Novel Method to Control Release of Lipophilic Drugs with High Potency from Silicone

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Silicone has been utilized as a carrier material for sustained release system of lipophilic drugs. Extensive studies revealed that drug release rate is influenced by factors such as physicochemical properties of the drug and additives.[1—5] When a lipophilic drug is highly potent at low concentrations, the drug release rate should be strictly controlled so as to avoid side effects. In this study, using vitamin D_3 (VD_3) as an example of such drugs, we investigated novel method to suppress initial burst and to modify drug release rate from silicone matrix. As a result, it was found that (a) addition of human serum albumin (HSA) suppressed initial burst and enhanced release rate in the later stage, resulting constant release of VD_3, (b) covering a matrix formulation with a membrane of low diffusivity (core-rod formulation) suppressed initial burst and released drug in a constant rate, and (3) using materials for which the drug has high affinity as dissolution solvent (reservoir formulation), the drug release rate was reduced.

Key words controlled release; silicone; lipophilic drug; diffusion

Silicone, which is mechanically flexible and biologically inert, has been extensively used for many biomedical applications. In the 1970s, much interest was focused on the use of silicone as a delivery system for lipophilic drugs. Norplant[®6] and Compudose[®7] are examples of commercialized silicone DDS and effective for long term with single administration, that is, five years and 100 d, respectively. In this way silicone was found to be suitable as DDS carrier material for lipophilic drugs. When a lipophilic drug which has high potency at low concentrations is applied for a silicone DDS, drug release rate should be strictly controlled. It has been reported that factors such as physicochemical properties of drugs, additives, membrane thickness and drug loading influence drug release rate from silicone matrix.[1—5] In this study, using vitamin D_3 (VD_3) as an example of lipophilic drugs which are highly potent at low concentrations, we investigated novel method to suppress initial burst and to modify drug release rate from silicone. This is the first report on continuous release of VD_3 from silicone.

Experimental

Materials Silicone samples (Silastic® MDX4-4210 Medical Grade Elastomer with Catalyst, Silastic® RX-50 Medical Grade Tubing, Silastic® Medical Adhesive Silicone Type A and Silastic® Q7-4750 Biomedical Grade ETR Elastomer Kit) were provided by Dow Corning Corporation (MI, U.S.A.). The MDX4-4210 is cross-linked by hydrosilylation when a base and a curing agent are mixed in a mass ratio of 10:1. The base consists mainly of dimethylvinylsiloxy-terminated polydimethylsiloxane, and the curing agent consists of a platinum catalyst and a cross-linker. Q7-4750 is cross-linked by hydrosilylation when Part A and Part B are mixed in equal portions. Part A consists of dimethylvinylsiloxy-terminated poly(dimethylsiloxane-co-methylvinylsiloxane) and a platinum catalyst. Part B consists of the same siloxane as Part A and a cross-linker. RX-50 is a tube sample prepared using Q7-4750. The tensile strength of MDX4-4210 and Q7-4750 is higher than 550 and 1250 psi, respectively. Medical Adhesive Silicone Type A is a one-component silicone adhesive.

$1\alpha,25$-$(OH)_2$ VD_3 was purchased from Biomol Research Laboratories, Inc. (PA, U.S.A.). 2,6-Di-t-butyl-p-cresol (BHT), DL-α-tocopherol (TP) and sodium azide were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Sudan II, which is a dye modeling for lipophilic drugs, was purchased from

Wako Pure Chemicals Industries, Ltd. (Osaka, Japan). Bovine serum albumin (BSA) and human serum albumin (HSA) Buminate® were purchased from SIGMA CHEMICAL CO. (MO, U.S.A.) and Baxter Healthcare Corporation (IL, U.S.A.), respectively.

Preparation of VD_3 Silicone Formulations Figure 1 shows the structure of the silicone formulations, and Table 1 lists their compositions.

Matrix Formulation (VD-1 and VD-2): The base and the curing agent of MDX4-4210 were mixed in a mass ratio of 10:1. TP and BHT (0.5% w/w each) were added to this mixture as anti-oxidants. Freeze-dried HSA powder (434.8 mg) was mixed with 1.00 g of MDX4-4210 to prepare VD-2. Each mixture was cast into a sheet, and 130 μl of VD_3 ethanol solution (concentration: 1.0 mg/ml) were placed on each film. Then, ethanol was removed under nitrogen flow and each mixture was kneaded to have VD_3 homogeneously distributed. Each mixture was then centrifugally deformed, filled into a Teflon tube with an inner diameter of 5.0 mm, and allowed to stand for 24 h to cure. After curing, each mixture was taken from the Teflon tube and cut into 10-mm-long pieces.

Core-rod Formulation (VD-3): MDX4-4210 (277 mg) containing 0.5% w/w TP and 0.5% w/w BHT was mixed with 186 μg VD_3 and centrifugally deformed *via* the same method as for matrix formulation. The mixture (52 mg) was filled in the middle of an RX-50 tube (3.0 mm outer diameter, 2.0 mm inner diameter, 50 mm length) and allowed to stand for 24 h to cure
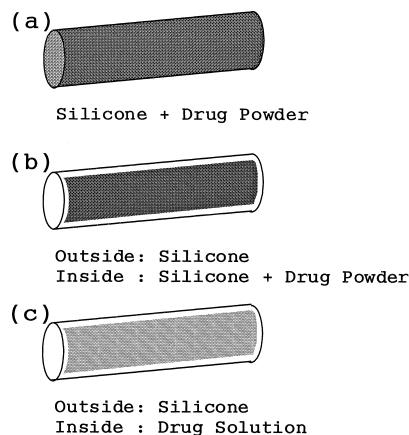

Fig. 1. Silicone Formulation

(a) Matrix formulation (VD-1 and VD-2), (b) core-rod formulation (VD-3), (c) reservoir formulation (VD-4).

Table 1.　Composition of VD$_3$ Silicone Formulations

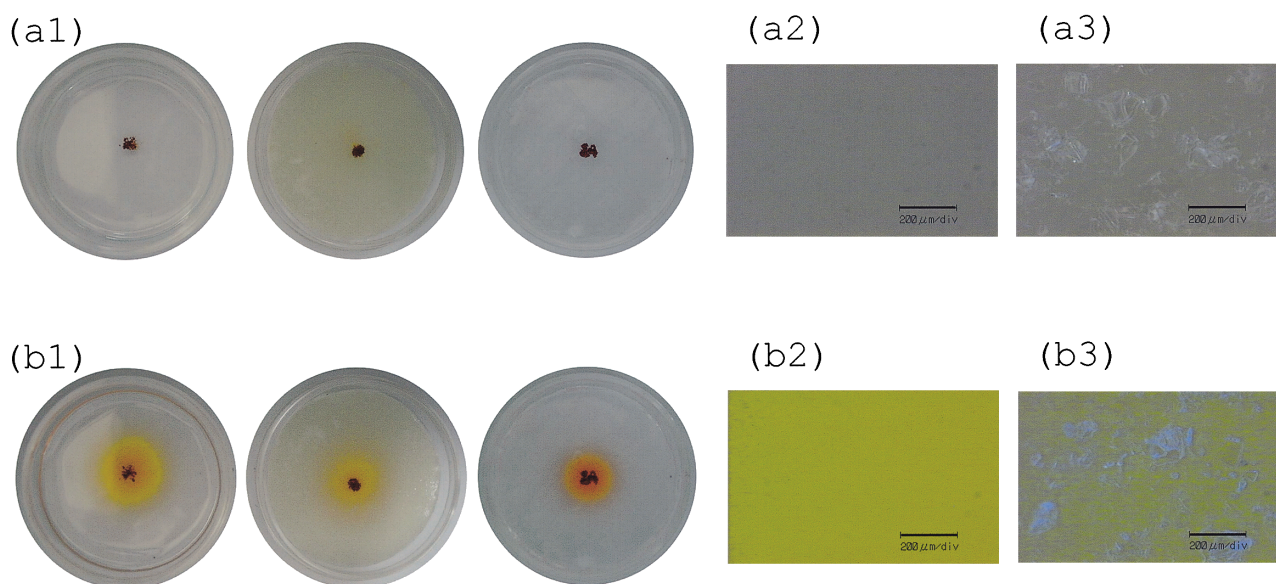|	Content (μg)	Formulation			
		Type	Size	Additive	Silicone
VD-1	43	Matrix	5φ×10	—	MDX4-4210
VD-2	45	Matrix	5φ×10	HSA 30% w/w	MDX4-4210
VD-3	32	Core-rod	3φ×15	—	Inside: MDX4-4210 Outside: Q7-4750
VD-4	38	Reservoir	3φ×15	TP	Q7-4750

Fig. 2.　Diffusion of Sudan II in Silicone

(a1) Initial; from the left, MDX4-4210, 30% w/w HSA MDX4-4210, Q7-4750, (a2) MDX4-4210 initial (×300), (a3) 30% w/w HSA MDX4-4210 initial (×300), (b1) after 72 h; from the left, MDX4-4210, 30% w/w HSA MDX4-4210, Q7-4750, (b2) MDX4-4210, after 72 h (×300), (b3) 30% w/w HSA MDX4-4210, after 72 h (×300). Bars in (a2), (a3), (b2) and (b3) indicate 200 μm.

the core section. MDX4-4210 was introduced into the tube at both ends of the tube to seal the ends; the mixture was allowed to stand for 24 h and the ends of the tube were cut off to adjust the length of the sealed portion at 2 mm.

Reservoir Formulations (VD-4): A small amount of MDX4-4210 was filled into an RX-50 tube (3.0 mm outer diameter, 2.0 mm inner diameter, 50 mm length) from both ends of the tube and cured to prepare a container with the length of the hollow-cylinder of 15 mm. The container was degassed by sticking one end with a needle, and a TP solution (46 μl) of VD$_3$ (concentration: 0.94 mg/ml) was injected from the other end using an syringe. The two holes were sealed with Medical Adhesive Silicone Type A.

Diffusion of Sudan II in Silicone　MDX4-4210, MDX4-4210 containing 30% w/w HSA, and Q7-4750 were cured in a 35-mm plastic petri dish. Sudan II (1 mg) was placed in the middle of the petri dish, and the diffusion of Sudan II was inspected either visually or with a digital microscope VH-6200 (KEYENCE CORPORATION, Osaka, Japan). Diffusion area (diameter) was measured at three points of the photographs (magnification; ×2) and the average was calculated.

VD$_3$ Release Study　Formulations were placed in a brown-glass test tube containing 3 ml of phosphate-buffered saline (PBS, pH 7.4) containing 0.05% BSA and 0.01% sodium azide and allowed to stand at 37 °C. The amount of VD$_3$ released into PBS during a specified period was determined by reversed-phase HPLC. HPLC was performed by an isocratic condition and the mobile phase was 55% acetonitrile. The flow rate was 1.0 ml/min. Waters μ-Bondasphere 5 μ C18-100 Å column (3.9×150 mm) was used and UV detection was performed at 265 nm.

Formulations which rapidly released VD$_3$ *in vitro* elevated blood calcium concentration soon after administration *in vivo*, indicating *in vitro* release study has correlation with *in vivo* study.

Table 2.　Diffusion Area of Sudan II

	24 h Diffusion area (mm)	72 h Diffusion area (mm)
MDX4-4210	10.5±0.4	18.3±0.7
30% w/w HSA MDX4-4210	8.1±0.1	14.4±0.7
Q7-4750	6.4±0.1	10.3±0.2

Results

Diffusion of Sudan II in Silicone　We investigated the effect of HSA added to MDX4-4210 on the diffusion of lipophilic drugs using Sudan II as a model. We also investigated the diffusion rates of Sudan II in different silicone matrices. Since silicone is transparent and Sudan II colors red, the trace of Sudan II diffusion was identified by color change. The region of Sudan II diffusion was largest with MDX4-4210, followed by MDX4-4210 containing 30% w/w HSA (Table 2, Fig. 2-b1). With Q7-4750, the region of diffusion was smallest. Observation by a digital microscope (×300) showed that the MDX4-4210 sheet was dyed homogeneously (Fig. 2-b2). On the other hand, in the MDX4-4210 sheet containing 30% w/w HSA, only silicone was dyed, keeping HSA unchanged (Fig. 2-b3). These results showed that diffusion profile of Sudan II, modeling for a lipophilic
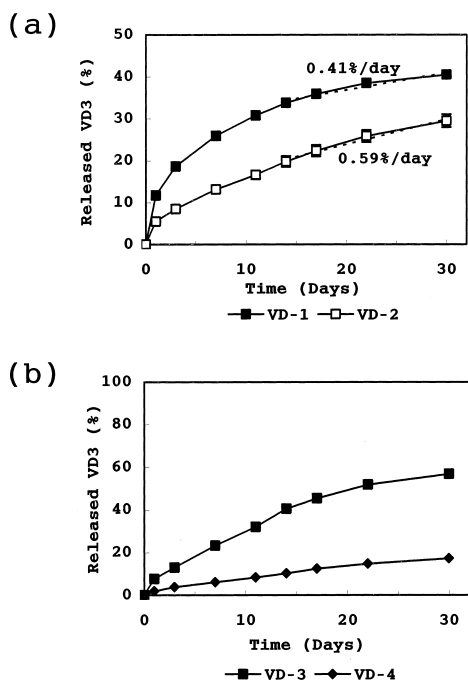
(a)

(b)

Fig. 3. Release of VD₃ from Silicone Formulations

(a) Controlled release by addition of HSA, (b) controlled release from different types of formulations (average for $n=2$).

drug, could be controlled by adding HSA to a silicone matrix.

Controlled Release of VD₃ by HSA Matrix formulations VD-1 and VD-2, which contained no additives and 30% w/w HSA respectively, continuously released VD₃ over one month (Fig. 3a, solid lines). While VD-1 released 11.8% of VD₃ in the first day, VD-2 released only 5.5%. The VD₃ release rates in the later stage, that is, 14—30 d, were calculated by the least-squares method and indicated in Fig. 3a as dotted lines. The results were 0.41%/d for VD-1 and 0.59%/d for VD-2. The monthly amount of release was 41% for VD-1 and 30% for VD-2. Thus, the release of VD₃ representing a lipophilic drug could be controlled by adding HSA to a silicone matrix.

Controlled Release of VD₃ from Different Formulation Types The release of VD₃ from VD-1 (matrix formulation) was initially rapid and gradually slowed down (Fig. 3a). In contrast, in the case of VD-3 (core-rod formulation) and VD-4 (reservoir formulation), the initial burst was suppressed and the release continued in almost same rate (Fig. 3b). The release of VD₃ from VD-4 was slower than that from VD-3, and the monthly amount of release was 57% for VD-3 and 17% for VD-4. Thus, the release of VD₃ could also be controlled by VD₃ incorporating form in silicone matrix.

Discussion

A number of investigations have been carried out on the sustained release of lipophilic drugs from silicone matrices. It has been reported that substances such as glycerin and polyethylene glycol (PEG) promoted the release of lipophilic drugs by inducing swelling of the formulation.[1—5] Pfister *et al.*[4] reported that the release rate of testosterone was decreased by adding titanium dioxide or barium sulfate to a silicone matrix. However, they did not clarify what factors were

affected by these additives.

When a drug is dissolved in a cylindrical matrix formulation, the rate of drug release is given by Eq. 1,[8]

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{pr^2}\right)^{1/2} - \frac{Dt}{r^2} \quad \left(\text{in case of } \frac{M_t}{M_\infty} \leq 0.4\right) \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the total amount of drug contained in the formulation, D is the diffusion coefficient in a carrier material, and r is the diameter of the formulation. Equation 1 shows that the rate of drug release can be controlled by varying D under a constant r.

In general, matrix formulations show an initial rapid release. According to Eq. 1, decrease of D in the initial period should be effective to suppress initial rapid release. From the fact that the release rate of testosterone was decreased by insoluble substances such as titanium dioxide, D of testosterone in silicone should have been suppressed by these substances. We considered that titanium dioxide, which does not have affinity either with testosterone or with silicone, blocked the diffusion of testosterone. We expected that HSA, which is water-soluble and therefore has a low affinity with lipophilic drugs and silicone, should have a similar effect. Since HSA does not swell strongly, significant promotion of drug release would not occur unlike glycerin or PEG. In addition, when 30% w/w HSA is added to silicone, it is gradually released from silicone matrix.[9] Therefore, decrease of D by HSA addition should be observed only in the early period of release experiments.

In this investigation, it was found that the addition of HSA to a silicone matrix obviously delayed the diffusion rate of Sudan II (Fig. 2-b1). This might have occurred by the HSA powder blocking Sudan II diffusion in the silicone matrix. In a digital microscope observation, silicone matrix in the route of Sudan II diffusion was colored red, but HSA powder was not dyed (Fig. 2-b3). From this observation, VD₃ is considered not to diffuse through HSA powder, but through silicone phase. This finding supports the above consideration, that is, HSA blocked the diffusion of VD₃ in a silicone matrix.

The change in D by the addition of HSA was reflected in the release of VD₃ from a silicone matrix. The initial release rate of VD-2 was slower than that of VD-1 which does not contain any additives (Fig. 3a). However, the VD₃ release rate in 14—30 d from VD-2 was 1.4 fold of VD-1. This reversal could be explained as follows; when HSA exists in silicone matrix, it disturbs VD₃ diffusion. However, once HSA is released, VD₃ diffusion is no longer suppressed. On the contrary, since water-filled channels were formed inside the formulation,[9,10] remained VD₃ contacts with water easier than initial phase and the fact accelerates VD₃ release (Fig. 4a).

Aiming at a constant release, we investigated the core-rod (VD-3) and reservoir (VD-4) formulations. When a lipophilic drug is enclosed within a polymer container above the saturated concentration, the release rate of the drug is given by Eq. 2,[8]

$$\frac{dM_t}{dt} = \frac{2\pi h D K \Delta C}{\ln\left(r_o / r_i\right)} \quad (2)$$

where dM_t/dt is the drug release rate at time t, h is the core-
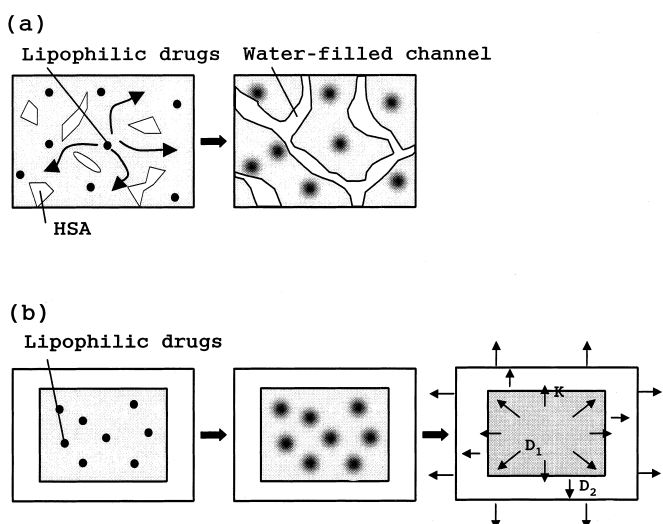
Fig. 4. Diagram Showing the Process of Lipophilic Drug Release from Silicone Formulations

(a) addition of HSA suppressed initial burst and enhanced release rate in the later stage, and (b) covering a matrix formulation with a membrane of low diffusivity (core-rod formulation) suppressed initial burst and released drug in a constant rate. In addition, using materials for which the drug has high affinity as dissolution solvent (reservoir formulation), the drug-release rate was reduced.

section length of the formulation, K is the distribution coefficient of the drug between the membrane and the core section, ΔC is the difference in concentration between the outside and the inside of the membrane, and r_0 and r_i are the outer and inner diameters of the formulation, respectively. While drug exists over the saturated concentration, ΔC is constant and the drug is released at a constant rate during the steady state. In the case of core-rod formulations, diffusion rate of drugs in membrane material (D_2 in Fig. 4b) has to be smaller than that in core material (D_1 in Fig. 4b) in order to have a constant release. We observed that the diffusion rates of Sudan II in MDX4-4210 and Q7-4750. The distance of Sudan II diffusion during 3 days was shorter with Q7-4750 than that with MDX4-4210 (Fig. 2-b1). Therefore, the diffusion of lipophilic drugs in Q7-4750 should be slower than that in MDX4-4210. While a base siloxane of MDX4-4210 has vinyl groups only at ends of molecules, that of Q7-4750 has vinyl groups not only at ends but also at side chains. This fact should result in higher cross-linking density of Q7-4750 than MDX4-4210, leading to slower drug diffusion in Q7-4750 than in MDX4-4210. Based on the result, we used an RX-50 tube made from Q7-4750 as a matrix membrane for VD_3. It was found that VD_3 was released from VD-3 *in vitro* at an almost constant rate (Fig. 3b). Based on this finding, we consider that the VD_3 concentration in the core section of VD-3 exceeded the saturation value, and that the RX-50 tube acted as a diffusion barrier. This is also supported by the fact that, although VD_3 content per unit volume of the VD-3 core section is higher than that of VD-1, the amount of VD_3 released per unit surface area on the first day was smaller for

VD-3 ($0.016\,\mu g/mm^2$) than for VD-1 ($0.025\,\mu g/mm^2$). In contrast, with respect to VD-3, the release rate gradually decreased from 14 d (accumulated amount of release: approximately 40%). Based on this finding, we consider that approximately 60% of the initial amount of VD_3 in VD-3 (approximately $400\,\mu g/cm^3$) is the saturated concentration in MDX4-4210. VD_3 was also released at a constant rate from VD-4 as well as VD-3, but the release rate of VD-4 was approximately 1/3 as low as that of VD-3. Among the parameters shown in Eq. 2, VD_3 content, formulation size and membrane material are the same in VD-3 and VD-4. The only difference exists in K. VD_3 exists in MDX4-4210 in the case of VD-3, and in TP in the case of VD-4. Probably K is smaller in the RX-50/TP pair than in the RX-50/MDX4-4210 pair. It is reported that octanol-water partition coefficients ($\log P$) are 1.28,[11] 1.09[12] and 5[13] for VD_3, TP, and polydimethylsiloxane fluid, respectively. Since RX-50 and MDX4-4210 are highly cross-linked polydimethylsiloxane rubber, their lipophilicity should be higher than fluid. VD_3 should have higher affinity to TP than MDX4-4210, because $\log P$ values are quite similar between VD_3 and TP.

In conclusion, addition of HSA to a silicone matrix suppresses the initial burst of VD_3 by reducing the diffusion rate. Having HSA released, the rate of VD_3 release is increased. Namely, addition of HSA enables to release VD_3 from matrix formulation in almost constant rate. Covering the surface of a matrix formulation with a membrane of low diffusivity can suppress initial burst and maintain constant rate of drug release. In addition, using materials for which the drug has high affinity as dissolution solvent, the drug-release rate can be reduced.

References and Notes
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