Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 261 (2003) 9–19
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

# Design of controlled-release formulation for ivermectin using silicone

H. Maeda [a,*], M. Brandon [b], A. Sano [a]

[a] *Formulation research Laboratories, Sumitomo Pharmaceuticals Co. Ltd., 3-45 Kurakakiuchi 1-Chome, Ibaraki-shi, Osaka 567-0878, Japan*

[b] *Smart Drug Systems, 181 South Broad Street, Suite 102, Pawcatuck, CT 06379, USA*

Received 11 December 2002; received in revised form 3 March 2003; accepted 13 April 2003

**Abstract**

The purpose of this study was to design a formulation using silicone as carrier, so that release of ivermectin (IVM) can be controlled for a long period of time. The lateral side of a cylindrical matrix-type formulation composed of IVM and silicone was covered with silicone to obtain a covered-rod (CR) formulation. With this formulation, linear release of IVM was obtained. With addition of polyethylene glycol 4000 (PEG), release of IVM was accelerated. In a trial with subcutaneous administration to mice, blood concentration of IVM was maintained within one-order over a period of 3 months. The velocity of release of IVM from CR preparation depended on the change in solubility of IVM by additives, and in the case of a formulation with addition of desoxycholate sodium, linear in vitro release of IVM was observed over a period of 1 year.


*Keywords:* Silicone; Controlled release; Ivermectin; Covered-rod; Solubility

## 1. Introduction

Ivermectin (IVM) (Campbell et al., 1983) is being used widely as an anthelminthic for endoparasites or ectoparasites in cattle, swine, horses, dogs, etc. (Plumb, 1999; Williams and Broussard, 1995). For livestock, such as cattle and swine, IVM formulations are mainly being used in the form of liquid injection. However, the duration of effect is about 1 month (Toutain et al., 1997). Therefore, in order to maintain anthelminthic effect for a long period of time, repeated administration is necessary. Oral formulations are being used for heartworm in dogs. However, administration once a month is necessary. Thus, from the standpoint of reducing the labor of administration to livestock, and preventing infection resulting from forgetting administration to dogs, a long sustained-release formulation that can reduce administration frequency would be useful.

We have studied long sustained-release formulations for protein drugs, i.e. interferon (IFN) or human serum albumin (HSA) with silicone as a carrier. The product is a cylindrical sustained-release formulation of covered-rod type (CR silicone formulation). The inner component is silicone matrix containing a protein drug, and the lateral side of the matrix is covered with a silicone outer layer. This formulation makes it possible to obtain zero-order release of protein drugs (Kajihara et al., 2001). It is considered possible to obtain a long sustained-release formulation of IVM by expanding

* Corresponding author. Tel.: +81-726-27-8146; fax: +81-726-27-8140.
*E-mail address:* maedah@sumitomopharm.co.jp (H. Maeda).

0378-5173/$ – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0378-5173(03)00293-X

this CR silicone formulation. On the other hand, drug release from CR silicone formulation differs considerably between protein drugs, which are highly soluble in water, and IVM, which is hydrophobic. Therefore, it is necessary to establish a new method of release control. In this study, therefore, we studied a new method of release control for the purpose of designing a sustained-release formulation of IVM.

## 2. Materials and methods

### 2.1. Materials

Silicone elastomer (Silastic Q7-4750) was obtained from Dow Corning (MI, USA). Ivermectin was obtained from Sigma (Missouri, USA), polyethylene glycol (average molecular weight is 4000) from Sanyo Chemical Industries, Ltd. (Kyoto, Japan), desoxycholate sodium (DOC) from Wako Pure Chemical Industries, Ltd. (Osaka, Japan), sucrose (SUC) from Dainihon Meiji Seitou Co., Ltd. (Tokyo, Japan), and polyoxyethylene polyoxypropylene glycol (Pluronic F-68 PEPPG) from Asahi Denka Co., Ltd. (Tokyo, Japan).

Normal BALB/c mice (4.5 weeks of age, males) were purchased from Charles River Japan Inc., and were used after quarantine for 1 week. During the experiment, animals were given feed and water ad libitum.

### 2.2. Preparation of silicone formulation

The formulations prepared are shown in Table 1.

Drug powders contained in the formulations were prepared as follows: For drug powders consisting of IVM that were used in Samples C–G, the raw materials obtained were crushed and sieved (212 μm). For drug powders consisting of 17% IVM and 83% PEG used for Sample A or B, a solution of 0.2 g of IVM in 1 ml of methanol was mixed with a solution of 1.0 g of PEG in 5 ml of methanol, and the mixture was dried under a nitrogen stream, followed by drying under reduced pressure. The substance obtained was crushed and sieved (212 μm). Drug powders of other composition ratios, used for Samples H and I, were each prepared by changing mixing ratios of IVM and PEG. The drug powder consisting of IVM and PEPPG that was used for Sample K was prepared in the same manner as above, using PEPPG instead of PEG. The drug powder consisting of 17% IVM and 83% SUC that was used for Sample J was prepared by violently mixing 0.2 g of sieved (212 μm) IVM powder with 1.0 g of sieved (212 μm) SUC powder. The powder drug consisting of 50% IVM and 50% SUC that was used for Sample L was prepared in the same manner by mixing 3.38 g each of the powders. The powder drug consisting of 50% IVM, 33% DOC, and 17% SUC that was used for Sample M was prepared as follows: 6.75 g of IVM and 4.50 g of DOC were dissolved in 50 ml of methanol. The solution was dried under a nitrogen stream, followed by drying under reduced pressure, and 5.63 g of drug powder consisting of IVM and DOC obtained by crushing and sieving (212 μm) and 1.13 g of sieved (212 μm) SUC powder were violently mixed.

Silicone elastomer (Silastic Q7-4750) is supplied as a two-component (Part A and Part B) kit. Part A contains a platinum catalyst and Part B a cross-linker with a silicone hydride group (Si–H). When Part A is mixed with Part B, the silicone hydride group and silicone vinyl unit produce an addition reaction in the presence of catalyst, with resultant crosslinking.

Sample A, which is a matrix-type formulation without covering by an outer layer, was prepared as follows: Part A (526 mg), Part B (526 mg), and drug powder (450 mg) were kneaded together. The kneaded product was filled in a cylinder, and extruded through an extruding nozzle to obtain a cylindrical rod. The extruded rod obtained was incubated for a week at 37 °C to cure it. While testing, it was cut into lengths needed to conduct the test.

The following is an example of preparation of Sample B, which is a CR type formulation with a covering. Other Samples C–M were also prepared in the same manner, though on difference scales. Part A (526 mg), Part B (526 mg), and drug powder (450 mg) were kneaded together, and used as an inner layer component. Separately, Part A (50 g) and Part B (50 g) were kneaded together, and used as an outer layer component. The inner layer component and the outer layer component were each filled in a separate cylinder, and extruded simultaneously through an extruding nozzle for concentric cylindrical molding, thereby obtaining a cylindrical rod. The extruded rod obtained was incubated for a week at 37 °C to cure it. For testing, the rod was cut into lengths needed to conduct the test.

Table 1
Composition of silicone formulations

| Sample number | Type | Diameter (mm) | Length (mm) | Powder/inner layer (%) | Composition of powder (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | IVM | PEG | SUC | PEPPG | DOC |
| A | M | 1.5 | 5 | 30 | 17 | 83 | | | |
| B | CR | 2 | 5 | 30 | 17 | 83 | | | |
| C | CR | 2 | 5 | 30 | 100 | | | | |
| D | CR | 1.7 | 5 | 20 | 100 | | | | |
| E | CR | 1.7 | 5 | 30 | 100 | | | | |
| F | CR | 1.7 | 5 | 40 | 100 | | | | |
| G | CR | 1.7 | 5 | 50 | 100 | | | | |
| H | CR | 2 | 5 | 30 | 83 | 17 | | | |
| I | CR | 2 | 5 | 30 | 50 | 50 | | | |
| J | CR | 2 | 5 | 30 | 17 | | 83 | | |
| K | CR | 2 | 5 | 30 | 17 | | | 83 | |
| L | CR | 3 | 10 | 30 | 50 | | 50 | | |
| M | CR | 3 | 10 | 30 | 50 | | 17 | | 33 |

IVM: ivermectin, PEG: polyethylene glycol (average molecular weight is 4000), SUC: sucrose, PEPPG: polyoxyethylene polyoxypropylene glycol (Pluronic F-68), DOC: desoxycholate sodium. M: matrix, CR: covered-rod.

### 2.3. Measurement of drug content in a formulation

After measurement of the weight of the formulation, the formulation was axially cut into four parts, and methanol was added at 2 ml per 10 mg of the formulation. The formulation was incubated for 3 days at 37 °C, and IVM was eluted. Then, IVM concentration in the eluate was measured by reverse-phase high performance liquid chromatography (HPLC) to determine drug content in the formulation. Analysis by HPLC was performed under the following conditions: With a C18 symmetry column (0.46 cm i.d × 5 cm, mean particle size 3.5 μm; Waters MA, USA), water was used as mobile phase A and methanol as mobile phase B. The flow rate of mobile phase was set at 1.5 ml/min. Mobile phase B was increased from 70 to 80% in 4 min, and then 80% was maintained for 8 min. Column temperature was set at 50 °C, and detection was performed by measuring absorption at 245 nm.

### 2.4. In vitro release test

Each of the Samples A–G shown in Table 1 was immersed in 1 ml of phosphate-buffered salts (PBS) containing 0.3% (w/w) Tween20 (release test solution), which was allowed to stand at 37 °C. (A–C, $n = 2$; D–G, $n = 3$). At a prearranged time point, the release test solution was entirely replaced, and the IVM concentration in the collected release test solution was measured by HPLC (under the same conditions as for IVM content in the formulation) to obtain the release profile. For Samples L and M shown in Table 1, the release profiles were obtained in the same manner ($n = 3$). In these cases, IVM content remaining in the sample was determined after completion of the test in the same manner as for measurement of drug content in the formulation.

Separately, each of Samples A–C was immersed in 1 ml of release test solution to which pigment (blue No. 1) had been added. After 2 weeks of incubation at 37 °C, each formulation was axially cut into two parts, and penetration of release test solution into each preparation was observed by examining the cut aspect of the preparation.

### 2.5. Measurement of solubility of IVM in the drug powder

The drug powders shown in Table 2 were prepared as follows: A mixture of IVM and PEPPG of the same quantity was dissolved in methanol, and dried under a nitrogen stream, followed by drying under reduced pressure. The substance obtained was crushed and sieved (212 μm), thereby obtaining Powder 1. Powder 5 with DOC as additive was prepared in the same manner. For Powder 2 with PEG as additive, the drug

Table 2
Solubility of IVM contained in various drug powders in PBS containing 1.5% (w/w) BSA at 25 °C

| Drug powder number | Composition | Form | Solubility of IVM (μg/ml) |
|---|---|---|---|
| 1 | IVM + PEPPG (50:50) | Homogeneous | 1805 |
| 2 | IVM + PEG (50:50) | Homogeneous | 20 |
| 3 | IVM + SUC (50:50) | Mixed | 8 |
| 4 | IVM | – | 4 |
| 5 | IVM + DOC (50:50) | Homogeneous | >30000 |

powder used for Sample I of the CR silicone formulation was used. For Powder 3 with SUC as additive, the drug powder used for Sample L of the CR silicone formulation was used. For Powder 4 containing IVM alone, the drug powder used for Sample C of the CR silicone preparation was used.

Sixty milligrams of each drug powder (30 mg of Powder 4 containing only IVM) was weighed, to which was added 1 ml of PBS containing 1.5% (w/w) bovine serum albumin (IVM concentration, 30 mg/ml). After vigorous stirring, the mixture was allowed to stand for 1 h at 25 °C. After vigorous stirring again, it was centrifuged, and 400 μl of the supernatant was collected, which was centrifuged again. Seventy microliters of the supernatant was collected, and diluted appropriately (two-fold or more) with PBS containing 3% (w/w) Tween20. Then, IVM concentration was measured with HPLC (under the same conditions as for measurement of drug content) to determine the solubility of IVM in each drug powder.

### 2.6. Plasma IVM concentration, and profile of remaining IVM in the formulation

Sample B shown in Table 1 was administered subcutaneously at one pellet per head (dose 700 μg per pellet per head) in the back of mice under anesthesia. At 3, 7, 14, 28, 56 or 84 days after administration, all blood was collected from the heart under ether anesthesia, after which the preparation was collected ($n = 6$ at each time point). Collected blood was treated with ethylenediaminetetraacetic acid (EDTA) and then centrifuged to obtain plasma, which was preserved at −40 °C until measurement. Plasma IVM concentration was measured according to the reported method (Chiou et al., 1987). The IVM remaining in the collected samples was measured using the above-mentioned method for measurement of drug content in the formulations. In the present study, mice, which are the smallest experimental animals available, were used to detect sufficient IVM plasma levels.

IVM solutions obtained by diluting commercially available Ivomec injection (10 mg/ml), 10-fold (1 mg/ml), and 100-fold (0.1 mg/ml) with 40% glycerol formal–60% propylene glycol were each administered subcutaneously in the back of mice (100 μg per head and 10 μg per head). As for Sample B, plasma was collected at 3 and 7 h, and 1, 2, 3, 7, 14 and 21 days after administration, and plasma IVM concentration was measured ($n = 3$ at each time point).

Also, for Samples H–K shown in Table 1, IVM remaining in the sample after subcutaneous administration to mice was measured ($n = 3$ at each time point), as for Sample B.

## 3. Results

### 3.1. Release profile

Fig. 1 shows a covered-rod type cylindrical sustained-release preparation (CR silicone formulation), consisting of a silicone inner layer component containing IVM and a silicone outer layer which covers the lateral side of the inner layer. In vitro release tests were conducted, using Sample C, which is a CR silicone formulation, Sample B, which is a CR silicone formulation whose inner layer contains drug powder of IVM and PEG (17:83), and Sample A, which is a matrix-type formulation obtained by removing the outer layer from Sample B. The results are shown in Fig. 2. The CR silicone preparation not containing PEG (Sample C) exhibited a zero-order release profile. By adding PEG to Sample C (Sample B), IVM release was accelerated while maintaining a zero-order profile. On the other hand,

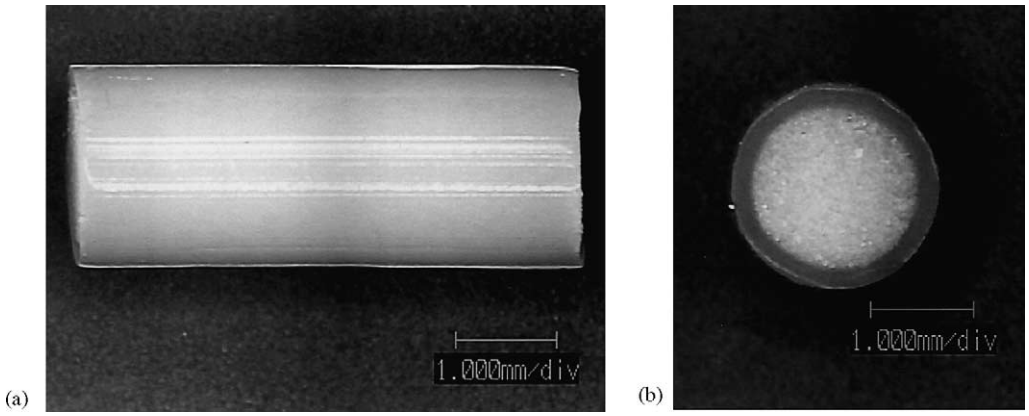


Fig. 1. The lateral side (a) and cross-section (b) of CR silicone formulation.

with matrix-type Sample A obtained by removing the outer layer from Sample B, IVM release was rapid in the early stage, with a first-order release profile.

For infiltration of the release test solution into the formulation, the results of observation are shown in Fig. 3. In Sample A of matrix type, the test solution infiltrated from the entire surface of the formulation. In Samples B and C of CR type, however, no infiltration was observed from the covering layer, and infiltration was noted only at the cross-sections where the inner layer was exposed to the surface.

The time course of change in plasma IVM concentration after subcutaneous administration of Sample B to mice (dose 700 μg per pellet per head, $n = 6$), and the profile of IVM remaining in the formulation are shown in Figs. 4 and 6a. The time course of change in plasma IVM concentration after administration of IVM solution (dose 100 μg of IVM per head and 10 μg of IVM per head, $n = 3$) is also shown in Fig. 4. With Sample B, a CR silicone formulation containing PEG, the plasma concentration of IVM maintained a range of one-order over a period of 84 days examined, and after day 84, IVM of 20 ng/ml or more was detected. Concerning the plasma concentration of IVM in administration of IVM solution, none was detected 21 days after administration at 100 μg of IVM per

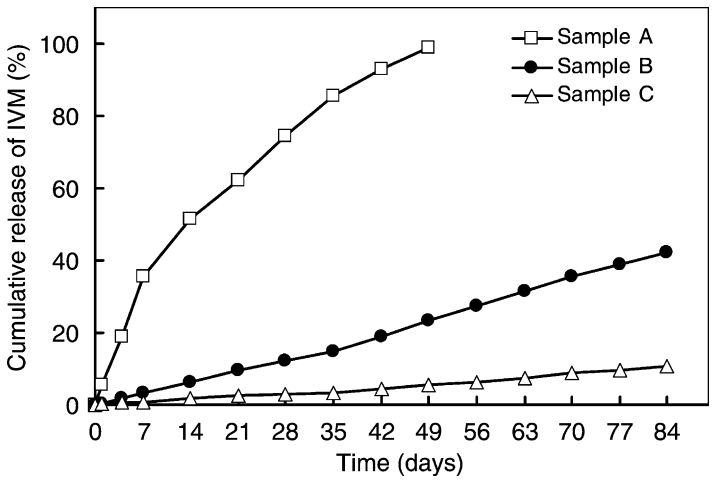


Fig. 2. In vitro release profile of IVM from: (□) matrix formulation (Sample A), (●) CR silicone formulation with addition of PEG (Sample B), and (△) CR silicone formulation not containing additive (Sample C). The numerical value at each time point is the mean value ($n = 2$).

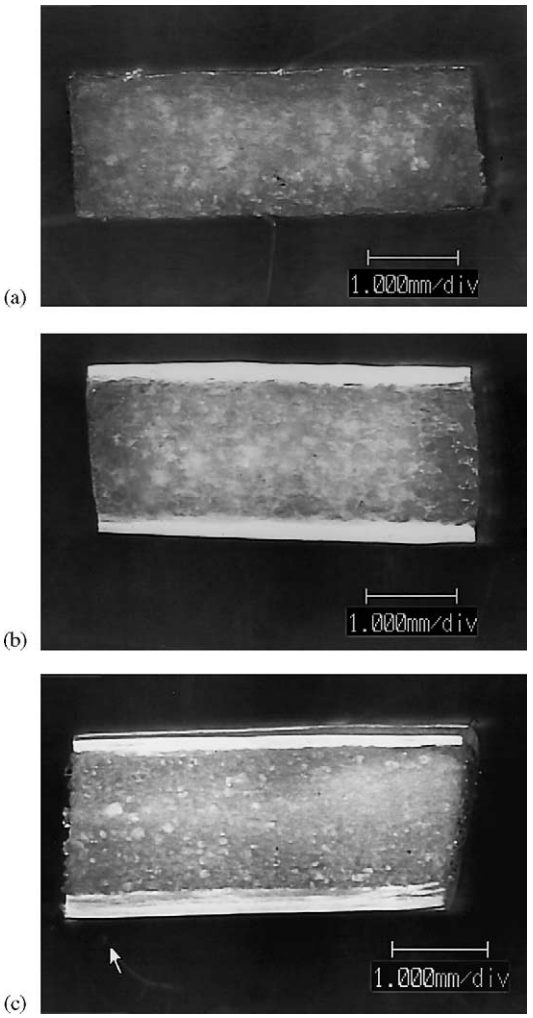


Fig. 3. Infiltration into sample of the release test solution with addition of pigment: picture of the inside of the formulation when it was axially cut into two parts 2 weeks after the test: (a) matrix formulation (Sample A), (b) CR silicone formulation with addition of PEG (Sample B), and (c) CR silicone formulation not containing additive (Sample C).

head; and with administration at 10 μg of IVM per head, none was detected 14 days after administration (1 ng/ml or less). In the case of Sample B, about 30% of IVM was released during the first week. After that, about 70% of IVM was released by day 84, the last time point of the period examined. Thus, linear release of IVM was maintained.

### *3.2. Influence of IVM content of formulation on release profile*

The content of IVM powder contained in the inner layer of the formulation was changed, and resultant changes in release behavior were examined. The results are shown in Fig. 5. With increase in content of IVM powder, the ratio of the amount of IVM released against the amount of IVM contained in the formulation before the test, i.e. the release rate, decreased.

### *3.3. Influence of composition of drug powders on release profile*

With regard to the composition of drug powders contained in the inner layer of the formulation, the profile of IVM remaining in the formulation was examined after subcutaneous administration to mice in the back, of the aforementioned Sample B containing IVM and PEG at 17:83, Sample I with IVM and PEG at 50:50, and Sample H with IVM and PEG at 83:17. When the ratio of IVM and additive was 17:83, the same examination was made of Sample J with SUC as additive, and Sample K with PEPPG. The results of each examination are shown in Figs. 6 and 7. The ratio of IVM remaining increased with decrease in the ratio of PEG in formulation with IVM and PEG. When the additive was changed, the ratio of IVM remaining increased in the order of PEPPG < PEG < SUC.

### *3.4. Solubility of drug powder*

As shown in Table 2, a study was made of the solubility of drug powder consisting of IVM and various additives in PBS containing 1.5% (w/w) bovine serum albumin. Compared with IVM powder not containing additive, the additive improved the solubility of IVM, and the effect increased in the order of SUC < PEG < PEPPG < DOC. With addition of SUC, the solubility of IVM was 8 μg/ml. In contrast, IVM was completely dissolved with addition of DOC at a special study rate of 30 mg/ml.

### *3.5. Formulation with addition of DOC*

In designing the formulation, it is necessary to increase the IVM content of the formulation. On the other hand, as seen from Fig. 5 and 6a, it was shown

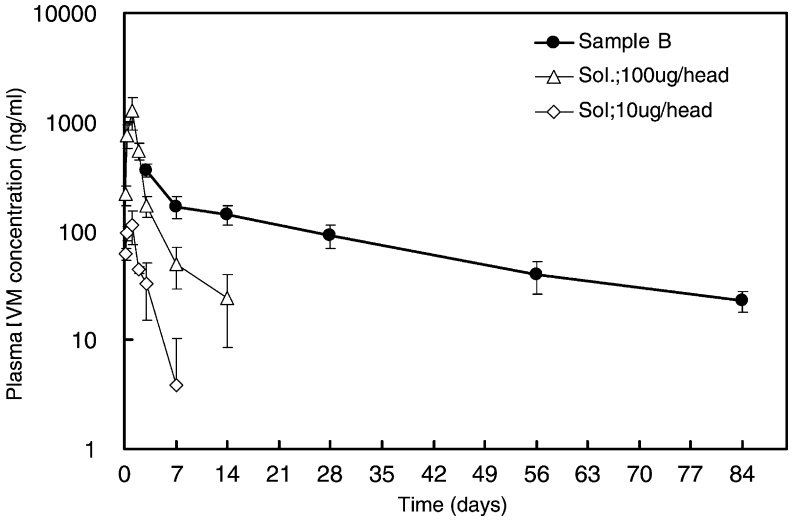


Fig. 4. Time course of changes plasma IVM concentration after subcutaneous administration to mice: (●) CR silicone formulation (Sample B), (△) IVM solution (100 μg of IVM per head), and (◇) IVM solution (10 μg of IVM per head). The numerical value at each time point is the mean ± S.D. (CR silicone formulation, $n = 6$; IVM solution, $n = 3$).

that with increasing IVM content in the formulation, release of IVM was suppressed. It was also found that DOC markedly increased the solubility of IVM (Table 2). Therefore, it was expected that the addition of DOC to a formulation would accelerate release of IVM from formulation containing a high level of IVM. Consequently, comparison was made of in vitro release profile between Sample M containing IVM, DOC, and SUC at 50:33:17 and Sample L which does not contain DOC, and contains only IVM and SUC at 50:50. With Sample L which does not contain DOC, release rate decreased about 8 weeks after the test.

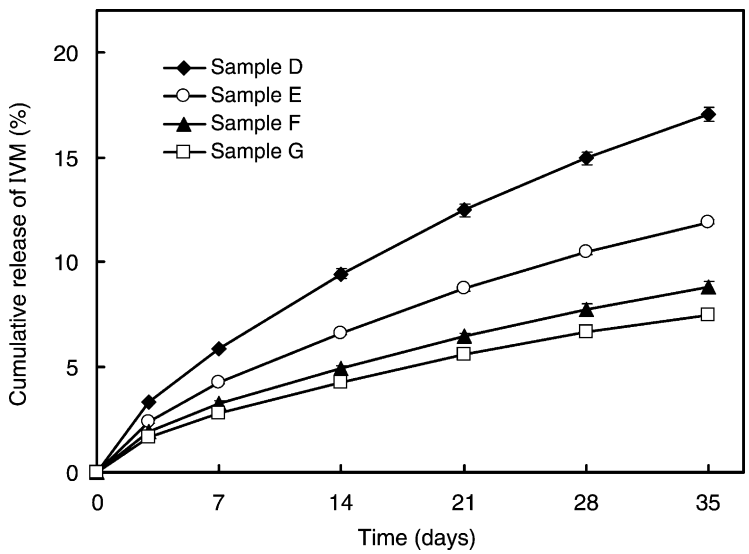


Fig. 5. In vitro release profile from CR silicone formulations with different contents of IVM powder: (◆) 20% (Sample D), (○) 30% (Sample E), (▲) 40% (Sample F), and (□) 50% (Sample G). The numerical value at each time point is the mean ± S.D. ($n = 3$).

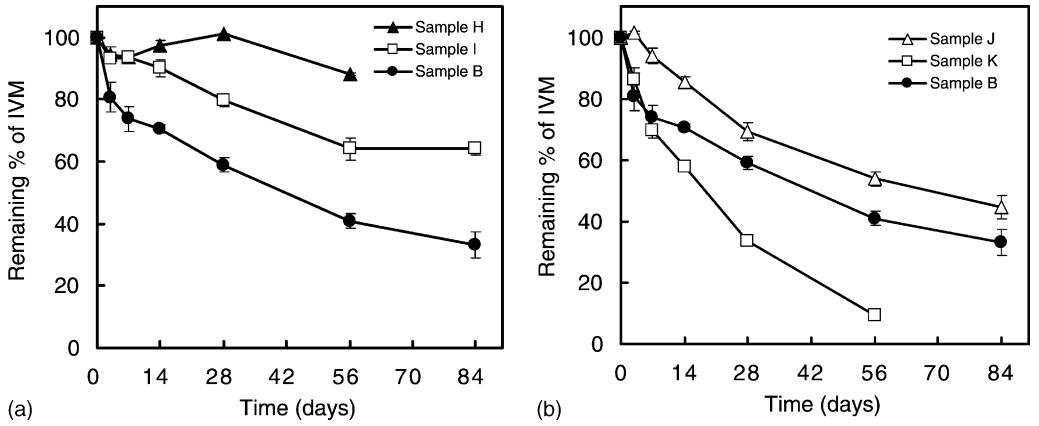


Fig. 6. Profile of IVM remaining in the CR silicone formulation after subcutaneous administration to mice. (a) Ratio of IVM:PEG is (▲) 83:17 (Sample H), (□) 50:50 (Sample I) and (●) 17:83 (Sample B). (b) Ratio of IVM:additive is 17:83, with additive (△) SUC (Sample J), (□) PEPPG (Sample K), and (●) PEG (Sample B). The numerical value at each time point is the mean ± S.D. ($n = 6$, Sample B; $n = 3$ for the other samples).

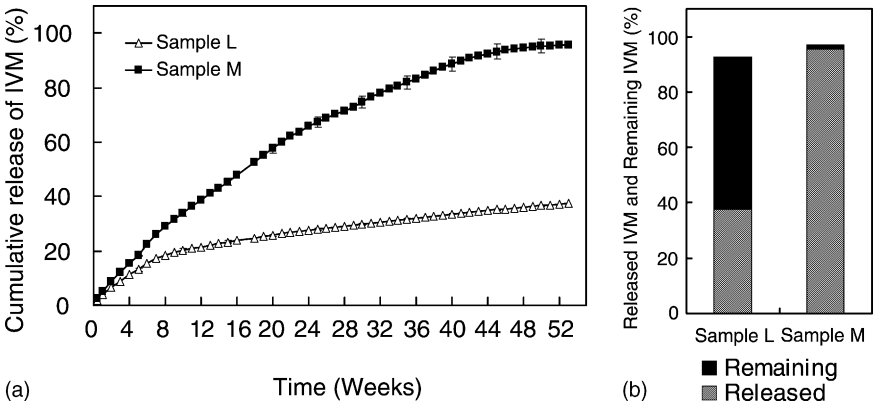


Fig. 7. In vitro release profile of IVM from: (△) CR silicone formulation (Sample L) containing IVM:SUC (50:50) and (■) CR silicone formulation (Sample M) containing IVM:DOC:SUC (50:33:17), and IVM released and remaining in the formulation. The numerical value at each time point is the mean ± S.D. ($n = 3$).

On the other hand, with Sample M containing DOC, linear release of IVM was maintained over a period of nearly 1 year. At the end of the test, the total of IVM released and the remaining IVM in the sample was more than 95%.

## 4. Discussion

The release profiles of protein drugs of CR silicone formulations have been reported as follows (Kajihara et al., 2001). First, the protein drug on the surface of both ends (cross-sections) of the formulation is dissolved and released. Since water cannot permeate silicone, water infiltrates into the formulation only through its cross-sections (both ends of the formulation), thereby dissolving the protein drug. The dissolved protein drug is diffused and released through the channel formed in the space created by dissolution of the protein drug. In this way, covering with silicone not only controls the initial burst caused by initial dissolution of the drug on the surface of cross-sections

but also confines water infiltration and drug release to the cross-sections. Linear release of the protein drug is thus achieved.

In the case of the hydrophobic drug IVM tested in this study as well, water infiltration occurs only at the cross-sections (Fig. 3), and long sustained-linear release of the drug is achieved by covering the formulation with an outer layer made of silicone (Sample B)(Figs. 2 and 4), compared to the uncovered matrix-type formulation (Sample A). Thus, covering was found to have effects on drug release profiles.

However, factors which determine the release profiles differ between water-soluble protein drugs and hydrophobic drugs. In the case of protein drugs, which are highly soluble in water, the drug is easily dissolved in the infiltrating water, leading to continuous diffusive release of the drug through the channel formed, as shown above. In such cases, dissolution does not work as a rate-limiting factor in release of the drug. On the other hand, release of a hydrophobic drug such as IVM differs from that of protein drugs, and dissolution of the drug is a rate-limiting factor in release of hydrophobic drugs. That is, since hydrophobic drugs are less soluble in water, water infiltration is slower than with formulations of protein drugs. Even when water infiltration occurs, the hydrophobic drug is not completely dissolved in the infiltrating water, and as a result the drug reaches a state of saturation. Thus, it seems likely that release of hydrophobic drugs from the cross-sections of a formulation is closely related to the solubility of the drug contained in the formulation. In cases of CR silicone formulations containing a mixture of protein drugs, i.e. IFN and HSA, within the inner layer, the release of IFN became more rapid as the protein content in the inner layer is increased, that is, as the volume of the channel is increased (Kajihara et al., 2001). In case of hydrophobic IVM, on the other hand, drug release decreased as IVM content increased (Fig. 5 and 6a). These results suggest that the solubility of drugs greatly affect their release from the cross-sections of this kind of formulation.

Therefore, changing the drug solubility appeared to be useful for controlling the release of IVM. The present study was undertaken to examine additives effective in controlling IVM release. In the study using PEG, replacement of 83% of IVM with PEG (IVM:PEG = 17:83, Sample B) resulted in an approximately four-fold increase in the velocity of IVM release, compared to the CR silicone formulation without PEG (Sample C) (Fig. 2). The velocity of IVM release varied as the IVM:PEG ratio was changed to 83:17 (Sample H) and to 50:50 (Sample I). The percentage of IVM remaining within the formulation 56 days after administration was $88.2 \pm 0.3\%$ for Sample H, $64.2 \pm 3.6\%$ for Sample I and $40.8 \pm 2.3\%$ for Sample B, as shown in Fig. 6a. We also analyzed the relationship between the solubility of IVM and the release of IVM from the formulation, using different additives (PEG, SUC, and PEPPG), as shown in Table 2 and Fig. 6b. The solubility of IVM increased in the following order in the presence of additives: SUC (8 μg/ml) < PEG (20 μg/ml) < PEPPG (1805 μg/ml). The percentages of IVM remaining in the formulation for 56 days after subcutaneous administration were $53.8 \pm 2.2\%$, $40.8 \pm 2.3\%$, and $9.3 \pm 0.6\%$ when SUC, PEG, and PEPPG were used as additives, respectively. Thus, release of IVM from the formulation was fastest in the presence of PEPPG and slowest in the presence of SUC (SUC ≤ PEG < PEPPG). This result, combined with the finding that SUC slightly promoted the dissolution of IVM, while PEG and PEPPG promoted its dissolution well, suggests that an increase in the concentration of dissolved IVM within the inner layer's channel promoted the release of the drug via this channel. It was thus confirmed that drug formulations with varying drug release profiles can be designed by using different additives.

Differences in drug release profiles depending on the additives used were examined by calculating the release rate parameters using the following equation:

$Mt/M = k \times t^n$, where $Mt/M$ denotes the fraction released by time $t$, $n$ is an exponent related to the drug release mechanism, and $k$ is a rate constant. In this equation, $n = 1$ corresponds to zero-order release, and $n = 0.5$ indicates a Fickian diffusion (Peppas, 1985). For Sample J (with SUC added), which exhibited slow release, and Sample K (with PEPPG added), which exhibited markedly faster release, we calculated the amount of IVM released by deducting the post-dosing IVM level from the pre-dosing IVM level, and the results of calculation were used for analysis of release rate parameters. Since the amount of IVM remaining in Sample J 3 days after administration was greater than the amount of IVM administered, the measurement at this point of time was deemed an error and

excluded from analysis. The value of $n$ was calculated to be 0.886 for Sample J (SUC) and 0.630 for Sample K (PEPPG).

Basically, matrix-type formulations exhibit Fickian diffusion with an $n$ of 0.5, and capsule-type formulations exhibit zero-order release with an $n$ of 1. The CR silicone formulation is a cylindrical matrix-type formulation containing the drug with the lateral side of the formulation covered with silicone membrane (Fig. 1). Structurally, this formulation can be said to be a combination of matrix type and capsule type. When the $n$ value was compared between Sample J (SUC) and Sample K (PEPPG), the value of Sample K ($n = 0.630$) was closer to Fickian diffusion than the value of Sample J ($n = 0.886$). This indicates that Sample K has properties closer to those of a matrix-type formulation. It therefore seems likely that increasing the solubility of IVM by using additives promotes matrix-type release, i.e. release through the channel of the cross-sections of the formulation.

Silicone is one of the materials for which research and development is being conducted as a carrier of hydrophobic drugs for sustained-release formulations. Well-known as representative sustained-release formulation of hydrophobic drug is Norplant, a capsule-type formulation in which levonorgestrel powder is entrapped in a silicone container (Robertson et al., 1983), and Compdose, a matrix-type formulation in which estradiol is dispersed in silicone (Ferguson et al., 1988).

With capsule-type formulations, it is possible to obtain zero-order release for a long period of time. However, in order to control release velocity, it is necessary to change the drug permeability in the silicone film. This permeability is thought to depend on the diffusion coefficient specific to the drug. There have been studies performed to change dispersion of a hydrophobic drug by using an additive in the silicone film, and their results have been reported (Pfister et al., 1985). However, a solid additive, such as lactose, decreases permeability. Use of tens of percent of a liquid additive, such as isopropyl palmitate, is reported to increase drug permeability. However, it is considered practically impossible to add a large quantity of liquid additive to the formulation. Therefore, in controlling drug release in capsule-type formulations, a problem exists in controlling drug permeability through silicone film.

In the matrix-type preparations, it is comparatively easy to change drug release by changing composition. However, since the drug present on the surface of the formulation dissolves and is released in the early stage of administration, a large volume of drug is quickly released in the early stage (initial burst). As a result, the problem of drug concentration in excess of the safety margin arises, with resultant adverse reactions. In addition, there are cases in which a large part of the drug administered cannot exhibit efficacy because drug concentration far exceeds the range of efficacy. Thus, with matrix-type formulations, there are cases in which it is necessary to avoid the initial burst.

The CR silicone formulation examined in the present study can be viewed as a dosage form combining matrix-type and capsule-type features, as mentioned above. By virtue of this structure, CR formulations can improve the limit of drug permeability in silicone film of capsule type, by exposing the inner layer containing the drug at the cross-sections, it becomes possible to adjust the drug release velocity. Furthermore, by covering the lateral side of the formulation with silicone film, the initial burst with the matrix-type formulation can be avoided.

CR formulations thus have combined functions of capsule type, which can maintain long-term release without initial burst, and matrix type, in which it is easy to adjust release by changing composition.

When DOC, which markedly increases the solubility of IVM (Table 2), was used as an additive in combination with SUC, a formulation releasing IVM linearly for approximately 1 year in vitro was obtained.

The use of IVM as an anthelminthic agent for cattle and swine is usually as a liquid formulation, which is mainly delivered by subcutaneous administration. It has been shown that by maintaining anthelminthic effect for a long period with the use of IVM in grazing cattle, the rate of increase in body weight becomes higher (Aizawa et al., 1997), and sexual maturation occurs earlier (Oikawa et al., 1998) compared with non-treatment animals. Use of IVM is thus economically beneficial. However, with subcutaneous injection of IVM, blood concentration is maintained for only about 1 month. Therefore, in order to maintain anthelminthic effect for a long period, it is necessary to repeat administration. An oral formulation of IVM has been developed for heartworm in dogs.

It is necessary to administer this oral formulation once a month, and therefore, because of long intervals between administration, the possibility exists of forgetting administration. With the CR silicone formulations examined in the present study, it is possible to maintain blood concentration for a long time, and the duration of effect can be adjusted with an additive. To put these formulations to practical use, it is necessary to optimize the duration of release, and to design the doses and sizes of the formulation. However, it is expected that through further developmental work, these formulations will become available as sustained-release formulations of IVM. It is possible to apply these formulations to other hydrophobic drugs, as well. Thus, it is expected that they will be applied to other medicinal treatments as well.

## References

Aizawa, T., Miyamoto, K., Yoshida, T., Nishino, Y., Yamane, I., 1997. A clinical trial to evaluate the effect of ivermectin injection for grazing heifers. Jyuuiekigakuzasshi 1, 17–22.

Campbell, W.C., Fisher, M.H., Stapley, E.O., Albers-Schonberg, G., Jacob, T.A., 1983. Ivermectin: a potent new antiparasitic agent. Science 221, 823–828.

Chiou, R., Stubbs, R.J., Bayne, W.F., 1987. Determination of ivermectin in human plasma and milk by high performance liquid chromatography with fluorescence detection. J. Chromatogr. 416, 196–202.

Ferguson, T.H., Needham, G.F., Wagner, J.F., 1988. COMPUDOSE: an implant system for growth promotion and feed efficiency in cattle. J. Control. Release 8, 45–54.

Kajihara, M., Sugie, T., Hojo, T., Maeda, H., Sano, A., Fujioka, K., Sugawara, S., Urabe, Y., 2001. Development of a new drug delivery system for protein drugs using silicone (II). J. Control. Release 73, 279–291.

Oikawa, S., Kawawa, F., Hiraga, K., Motokawa, M., Chiba, Y., Ogawa, T., Fukumoto, S., 1998. Deworming effect of ivermectin on gastrointestinal nematodes in Holstein heifers on pasture. J. Jpn. Vet. Med. Assoc. 51, 237–240.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release polymers. Pharm. Acta Helv. 60, 110–111.

Pfister, W.R., Sweet, R.P., Weaver, M.E., Walters, P.A., 1985. Modification of physical properties and drug delivery rates from polydimethylsiloxane by use of selected oil and water soluble additives. Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 12, 145–146.

Plumb, D.C., 1999. Veterinary Drug Handbook, 3rd ed. Iowa State University Press/Ames, Minnesota, pp. 357–361.

Robertson, D., Sivin, I., Nash, H., Braun, J., Dinh, J., 1983. Release rates of levonorgestrel from silastic capsules, homogeneous rods and covered rods in humans. Contraception 27, 483–495.

Toutain, P.L., Upson, D.W., Terhune, T.N., Mckenzie, M.E., 1997. Comparative pharmacokinetics of doramectin and ivermectin in cattle. Vet. Parasitol. 72, 3–8.

Williams, J.C., Broussard, S.D., 1995. Persistent anthelmintic activity of ivermectin against gastrointestinal nematodes of cattle. Am. J. Vet. Res. 56, 1169–1175.