Prolonged Release of 4,4'-Diaminodiphenylsulphone (DDS) by Incorporation in Silicone Rubber A Preliminary Report [1, 2]

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DDS is widely accepted as the drug of choice in leprosy and is used with considerable safety under medical supervision. It is given orally in dosage varying from 5 mg to 100 mg per day for six days a week. For effective control of the disease the drug must be taken at least for five to ten years and often for life ([11]). In practice it has been demonstrated that many patients find it difficult to take the drug regularly each day and the majority of them are irregular or drop out of treatment after a few years, specially after clinical improvement. In 1968 Shepard *et al* ([12]) reported clinical trials of a repository sulfone, 4,4'-diacetyldiaminodiphenylsulphone (DADDS). They found that patients given DADDS intramuscularly in a dose of 225 mg every 77 days responded as rapidly as those in a control group treated with 100 mg DDS. Though therapy with DADDS is prolonged as compared to most drug treatment regimes, it is still not long enough for an extremely chronic infection like leprosy. Also one of the disadvantages of this mode of treatment is that once it is injected into the body it is irretrievable and cannot be removed if toxic reactions occur. The reports with DADDS noted, fortunately, that no toxic reactions were observed.

The property of gradual diffusion of drug through silicone rubber has been demonstrated by Folk and Long ([4, 9]). Since then it has been used clinically for slow and prolonged release of hormones ([2, 10]), vitamins ([9]), antibiotics ([8]), histamine and atropine ([1]), and various other drugs ([5]). Thus, a small silicone rubber capsule containing the drug can provide enough medication to last a patient for many months or even years ([4, 9]). Experiments conducted in our laboratory with DDS-silicone blocks have shown that DDS can diffuse into distilled water at a gradual rate over a period of 12 to 18 months ([13]). To confirm and extend these findings further experiments were carried out to study the rate of DDS diffusion in plasma, *in vitro*, and by implantation of DDS silastic carrier into rabbits *in vivo*.

MATERIALS AND METHODS

The following types of carriers were employed:

a. Dow Corning's silastic RTV tubings of different internal and external diameters, were cut to varied lengths, filled with DDS and sealed with silicone medical adhesive. Details are given in Table 1.
b. 1 cm square DDS silastic blocks containing DDS to RTV 382 in the ratio of 2:1.
c. Thin 10 cm square DDS silastic sheets of 0.05 cm thickness were prepared as follows: 40 mg DDS were added to 8.5 gm RTV 382, mixed well, catalyzed and spread on a ceramic tile to give a thin DDS-RTV sheet. This was cut into four equal squares and rolled 1) either loosely or 2) tightly into cylindrical forms. A drop of silastic medical adhesive was used to seal the outer flap of these cylinders.
d. The above (c) was repeated using 1 gm of DDS per sheet. The sheet was cut into four squares and rolled loosely to form cylinders.
e. 1 cm silastic block without DDS.
f. Silastic sheet cylinders were prepared as in (c), but no DDS was added to RTV 382.

Before use, silastic tubings, block and sheet cylinders were washed in distilled

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water to remove any externally adherent DDS, sterilized by autoclaving at 15 lbs steam pressure for 15 minutes, immersed in sterile human plasma and incubated at 37°C for seven days. Thereafter the plasma was removed for DDS estimation by the Bratton-Marshall reaction [14] and the DDS silastic moulds were reimmersed in fresh sterile plasma and incubated at 37°C for seven more days. In this way DDS estimation in plasma was done every seven days for six months.

In vivo experiments. Three male albino rabbits, HI strain weighing about 1.5 kg, were selected for the study. In both rabbits type D of DDS-RTV sheet cylinders were implanted. In rabbit 1 it was inserted subcutaneously on the outer aspect of each thigh while in rabbit 2 one such cylinder (DDS-RTV) was implanted intraperitoneally. Rabbit 3 was kept as normal control and was implanted with DDS-free RTV sheet as in rabbit 1.

RESULTS

The *in vitro* results are presented in Tables 1 and 2. The rate of diffusion of DDS is very low from silastic tubings used in the experiments. Only about 1.5-2 μg of DDS was found to diffuse per ml per day for a period of six months. Diffusion through DDS block was greater than that obtained with silastic tubings, being in the region of 5 to 12 μg per ml. Maximum amount of DDS diffusion was noted with DDS-RTV sheet rolled into cylinders (Table 2, C1, C2 and D). Even with cylinders, differences in the rate of DDS diffusion were observed, depending on the amount of DDS incorporated in the sheet and also on the mode of rolling sheets into cylinders. Cylinders D, containing 1 gm of DDS per sheet gave much better diffusion (19-30 μg per ml) than sheet C1 containing 40 mg DDS per sheet (11-23.0 μg per ml), Table 2. Moreover, with cylinders prepared from the same sheet, better diffusion of DDS occurred when the sheets were rolled loosely into cylindrical shape (11-23.0 μg per ml) than when rolled tightly (8.16.0 μg per ml).

The in vivo results of DDS implantation in rabbits were as follows. In the first five days after DDS silastic implant the amount of DDS excreted in urine was quite high giving peak values of 47 μg per ml with subcutaneous implantation and 37 μg per ml with the intraperitoneal implantation. After five days the amount of DDS excretion in urine was considerably reduced with time till the 90th day. Thereafter, with the subcutaneous implant, a steady level of DDS was maintained up to 150 days of the experiment, being in the region of 11-14 μg per ml. With the intraperitoneal implant, however, the level of DDS in urine fell from 8 μg per ml at 90 days to 2 μg per ml at 150 days. With both the subcutaneous and intraperitoneal inserts, DDS concentration in the blood of rabbits was about 0.5-1 μg per ml for all the five months after DDS-RTV insertion. This concentration is about 25-50 times that required for inhibition of *M. leprae in vivo* [12].

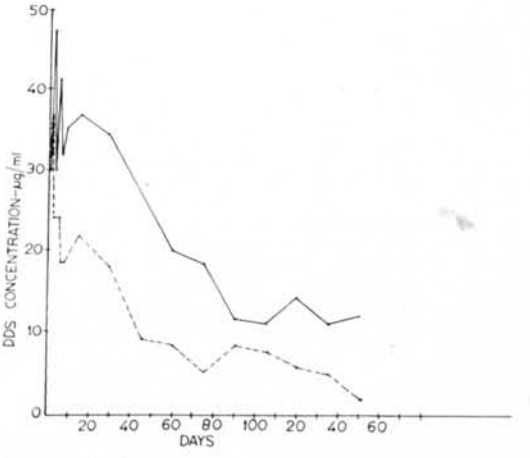

FIG. 1. Urinary excretion levels of DDS in rabbits. Continuous line for subcutaneous implant. Dotted line for intraperitoneal implant.

DISCUSSION

Dow Corning's silicone rubber is an inert substance well-tolerated by the body. It is highly resistant to body fluids and causes no irritation to body tissues. Because of its non-reactivity with body fluids and its stability to environmental conditions of stress and strain, silastic RTV has been used extensively, in recent times, both in medicine and surgery. In our department it has been used for repair of flexor tendons and nerves and as implants in case of internal prosthesis. The discovery of the ability of silastic RTV to dissolve drugs and slowly release them [4, 9] has greatly extended its use. It has been used in the field of general anesthesia [5, 6],

TABLE 1. *Results of* in vitro *silastic experiment.*

Material	ID	X	OD	Length in cm	DDS content in gm	Amount of plasma used ml	Diffusion per ml for a period of six months	
							7 days	per day
Tube 1	0.062	x	0.095 cm	20	0.030	10	7-10 μg	1.5-2 μg
Tube 2	0.062	x	0.125 cm	20	0.030	10	"	"
Tube 3	0.132	x	0.183 cm	5	0.016	10	"	"
Tube 4	0.104	x	0.192 cm	5	0.016	10	"	"
Tube 5	0.078	x	0.125 cm	5	0.005	10	"	"
Tube 6	0.3	x	0.6 cm	10	0.031	15	"	"
Tube 7	0.2	x	0.4 cm	10	0.0194	15	"	"
Tube 8	0.9	x	1.1 cm	8	8.00	15	"	"
Tube 9	1/2	x	11/16 inch	5	3.614	15	"	"
Tube 10	3/8	x	1/2 inch	5	1.586	15	"	"

TABLE 2. In vitro *results continued.*

Different silastic moulds in 10 ml plasma	Daily averages per month for a period of six months
B	5.3 μg per ml in the 1st month
C1	11.42 "
C2	8.1 "
D	19.1 "
E	Nil "
F	Nil "
B	6.0 μg per ml in the 2nd month
C1	19.9 "
C2	16.0 "
D	24.4 "
E	Nil "
F	Nil "
B	7.8 μg per ml in the 3rd month
C1	21.0 "
C2	15.5 "
D	24.5 "
E	Nil "
F	Nil "
B	12.0 μg per ml in the 4th month
C1	22.0 "
C2	15.0 "
D	28.1 "
E	Nil "
F	Nil "
B	10.95 μg per ml in the 5th month
C1	22.3 "
C2	14.4 "
D	29.8 "
E	Nil "
F	Nil "
B	8.6 μg per ml in the 6th month
C1	23.0 "
C2	12.2 "
D	28.65 "
E	Nil "
F	Nil "

TABLE 3. In vivo *results.*

Sample collection Days	RESULTS TEST SAMPLES DDS SC [a]	in urine IP [a]	DDS SC	in blood IP
1	30 μg/ml	32 μg/ml	0.5-1 μg/ml	0.5-1 μg/ml
2	47 "	37 "	"	"
3	30 "	24 "	"	"
4	34 "	24 "	"	"
5	41.5 "	22 "	"	"
6	32 "	18.5 "	"	"
7	35 "	18.5 "	"	"
15	37 "	22 "	"	"
30	34 "	18 "	"	"
45	27 "	9.5 "	"	"
60	20 "	8 "	"	"
75	18.5 "	5 "	"	"
90	12 "	8 "	"	"
105	11.0 "	7.5 "	"	"
120	14 "	6 "	"	"
135	11 "	5 "	"	"
150	12 "	2 "	"	"

[a] SC = subcutaneous implantation; IP = intraperitoneal implantation.

and as hormone releasing intrauterine or subcutaneous contraceptives for reducing fertility ([2, 10]). It is seen from the experimental results, presented in this paper, that DDS can diffuse through silastic RTV. Therefore, introduction of DDS silastic in the treatment of leprosy may be a feasible proposition, this would help to simplify and facilitate the chemotherapy of leprosy, by eliminating the necessity of daily drug intake. However before its use in man, more work will have to be done with DDS silastic. In our department further *in vivo* experiments are being undertaken to determine the concentration of DDS in the blood of rabbits implanted with DDS silastic carriers, employing the highly sensitive fluorometric methods of DDS estimation in body fluids ([3, 7]).

SUMMARY

Prolonged release of DDS by incorporation into silastic RTV sheets has been demonstrated in *in vitro* and *in vivo* studies in rabbits up to a period of 150 days. This is a preliminary report of a continuing study.

RESUMEN

La eliminación retardada de DDS mediante la incorporación en láminas de Silastic RTV ha sido demostrada en studies *in vitro* y *in vivo* en conejos durante 150 días. Esta es una communicación preliminar de un estudio en proceso.

RÉSUMÉ

L'élimination retarde de DDS avec l'incorporation dans des Silastic RTV feuilles est démontre par *in vitro* et *in vivo* études chez le lapin. Ce travail préliminaire est une partie de études plus prolonge.

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