DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(9-11), 1915-1932 (1987)

EVALUATION OF THE COMPATIBILITY AND PHYSICAL PROPERTIES OF SILICONE ELASTOMER CONTAINING HYDROPHILIC AND/OR HYDROPHOBIC ADDITIVES

Frank Rankin
Dow Corning Ltd
Cardiff Road
Barry
South Glamorgan
CF6 7YL
UK

and

Louis Aguadisch
Dow Corning France S.A.
European Health Care Centre
Route des Cretes BP43
Sophia Antipolis - Les Bouillides
06561 Valbonne Cedex
France

ABSTRACT

Hydrophilic additives viz water, PEG 200, 400 and 600 have been successfully incorporated into medical grade silicone elastomer via the pre-formation of a water-in-oil emulsion. The formulation, including an emulsifier, has been optimised and hydrophilic particles of low, narrow size distribution incorporated into the silicone matrix. These additions were shown to have insignificant effect on the curing characteristics of the polymer. Various amounts of PEG were loaded into the elastomer and physical properties measured. There was no significant variation in these properties for the PEG MWt range chosen. However, at high loadings (greater than 20 wt %) these properties are significantly reduced. The use of such a system for incorporating, and subsequently controllably releasing hydrophilic drugs, is discussed.

INTRODUCTION

Polydimethylsiloxane, (silicone) medical grade materials are now widely accepted for the construction

of devices for the controlled delivery of drugs[1][2]. This is due in part to the relatively high permeability of silicone elastomers when compared with other types of synthetic material, and to their excellent bio-compatibility. For example Searles Nitrodisc[3] is a transdermal system for delivering nitroglycerin and utilises a silicone matrix. Alza describes a transdermal device[4] for nitroglycerin, utilising a silicone fluid carrier and a silicone pressure sensitive adhesive. Alza's Progestasert[5] is an IUD membrane system delivering progesterone and utilising silicone fluid carrier. Upjohns vaginal ring device[6] employs a silicone matrix for delivering medroxyprogesterone. Beecham[7] describe an injectable cold-curing system incorporating antibacterial agent for the protection of cow-teats, from mastitis. The Norplant® contraceptive implantable device utilises a heat vulcanised silicone material as membrane[8]. Finally Eli Lilly's Compudose®[9] is an implantable system utilising a silicone matrix to deliver a growth promotant, in cattle.

There are various ways of modifying the release characteristics of drugs from, or through such matrices. Co-formulating with water in soluble solid excepient, such as silica, reduces permeation rates[10] whereas co-formulating with pharmaceutically acceptable solvents such as glycerol or polyethylene glycol results in enhanced permeation rates[11]. Other ways of regulating drug permeation rates include altering the pendant groups[12] and/or modification of the backbone structure[13] of the silicone polymer and the use of copolymer/terpolymer compositions[14].

Currently, the simplest and most convenient approach is to co-formulate using selected additives. Pfister et al [15,16] describe the use of various hydrophilic and hydrophobic excipients to modify drug release characteristics.

Silicones are hydrophobic in nature so that hydrophilic drugs have limited solubility. In many cases, high loadings of hydrophilic drug are required so as to provide required dosage quantities. One way of achieving such high loadings is to incorporate hydrophilic additives into the polymer matrix. Polyethylene glycol (PEG) appears to be one additive which has been extensively used for such purposes. However, depending upon the amount of PEG used, the resulting silicone matrices can lose little or virtually all of their physical strength, often limiting their subsequent use to non-implantable devices. It is important that the effect of amount, and MWt of PEG on the polymer structure be assessed in terms of its physical characteristics and subsequent use; the objective of this work was to make such an evaluation.

EXPERIMENTAL

Materials

Polydimethylsiloxane elastomer (Dow Corning® MDX4-4210 Medical Grade Elastomer), polydimethylcyclosiloxane (Dow Corning® 344 Fluid) and emulsifying agent (5 wt % polydimethylsiloxane/ polycarbinol copolymer [X] in polydimethylcyclo-

siloxane) were provided by Dow Corning Ltd., Barry, South Glamorgan, UK. Polyethylene glycols 200, 400 and 600 were provided by BDH Chemicals Ltd., Poole, UK.

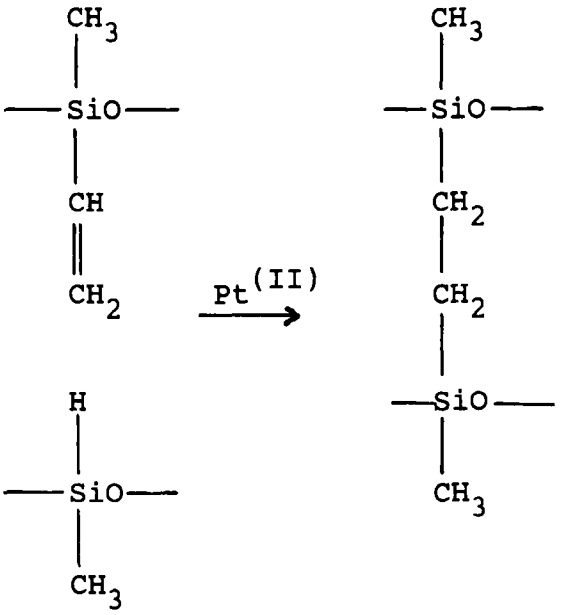
X $Me_3SiO(Me_2SiO)_{370}(MeSiO)_5SiMe_3$ 5 pbw

$(CH_2)_3(OCH(CH_3)CH_2)_{18}(OCH_2CH_2)_{18}OH$

Dow Corning® 344 Fluid 95 pbw

Preparation of Matrices

All matrices were prepared from Dow Corning MDX4-4210 Medical Grade Elastomer, a room temperature vulcanising system based upon the following reaction:



This is a two-part system, consisting of a silicone "base" and "curing agent".

In order to achieve good dispersion of the PEG within the polymer matrix, the PEG was initially emulsified using silicone oil (Dow Corning 344 Fluid) and emulsifying agent X, to form a water-in-oil (W/O) emulsion. This was then incorporated into the elastomer base prior to curing. Thus in a typical experiment, the water phase (consisting of PEG, 22gm, in distilled water, 20gm) was added to oil phase (consisting of emulsifier X, 4gm, in Dow Corning 344 fluid, 20gm) using a high-shear mixer (Citenko FHP Motor, Park Products Ltd., Blackburn, UK). The elastomer base (200gm) was added to the emulsion, with continued mixing, followed by the addition of the curing agent. The product was degassed to remove entrapped air and cured by compression moulding at 60°C, 45 minutes.

Rheometry

The rate and extent of cure of the modified elastomer was measured using a Monsanto Rheometer, Model 100, at 100°C, arc setting 1°.

Microscopic observations and particle size analysis

Emulsions were observed using a Leitz Laborlux 12 optical microscope. Elastomer microstructure was observed using an Hitachi S450 scanning electron microscope at 10kV; particle size analysis was carried out using a Malvern particle sizer 3600 E type machine (Malvern Instruments, England).

Physical property measurements

Tensile strength, and elongation measurements were made, according to ASTM D412, and tear strength measured according to ASTM D642, using a Zwick tensiometer, model 1445. Hardness was measured according to ASTM D2240, using a Shore hardness tester.

RESULTS AND DISCUSSION

Preliminary investigations

A series of preliminary compositions were prepared to determine whether any of the emulsion components, either alone or in combination, would produce an inhibiting effect on the curing characteristics of the silicone polymer. Such a possibility was investigated via rheometric measurements, during cure, and two parameters (maximum torque, M_x; and time to reach 90% maximum torque, t_{90}) observed. Results are shown in Table 1.

It can be seen that each component alone, or in combination, produced no significant effect on the cure time (t_{90}). Furthermore, emulsifier, and distilled water, at the levels chosen, do not significantly affect the extent of reaction, M_x. (Compare samples 1, 3, 5 with control C). However, the relatively large loading of 344 fluid did produce a significant reduction in M_x (compare samples 2, 4, 6, 7 with C). In other preliminary investigations, a range of silicone fluids, of varying molecular weight, were used in place of the 344 fluid; the latter material, being

TABLE 1

Component		Sample							
		C	1	2	3	4	5	6	7
MDX4-4210 base	(gm)	50	50	50	50	50	50	50	50
MDX4-4210 curing agent	(gm)	5	5	5	5	5	5	5	5
Emulsifier X	(gm)	-	1	-	-	1	1	-	1
344 Fluid	(gm)	-	-	25	-	25	-	25	25
Distilled Water	(gm)	-	-	-	5	-	5	5	5
M_x	(N.m)	1.51	1.40	0.61	1.41	0.52	1.17	0.44	0.44
t_{90}	(sec)	117	117	132	99	150	107	126	153

Rheometric studies of Silicone Elastomer mixed with "Emulsification Additives"

of low viscosity (2.5 m^2s^{-1} at 25°C) was chosen because it could be easily formulated into the W/O emulsion and had the effect of "thinning" the elastomer base (viscosity $8x10^6$ m^2s^{-1} at 25°C), However, because of its drastic effect on the polymer structure, the level of incorporation was reduced from 25 to 5 parts by weight, per 50 parts by weight of MDX4-4210 base.

Emulsification process

W/O emulsification techniques were employed as the method of incorporation of hydrophilic components into the silicone matrix. This had the advantage of being able to easily predisperse the hydrophilic components within a controllable, narrow particle size distribution, prior to its incorporation into the silicone matrix. The basic W/O emulsion comprising 344

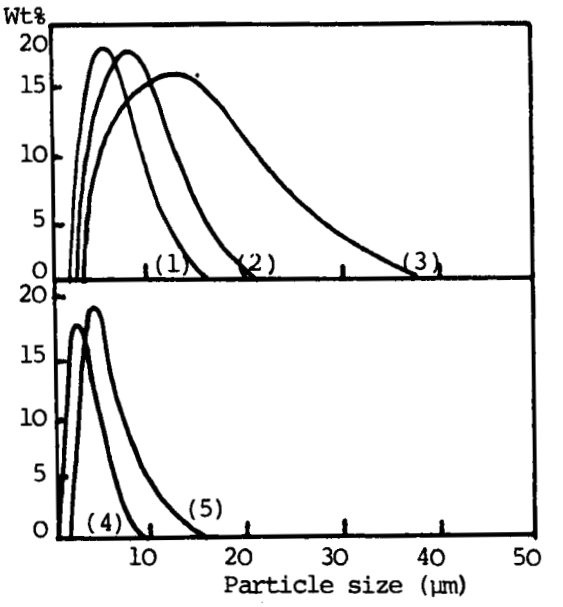


FIGURE 1

Particle Size Distribution of Emulsions prepared using PEG 200(1), PEG 400(2), PEG 600(3), PEG 600 and high shear (4), PEG 600 Emulsion in MDX4-4210 base (5).

fluid, emulsifier, and water (weight ratio 20:4:20) was stable, having a particle size population entirely below 10.5 μm.

Hydrophilic additives PEG 200 or PEG 400 or PEG 600 were incorporated into the water phase of the emulsion (weight ratio 344 fluid : emulsifier : water : PEG equals 20:4:20:22). Stable emulsions were obtained with particle size distributions as shown in Figure 1, curves (1)(2) and (3) respectively. It can be seen that the peak particle size decreases with increasing PEG MWt; this is due to the corresponding increase in viscosity and the ability to generate greater shear.

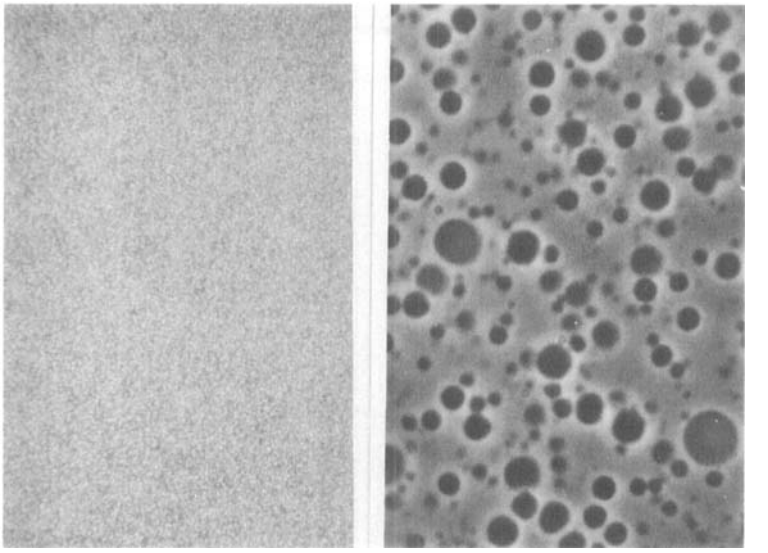


FIGURE 2

Magnification x 125 Magnification x 1250
Optical Microscope Photographs of Emulsion prepared using PEG 600, and High Shear

Indeed at very high shear rates, for PEG 600, the peak particle size was further reduced, Figure 1, curve (4); optical microscopy, Figure 2, confirmed the homogeneity of the emulsion.

In a further experiment, the PEG 600 emulsion was incorporated into the MDX4-4210 elastomer base (no addition of curing agent. Figure 1, curve (5) shows the particle size distribution of an aliquot of this mixture dissolved in 344 fluid; it can be seen that there is a significant decrease in peak particle size due to the extra shear exerted during mixing into the elastomer base; once again, optical microscopy, Figure 3, confirmed the homogeneity of the emulsion.

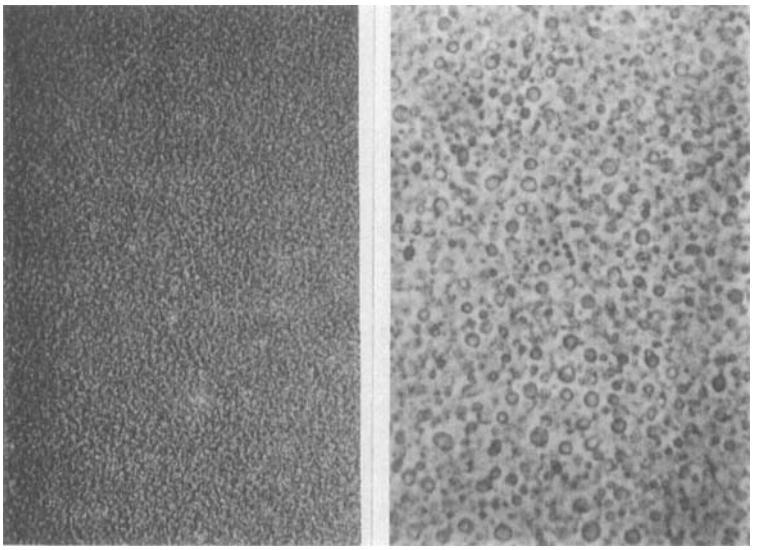


FIGURE 3

Magnification x 125 Magnification x 1250
Optical microscope photographs of PEG 600
Emulsion dispersed in MDX4-4210 Base

Physical properties of elastomers

Elastomer samples without PEG or incorporating PEG 200, or PEG 400 or PEG 600 were prepared as described under 'Preparation of matrices'; rheometric studies confirmed that the curing characteristics were not affected by the incorporation of PEG. The physical properties of the elastomers are reported in Table 2.

The effect of incorporating PEG into the silicone matrix is to reduce physical properties, though there are no significant differences between matrices prepared with PEG 200, PEG 400 or PEG 600.

TABLE 2

Property	MDX4-4210 (Control)	Sample containing emulsion: Without PEG	With PEG 200	With PEG 400	With PEG 600
Tensile Strength (Nmm^{-2})	4.2	2.1	2.0	2.1	2.2
Tear Strength (kNm^{-1})	9.1	6.9	3.7	3.7	3.7
Elongation (%)	539	477	485	488	501
Hardness (Shore A)	30	22	15	18	16

Physical Properties of MDX4-4210 Elastomer incorporating PEG 200 or PEG 400, or PEG 600.

The effect, on physical properties, of incorporating various amounts of PEG 600 into the matrix was next investigated: PEG 600 was chosen because of its ability to provide a fine W/O emulsion. The formulation used was:

MDX4-4210 base	50 (parts by weight)
MDX4-4210 curing agent	5
Emulsifier X	1
344 Fluid	5
Distilled Water	5
PEG 600	2.8, 5.5, 8.3, 11.0, 16.5 or 19.3

Table 3 shows the physical properties of films prepared from these formulations.

There is no significant variation in physical properties of films containing up to 11.0 parts by weight of PEG 600; above this figure, physical

TABLE 3

Property		Parts by weight of PEG 600 per 55 parts by weight of MDX4-4210 base plus curing agent					
		2.8	5.5	8.3	11.0	16.5	19.3
Tensile Strength	(Nmm^{-2})	2.2	2.2	2.2	1.7	1.3	1.1
Tear Strength	(kNm^{-1})	3.9	3.7	3.5	3.0	2.8	1.9
Elongation	(%)	472	501	540	504	493	518
Hardness	(Shore A)	21	16	18	16	15	7

Physical Properties of MDX4-4210 Elastomer incorporating PEG 600 at various levels

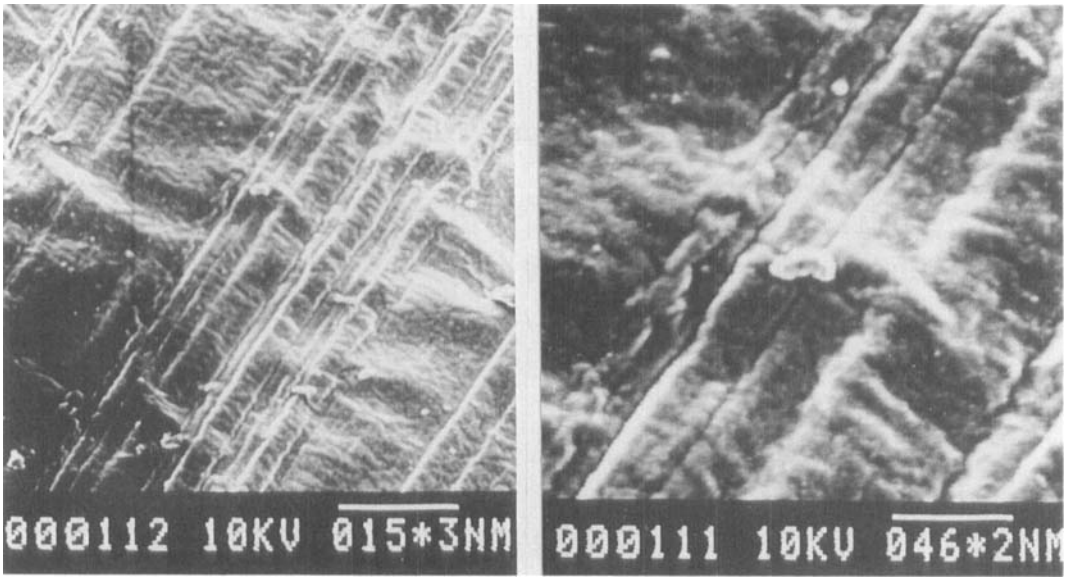


FIGURE 4

Photomicrographs of MDX4-4210 Elastomer

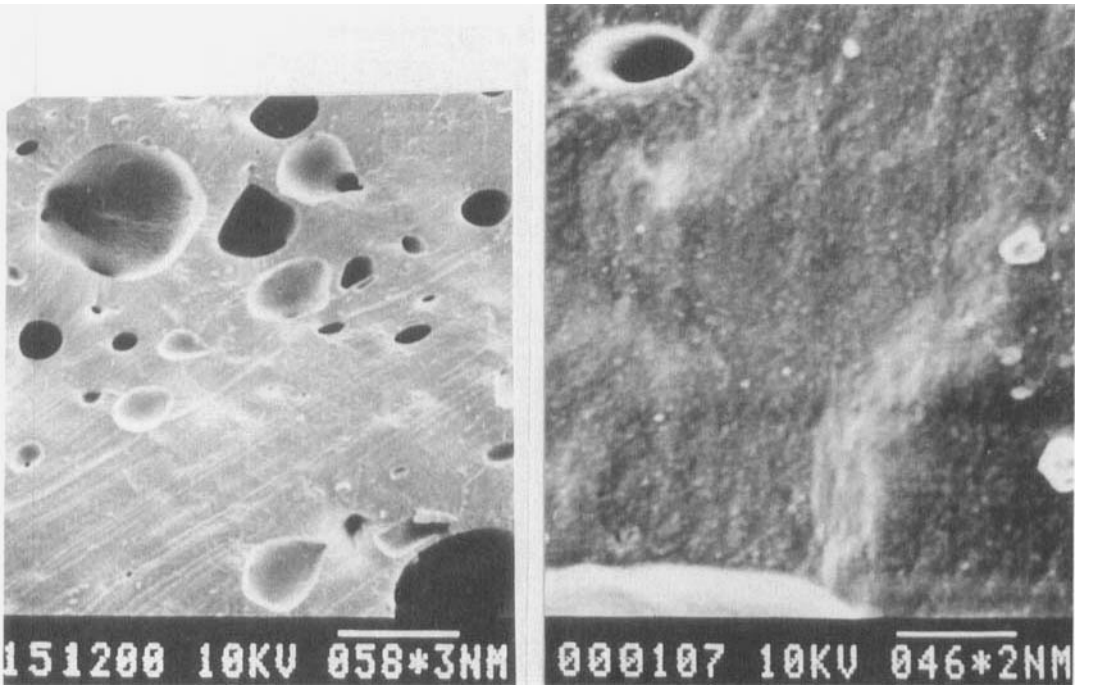


FIGURE 5

Photomicrographs of MDX4-4210 Elastomer incorporating W/O Emulsion, no PEG

properties are significantly reduced, often limiting their subsequent use to non-implantable devices.

Microstructure of elastomers

Scanning Electron Microscopy was used to observe elastomer microstructure. Figure 4 shows the homogeneous surface exhibited by MDX4-4210 with no additives. Figure 5 shows the crater-like structure obtained when the W/O emulsion, without PEG, has been incorporated; there appear to be interconnecting

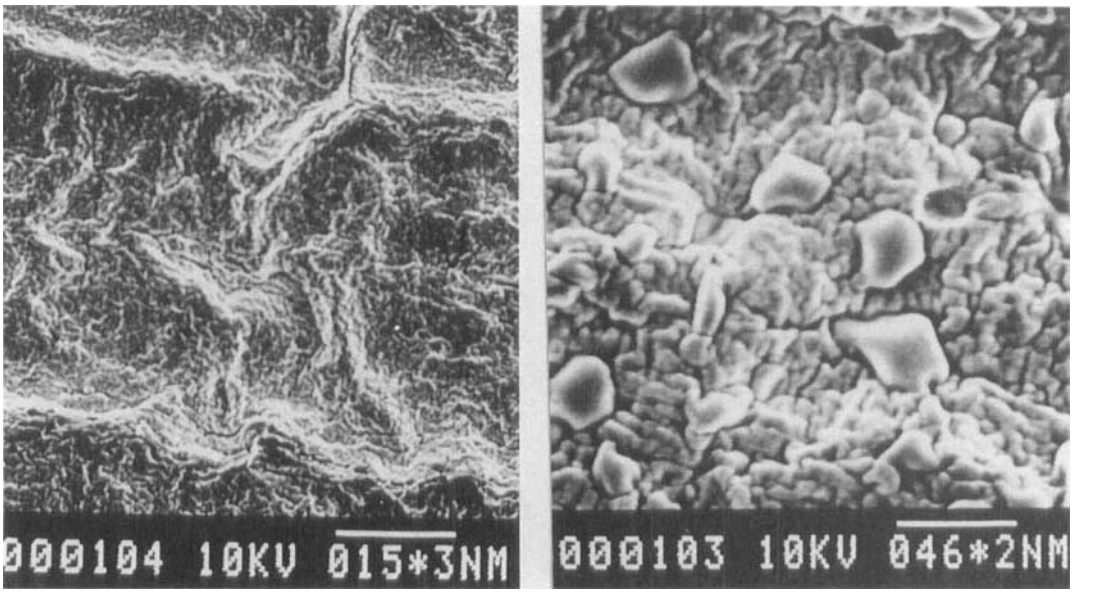


FIGURE 6

Photomicrographs of MDX4-4120 Elastomer incorporating W/O Emulsion and PEG 600

channels possibly rendering the structure porous. Incorporation of PEG 600 significantly modifies the polymer structure (Figure 6).

CONCLUSIONS

Hydrophilic and hydrophobic additives, combined in emulsion form, have been successfully incorporated into a silicone matrix. This novel approach offers the advantage of being able to easily predisperse the hydrophilic components within a controllable, narrow particle size distribution. It has been shown that W/O

emulsions based upon water, PEG (MWt 200-600), silicone fluid and an appropriate emulsifier, do not significantly affect the cure characteristics of the silicone elastomer (comprised of up to 35% by weight of emulsion). The particle size distribution (typically 1 to 10 μm) appears to be much lower than that reported elsewhere eg Chien[17] has obtained 10-200 μm distribution. The capability of being able to incorporate small particles will undoubtedly have a significant effect on the loading efficiency of hydrophilic drug and its subsequent release.

The action of these additives appears to be the creation of pores, possibly providing preferential transport of drug loaded into the system.

The physical properties of matrices incorporating 8 wt% PEG 200, or PEG 400 or PEG 600 were reduced; at loadings of 20 wt% or greater PEG 600, physical properties were significantly reduced, possibly limiting their subsequent use to non-implantable devices.

The systems developed here, offer exciting possibilities for the incorporation and subsequent release of hydrophilic drugs from silicone matrices. However, further work is necessary to fully understand the effects of the various components on polymer structure, and indeed to study the release kinetics of chosen drugs from such systems. This work is in progress.

REFERENCES

1. F.S. Rankin, "The Use of Silicones for the Controlled Release of Drugs", Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 12, 143, 1985.

2. F.S. Rankin, "Physical Property Measurements of Silicones Incorporated into Controlled Release Devices", Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 13, 218, 1986.

3. G.D. Searle & Co., "Transdermal Sustained Release Nitroglycerin Pad", UK Patent Application 2081582, 1981.

4. Alza Corporation, "Bandage for Administering Drugs", UK Patent 2100605, 1982.

5. Alza Corporation, "System for Delivering Drugs to the Vagina", USP. 4237885, 1980.

6. The Upjohn Co., "Pharmaceutical Devices and Method", USP. 3920805, 1975.

7. Beecham Group plc., "Intramammary Veterinary Compositions and Method for their Use", European Patent Application 0076068, 1982.

8. D.N. Robertson, I. Sivin, H.A. Nash, J. Braun, and J. Dinh, "Release Rates of Levonorgestrel from SILASTIC® Capsules, Homogeneous Rods and Covered Rods in Humans", Contraception, 27, No.5, 483, 1983.

9. Eli Lilly Co., "Implant for Controlled Release of Estradiol", UK Patent 2136688, 1984.

10. C.F. Most, "Some Filler Effects on Diffusion in Silicone Rubber", J. Appl. Pol. Sci., 14, 1019, 1970.

11. D. Hsieh, P. Mason, Y.W. Chien, "Enhanced Release of Drugs from Silicone Elastomers : Microstructure and in-vivo/in-vitro Correlation", Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 12, 212, 1985.

12. C.L. Lee and K.L. Ulman, "Relationships between Polymer Structure and Drug Permeability: I. Effect of Alkyl Substituent (R) in $(MeRSiO)_x$ Polymer", Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 12, 147, 1985.

13. C.L. Lee and K. Ulman, "Relationships between Polymer Structure and Drug Permeability : II. Effect of Polymer Backbone Structure", Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 12, 149, 1985.

14. K.L. Ulman, K.R. Larson and C.L. Lee, "Effect of Polymer Structure on the Drug Permeability of Polydimethylsiloxane - Polyethylene oxide-Polymethylmethacrylate Copolymers", Intern. Symp. Control. Rel. Bioact. Mater., 13, 228, 1986.

15. W.R. Pfister, R.P. Sweet, M.E. Weaver, and P.A. Walters, "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, 1985.

16. W.R. Pfister, R.P. Sweet, P.A. Walters and D. Sandvig, "Controlled Release of Progesterone, Testosterone, Indomethacin, and Propranolol from Silicone Membrane and Matrix Devices", Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 13, 220, 1986.

17. G.D. Searle & Co., "Microsealed Pharmaceutical Delivery Device," USP. 3946106, 1976.

18. G. Di Colo, V. Cartelli, E.Nannipieri, M.F. Serafini, D. Vitale and F. Bottari, "Effect of Different Water-Soluble Additives on the Sustained Release of Sulfanilamide from Silicone Rubber Matrices", Il Farmaco, 37, No.12, 377, 1982.