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Effect of water-soluble additives on drug release from silicone rubber matrices. II. Sustained release of prednisolone from non-swelling devices

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Summary

Multi-week release of 20% loading doses of micronized prednisolone from silicone rubber disks to isotonic pH 7.4 phosphate buffer is shown to be activated by liquid water carriers, such as glycerol, ethylene glycol and polyethylene glycol 200, through a mechanism not involving matrix swelling. Although the release pattern is of the $\sqrt{t}$ type, the solely diffusion-controlled mechanism for suspension slabs is ruled out by a dependence of the release "rate" (slope of the $\sqrt{t}$ plot) on the disk thickness. The "rate" is also shown to depend on the particular water carrier and water carrier-to-polymer ratio, and on the drug load and particle size.

Introduction

Aqueous pores have been generated in silicone rubber medicated matrices by dispersing liquid or solid water carriers in the polymer (Carelli and Di Colo, 1983; Di Colo et al., 1982; Di Colo et al., 1984; McGinity et al., 1979; Nippon Kayaku, 1984; Riffee et al., 1980). In Part I of this series (Di Colo et al., 1982) different carriers have been investigated with regard to their effectiveness in promoting osmotic hydration and swelling of the matrix and drug release from the matrix. With some carriers a strong influence was noticed with the drug loading dose on the drug release rate suggesting that the solid drug particles might be contributing to the development of pores by a polymer-breaking mechanism. Along these lines, the drug loads have been substantially increased in the present work, and the carrier effects with such increased loads have been evaluated. Prednisolone has been used as the model drug in view of the therapeutic and investigational applications an implantable controlled delivery form of this drug may offer. Typical water carriers were selected among those studied in the previous work. Release data are presented here, and their dependence on drug particle size, matrix thickness and formulation variables is discussed. A further report will follow, dealing with the mechanistic features of release.

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Materials and Methods

Materials

Prednisolone (Merck, Darmstadt, F.R.G.), polydimethylsiloxane elastomer and silica filler (PDS) (Silastic 382 medical grade elastomer, Dow Corning, Midland, MI, U.S.A.), stannous octoate (Catalyst M, Dow Corning, Midland, MI, U.S.A.), ethylene glycol RPE and glycerol FU (Carlo Erba S.p.A., Milano, Italy), polyethylene glycol (PEG) 200 (Merck-Schuchardt, Munchen, F.R.G.) were all used as received. PDS and catalyst, and prednisolone were each from a single batch. Sodium chloride RPE (Carlo Erba S.p.A., Milano, Italy) was ball-milled, then passed trough a 140-mesh (105 μm) screen prior to use. For some experiments the drug powder was sized to the 0–10, 20–40 and 40–105 μm ranges by the procedure described below.

Powder sizing procedures

Particle size analysis of the commercial prednisolone powder was carried out with a Reichert-Jung Microstar 120 projection microscope (American Optical, Buffalo, NY, U.S.A.), following the procedure recommended by Speiser (1967). A total number of 412 particles were classified according to their projected diameter. The arithmetic number and volume mean diameters were calculated to be 3 μm and 12 μm, respectively. Higher sizes were obtained through re-crystallization of the commercial product from quiescent ethanol. The macro-crystals were ground in a mortar, then sieve-sized to the 0–10, 20–40 and 40–105 μm ranges with the Analysette 3 microsieving apparatus (Fritsch GMBH, Idar-Oberstein, F.R.G.) using petroleum ether (60–80°C) as the suspending medium. An ultrasonic probe was used to prevent particle aggregation.

TABLE 1
FORMULAE OF MATRICES

Matrix	Water carrier	Drug load (%)	Water carrier–PDS ratio $\times 10^2$ (w/w)
G 20/14	Glycerol	20	14
G 20/25	Glycerol	20	25
G 10/14	Glycerol	10	14
EG 20/14	Ethylene glycol	20	14
P 20/14	PEG 200	20	14
SC 20/14	Sodium chloride	20	14
Control	None	20	0

Preparation of matrices

The formulae of the matrices tested in this study are specified in Table 1. Disk matrices (1 cm diameter, 0.1 cm or 0.05 cm thick) were prepared by the procedure described in the previous paper (Di Colo et al., 1982) with the following modifications: 2% catalyst was always employed; the term of cure was extended over ~ 65 h; and the order in which the carrier and the drug were added to the PDS prepolymer was reversed. Dispersing the drug as first, indeed, apparently facilitated dispersal of the liquid carriers, probably due to adsorption of these onto the drug particle surface. In fact, the G 20/25 specimens could not be made up but with the reversed sequence. The commercial drug powder was always used to prepare the matrices except in some specified instances. All matrices exhibited elastic properties. Their surfaces were visually smooth and hydrophobic.

Kinetic measurements

The procedure for determination of drug release and matrix swelling kinetics was the same as that reported previously (Di Colo et al., 1982). The matrices were shaken in isotonic 0.13 N pH 7.4 phosphate buffer at 37°C. In some cases pure water was used as the release medium over a week, then it was replaced by the buffer. The release medium, whether buffer or water, was spectrophotometrically analyzed for prednisolone at 248 nm. At this wavelength no carrier leaching from matrix could ever interfere with the measurements. Each experiment was run in triplicate, using three batches of identical formula, and data were averaged to draw the plot of the amount of drug released per unit initial surface area (Q/S), or the ratio of swollen to dry matrix weights (γ), versus square-root of time. Where the plot showed apparently linear portions, these were separately analyzed by linear regression. The analysis was generally extended to data points in the portion of plot which gave the best fit. All regressions were highly significant ($P < 0.001$).

Drug stability tests

Prednisolone is known to be liable to degrade oxidatively yielding acidic steroidal compounds as the main products (Guttman and Meister, 1958; Khalil et al., 1984). According to Guttman and Meister (1958) roughly 84% and 16% of acidic and neutral material, respectively, under aerobic conditions, or 50% and 50% under anaerobic conditions are formed in aqueous solution. These authors also reported that the acidic products have the same absorptivity as the undegraded drug at 248 nm. Since aqueous pores were thought to form in the matrices under study, the drug stability in such matrices under the conditions of the release experiments was to be checked. This was done by the following procedure. Some representative specimens formulated with the different water carriers were withdrawn after 1 month of elution, then extracted with 40 ml absolute ethanol (overnight, at 37°C). The extracts were evaporated to dryness at 40°C, under reduced pressure; the residue re-dissolved in water; and the resulting aqueous solutions spectrophotometrically analyzed for steroid content: in all cases this corresponded reasonably well to the amount calculated by difference between initial matrix load and amount released throughout elution. The aqueous solutions of residue were then carried through a reported procedure for determination of the acidic steroids, based on extraction of the alkalinized solution with chloroform and determination of the acidic material concentration from absorbance of the aqueous residue (Guttman and Meister, 1958). In no case could a significant fraction of acidic product be detected. This was considered a satisfactory proof of drug stability in matrices. On the other hand, checks on the elution medium revealed some degradation occurring in the receiving buffer. Such a degradation, nevertheless, could not impair the accuracy of the release data since, as stated before, the drug and its degradation products have the same absorptivity at 248 nm. In fact, the absorbance of standard drug solutions in buffer was constant over 4 days, i.e. the longest sampling interval used in the kinetic experiments.

Solubility determinations

The solubility of prednisolone in water, glycerol, ethylene glycol or PEG 200 at 37°C was determined by the procedure described in Part I for sulfanilamide (Di Colo et al., 1982). The chemical stability of prednisolone in the solvents was checked by the extraction procedure outlined above, after water dilution of the equilibrated solutions. No important fractions of degradation product could ever be detected.

Results and Discussion

Effects of the water carriers

Fig. 1 compares the $\sqrt{t}$ plots of the drug release data for matrices compounded with the liquid water carriers. The important difference from the formulae of the previous work employing the same carriers (Di Colo et al., 1982) is in the drug loading dose (20% vs 4% or 8%), whereas the water carrier-to-polymer ratio is unchanged. Data for the carrierless matrix also are reported for comparison. Silicone rubber appears from these data to be, by itself, rather a poor vehicle for prednisolone. Release of drug, however, was largely enhanced by the carriers, of which glycerol was the most effective, followed by ethylene glycol and

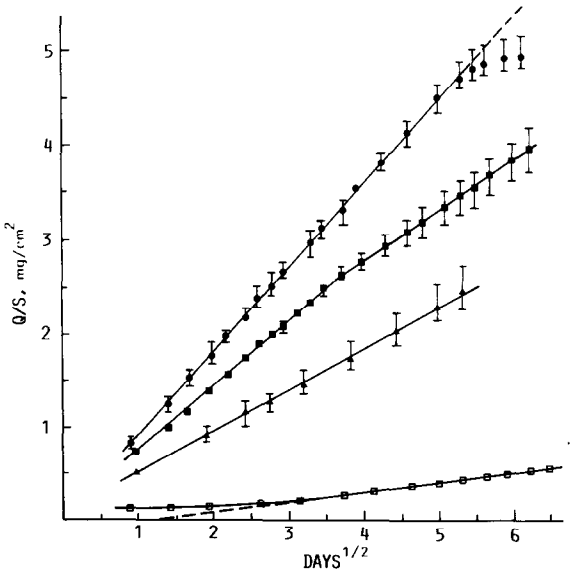

Fig. 1. Prednisolone release from matrices 0.05 cm thick, compounded with the liquid water carriers. Key: ●, G 20/14; ■, EG 20/14; ▲, P 20/14; □, control. Vertical bars represent the range. Where not shown, they fall within the drawn symbol.

PEG 200 in the order. Glycerol and PEG 200 yielded apparently linear $\sqrt{t}$ patterns, with a tailing off for the former at about 90% matrix depletion, whereas a breakpoint was evident in the plot for ethylene glycol. The plot for the control attained linearity after a lag time, in line with the usual behaviour of non-porous monoliths. In striking contrast with the previous findings with the carriers in hand (Carelli and Di Colo, 1983; Di Colo et al., 1982), none of the three was found to cause any water swelling of the present matrices. This is felt to be an effect of the increased drug load. With such a load of dispersed solids, indeed, small volumes of imbibed water were possibly sufficient to start a system of cracks in the polymer. Pores developed in this way could allow liquid flow and hence, prevent matrix swelling, if the osmotic agents were so finely dispersed as to make the fraction of blind pores insignificant. As noticed in the experimental section of this report, carrier dispersion was favoured by adsorption onto the drug particle surfaces. A further source of unswollen porosity could be clusters of drug particles and adsorbed carrier extending from the matrix surface deep into the matrix. Such aggregates should result in connected pores upon carrier hydration (Siegel and Langer, 1984). Differences in the porous structures generated by the various carriers must be admitted to account for the differences in drug release from the respective matrices. The drug-solubilizing power of the single carriers should be of little importance in this respect as far as the solubility values listed in Table 2 do not rank in the same order as the release-enhancing effects seen in Fig. 1. The break in the plot for ethylene glycol points to two sequential rate-controlling mechanisms, possibly

TABLE 2
SOLUBILITIES OF PREDNISOLONE IN WATER AND IN THE LIQUID WATER CARRIERS AT 37°C

Solvent	Solubility (mg/ml)
Water	0.32
Glycerol	2.97
Ethylene glycol	19.19
PEG 200	34.62

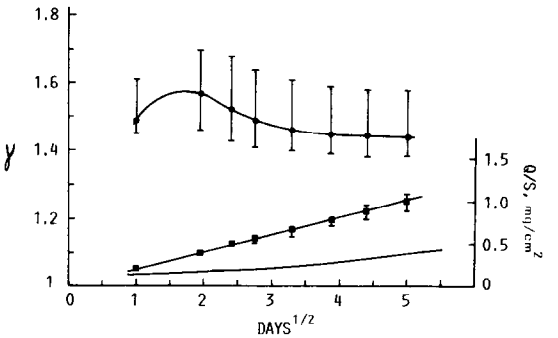

Fig. 2. Prednisolone release (■) and matrix swelling (●) data for the matrix SC 20/14, 0.05 cm thick. Vertical bars represent the range. Where not shown, they fall within the drawn symbol. The bare line represents the control (data points found in Fig. 1).

related to the different environmental conditions, e.g. aqueous or rubbery, the drug particles might experience in the porous matrix. Less pronounced breaks in the plots for the other carriers may be hidden by the scatter of points.

With sodium chloride as the water carrier the matrix did swell upon hydration. Its swelling pattern as appears in Fig. 2 is similar to that seen in the previous work with this carrier (Di Colo et al., 1982). Such a behaviour points to the presence in the porous structure of the matrix SC 20/14 of a significant fraction of blind pores, probably due to inadequate carrier dispersion. Hence from this may follow the poor release enhancing effect of sodium chloride, easily seen in the figure. The most effective carrier in this respect, i.e. glycerol, was used to carry on the study of the important factors in drug release from the present type of systems.

Effects of drug particle size

Matrices of the G 20/14 type were loaded with drug powder in the 0–10, 20–40 or 40–105 μm range to investigate the relevance of the drug particle size. None of the ranges tested allowed any important matrix swelling. The data plotted in Fig. 3 show that the powders containing high number fractions of micronized particles, namely, the commercial product (mean number diameter, 3 μm) and the 0–10 μm range were released faster than the higher size ranges. Interestingly, the presence of sizes greater than 10 μm in the commercial product (mean volume diameter, 12 μm) made its

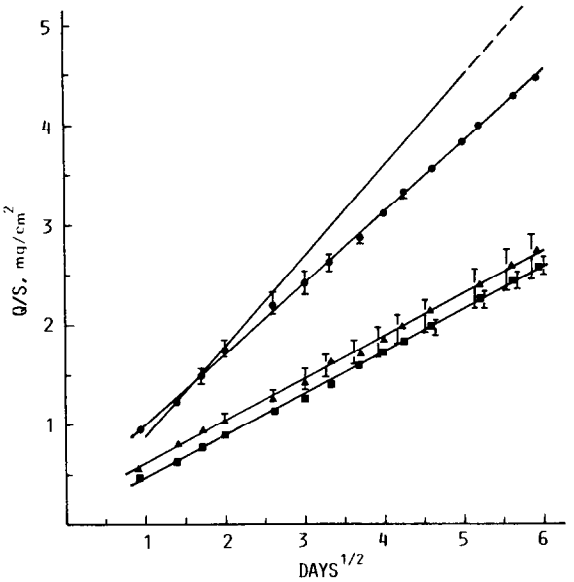

Fig. 3. Effects of drug particle size on prednisolone release from the matrix G 20/14, 0.05 cm thick. Key: ●, 0–10 μm; ■, 20–40 μm; ▲, 40–105 μm, ———, commercial powder (data points found in Fig. 1). Vertical bars represent the range. Where not shown, they fall within the drawn symbol

release "rate" (slope of the $\sqrt{t}$ plot) exceed somewhat that of the 0–10 μm range.

Effects of formulation variables

These effects are shown in Fig. 4 by $\sqrt{t}$ plots for matrices of the G 20/14, G 20/25 and G 10/14 types, and in Table 3 (2nd column), where the respective "rates" (slopes) are compared. Increasing the carrier-to-polymer ratio from 0.14 (as in G 20/14) to 0.25 (as in G 20/25) brought into evidence a break in the release line, thus supporting the aforesaid hypothesis of two sequential rate-controlling mechanisms. Of these, only the early, shorter lasting one should be substantially affected by such increased carrier levels, since only the first stage "rate" was practically increased. As expected, no swelling was noticed of the matrix G 20/25. Less expected was, on the other hand, the absence of any important swelling found of the matrix G 10/14. A maximum swelling degree of 3 was indeed reported in the previous paper (Di Colo et al., 1982) of sulfanilamide matrices formulated with the same glycerol-to-PDS ratio as in G 10/14 and an almost as high drug

TABLE 3

EFFECTS OF FORMULATION VARIABLES, MATRIX THICKNESS, AND WATER PRE-ELUTION ON THE "RATE" OF PREDNISOLONE RELEASE FROM MATRICES FORMULATED WITH GLYCEROL AS THE WATER CARRIER

Matrix	"Rate" ($mg \cdot cm^{-2} \cdot day^{-1/2}$)		
	0.05 cm thick	0 1 cm thick	0.1 cm thick pre-eluted [a]
G 20/14	0.88	1.08	1.10
G 20/25	1.50 (1st stage) 0.99 (2nd stage)	1.36	1.33
G 10/14	0.40	0.41	0 53

[a] Values derived from plots in Fig. 6, section B.

load (8%). These findings can nevertheless be reconciled by taking notice of the much lower solubility either in water or glycerol and finer dispersion in matrix of prednisolone compared to sulfanilamide. On the other hand, the strong dependence of the "rate" on the drug load which

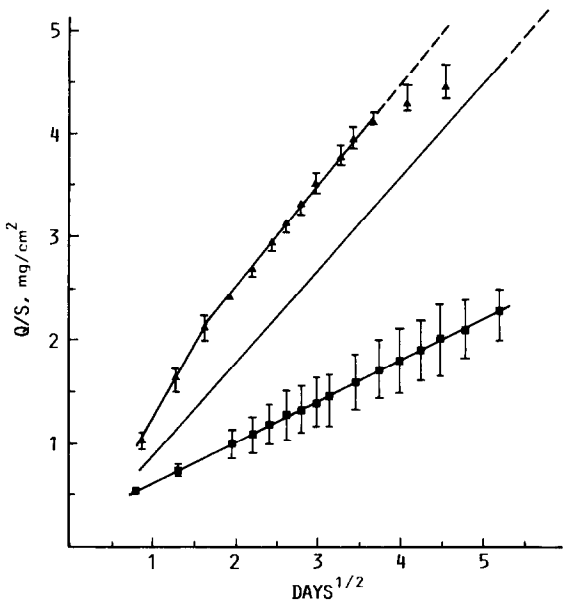

Fig. 4. Influence of formulation variables on prednisolone release from matrices 0.05 cm thick, compounded with glycerol as the water carrier. Key: ▲, G 20/25; ■, G 10/14, ———, G 20/14 (data points found in Fig. 1). Vertical bars represent the range. Where not shown, they fall within the drawn symbol.

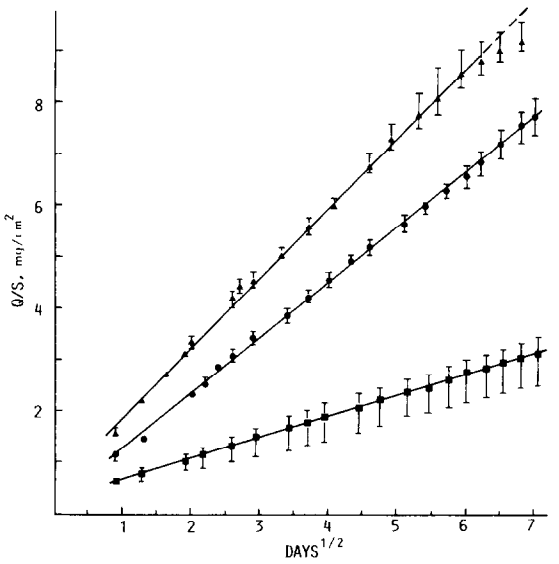

Fig. 5. Prednisolone release from matrices 0.1 cm thick, formulated as in Fig. 4. Key: ▲, G 20/25; ●, G 20/14; ■, G 10/14. Vertical bars represent the range. Where not shown, they fall within the drawn symbol.

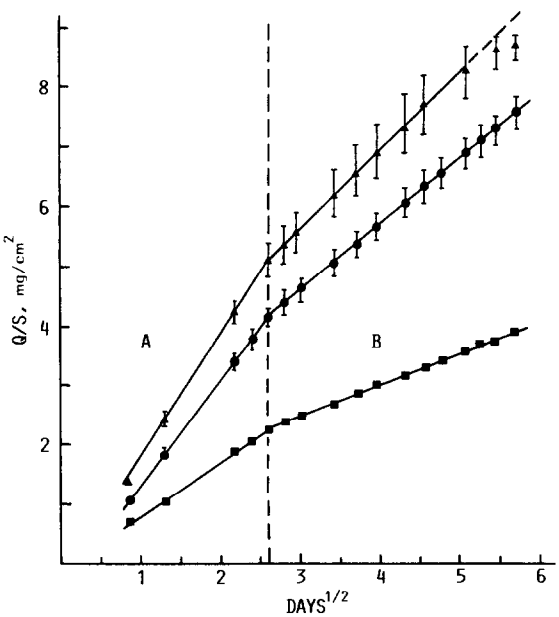

Fig. 6. Influence of the elution medium on prednisolone release from matrices 0.1 cm thick, formulated with glycerol as the water carrier. Section A, water was the elution medium; section B, the buffer was the elution medium. Key. ▲, G 20/25; ●, G 20/14; ■, G 10/14. Vertical bars represent the range. Where not shown, they fall within the drawn symbol.

was observed with sulfanilamide still holds here, as a comparison between the "rates" for the matrices G 20/14 and G 10/14 clearly shows. To be noted in Fig. 4 is the comparatively wide variation range for the latter.

Effects of matrix thickness

The matrix volume was doubled, without practically altering either shape or surface area, by doubling the disk thickness (0.1 cm vs 0.05 cm). The effects of such a change on drug release will appear on comparing relevant data in Figs. 4 and 5 and Table 3. The plot for the matrix G 20/25 was straightened, due to an increase of the 2nd stage "rate". The "rate" for the matrix G 20/14 also was increased, even if little beyond the variation range, whereas that for G 10/14 was practically unaffected. These volume effects will be discussed in mechanistic terms in Part III of this series. We can state now that they rule out the solely diffusion-controlled model for suspension slabs from applying to either the system G 20/25 or G 20/14. Such a model, indeed, is well known to be thickness-independent.

Effects of elution medium

In order to investigate these effects, the release kinetics of matrices of the G 20/25, G 20/14 and G 10/14 types was measured with water as the elution medium over a week, then the water was replaced by the buffer. The results plotted in Fig. 6 show drug release to water to be generally faster, thus proving the external medium to be part of the release mechanism. Water, however, should not affect the rate-controlling factors irreversibly, except for the less loaded matrix G 10/14. Only in this case, indeed, was the "rate" in buffer significantly higher than that for the matrix not pre-eluted with water (compare values in columns 3 and 4 of Table 3). Pre-elution also strikingly reduced the variation range of the data for this matrix.

Conclusions

Strong release-enhancing effects of the liquid water carriers not accompanied by any matrix

swelling effects were the outstanding results of the increased drug loads. The high fineness and low solubility of the commercial prednisolone powder, and the high dispersion degree of the liquid additives were concurrent factors in determining such results. Glycerol was the most effective activator of the present matrices, as was previously found to be of the sulfanilamide ones because of its comparatively high osmotic power and weak interactive properties. The drug load and matrix volume effects discussed in this report show promise for an off-hand control of either the time scale or the "rate" of prednisolone release. A more in-depth study of the mechanistic features of release is needed, however, for a better understanding of the present findings altogether. Also the hypotheses advanced here about the porous nature of the matrices need to be substantiated by experimental evidence. This is going to be the purpose of a subsequent report.

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References

Carelli, V. and Di Colo, G., Effect of different water-soluble additives on water sorption into silicone rubber J. Pharm. Sci., 72 (1983) 316–317.

Di Colo, G., Carelli, V., Nannipieri, E., Serafini, M.F., Vitale, D. and Bottari, F., Effect of different water-soluble additives on the sustained release of sulfanilamide from silicone rubber matrices. Il Farmaco, Ed. Pr., 37 (1982) 377–389.

Di Colo, G., Campigli, V., Carelli, V., Nannipieri, E., Serafini, M F. and Vitale, D., Release of osmotically active drugs from silicone rubber matrixes Il Farmaco, Ed Pr., 39 (1984) 310–319

Guttman, D.E. and Meister, P.D., The kinetics of the base-catalyzed degradation of prednisolone. J. Am. Pharm. Ass., 47 (1958) 773-778.

Khalil, S.A.H., El-Fattah, S.A. and Mortada, L.M., Stability and dissolution rates of corticosteroids in polyethylene glycol solid dispersions. Drug Dev. Ind. Pharm., 10 (1984) 771–787.

McGinity, J.W., Hunke, L.A. and Combs, A.B., Effect of water-soluble carriers on morphine sulfate release from a silicone polymer. J. Pharm. Sci., 68 (1979) 662–664.

Nippon Kayaku Co., Ltd., Sustained-Release Formulations, Jpn. Kokai Tokkio Koho JP 59 44, 310, 12 Mar 1984 Chem. Abstr., 100 (1984) 215561c.

Riffee, W.H., Wilcox, R.E., Anderson, J.A. and McGinity, J W., Polydimethylsiloxane pellets for sustained delivery of morphine in mice. J. Pharm. Sci., 69 (1980) 980–982.

Siegel, R.A and Langer, R., Controlled release of polypeptides and other macromolecules. Pharm. Res., 1 (1984) 2–10