DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(6&7), 1391-1410 (1985)

ENHANCED RELEASE OF DRUGS FROM SILICONE ELASTOMERS (I) RELEASE KINETICS OF PINEAL AND STEROIDAL HORMONES

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ABSTRACT

The release of melatonin, estradiol, and flourogestone acetate from subdermal implants was enhanced when implants were fabricated from silicone elastomers containing co-solvents. This enhancement followed a Q vs. $t^{1/2}$ relationship. As glycerol concentration increased, the increments in release rate were greater for hydrophilic drugs than for hydrophobic drugs. When drug loading in the implants was held constant, release rates were found to be a function of glycerol concentrations in the device. A synergistic enhancement of release rate was observed when both glycerol

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and sodium chloride were added to the silicone matrix. The fact that co-solvents enhance the rate of drug release from silicone elastomers indicates that a reduction in the activation energy required for drug release may occur.

INTRODUCTION

Polydimethylsiloxanes have been sucessfully used in the development of rate-control drug delivery systems for the controlled delivery of pharmaceuticals and veterinary drugs (1-10). For example, polydimethylsiloxanes have been utilized in the preparation of transdermal patches (10, 11), like Nitrodisc®, for 24-hour treatment of angina pectoris (12), and subdermal implants, like Compudose®, for 200 to 400-day growth promotion in cattle (13). The method of fabrication is critical in determining the mechanisms and rate profiles of the devices which control the release of medicant (14). Polydimethylsiloxanes have been used to fabricate various forms of controlled-release drug delivery systems (15): (i) capsule-type (1-6), (ii) matrix-type (7-9, 13), and (iii) hybrids of the capsule- and matrix-types, such as the microsealed drug delivery system (10-12, 16-18).

Nevertheless, polydimethylsiloxanes are hydrophobic in nature, and thus, these types of drug delivery systems are limited to the controlled delivery of relatively non-polar and lipophilic compounds. The use of polydimethylsiloxanes as carriers for the delivery of polar molecules is limited, because polar compounds diffuse out of polydimethylsiloxanes only with difficulty (19). In order to improve the release of polar compounds, such as morphine sulfate, from polydimethyl-

siloxanes, McGinity et al. (20) first incorporated water-soluble carriers, like sodium alginate, into polydimethylsiloxane-based matrix-type pellets. The water-soluble carrier caused the pellets to swell in the aqueous media, leading to an increase in the release of hydrophilic compounds. Recently, Di-Colo et al. (21, 22) further investigated the swelling phenomenon of silicone elastomers by incorporating some water-soluble additives having different physical and chemical properties. Liquid-type co-solvents, such as glycerol, and solid-type salts, such as sodium chloride, were used. Incorporating these additives into silicone elastomers to form a matrix was reported to enhance the release rate of sulfanilamide (21). The extent of the enhancing effect was found to be dependent upon the type of additive used. The observed enhancement in release rate was hypothesized to be due to the formation of aqueous pores in the matrix, thus providing a preferential pathway for drug release. However, no experimental evidence has been obtained yet to demonstrate the formation of pores.

In this study, the first of a series of investigations, the effect of water-soluble co-solvents and salts on the kinetics and the thermodynamics of the release of steroidal drugs and pineal hormones from the silicone elastomer-based subdermal implants will be discussed.

EXPERIMENTAL

A. Preparation of Silicone Implants

1) Estradiol implants

Medical grade silicone elastomer 382 (*1) and varying weight fractions of glycerol, propylene glycol, and

polyethylene glycol 400 (*2) were mixed in a laboratory mixer (*3). Nine grams of this combination were mixed with one gram of estradiol (*4) to make implants containing 10% w/w estradiol. While it was stirred constantly, one drop of catalyst M was added to the mixture. After deaeration, the resultant mixture was extruded via a 30-ml syringe into the molds, which were sections of Tygon tubing, and then cured overnight at room temperature.

2) Fluorogestone acetate implants

Implants containing 1% w/w fluorogestone acetate (FGA) were also prepared in the same way as outlined above for the estradiol implants, except that the 0.1 gram of FGA was first dissolved in ethanol (one ml for every 10 mg of FGA) by sonication. It was then mixed into the silicone elastomer/co-solvent combination with the laboratory mixer. The drug/polymer mixture was agitated and heated at 80°C until all of the added ethanol had evaporated and a uniform dispersion of the drug in the polymer matrix was achieved.

3) Melatonin implants

Implants containing 10% w/w melatonin (*5) were prepared in the same way as that outlined earlier for estradiol implants.

B. In Vitro Drug Release from Silicone Implants

Estradiol- and FGA-containing silicone implants (3 cm x 0.32 cm) were each suspended in 10 ml of aqueous PEG solution, which contained 50% w/w PEG 400, to maintain the required sink condition, while shaking in a waterbath (*6) at 37 °C. For melatonin implants, however, 10 ml of an aqueous solution of 20% w/w PEG 400 were used as the drug release

medium. For each type of implant, triplicate experiments were run for a duration of at least 7 days. After each twenty-four hour period, the implants were transferred to a new set of elution media.

The amount of drug released per day was determined by measuring the drug concentration in the daily samples by UV spectrophotometry (*7). The drug release profile for each implant was expressed as the cumulative amount of drug released from a unit surface area of the implant (Q, mcg/cm^2) and was plotted as a function of the square root of time ($t^{1/2}$). The flux of drug release ($Q/t^{1/2}$) was determined from the slope of the linear Q vs. $t^{1/2}$ plots and was used to compare the effects of co-solvents and temperature.

1) Effect of different co-solvents

Ten percent w/w estradiol implants were prepared from the co-solvent/polydimethylsiloxane combinations containing 10% w/w of either glycerol, propylene glycol, or PEG 400.

2) Effect of glycerol concentrations

Ten percent w/w estradiol implants were prepared from the co-solvent/polydimethylsiloxane combinations containing varying weight fractions (0-30% w/w) of glycerol.

3) Effect of temperature

To determine the activation energy required for the release of estradiol or FGA from the silicone implants and the effect of co-solvent on energy requirements, the in vitro drug release studies were conducted at 32, 37, and 44° C. The fluxes of drug release at different temperatures were then analyzed by using the Arrhenius relationship (15).

4) Synergistic effect

Implants were prepared to contain 10% w/w melatonin in the co-solvent/polydimethylsiloxane combinations having 20% w/w glycerol and 10% w/w NaCl. Three types of control implants were also prepared for comparison: (i) implants containing 10% w/w melatonin alone in the polymer base, (ii) implants containing 10% w/w melatonin in a polymer base having 20% w/w glycerol, and (iii) implants containing 10% w/w melatonin in a polymer base having 10% w/w NaCl. For further elucidation of the synergistic effects, 10% w/w melatonin implants were prepared from the co-solvent/polydimethylsiloxane combinations having 10% w/w NaCl and 5, 10, 15, or 20% w/w glycerol.

RESULTS

A. Drug Release Profiles from Silicone Implants

Figure 1 shows the effect of co-solvent on the release flux of water-soluble melatonin, a pineal hormone, from matrix-type silicone implants. The addition of 10% w/w glycerol, a water-miscible co-solvent, did not affect the matrix diffusion-controlled drug release mechanism, but only accelerated the release flux from 28 to 150 mcg/cm^2/hr$^{\frac{1}{2}}$. This phenomenon was also observed in the release of amino acids and sulfa drugs from silicone devices containing glycerol (23).

B. Effect of Different Co-solvents

Figure 2 shows the effect of different co-solvents on the release flux of estradiol, a hydrophilic steroid, from silicone implants. When 10% w/w glycerol, propylene glycol,

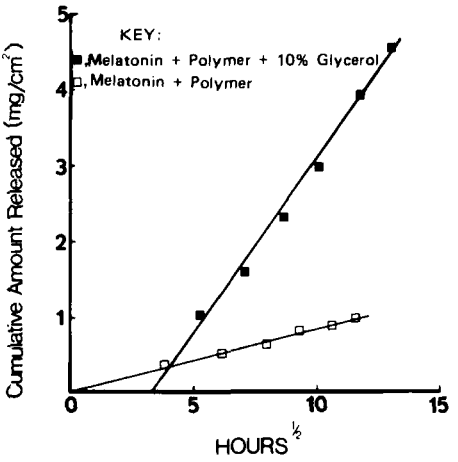

Figure 1. Q vs. $t^{1/2}$ release profiles of melatonin from silicone implants at 37°C and the effect of glycerol. The standard deviation is within 5% for all data points.

Key: ■ Release of melatonin from silicone polymer containing 10% w/w glycerol,

□ Release of melatonin from silicone polymer (no glycerol).

or PEG 400 was added, the release flux ($Q/t^{1/2}$) of estradiol, calculated from the slope of the linear Q vs. $t^{1/2}$ plots in Figure 2, was found to be enhanced by 64, 67, and 89%, respectively, when compared with virgin implants containing no co-solvent (Table I). No correlation with the solubility of the pure co-solvent could be established.

C. Effect of Co-solvent Concentration

Using glycerol, the effect of co-solvent concentration in the polymer matrix on the release of estradiol, FGA, and melatonin was evaluated. Figure 3 shows the enhancement of

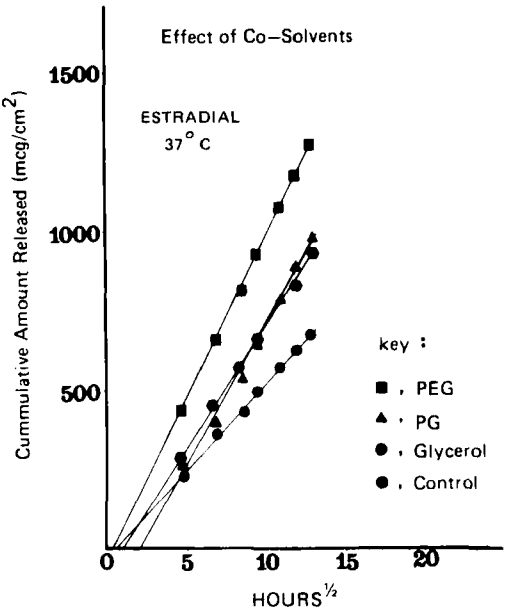

Figure 2. Effect of co-solvents on the release profile of estradiol from silicone implants. The standard deviation is within 5% for all points.

Key: ● Control,
⬢ 10% Glycerol,
▲ 10% Propylene glycol,
■ 10% PEG 400.

Table I. Effect of Co-solvents on the Release of Estradiol[1)]

Co-solvent[2)]	Release flux[3)]	Extent of increase	Solubility[4)]
	(mcg/cm²/hr½)	(%)	(mg/ml)
None	54.47	-	-
Glycerol	89.40	64	0.15
Propylene glycol	91.20	67	5.60
PEG 400	102.95	89	4.56

1) 10% w/w of estradiol in silicone Medical-grade elastomers 382.
2) 10% w/w of co-solvent in silicone Medical-grade elastomers 382.
3) Calculated from the data in Figure 2.
4) In pure co-solvent.

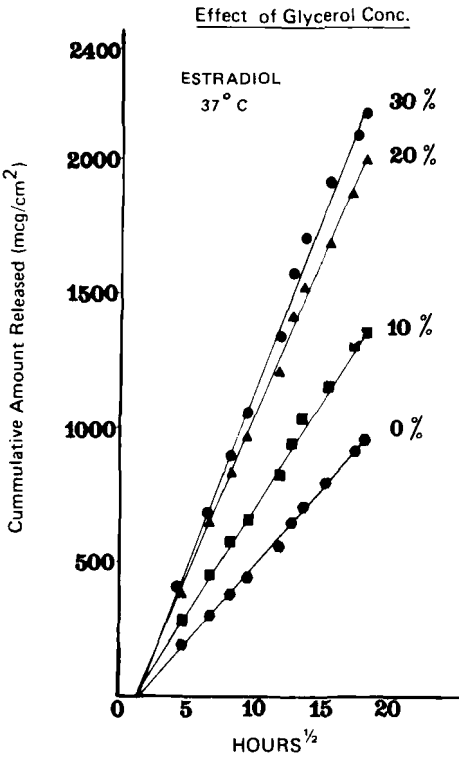

Figure 3. Effect of glycerol concentration on the release profile of estradiol from silicone implants. The standard deviation is within 5% for all data points.

estradiol release from silicone implants containing 10, 20, or 30% w/w of glycerol. The linear Q vs. $t^{1/2}$ relationship was followed at each glycerol concentration studied. The release flux ($Q/t^{1/2}$) of estradiol, calculated from the slopes in Figure 3, was found to increase from 49.29 to 141.42 mcg/cm^2/hr$^{1/2}$ when the concentration of glycerol increased from 0 to 30% (Table II). The release flux of FGA also increased progressively from 13.96 to 53.59 mcg/cm^2/hr$^{1/2}$ as the concentration of glycerol increased gradually to 30% (Table II), while the release flux of melatonin was increased even more remarkably

Table II. Effect of Glycerol Concentrations on Release Rates of Estradiol and Flourogestone Acetate (FGA) from Silicone Implants

Glycerol conc. (%w/w)	Release Rate ($mcg/cm^2/hr^{1/2}$)	
	Estradiol	FGA
0	49.29	13.96
5	-	15.88
10	88.98	20.55
15	-	21.33
20	129.84	34.05
30	141.42	53.59

from 28.31 to 253.81 $mcg/cm^2/hr^{1/2}$ with the incorporation of up to 20% w/w of glycerol (Table III).

D. Synergistic Effect

Figure 4 and Table III show the synergistic effect of co-solvent and water-soluble salt in melatonin release from silicone implants. The release flux of melatonin, calculated from the slope of the linear Q vs. $t^{1/2}$ plots in Figure 4, increased from 28.31 $mcg/cm^2/hr^{1/2}$ for the implants containing neither glycerol nor NaCl, to 78.57 $mcg/cm^2/hr^{1/2}$ for the implants containing 20% w/w NaCl, to 253.81 $mcg/cm^2/hr^{1/2}$ for the implants containing 20% w/w glycerol, and to 549.92 $mcg/cm^2/hr^{1/2}$ for the implants containing 10% w/w NaCl and 20% w/w glycerol. There was a 2.2-fold increase attributable to

Table III. Effect of Glycerol and NaCl on the Release Fluxes of Melatonin from Silicone Implants

Glycerol		NaCl		Glycerol + NaCl	
Conc.	flux	Conc.	flux	Conc.	flux
5	90.45	5	56.49	$5^{g}+10^{s}$	125.65
10	149.58	10	61.47	$10^{g}+10^{s}$	231.27
15	218.57	15	64.75	$15^{g}+10^{s}$	372.41
20	253.81	20	78.57	$20^{g}+10^{s}$	549.92

Units: concentration in % (w/w) and flux in mcg/cm^2/hr$^{\frac{1}{2}}$.
Superscript: 'g' represents glycerol, 's' represents NaCl.

the addition of 10% w/w salt, a 9-fold increase attributable to the incorporation of 20% glycerol, and a 19-fold increase attributable to the combination of 10% w/w salt and 20% glycerol. When glycerol concentration was increased gradually, as the level of NaCl concentration remained constant (i.e. 10% w/w), the release fluxes of melatonin from the silicone implants were observed to increase progressively (Table III). There was a 4.4-fold increase in the release flux due to the addition of a combination of 5% w/w glycerol and 10% w/w NaCl, an 8.2-fold increase due to the addition of a combination of 10% w/w glycerol and 10% w/w Nacl, a 13.2-fold increase due to the addition of a combination of 15% w/w glycerol and 10% w/w NaCl, and a 19.4-fold increase due to the addition of a combination of 20% w/w glycerol and 10% w/w NaCl. The release of melatonin from silicone implants containing a combination of glycerol and NaCl was enhanced

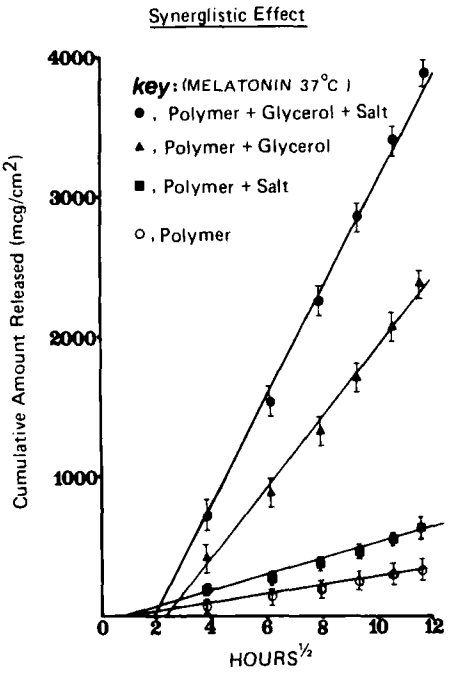

Figure 4. Synergistic effect of the water-soluble carriers on the release of melatonin from silicone implants.

Key: ○ Control,
■ 20% NaCl,
▲ 20% Glycerol,
● 20% Glycerol with 10% NaCl.

more than that from silicone implants containing either NaCl or glycerol alone.

E. Reduction in Activation Energy for Drug Release

The Arrhenius plot of the release fluxes of FGA from silicone implants containing various glycerol concentrations is shown in Figure 5. A linear relationship exists between the logarithm of release flux and the reciprocal of the

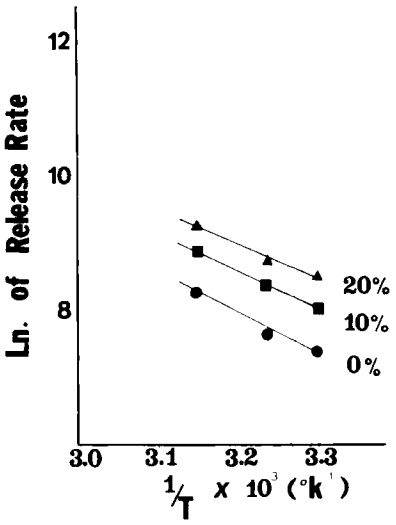

Figure 5. Arrhenius plot of the FGA release fluxes from silicone elastomers containing:

● 0% Glycerol,

■ 10% Glycerol,

▲ 20% Glycerol.

absolute temperature, confirming that the release of FGA is an energy-requiring process. The activation energy for drug release can be determined from the slope of the following relationship (15):

$$\ln (Q/t^{1/2}) = \text{Constant} - \frac{E_a}{2R}\frac{1}{T} \qquad \text{(Eq. 1)}$$

where E_a is the activation energy for drug release, R is the gas constant, and T is absolute temperature. The activation energies thus calculated for estradiol and FGA are summarized in Table IV. The results suggest that the higher the concentration of glycerol, the lower the activation energy required for the release of drugs.

Table IV. Effect of Glycerol Concentration on Activation Energy Required for Drug Release from Silicone Implants

Glycerol conc. (%w/w)	E_a (Kcal/mole)*	
	Estradiol	FGA
0	20.12	12.10
10	15.50	11.20
20	11.84	10.04
30	11.72	-

* Triplicate runs in aqueous solution containing 50% PEG 400.

DISCUSSION AND CONCLUSIONS

Although the use of silicone elastomers in the fabrication of controlled-release drug delivery systems has been well documented in the literature, one of the major deficiencies, concerning the impermeability of "polar" compounds and low permeability of "water-soluble" drugs through the silicone elastomers, has not yet been overcome (19). This investigation has demonstrated that it is feasible to develop controlled-release drug delivery devices from lipophilic silicone elastomers for the delivery of "polar" and "water-soluble" drugs, by incorporating glycerol and other water-soluble co-solvents into the polymer. The enhanced release of hydrophilic melatonin from glycerol-containing silicone implants is a typical example (Figure 1). The release of drugs from co-solvent-containing matrix-type

silicone devices was noted to follow the same matrix diffusion-controlled process as did the co-solvent-free matrix-type silicone devices. The incorporation of water-soluble co-solvents did not appear to affect the mechanism of matrix-controlled drug release, but it enhanced the flux of release (Figures 1, 2, and 3). Using the well established model for matrix diffusion-control devices (15), the fluxes of drug release can be described mathematically by the following equations:

(1) without co-solvent:

$$(Q/t^{\frac{1}{2}})_o = \{ (2A - C_p) C_p D_p \}^{\frac{1}{2}} \qquad \text{(Eq. 2)}$$

(2) with co-solvent:

$$(Q/t^{\frac{1}{2}})_x = \{ (2A - C_{px}) C_{px} D_{px} \}^{\frac{1}{2}} \qquad \text{(Eq. 3)}$$

where $(Q/t^{\frac{1}{2}})_x$ is the flux of drug release from a polymer matrix containing a given concentration of co-solvent f_x; $(Q/t^{\frac{1}{2}})_o$ is the flux of drug release from a polymer matrix containing no co-solvent; A is the initial drug loading dose; C_p and D_p are the solubility and diffusivity of the drug in the polymer matrix containing no co-solvent; and C_{px} and D_{px} are the solubility and diffusivity of the drug in the polymer matrix containing a co-solvent.

Based upon the experimental results in Figures 1 to 4, the rate of drug release was observed to increase following the addition of co-solvents to the silicone matrix. One possible interpretation of this phenomenon is that the increase in drug

release rate results from an improvement in drug solubility and diffusivity in the polymer matrix, such that $C_{px} > C_p$ and $D_{px} > D_p$. In other words, the changes in the physical nature of the silicone network accelerate the release of the water-soluble drug. Nevertheless, the increase in drug release flux in response to the addition of a co-solvent depends upon the type of co-solvent (Figure 2 & Table I), the weight fraction of the co-solvent (Figure 3 & Table II), and the combination of the two different types of water-soluble carriers (Figure 4 & Table III). Among the co-solvents tested, polyethylene glycol 400 appeared to be the most effective in promoting the release of estradiol (Table I). The synergistic effect on the release of melatonin from the silicone implants containing both glycerol and sodium chloride could be the result of an osmotic effect, exerted by sodium chloride, and an enhancing effect, exerted by glycerol, in combination.

A semilogarithmic relationship was established between the release flux of drug and the concentration of water-soluble carrier added to the silicone implant (Figure 6). The correlation coefficients of the linear relationship were 0.961 for NaCl-containing implants, 0.987 for glycerol-containing implants, and 0.995 for implants containing both glycerol and NaCl. The slope of the linearity was 0.036, 0.132, and 0.172 for implants containing NaCl, glycerol, and both, respectively. The usefulness of this empirical relationship is that it can be used in the development of a drug delivery device to achieve a specifically desired release rate. In a separate study, this empirical relationship was applied to

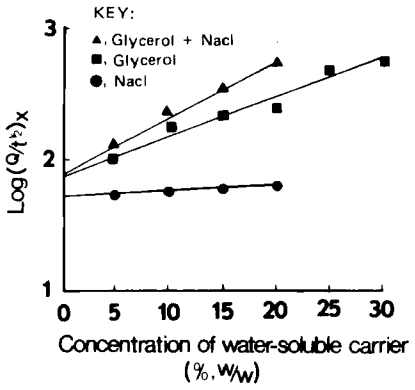

Figure 6. Semi-logarithmic relationship between the release flux of melatonin and the concentration of the following water-soluble carriers in the silicone implants:

■ Glycerol,

● NaCl,

▲ Glycerol and NaCl.

obtain an enhancement of the release of sulfa drugs, the results of which will be reported at a later date.

Examination of Figures 1-4 suggests that an extrapolation of the steady-state drug release profile (Q vs. $t^{\frac{1}{2}}$) will intercept the x-axis at a finite time, implying the existence of a non-steady-state diffusion process in the initial stage of drug release. In this stage the water molecules in the drug releasing medium diffuse into the silicone matrix to make the polymer swell, which faciliates the release of drug molecules at a steady state release rate.

Before a theoretical model can be established, the following questions must be investigated: (i) Is the swelling phenomenon of silicone implants containing co-solvents reversible? (ii) Are there differences in the micro-structure

of implants before and after swelling (as determined by using scanning electron microscopy)? (iii) To what extent does the co-solvent leach from implants which contain glycerol? (iv) Is there an interaction between glycerol and the polydimethylsiloxanes? (v) What are the diffusivity and solubility of drugs in silicone membranes containing glycerol? All of these investigations will be conducted in the near future. Once these experiments are completed, the role of co-solvents and other water-soluble carriers in enhancing the release of drugs from silicone elastomers will be more clearly understood.

In conclusion, this study shed new light on the formulation of drug delivery systems using lipophilic polymers, such as silicone elastomers, for the controlled delivery of hydrophilic compounds. The exponential relationship between release flux ($Q/t^{\frac{1}{2}}$) and glycerol concentration provides a guideline in the development of formulations for matrix-type drug delivery systems to deliver drugs at specific release rates. The data obtained so far tend to suggest that an increase in the release rate, due to the addition of co-solvents, may be a result of a reduction in the activation energy required.

Footnotes

*1. MDX 4-4210, Dow Corning Co., Midland, MI.

*2. Fisher Chemical Co., Fair Lawn, NJ.

*3. Lab stirrer, Model 43800-00, Cole Parmer, Chicago, IL.

*4. Sigma Chemical Co., St. Louis, MO.

*5. See footnote 4.

*6. Shaking water-bath, Model 127, Fisher Scientific Co., Fair Lawn, NJ.

*7. UV/Vis Spectrophotometer, Model 559A, Perkin Elmer Corp., Chicago, IL.

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