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Transport of Prostaglandins through Silicone Rubber

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Abstract □ The *in vitro* release profiles of the F-series of prostaglandins were determined from a silicone rubber matrix of constant surface area. Silicone rubber was selective toward prostaglandin transport and offers potential as a controlled-release delivery system. Drug release patterns were dependent on the lipophilicity of the prostaglandin molecule. For dinoprost (prostaglandin $F_{2\alpha}$), the following sequence was observed: methyl ester > free acid > tromethamine salt. The biologically potent carboprost methyl [(15*S*)-15-methylprostaglandin $F_{2\alpha}$ methyl ester] was released considerably faster than the methyl ester of the parent dinoprost molecule, while release of the tromethamine salts of the two prostaglandins was similar. Permeability rates of the salts were depressed substantially when compared to their respective C-1 methyl esters. Results from independent membrane transport studies supported the observed dependence of steady-state flux on the chemical structure of the prostaglandin molecule. Plots of the amount released per unit area *versus* the square root of time were linear except for the initial drug release phase, and the total amount of prostaglandin released increased as the initial loading dose was raised. The data were analyzed according to a physical model describing drug release from inert matrix systems. The observed concentration dependence was consistent with the predictions of the model.

Keyphrases □ Prostaglandins—transport through silicone rubber, effect of lipophilicity, *in vitro* release profiles □ Dinoprost—transport through silicone rubber □ Carboprost—transport through silicone rubber □ Controlled-release delivery—transport of prostaglandins through silicone rubber □ Dosage forms—transport of prostaglandins through silicone rubber

Prostaglandins are a class of C_{20} lipid-like substances that produce a wide spectrum of biological responses (1). Their clinical application in fertility control is well recognized since they possess luteolytic and abortifacient properties, alter ovum transport, and induce menses (2). Naturally occurring dinoprost[1] (prostaglandin $F_{2\alpha}$) and dinoprostone[2] (prostaglandin E_2) have been tested clinically by numerous routes of administration in solution, tablet, and suppository dosage forms. The (15*S*)-15-methyl analogs also are being explored as fertility-regulating agents and are considerably more potent (3, 4).

Intrauterine administration reduces undesirable side effects associated with the systemic intravenous route since drug is delivered closer to the uterus. The vaginal route, however, allows for self-administration, and it has been used successfully to terminate pregnancy with dinoprostone suppositories given by a multiple-dosing regimen (5) and with a single carboprost methyl[3] [(15*S*)-15-methylprostaglandin $F_{2\alpha}$ methyl ester] vaginal suppository (6).

BACKGROUND

Studies in these laboratories have been directed toward the development of a prostaglandin delivery module that can be self-administered, is reversible, and provides continuous drug release for the treatment period following a single administration. Structural modifications of polymeric materials have been made to attain satisfactory prostaglandin release rates.

Nuwayser and Williams (7) showed that the permeability rate of dinoprost in deacetylated cellulose acetate was much greater than in other cellulose derivatives; in the rabbit, Akkapeddi *et al.* (8) demonstrated the abortifacient effectiveness of dinoprost and dinoprostone when incorporated into a series of hydrophilic polymeric materials. Polyacrylamide and polyvinylpyrrolidone gels containing dinoprostone or dinoprost also were effective in fertility control in several animal systems (9–12). Silicone rubber, however, was impervious to dinoprost transport and was discounted as a possible delivery system (9). Yet Spilman and Roseman (13) showed that silicone vaginal rings impregnated with carboprost methyl were effective in producing increased uterine muscle activity, luteolysis, and abortion in the Rhesus monkey.

The delivery system design, therefore, not only depends on the delivery module but also on the chemical form of the drug molecule. The present article provides a physicochemical analysis of the transport mechanism of prostaglandins through silicone rubber. The influence of lipophilicity on release is a dominant factor in assessing the utility of silicone rubber as a delivery system. In this regard, these findings parallel an earlier study with steroids (14).

EXPERIMENTAL

The prostaglandins[4], dinoprost, dinoprost tromethamine, dinoprost

[1] Prostin F_2 alpha, The Upjohn Co., Kalamazoo, MI 49001.
[2] Prostin E_2, The Upjohn Co., Kalamazoo, MI 49001.
[3] Prostin M/15, The Upjohn Co., Kalamazoo, MI 49001.
[4] Supplied by the Pharmaceutical Research and Development Division, The Upjohn Co., Kalamazoo, MI 49001.

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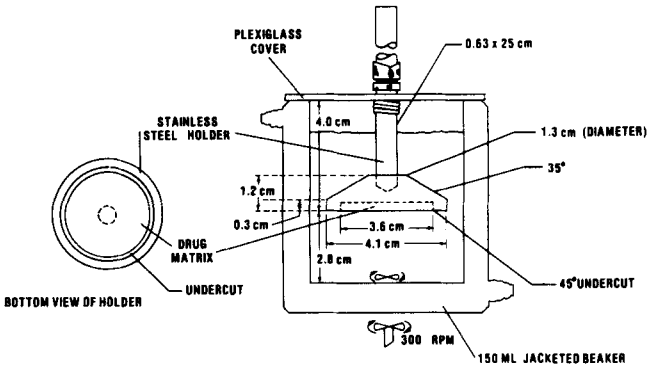

Figure 1—*Sketch of release apparatus and mold used to study the release of prostaglandins from silicone rubber.*

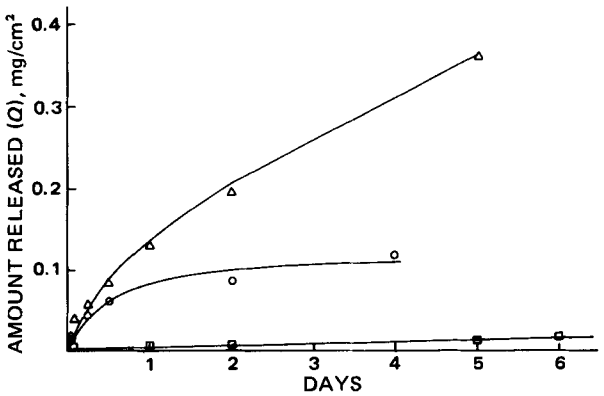

Figure 2—*Release profiles of dinoprost (prostaglandin $F_{2\alpha}$) from silicone rubber at a loading of 2%. Key: △, dinoprost methyl ester; ○, dinoprost free acid; and □, dinoprost tromethamine.*

methyl ester, carboprost methyl, and carboprost tromethamine, were at least 99% pure by GLC and showed a single major zone by TLC. Compression-distilled water and analytical reagent grade chemicals were used. Distilled-in-glass chloroform was used for prostaglandin extraction.

Release Method—The preparation of the prostaglandin matrixes and the experimental design of the release rate studies were similar to those reported previously (15). The methyl esters of dinoprost and carboprost first were triturated in a mortar to reduce their particle size. After the prostaglandins were suspended in the silicone monomer[5] and catalyzed with stannous octoate, the mix was placed into a stainless steel circular mold having an exposed surface area of 10 cm^2 (Fig. 1). During the curing step, an acrylic resin plate was placed over the elastomer to provide a smooth surface for the subsequent release experiments. The matrix was cured overnight at room temperature, the acrylic resin plate was removed, and the excess flashings were trimmed before release determinations were made.

Release measurements were performed in 100 ml of 0.1 *M* tromethamine buffer (pH 7.0) at 37°. Agitation of the solution was provided by a 300-rpm synchronous motor which rotated a magnetic stirrer. Samples (15–25 ml) were withdrawn through the acrylic resin cover with a syringe and needle, extracted with chloroform, and assayed. The withdrawn solution was replaced with an equal volume of buffer preequilibrated at 37°. For dinoprost tromethamine and dinoprost (free acid), the procedures were identical except that the tromethamine salt was micronized and the waxy free acid was levigated directly into the silicone phase.

The dissolution medium pH was selected to maintain sink conditions for dinoprost when used as the tromethamine salt and free acid. Since concentrations were <0.01 mg/ml and the aqueous solubility at this pH is >200 mg/ml (16), the sink condition was met. This same pH was used for the esters to maintain uniformity of dissolution and to retard any drug decomposition during the experiment. For the methyl esters, the concentrations during dissolution were <10% of their equilibrium solubility values. Stability studies with the methyl ester prostaglandins indicated that no decomposition occurred during sample preparation for dissolution. However, after about 1 week, some degradation of carboprost methyl was noted in the elution medium. When necessary, the concentrations were corrected to reflect accurately the total prostaglandin released. To avoid the potential effect of surface diffusion of drug on the release profiles, dissolution studies were performed within 1 week after device preparation.

The methyl ester samples (15–25 ml) were extracted directly with three equal volumes of chloroform and dried under vacuum with mild heat[6]. For the tromethamine salt and free acid runs, the pH of the withdrawn samples was lowered to 3 with 0.2 *M* citrate buffer (pH 3) and extracted with chloroform as outlined for the esters.

Membrane Transport—Fillerless silicone membranes were prepared by polymerizing the silicone monomer[7] with stannous octoate and placing the mix between metal plates separated by the appropriately sized spacers. After curing, the sheet was removed and circular membranes of the desired diameter were punched out. The membrane was soaked overnight in water and then mounted into a diffusion cell originally designed by Flynn and Smith (17), without the screen and with a 60-rpm motor. Throughout the experiment, temperature was maintained at 37°.

At time zero, a preequilibrated saturated solution containing excess prostaglandin in pH 7.0 tromethamine buffer was placed in the donor compartment, while the receptor side contained the buffer with no drug. Samples were taken as a function of time by flushing the receptor compartment with three volumes of fresh buffer. The entire sample then was extracted with chloroform (3 × 25 ml).

The diffusion coefficient of tritium-labeled carboprost methyl [(15*S*)-15-methylprostaglandin $F_{2\alpha}$-11β-[^{3}H]methyl ester] was determined using the described diffusion cell. Samples (1 ml) were withdrawn, diluted with 10 ml of scintillation fluid[8], and then counted on a liquid scintillation counter[9].

Analytical Procedures—GLC was employed to determine prostaglandin concentrations. The dried prostaglandin extracts were treated with 3–4 drops of dry pyridine and 0.5 ml of silylating reagent containing 1 or 3 mg of cholesteryl acetate (internal standard)/ml. For the 15-methylprostaglandin $F_{2\alpha}$ compounds, the silylating reagent was bis(trimethylsilyl)trifluoroacetamide plus 1% trimethylchlorosilane[10], and the solution was allowed to react overnight at room temperature. With the dinoprost compounds, a silylation mixture of *N,O*-bis(trimethylsilyl)-acetamide–trimethylchlorosilane[11] (4:1) was utilized; the reaction was completed in 30 min. Reference standards were prepared by direct treatment of 1 mg of prostaglandin with the appropriate silylating reagent.

After the reaction was complete, 1 μl was injected onto the glass (0.63-cm i.d. × 1.2-m length) column[12] packed with 3% UCW-98 on 80–100-mesh Gas Chrom Q[13]. The flash heater was off, and the column and detector temperatures were 260 and 270°, respectively. The helium gas flow was 60 ml/min, and air and hydrogen rates were adjusted to maximize response; the attenuation was 10 × 32. Unknown prostaglandin concentrations were determined by peak area ratios with standards injected with the samples.

Extraction of solution from a placebo run showed no interfering peaks. The efficiency of the analytical procedures was checked by analyzing samples of known concentrations. Complete prostaglandin recovery resulted from the extractions from aqueous media.

RESULTS AND DISCUSSION

Release Profiles of Dinoprost (Prostaglandin $F_{2\alpha}$)—Studies on prostaglandin release from silicone rubber were initiated using the naturally occurring dinoprost as the model compound. Figure 2 illustrates the release pattern of dinoprost as a function of its chemical form at the C-1 position. Silicone rubber was almost impervious to the transport of dinoprost as the tromethamine salt, while the methyl ester was released continuously as a function of time. The release profile of dinoprost (free acid) fell in between the methyl ester and tromethamine salt. Qualitatively, the release data correlated directly with the expected degree of lipophilicity of the prostaglandin molecule in the silicone matrix phase, *i.e.*, methyl ester > free acid > tromethamine salt.

[5] Silastic 382, Dow Corning Corp., Midland, MI 48640.
[6] Büchi-Rotavapor-R, Switzerland.
[7] Fillerless Silastic 382 was supplied by the Dow Corning Corp., Midland, MI 48640.
[8] PCS, Amersham Co., Arlington Heights, IL 60005.
[9] Mark III model 6880, Searle Analytical Inc., Des Plaines, IL 60016.
[10] Regisil, Regis Chemical Co., Morton Grove, IL 60053.
[11] Pierce Chemical Co., Rockford, IL 61105.
[12] Model 402, Hewlett-Packard, Skokie, IL 60076.
[13] Applied Science Laboratories, State College, PA 16801.

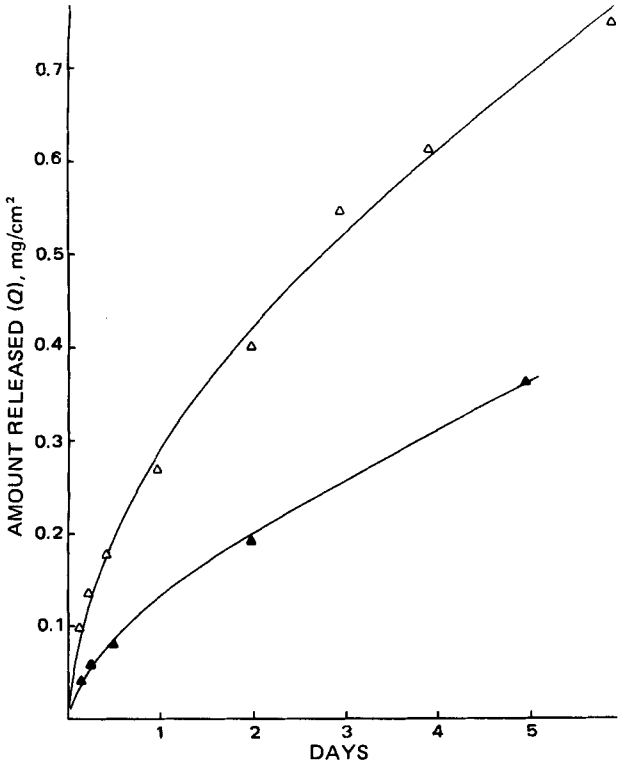

Figure 3—*Release profile of dinoprost methyl (prostaglandin $F_{2\alpha}$ methyl ester) from silicone rubber. Key: ▲, 2%; and △, 5%.*

Earlier work on the release of neutral steroidal compounds from silicone rubber suggested that drug transport is due mainly to diffusion through the matrix phase (18). The extremely slow release of dinoprost tromethamine supports this mechanism. At pH 7.0, dinoprost has a solubility in excess of 200 mg/ml. If transport through aqueous channels or pores is an important route for drug release, then the large aqueous solubility of the salt would provide a highly favorable driving force (concentration gradient) for the rapid diffusion of prostaglandin. The lower release rate of the salt form was probably due to a rather limited solubility in the silicone rubber phase. In contrast to the methyl ester of dinoprost, the free acid form was released for only about 2 days. The polymerization reaction for dinoprost (free acid) required a two- to threefold increase in the catalyst concentration, and it appears that the drug participated in the polymerization. If this is the case, the effective drug concentration in the matrix would be reduced and limit the availability of the prostaglandin molecule, as evidenced by the plateau region in Fig. 2. The dependence of release on the initial prostaglandin loading dose is shown in Fig. 3 for dinoprost methyl ester.

Comparison of Permeability Rates of Dinoprost Methyl (Prostaglandin $F_{2\alpha}$ Methyl Ester) and Carboprost Methyl [(15*S*)-15-Methylprostaglandin $F_{2\alpha}$ Methyl Ester]—The synthesis and biological activity of carboprost methyl was reported by Bundy *et al.* (19). This compound, along with other 15-methyl analogs of the A and E series of prostaglandins, was not a substrate for the enzyme, 15-hydroxyprostaglandin dehydrogenase, which rapidly inactivates the naturally occurring prostaglandins. The 15-methyl analog is 10 times more potent than dinoprost in promoting uterine activity and has been used successfully to terminate pregnancy by several administration routes (20). Silicone rings and devices containing carboprost methyl exhibit antifertility activity in the Rhesus monkey. A single intravaginal insertion of this device resulted in prolonged uterine activity, luteolysis, and termination of pregnancy (13, 15).

The *in vitro* release of this compound is presented in Fig. 4 for the 0.5–10% concentration range. Continuous drug release was observed for as long as 36 days, with the amount released at a given time increasing as the concentration was raised. This dependence is similar to the release of dinoprost methyl ester as seen in Fig. 3. However, the release rate of the 15-methyl analog was 1.4 times faster than the parent ester of dinoprost. At equal matrix concentrations, this factor reflects the ratio of the square root of the permeability constants (P), *i.e.*, the product of the drug solubility in the polymer (C_s) times the drug diffusivity in the polymer (D_s) (see *Theoretical Analysis*). Steady-state fluxes across a silicone

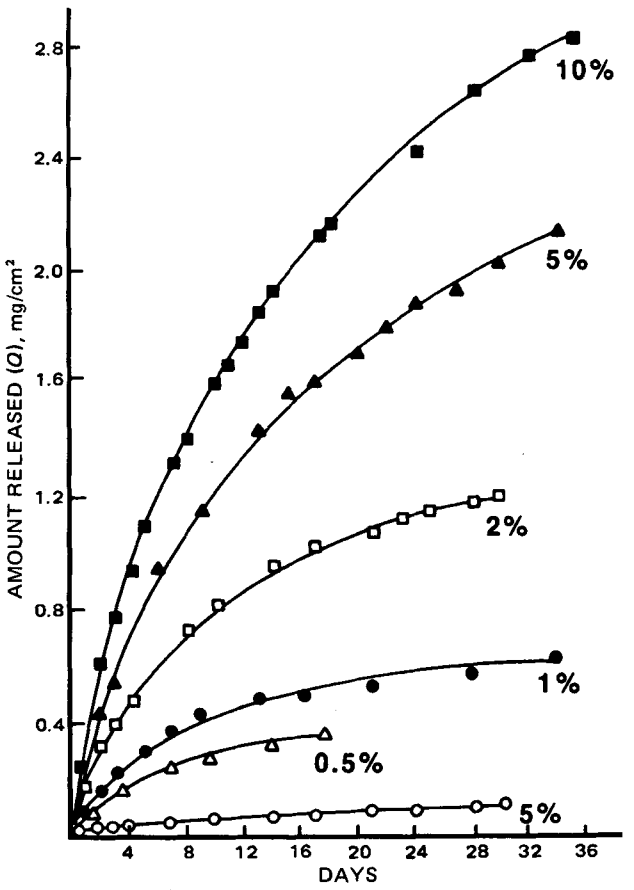

Figure 4—In vitro *release profiles of carboprost methyl [(15S)-15-methylprostaglandin $F_{2\alpha}$ methyl ester] from silicone rubber as a function of prostaglandin concentration in the matrix. Key:* ○, *5% tromethamine salt; and all other curves, methyl ester.*

membrane confirm the observed dependence on prostaglandin structure (Fig. 5). When the donor compartment in the diffusion cell is maintained at saturation, the following expression from Fick's law (21) is applicable:

$$\text{rate} = \left(\frac{dQ}{dt}\right)_{ss} = \frac{C_s D_s}{l} \qquad \text{(Eq. 1)}$$

where l is the membrane thickness. Steady-state diffusion rates are related linearly to C_sD_s and, as expected, the flux of the two prostaglandins is different at equal membrane thicknesses. Increasing the thickness decreases the transport in accord with Eq. 1. In contrast to the observed

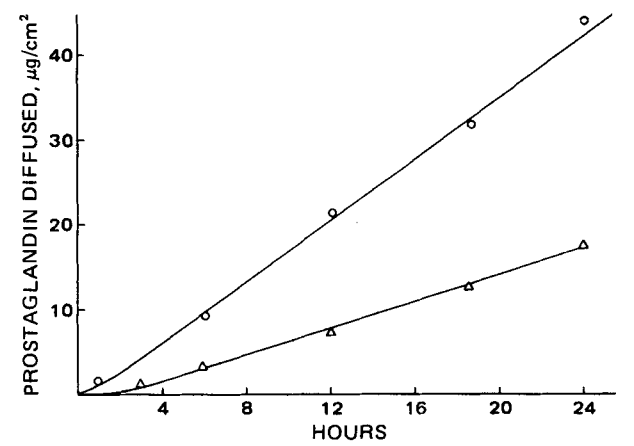

Figure 5—*Amount of prostaglandin diffused across a 0.047-cm thick silicone rubber membrane as a function of time. Key:* ○, *carboprost methyl [(15S)-15-methylprostaglandin $F_{2\alpha}$ methyl ester]; and* △, *dinoprost methyl (prostaglandin $F_{2\alpha}$ methyl ester).*

Table I—Comparisons of Prostaglandin Permeability Constants [a] (C_sD_s) from Matrix Release and Membrane Transport Experiments

	Matrix Release	Membrane Transport
Dinoprost methyl (prostaglandin $F_{2\alpha}$ methyl ester)	$0.84^b \times 10^{-8}$	0.98×10^{-8c}
Carboprost methyl [(15*S*)-15-methylprostaglandin $F_{2\alpha}$ methyl ester]	$1.6^b \times 10^{-8}$	$2.1^c \times 10^{-8}$, $2.6^d \times 10^{-8}$

[a] Units are milligrams per centimeter per second. [b] Calculated average from the least-squares slope of $(Q/t^{1/2})$ *versus* $A^{1/2}$. [c] Calculated using a 0.097-cm thick membrane. [d] Calculated using a 0.0470-cm thick membrane.

transport of the esters, the tromethamine salts diffused at negligible rates.

Theoretical Analysis—The general equation for drug release from a planar silicone rubber surface is:

$$Q = \frac{-D_s h_a K A \epsilon}{D_a \tau} + \left[\left(\frac{D_s h_a K A \epsilon}{D_a \tau}\right)^2 + \frac{2AD_sC_s\epsilon t}{\tau}\right]^{1/2} \quad \text{(Eq. 2)}$$

where:

Q = amount released per unit area
t = time
A = total concentration of drug in matrix
D_a = diffusion coefficient in the dissolution medium
D_s = diffusion coefficient in the matrix phase
K = partition coefficient (C_s/C_a)
C_a = solubility in the dissolution medium
C_s = solubility in the matrix phase
h_a = boundary diffusion layer thickness
ϵ = volume fraction
τ = tortuosity

Equation 2 was derived from a physical model which considers both diffusion through the matrix and transport away from its surface across a boundary diffusion layer[14]. For drugs that exhibit high permeability rates, the boundary diffusion layer can offer a major resistance to drug release. However, when the matrix is rate controlling, Eq. 2 reduces to:

$$Q = \left(\frac{2AD_sC_s\epsilon t}{\tau}\right)^{1/2} \quad \text{(Eq. 3)}$$

which was originally derived (22) for drug release from inert matrix systems. Plots of Q *versus* $t^{1/2}$ for the prostaglandin methyl esters are shown in Figs. 6 and 7. Except for an early nonlinear period, Eq. 3 is obeyed. The curvature at early times follows predictions from Eq. 2 when the resistance of the diffusion layer plays a significant role in the total diffusion. As noted in Fig. 7, where a wide range of concentrations are presented, the curvature becomes less as the concentration in the silicone rubber phase decreases. This finding supports the applicability of Eq. 2 at early times because the depleted region in the matrix recedes less at high

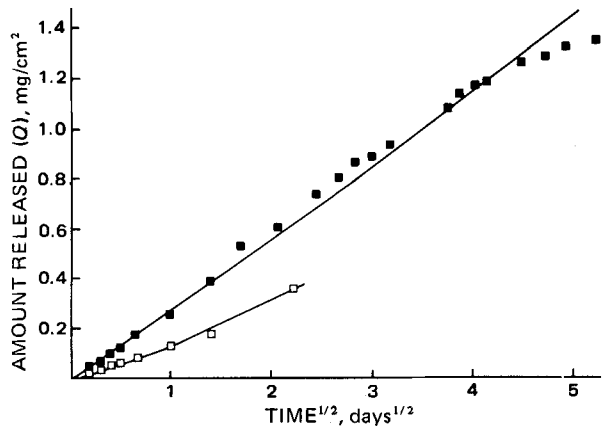

Figure 6—*Dependence of* Q *on* $t^{1/2}$ *for the release of dinoprost methyl (prostaglandin $F_{2\alpha}$ methyl ester) from silicone rubber at different loading doses. Key: □, 2%; and ■, 5%.*

[14] The assumptions in the derivation can be found in Ref. 18.

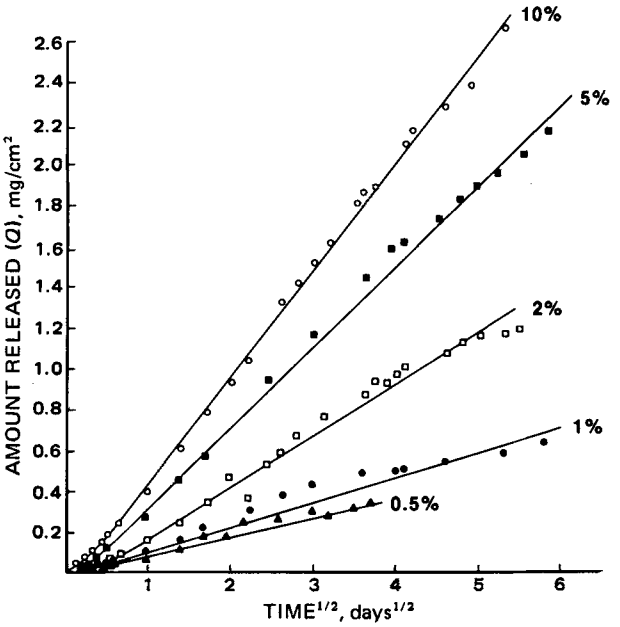

Figure 7—*Dependence of* Q *on* $t^{1/2}$ *for the release of carboprost methyl [(15S)-15-methylprostaglandin $F_{2\alpha}$ methyl ester] from silicone rubber at different loading doses.*

loading doses. At low matrix concentrations, drug diffusion occurs across a depleted zone of greater depth and Eq. 3 becomes operative sooner. This is evident in the 0.5% curve where Q *versus* $t^{1/2}$ plots are linear even during the early release stage.

Calculated values for the permeability constants, C_sD_s, are given in Table I. Considering the complexities of the studies, favorable agreement between the matrix release and membrane transport data is noted. The slightly higher numbers associated with the membrane transport experiments may be a consequence of faster drug diffusion through a fillerless polymer[15]. Fillerless material was used to obtain additional information on the diffusivity of the prostaglandins since silicone rubber reinforced with diatomaceous earth or silica was reported (23, 24) to increase the lag times (L) and yield anomalous diffusivity values calculated from the lag time expression (25):

$$D_s = \frac{l^2}{6L} \quad \text{(Eq. 4)}$$

where l is the membrane thickness and L is the lag time[16]. In the present study, extrapolation of the steady-state portions of the curve in Fig. 5 yielded lag times with high standard errors of the mean, and accurate values could not be determined. However, by utilizing radiolabeled carboprost methyl, the diffusion coefficient of the prostaglandin was determined to be 0.485×10^{-7} ($\pm 0.020 \times 10^{-7}$) cm^2/sec. The C-15 methyl group is not expected to alter the diffusivity of this series, and the same value can be reasonably assumed for dinoprost methyl ester. The estimated values of C_s for carboprost methyl and dinoprost methyl ester are 0.48 and 0.20 mg/cm^3, respectively. Methylation at the C-15 position of dinoprost methyl ester, therefore, appears to make the prostaglandin ester more lipophilic, resulting in increased transport rates.

Previous studies (26) demonstrated that substitution of a less polar carbonyl group for the hydroxyl moiety at C-9 (*i.e.*, dinoprost → dinoprostone) and the addition of lipophilic ester groups at C-1 significantly increase the transport rates of prostaglandins across silicone rubber. The agreement between the permeability constants in Table I for matrix release and membrane transport suggests that membrane transport studies can be used to predict *a priori* release profiles of prostaglandins from monolithic devices according to:

$$Q = \left[2Al\left(\frac{dQ}{dt}\right)_{ss}\right]^{1/2} t^{1/2} \quad \text{(Eq. 5)}$$

[15] Filler, such as silica, is incorporated in the polymer to increase its mechanical properties.

[16] This expression applies when the major resistance to diffusion resides in the membrane. It is valid for these prostaglandins since the resistance in the membrane is at least 100 times greater than in the diffusion layer.

and:

$$\text{rate} = \left[\frac{Al}{2}\left(\frac{dQ}{dt}\right)_{ss}\right]^{1/2} t^{-1/2} \qquad \text{(Eq. 6)}$$

where $(dQ/dt)_{ss}$ is the slope of the steady-state portion of the curve from a diffusion cell experiment (Fig. 5) and the other terms are as were defined. This approach is valuable in screening compounds to assess whether release rates are consistent with their biological dosing patterns.

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NOTES

Synthesis and Antibacterial and Antifungal Activities of Alkyl and Polyhalophenyl Esters of Benzo[*b*]thiophene-3-carbamic Acid

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Abstract □ Several alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid were prepared and tested for antibacterial and antifungal activities. Two compounds exhibited the highest activity of growth inhibition against some bacteria and fungi.

Keyphrases □ Antibacterial activity—alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid □ Antifungal activity—alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid □ Benzo[*b*]thiophene-3-carbamic acid—alkyl and polyhalophenyl esters, synthesis, antibacterial and antifungal activities

Dialkylaminoalkyl esters of benzo[*b*]thiophene-2-carboxylic acid[1] reportedly are useful as hypotensive, antiviral, and antifungal agents (1). Derivatives of benzo[*b*]thiophene-2-carboxamide were reported to have local anesthetic and analgesic activities (2). Some carbamic acids having the benzo[*b*]thiophene moiety showed pesticidal, fungicidal, and insecticidal activities (3).

In continuing studies on the chemistry and antibacterial and fungicidal activities of carbamic acid esters (4–7), alkyl and polyhalophenyl esters of benzo[*b*]thiophene-3-carbamic acid were synthesized and their efficacy was determined.

DISCUSSION

Chemistry—The desired compounds were prepared according to Scheme I.

The reaction of *N*-bromosuccinimide with readily available 3-chloromethylbenzo[*b*]thiophene (I) (8) afforded II. Hydrolysis of II gave benzo[*b*]thiophene-3-carboxylic acid (III) (9). Compound III was converted to benzo[*b*]thiophene-3-carboxyhydrazide (V) by a literature method (10). The hydrazide (V) then was transformed to the carboxazide (VI) by reaction with sodium nitrite in acetic acid. Curtius rearrangement of the azide was achieved readily through heating with alcohols or with polyhalophenols in refluxing benzene. The physical data of the compounds prepared are summarized in Table I.

Antifungal and Antibacterial Activities—All compounds listed in Table I were tested against *Candida albicans* (28012), *Penicillium not-*

[1] Benzo[*b*]thiophene also is known as thianaphthene.

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