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MECHANISTICAL ANALYSIS OF RELEASE KINETICS FOR LIPOPHILIC DRUG FROM MATRIX-TYPE DRUG DELIVERY DEVICES

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ABSTRACT

The release kinetics of lipophilic drug from hydrophobic polymer-based matrix-type drug delivery system was studied. Using the "intrinsic formula", several experimental problems can be analyzed and solved. The results reveal that intrinsic release, calculated from the model, shows the true properties of the drug delivery system, which might have been disguised by the boundary layer effect. The results also demonstrated the needs of maintaining sink condition and uniform distribution of dispersed phase in studying the matrix diffusion-controlled drug release.

INTRODUCTION

Because of its physiological inertness, biomedical compatibility and remarkably high permeability to organic substances, especially to steroidal drugs, considerable interests have been generated in the use of silicone elastomers for the controlled delivery of pharmaceuticals (1-7). The dependence of release rate upon the physicochemical properties of drug and loading dose in the polymer as well as the solubility in the external

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solution was investigated (8-9). It was discovered that the drug release profiles from the matrix-type device are influenced by the hydrodynamic properties of the in vitro drug release apparatus used for the investigations, i.e., the release profiles are dependent upon the flow pattern in the diffusion cells (10). Therefore, the hydrodynamics of in vitro drug release apparatus should be well characterized. Further, the physiological environments, such as gastrointestinal mobility in the case of oral drug administration, kinematic viscosity of the tissue fluid surrounding the implanted devices and the aqueous boundary layer between the drug device and vaginal surface, are important concerns as well, since they will affect the in vivo release and absorption profiles of a therapeutic agent from a drug delivery device. Accordingly, the hydrodynamic diffusion layer plays a very significant role in the rate profile of drug release and absorption; particularly, for a lipophilic drug species. The diffusion of the lipophilic drugs across the hydrodynamic diffusion layer sandwiched between the drug delivery device and absorption surface of tissue is often the rate-determining step.

Although Roseman et al. (10) have proposed a model to describe the release pattern of drugs from a matrix-type device with the consideration of a boundary diffusion layer, the concept of "intrinisic" diffusion rate has not been introduced until recently by Tojo et al. (11). A mathematical expression was derived on the basis of matrix-boundary diffusion layer model. Using the mathematical model, the "intrinsic release rate", which is defined as the maximum achievable release rate with minimum effect from a negligibly thin boundary layer, can be determined. Despite the variation in flow patterns in different diffusion cell designs, which are often used in diverse investigations, this intrinsic rate of release should be an invariant value. The intrinsic release rate obtained thus sheds light on standardization of the experimental values for inter-laboratory comparison; and, the results obtained in different laboratories can then be correlated in a scientific manner. Apparently, the effect of hydrodynamic diffusion layer could lead to a possible distortion of experimental data

and should be one of the important concerns in any analysis of drug release data.

The purpose of this investigation is to study the effect of hydrodynamic diffusion layer on the apparent release profiles of lipophilic drug from a hydrophobic polymer-based matrix-type drug delivery system. The determination and the significance of "intrinsic release rate" in the interpretation of experimental observations are illustrated as well, with emphasis on the experimental conditions and heterogeneity of matrix device.

EXPERIMENTAL

Material

Progesterone[1] was used as received. Silastic 382 medical grade elastomer, DC Silicone fluid 360 and catalyst M (Stannous Octanoate) were donated from the manufacturer[2].

Preparation of Matrix-Type Devices

Polymer discs with various loading doses (0.5 - 25% w/w) were prepared by mixing well a required amount of progesterone, 10% w/w silicone fluid, with 65-89.5% w/w of silastic elastomer 382 using a laboratory stirrer for a sufficient time to assure a uniform dispersion. The mixture was then deaerated in a dessicator under a mild vacuum to eliminate any air entrapped. Several drops of Catalyst M were added with constant stirring and the whole mixture was then again deaerated under the vacuum. The resulting mixture was quickly poured into molding equipment and cured for 24 hours at room temperature. The drug-dispersed polymer sheet was then cut into circular discs with a diameter of 6.7 cm and a thickness of 0.09 cm.

Determination of Progesterone Release

A well-calibrated Ghannam-Chien (G-C) membrane permeation system (12) was used, with some minor modifications, in this investigation for determination of progesterone release profile. Each pair of half cells was divided into two diffusion cells, making it possible to simultaneously

study the drug release from two matrix devices at one time (Figure 1). Impermeable aluminum foil-backed, progesterone-dispersed polymer discs were mounted, back to back, at the center of the two half cells, so that each of the half cells had a matrix device with one constant releasing surface exposed. After completely assembled, 170 ml of an elution medium (previously thermostated at 37°C) was charged into each half cell. At predetermined intervals, 10 ml samples were withdrawn and immediately replaced with the same volume of fresh, drug-free elution medium to maintain the same total volume. The samples were analyzed by UV spectrophotometer[3] at 240 nm. In the experimental design, the rotation speed of stirring magnets, elution medium and drug loading dose were varied to investigate the characteristics of matrix-diffusion-controlled drug release profile.

RESULTS AND DISCUSSION

The mechanism of drug release from various matrix-type system has been discussed previously (13). It was assumed that the rate-determining step resides on the diffusion of drug molecules across the matrix, i.e., matrix diffusion-control. However, it is conceivable that the rate of diffusion from the surface of the matrix-type device to the surrounding solution bulk could also play a significant role in the total diffusion process under certain experimental conditions. The difference in polarity between the drug solute released and the solvent molecules in the elution medium is one of the important factors that could determine the extent of diffusion layer effect. A typical concentration profile for a drug released from a monolithic matrix device, where the drug loading exists as a combination of dissolved and dispersed forms throughout a polymer matrix, is shown in Figure 2. The assumptions used in this physical model are: (1) the drug loading dose (A) in the polymer matrix is much greater than its solubility (C_p) in the polymer, i.e., $A \gg C_p$; (2) pseudo-steady state is achieved; (3) the diffusion coefficient (D) is constant; (4) diffusion, rather than dissolution, is the rate-determining step; (5) sink condition is maintained.

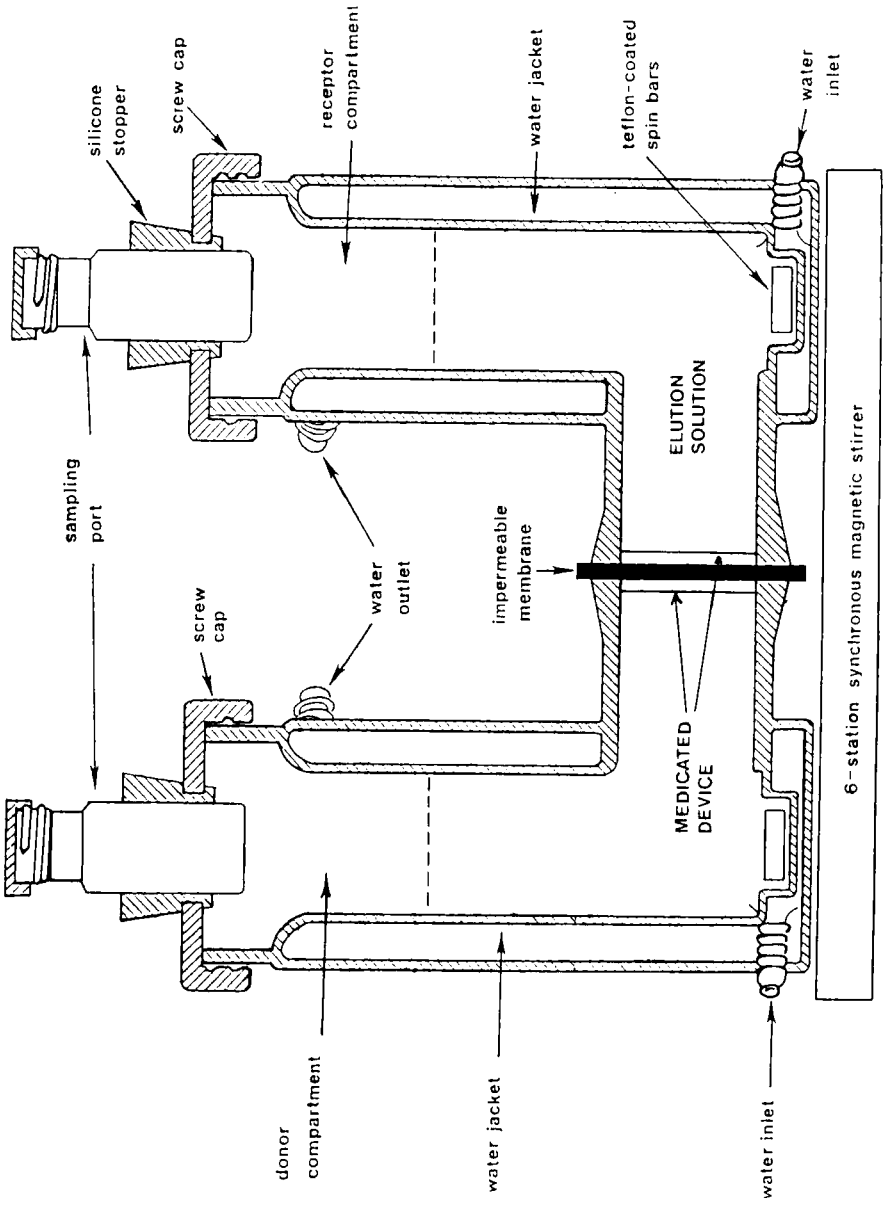

Figure 1

One cell unit of the modified Ghannam-Chien membrane permeation system for in vitro drug release studies.

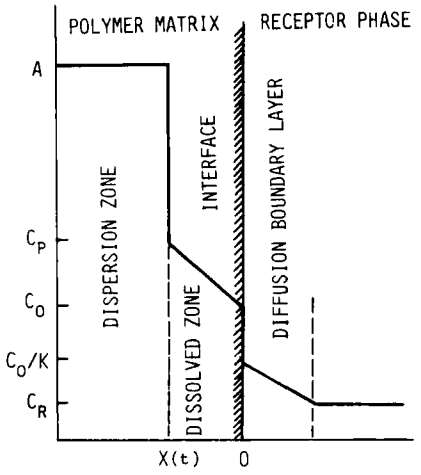

Figure 2

Hypothetical concentration profiles in the matrix-type drug delivery system under pseudo-steady state condition.

The apparent release rate can be represented by:

$$\frac{dQ}{dt} = D_p(C_p - C_o)/x = (A - C_p/2) = k_m(C_o/K - C_R) = k_m C_o/K \qquad (1)$$

where D_p is the diffusivity of drug in the matrix device; C_p is the drug solubility in the polymer; x is the eluting front (Figure 2); A is the loading dose; K is the partition coefficient as defined by the ratio of C_p/C_s, in which C_s is the drug solubility in the elution medium; C_R and C_o are drug concentrations in elution solution bulk and matrix surface, respectively; and k_m is the mass transfer coefficient in the hydrodynamic diffusion layer.

Solving Eqn (1) and taking the integration yield the apparent cumulative amount of drug released (Q), which is expressed as follows:

$$Q = \int_0^t \left(\frac{dQ}{dt}\right) dt = (A - C_p/2)\left[\sqrt{\frac{2C_p D_p t}{A - C_p/2} + \left(\frac{KD_p}{k_m}\right)^2} - \frac{KD_p}{k_m}\right] \qquad (2)$$

where boundary layer effect is illustrated by the terms of $(KD_p/k_m)^2$ and KD_p/k_m in Eqn (2). It was found that the mass transfer coefficient (k_m) would be large if the drug and elution medium have similar physicochemical

characteristics or same polarities. The effect of boundary layer becomes negligible if the drug released is very hydrophilic, while an aqueous solution is used as the elution medium with adequate mixing. Namely, Eqn (2) can be simplified and the resultant equation is the same as that given by Higuchi (13):

$$Q_\infty = \lim_{k_m \to \infty} Q(k_m) = \sqrt{(2A-C_p)D_pC_pt} \qquad (3)$$

where Q_∞ denotes the cumulative amount of drug released under ideal condition, (i.e., with an infinitely thin hydrodynamic diffusion layer) and is thus defined as the "intrinsic release".

From Eqn (2) and (3), a correlation between the apparent release (Q) and intrinsic release (Q_∞) can be determined:

$$Q/Q_\infty = Q/\ [1-(Q/t)/k_mC_s]^{\frac{1}{2}} \qquad (4)$$

Equation (4) is significant when dealing with the release of a lipophilic drug, in which the diffusion layer would affect the apparent amount of cumulative release (Q), but not the intrinsic release (Q_∞). For practical applications, intrinsic release, which is calculated from Eqn (4), can be used as a standard, to compare the experimental results obtained in different laboratories. Furthermore, intrinsic release provides the information that might be hidden by hydrodynamic diffusion layer effect, which will be discussed later.

Effect of Cosolvent and Non-sink Condition

Cosolvents are routinely used as aids to enhance the solubility of drugs in aqueous solution, particularly for non-polar compounds. Usually, the best cosolvent is the one which most closely matches the polarity of the compound (14). The addition of cosolvent into the elution medium to increase the aqueous solubility of drug has now become a common practice in laboratories to maintain a sink condition required for *in vitro* studies (15). The data in Figure 3 illustrate that the apparent amount of cumulative release (Q) of progesterone is greatly dependent upon the volume fraction

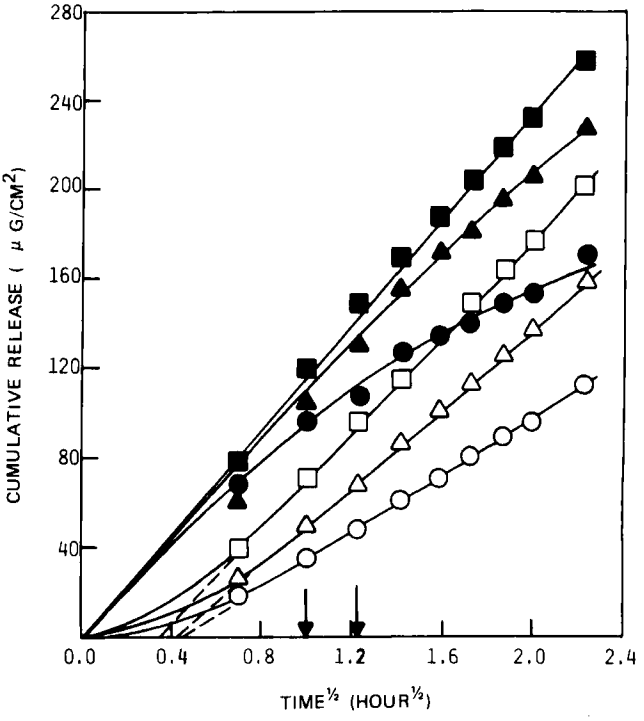

Figure 3

Effect of solution sink on the release profiles of progesterone from the matrix-type drug delivery system: (1) apparent drug release profiles in aqueous solution containing 0% PEG 400 (○), 20% PEG 400 (△) and 40% PEG 400 (□); (2) intrinsic drug release profiles in aqueous solution containing 0% PEG 400 (●), 20% PEG 400 (▲) and 40% PEG 400 (■).

of cosolvent (PEG 400) in the elution medium. Since progesterone molecules are very lipophilic (Table I) the diffusion process from the surface of the matrix disc into the elution medium could become the rate-determining step. The time lag phenomenon commonly observed can be attributed to the delaying effect of the aqueous boundary layer, which extend the path for the diffusion of drug molecules from the matrix device to its surrounding elution medium.

By the manipulation of Eqn (4), which converts the apparent release (Q) to intrinsic release (Q_∞), the time lag phenomenon can be corrected (Figure 3). Interestingly, a non-linear relationship was observed when the intrinsic cumulative release data generated in the aqueous solution

Table I - Physical Properties of Progesterone at 37°C

Physical Parameters	
Density	1.2 gm/ml
Solubility in	
0% PEG 400	12.5 µg/ml
20% PEG 400	48.0 µg/ml
40% PEG 400	198.0 µg/ml
Partition Coeff. (K) (Silicone polymer/water)	22.7[a]

[a]Data from Reference 16

containing no more than 20% v/v PEG 400 were plotted against square root of time ($t^{\frac{1}{2}}$), which suggests that the elution medium did not afford the sink condition required during the experiments. The concentration-time data in Table II indicate that only the elution solution containing 40% v/v of PEG 400 is able to maintain a good sink condition throughout the course of 5-hr drug release studies. The intrinsic drug release profiles for the elution solution containing less than 20% of PEG 400 (Figure 3) start to show curvature at the same time when sink condition is no longer prevailed. In contrast, a fairly linear Q vs. $t^{\frac{1}{2}}$ relationship was established for the apparent cumulative release even when the elution solution contains 0-20% of PEG 400. The results imply that the apparent cumulative release plot conceals some basic information and, thus, distorts the investigation. Therefore, the concept of intrinsic release is very important in not only providing the inter-laboratory standard, but also helping to analyze the mechanistics of controlled drug release.

Table II - Concentration-Time Profiles for Progesterone in Aqueous Media Containing Various Volume Fractions of Cosolvent:

Time (hr)	Progesterone Concentration[a] (μg/ml)		
	0% PEG 400	20% PEG 400	40% PEG 400
0.5	1.44	1.77	3.24
1.0	2.82 (N.S.)[b]	3.42	5.41
1.5	3.82 (N.S.)	4.96 (N.S.)[b]	7.13
2.0	4.33 (N.S.)	6.21 (N.S.)	8.19
2.5	4.94 (N.S.)	7.18 (N.S.)	9.35
3.0	5.42 (N.S.)	7.99 (N.S.)	10.08
3.5	5.78 (N.S.)	8.43 (N.S.)	10.79
4.0	6.13 (N.S.)	8.76 (N.S.)	11.23
5.0	7.09 (N.S.)	9.51 (N.S.)	12.46

[a]Each data point represents the average of triplicate determinations with standard deviation less than 8%.

[b]N. S. designates the data points obtained under non-sink condition.

Effect of Rotation Speed

Another important factor which will affect the extent of diffusion layer effect or mass transfer coefficient (k_m) is the flow pattern in the *in vitro* drug release medium.

The effect of flow field on the thickness of aqueous diffusion layer on the surface of a matrix-type device mounted in the G-C diffusion cells is shown in Table III. The data indicate that the thickness of diffusion layer decreases as the rotation speed increases. Accordingly, time lag phenomenon will be more obvious when the diffusion layer becomes thicker.

Table III - Effect of Rotation Speed on the Thickness of Hydrodynamic Diffusion Layer:

Rotation Speed (rpm)	Diffusion Layer Thickness[a] (microns)
225	99
425	67
625	53

[a]Calculated from Reference 11

The dependence of the apparent drug release profiles upon the flow field is one of the difficulties encountered when making comparison of the experimental data generated from different diffusion systems among various research laboratories.

The mass transfer coefficient (k_m) is also known to be a function of the flow pattern, or rotation speed, in the in vitro drug release apparatus; and, as a result, the apparent cumulative amount of drug release is affected, as expected from Eqn (2). Figure 4 shows the effect of rotation speed on the release profiles of progesterone from the matrix-type device containing 1% drug loading. As expected from Eqn (4), the apparent release profiles of progesterone increase as increasing the rotation speed, while the lag time also decreases in magnitude. On the other hand, the intrinsic drug release profile should be independent of rotation speed. According to Eqn (3), therefore, the lower intrinsic drug release profile obtained at the rotation speed of 225 rpm appears to suggest that the pseudo-steady state has not been achieved under this condition. The data in Table IV demonstrate that diffusion layer is of significance in affecting the release of progesterone from the matrix-type device to the surrounding elution medium in terms of the magnitude of release flux and time-lag value. The

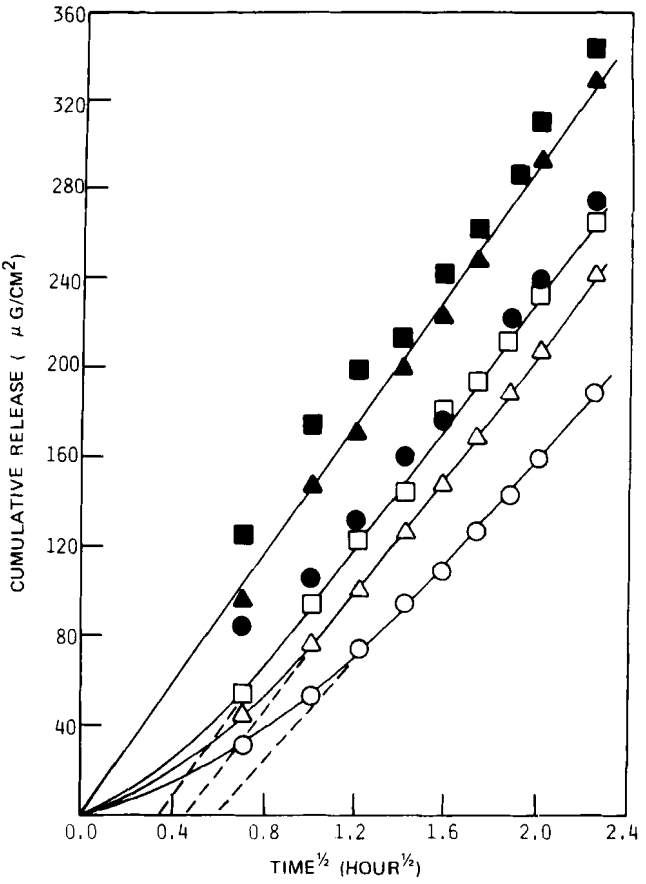

Figure 4

Effect of rotation speed on the release profiles of progesterone from matrix-type drug delivery device: (1) apparent release at 225 rpm (○), 425 rpm (△) and 625 rpm (□); (2) intrinsic release at 225 rpm (●), 425 rpm (▲) and 625 rpm (■).

observation of slightly scattering in the early phase of intrinsic drug release plot (Figure 4) could be attributed to the dissolution process of drug particles on the surface of the matrix-type device.

Effect of Drug Loading Dose

In the preparation of matrix-type drug delivery device, various drug loading doses (A) can be incorporated into the polymer for the attainment of different release profiles. The effect of drug loading dose on the magnitude of $Q/t^{\frac{1}{2}}$ values is depicted in Figure 5. In contrast to the

Table IV - The Flux and Time-lag Phenomena of Apparent and Intrinsic Release Profiles:

	Apparent			Intrinsic		
	225 rpm	425 rpm	625 rpm	225 rpm	425 rpm	625 rpm
Flux $(Q/t^{1/2})^a$	115	140	148	143	160	158
Time Lag (min.)	23.5	17.4	11.4	5.0	2.0	0

[a]The unit of flux is μg. cm^{-2}. hr^{-1}.

apparent drug release fluxes the intrinsic drug release fluxes demonstrate a linear relationship with the square root of the loading dose $(A)^{1/2}$. From Eqn (3), the loading dose-dependence can be derived, if the condition $2A>>C_p$ exists:

$$Q/t^{1/2} = (2D_pC_p)^{1/2}(A)^{1/2} \quad (5)$$

The negative deviation of apparent release flux at higher loading doses from the linear Q vs. $A^{1/2}$ relationship suggests that diffusion layer effect become more significant as increasing the loading level of progesterone.

Effect of Particle Size Distribution

The effect of the particle size distribution of dispersed drug in the matrix and the curing procedure in device fabrication on the release kinetics of drug from the matrix-type device was studied. The data in Figure 6 illustrate that in spite of the difference in the rotation speeds and the loading doses, (1% and 125 rpm vs. 20% and 425 rpm) the plots of intrinsic drug release exhibit the same time-lag ($t^{1/2}$ = 0.60 $hr^{1/2}$ or t_{lag} = 21.6 min.). This observation implies the homogeneity problem inherent

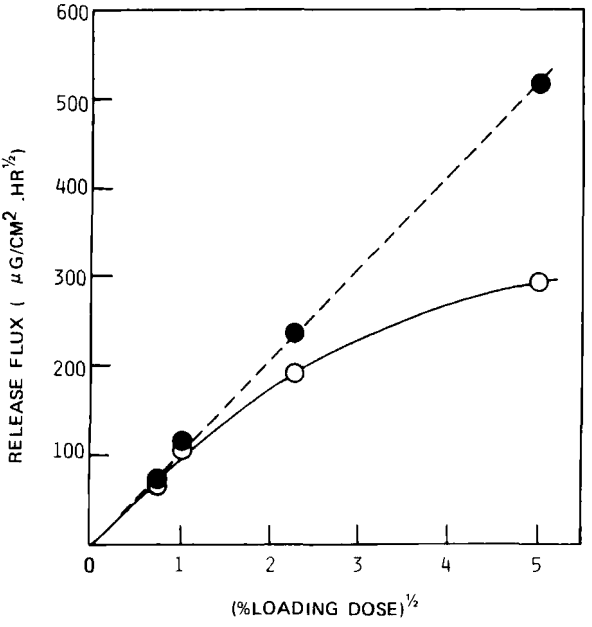

Figure 5

Effect of drug loading dose on the release flux ($Q/t^{\frac{1}{2}}$) of progesterone: apparent flux (○) and intrinsic flux (●).

in the dispersion of drug particles in the polymer matrix. The content uniformity is often one of the greatest problems encountered in the manufacturing of drug dispersion matrix-type system; hence, an optimum particle size distribution is required to eliminate the possibility of non-uniform dispersion.

Based on Stoke's law:

$$v = \frac{d^2 (\rho - \rho_m) g}{18 \eta} \qquad (6)$$

where v is the settling rate of sphere-shaped dispersed particles with a diameter of d, g is the gravitation constant, η is the viscosity of the polymer medium before curing and ρ, ρ_m are the densities of dispersed particles and polymer medium, respectively. It was experimentally found that homogeneous drug distribution in the polymer matrix could be achieved by incorporating drug crystals with mean particle size less than 37μ for

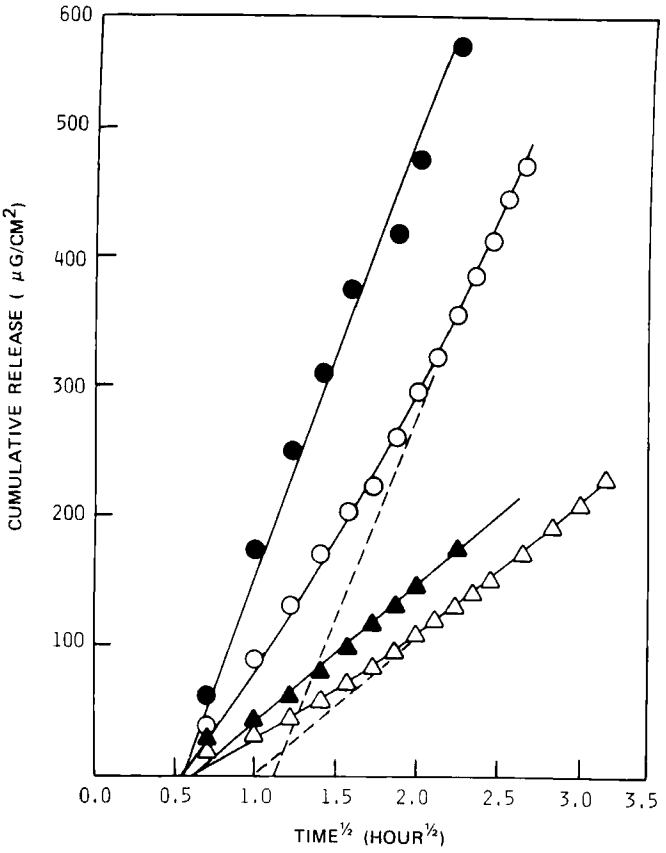

Figure 6

Release profiles of progesterone from the matrix-type drug delivery device with (1) 1% drug loading and a rotation speed of 125 rpm; key: apparent (△), intrinsic (▲); (2) 20% drug loading and a rotation speed of 425 rpm; key: apparent (○), intrinsic (●).

overnight curing procedure at room temperature with medical grade 382 silicone elastomer as the polymer medium, since the settling of drug particles is minimized during curing when smaller particles are used. In order to achieve a matrix-controlled release, the thickness of matrix disc should be much greater than the diameter of dispersed particles.

The data in Figure 6 were generated from the matrix-type device with progesterone of large particle size (with mean diameter of 128 μ) and wide distribution (37 to 250 μ). The large particles have a greater tendency

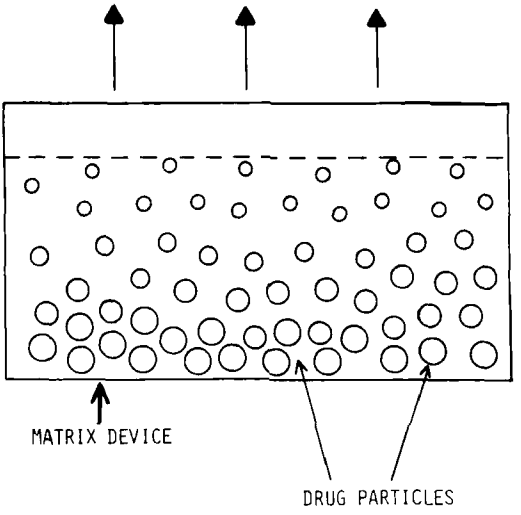

Figure 7

Cross-sectional view of the distribution of drug particles with different particle size in the matrix-type slab containing a wide particle size distribution.

to settle in the matrix, as expected from Stoke's law, during an overnight curing process; thus, a content uniformity problem was resulted. Figure 7 is a cross-sectional view of this type of drug particle distribution in the matrix to illustrate the possiblity of heterogeneous dispersion. The upper layer, which contains no drug particles, is resulted from the settlement of particles and accounts for the delay of drug release since the drug molecules have to diffuse through this layer before they can be released to the elution medium. It explains the observation that no burst drug release phenomenon was observed in this investigation. The thickness (h) of this upper layer could be estimated from the following equation:

$$h = 6\, t_{lag}\, D_p \qquad (7)$$

and is about 200 μ when the diffusion coefficient of progesterone in the silicone polymer matrix is to be 4.5×10^{-8} cm^2/sec.

CONCLUSION

The experimental results obtained in this investigation have demonstrated that the "intrinsic" concept can be very useful in the

interpretation of the matrix diffusion-controlled release of lipophilic drug from the matrix-type delivery systems fabricated from hydrophobic polymer. By eliminating the effect of hydrodynamic diffusion layer, the analysis of intrinsic drug release profiles disclose the problems which may not be realized otherwise, such as the maintainance of sink condition and fabrication specifications. Furthermore, intrinsic drug release profiles could also help the comparison of experimental data obtained from different laboratories.

FOOTNOTES

1. Sigma Chemical Company, Saint Louis, Missouri 63718
2. Dow Corning Corporation, Midland, Michigan 48640
3. Perkin-Elmer 559A UV/VIS Spectrophotometer, Perkin-Elmer Corporation, Elmwood Park, New Jersey 07407

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