Study of Progesterone Release Mechanisms from a Silicone Matrix by a New Analytical Method

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ABSTRACT: The release behavior of progesterone from a silicone matrix to release media containing 60% (v/v) alcohol and water was investigated and kinetically evaluated. For this purpose, samples containing 5, 10, or 15% (w/w) micronized progesterone were prepared through the mixing of two-component silicone and the drug in a thermomixer. The discs were cured with compression molding. Then, the release from a controlled surface area was experimentally determined by a high-performance thin-layer chromatography technique, a new method for progesterone analysis. With Higuchi's model, the drug-release behavior of the dispersion systems was determined by a partition-controlled process (the relationship between the accumulated amount of the drug released and the time) and a matrix-controlled process (the relationship between the accumulated amount of the drug released and the square root of time). The release profile determined by experimental data was in good agreement with Higuchi's model. Moreover, the product of the solubility and diffusivity of progesterone in the polymer matrix was evaluated and found to be 8.1×10^{-7} mg/cm/s. Finally, the effects of fillers on the release behavior were studied. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 91: 3040–3044, 2004

Key words: drug delivery systems; silicones; diffusion

INTRODUCTION

In recent years, the study of the controlled release of drugs and other bioactive agents from polymeric devices has attracted the interest of many researchers from around the world. Controlled drug delivery applications include both sustained delivery over days, weeks, months, and years and targeted delivery on a one-time or sustained basis.[1]

Controlled-release dosage forms can be classified according to their release mechanism. Various mechanisms can be used to control drug release. Diffusion, swelling, and degradation and erosion are the most important. Diffusion-controlled systems can be divided into monolithic and reservoir systems. In monolithic (matrix) systems, drug molecules that disperse homogeneously in the polymer matrix are released by permeation from its interior to the surrounding medium.[2]

Developing a matrix system with a constant release rate has always been a challenge for pharmaceutical scientists. According to Fick's first law of diffusion, the release of a drug from a monolithic matrix is inherently nonlinear because of the increase in the diffusional length resistance or the decrease in the inwardly releasing surface area with time.[3] Many researcher groups have been studied drug-release kinetics from polymers and the effects of different factors on release.[4–8]

The objectives of this work were (1) to study the release mechanism of progesterone from a silicone elastomer as a matrix system, (2) to investigate the initial-loading effect, (3) to study the solubility and diffusivity of progesterone in the silicone matrix, (4) to investigate the effects of calcium carbonate and silicone oil on the release profile as filler effects, and (5) to apply a new method to the evaluation of drug release.

EXPERIMENTAL

Materials

The materials used in this study were Elastosil 3003/40 (Wacker Co., München, Germany) and micronized progesterone (Xianju Pharmaceutical Factory, Xianju, China). All other chemicals and reagents were either medical-grade or high-performance-liquid-chromatography-grade and were used as received.

Preparation method

The samples containing 5 (SM 1), 10 (SM 2), and 15 wt % (SM 3) micronized progesterone were fabricated

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TABLE I
Disc Characteristics

Sample code	Drug loading (mg)	Hardness (Shore A)	Amount of drug released (mg/cm^2)	
			3.5 h[a]	48 h
SM 1	9.6	48	0.91	2.83
SM 2	19.2	49	1.13	5.12
SM 3	29.2	51.1	1.88	6.13

[a] Initial time of the partition-controlled process.

through the mixing of two-component silicone and the drug in Haake thermomixer (system 90, Haake, Madison, WI) for 1 h. Discs 10 mm in diameter and 2 mm thick were cured with compression molding at 150 bar and 115°C for 15 min. The disc characteristics are given in Table I.

Samples including 10 wt % micronized progesterone and 10 wt % silicone oil (SM 4) or 10 wt % calcium carbonate (SM 5) were prepared as mentioned previously, and the drug release was evaluated.

Progesterone release

The release of progesterone from silicone-based discs was measured in a hydrodynamically well-characterized Chien permeation system at 37°C (Perme Gear, Inc., Bethlehem, PA). An ethanol/water mixture (60% v/v) was prepared and heated to 37°C before being tested as a release medium. For the determination of the progesterone release profile, each disc was mounted in the orifice of a half-cell of the Chien permeation system. Each half-cell was filled with 3 mL of the aforementioned release solution. At different intervals, from 1 to 92 h, the release medium was completely withdrawn and immediately replaced with a fresh solution.

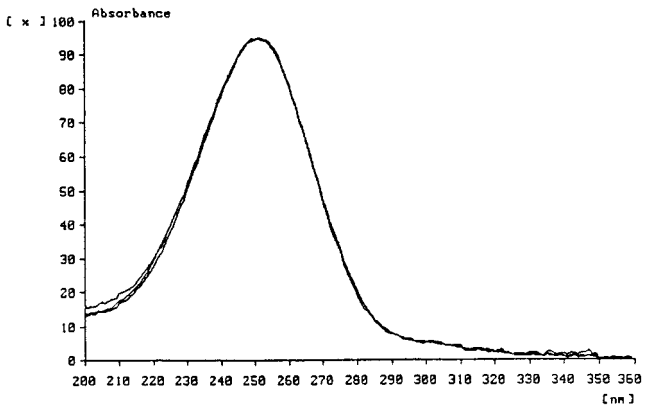

Figure 1 *In situ* UV spectra of progesterone on silica gel.

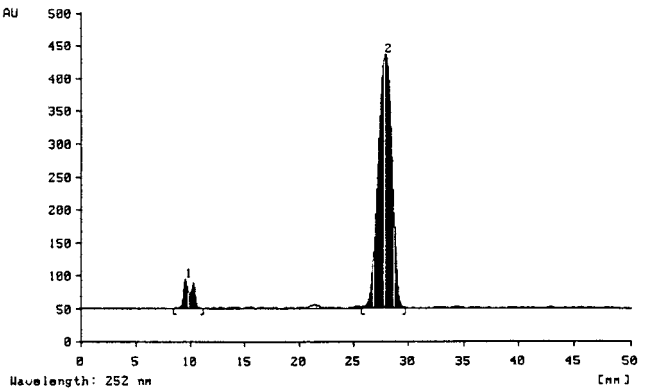

Figure 2 Separation of progesterone (peak 2) on silica gel 60F254 HPTLC plates.

Analytical method

Progesterone determination in the release medium was performed with a newly developed high-performance thin-layer chromatography (HPTLC) method. Chromatography was performed on silica gel 60F254 HPTLC plates (10 cm × 20 cm; Article no. 264; Merck, Darmstadt, Germany). The standards and samples were applied to the plates with a TLC Sampler III automated spray-on instrument (Camag, Muttenz, Switzerland). The band length was 2 mm, the distance between the bands was 4 mm, the distance from the plate edges was 20 mm, and the distance from the plate bottom was 10 mm. The plates were developed in a twin-trough thin-layer-chromatography chamber to 60 mm with toluene/2-propanol (10:1 v/v), without saturation. After development, the plates were air-dried, and the sample and standard zones were quantified by linear scanning at the maximum absorption wavelength of 252 nm (Fig. 1) with a Camag TLC Scanner III with a deuterium source. Baseline separation is shown in Figure 2. The regression equation was $Y = 1.1457X + 24.518$, where Y is the peak height and X is the amount of progesterone (ng); the correlation factor was 0.999 for 27–145 ng/zone. This method showed good recovery (99.8–100.9%) for various levels of spiked samples in the linear working range interval. The relative standard deviation of repetitive measurements ($n = 7$) was 0.08–0.39 ng/zone, and the limit of quantification was 5 ng/zone. The analyte weights in the sample zones were determined from their peak heights by interpolation from the regression curve.

Determination of the partition coefficient and solubility

The partition coefficient of progesterone was determined by the equilibration of three flat sheets (7 cm

TABLE II
Physical Parameters of Progesterone

	C_i (mg/mL)	C_f (mg/mL)	K	C_p (mg/mL)
Progesterone	0.00989	0.00719	53	0.53

$\times$ 2 cm $\times$ 0.05 cm) of the blank silicone elastomer in a filtered saturated solution of the drug at 37°C. The sheets were removed after 24 h. The partition coefficient (K) was calculated with the following expression:

$$K = \frac{V_1(C_i - C_f)}{V_2 C_f} \tag{1}$$

where V_1 and V_2 are the volumes of the solution and silicone sheets, respectively, and C_i and C_f are the initial and equilibrium concentrations of the solution, respectively. The solubility of progesterone in the polymer (C_p; mg/mL) was calculated with the following equation:

$$C_p = KC_s \tag{2}$$

where C_s is the water solubility. The values of C_p, C_s, and K for progesterone are listed in Table II.

RESULTS AND DISCUSSION

According to the Higuchi equations, the release pattern of a drug from a drug-dispersed polymer matrix can be defined as follows:[9]

$$\delta_m^2 + \frac{2(A - C_p)D_m\delta_d\delta_m}{\left(A - \frac{C_p}{2}\right)D_s\bar{k}k} = \frac{2C_pD_p}{\left(A - \frac{C_p}{2}\right)}t \tag{3}$$

$$Q = A\delta_m \tag{4}$$

where Q is the accumulated amount of the drug released from a unit of the surface area (mg/cm^2); A is the initial amount of the drug impregnated in a unit of the volume of the polymer matrix (mg/cm^3); δ_d and δ_m are the thicknesses (cm) of the hydrodynamic diffusion layer on the immediate surface of the matrix and of the depletion zone, respectively; D_s and D_p are the diffusivities (cm^2/s) of the drug molecule in the elution solution and in the polymer matrix, respectively; k is the partition coefficient of drug species from the polymer matrix to the solution phase; $\bar{k}$ is a constant accounting for the relative magnitude of the concentration gradients in both the diffusion layer and the depletion zone; and t is time.

The concentration profiles of a unit section of a polymeric matrix are schematically illustrated in Figure 3.[10] At the earliest stage of a drug elution study, δ_m is so small that the following condition exists:

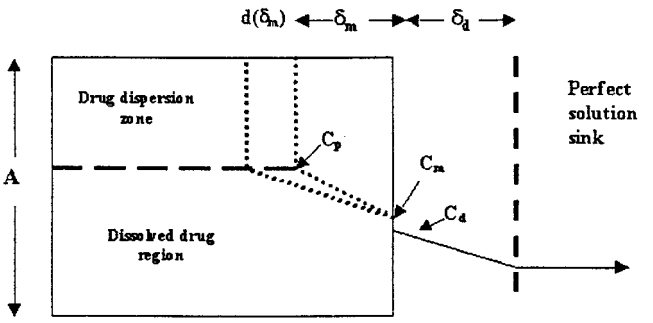

Figure 3 Theoretical concentration profile in a drug-dispersed silicone matrix.

$$\delta_m^2 << \frac{2(A - C_p)D_p\delta_d\delta_m}{\left(A - \frac{C_p}{2}\right)D_s\bar{k}k} \tag{5}$$

Therefore, eq. (3) can be reduced to

$$\delta_m = \frac{\bar{k}D_skC_p}{(A - C_p)\delta_d}t \tag{6}$$

Substituting eq. (6) for the δ_m term in eq. (4) gives

$$Q = \frac{\bar{k}D_skC_p}{\delta_d}t \tag{7}$$

Because the experiments were so designed that A was much greater than C_p of the drug in this polymer, $A - C_p$ was equal to A.

We know that C_s is equal to KC_p, so eq. (7) can be transformed as follows:

$$Q = \frac{\bar{k}D_sC_s}{\delta_d}t \tag{8}$$

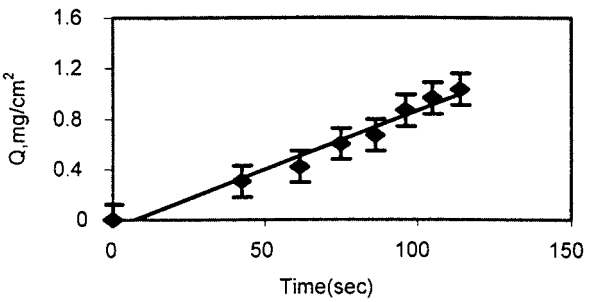

Figure 4 Initial-state release profile of progesterone from SM 2 (partition-controlled process).

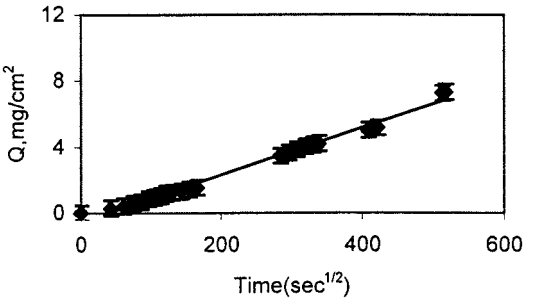

Figure 5 Release profile of progesterone from SM 2 (matrix-controlled process).

Equation 8 indicates that at a very early stage of the drug-release dynamics, the partition-controlled process at the hydrodynamic diffusion layer is the rate-limiting step. However, after the lapse of a finite time, δ_m becomes substantially greater, and it is impossible to ignore δ_m in eq. (5). Therefore, it is reduced to

$$\delta_m = \left(\frac{2C_pD_p}{\left(A - \frac{C_p}{2}\right)} t\right)^{1/2} \quad (9)$$

Substituting eq. (9) for the δ_m term in eq. (5), with $[A - (C_p/2)] \approx A$, gives

$$Q = [2AD_pC_p]^{1/2}t^{1/2} \quad (10)$$

In this work, the release of progesterone from a silicone polymer matrix containing 10% of the drug (SM 2) was evaluated, and at an early stage of drug release (≤3.5 h), it is illustrated in Figure 4. Theoretical analyses conducted earlier suggested that this initial-state drug release was predominately a partition-controlled process in the hydrodynamic diffusion layer (Fig. 3), and a zero-order drug-release profile should be observed.

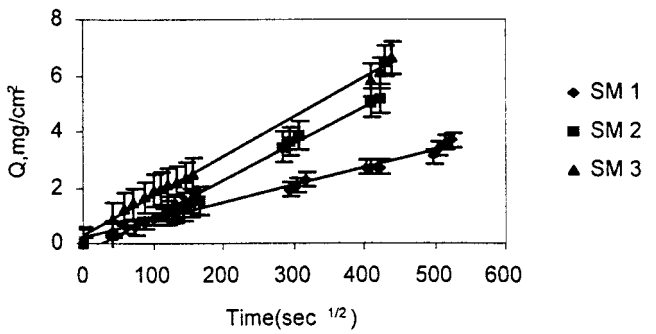

Figure 6 Initial-loading effect on progesterone release from a silicone matrix.

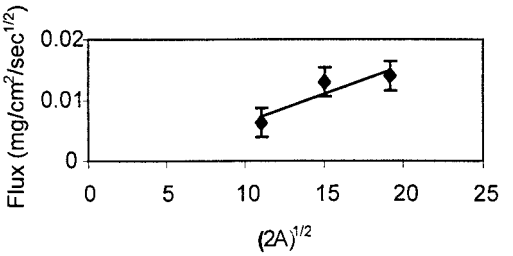

Figure 7 Linear relationship of $Q/t^{1/2}$ and $(2A)^{1/2}$ for progesterone release from a silicone matrix.

δ_m increases with time (Fig. 3). In this case, the matrix-controlled process is the predominant process. Therefore, the cumulative amount of drug release from a unit of the surface area of the polymeric matrix should become proportional to the square root of time. The results shown in Figure 5 confirm this linear relationship. Also, the initial-loading dose effect was studied (Fig. 6). According to eq. (4), the cumulative release was increased with an increasing loading dose of progesterone in the matrix. However, eq. (9) indicates that δ_m is proportional to $A^{-1/2}$. This means that in a specific time, δ_m is exponentially reduced with an increasing initial-loading dose. Therefore, the values of Q for samples that are 10–15% drug are lower than those for samples that are 5–10% drug. However, Q increases with increasing A.

According to eq. (10), the drug-release flux ($Q/t^{1/2}$) depends linearly on $(2A)^{1/2}$, this being a characteristic of matrix-type drug delivery systems (Fig. 7). Because, according to Table II, the progesterone solubility was 0.53 mg/cm^3, the slope $(C_pD_p)^{1/2}$ was used to calculate the diffusivity of progesterone in discs, which was found to be 1.52×10^{-6} cm^2/s.

The filler effect is shown in Figure 8. The addition of calcium carbonate as an inert filler reduced the diffusivity because it increased the tortuosity of the diffusion path; because the diffusional distance increased, the drug molecules had to migrate to reach the silicone surface. Silicone oil increased the diffusivity by increasing chain mobility.

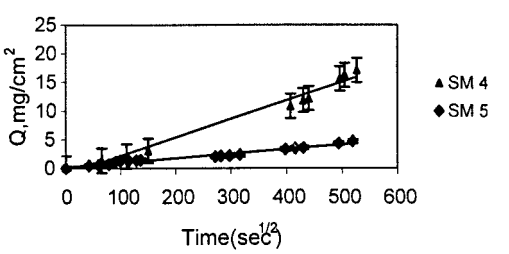

Figure 8 Effects of fillers on progesterone release from a silicone matrix.

CONCLUSIONS

The *in vitro* controlled release of progesterone from a drug-dispersed silicone polymer was investigated. The results indicated that drug release from discs in the initial state was predominately a partition-controlled process; after the drug diffused out, the release was mainly a matrix-controlled process. There was an increasing cumulative amount of drug release with an increasing initial-loading dose according to the Higuchi equations. There were different effects of the fillers on the release of the drug from the silicone matrix. The addition of silicone oil to the silicone increased, and the addition of calcium carbonate reduced, the *in vitro* release rate of progesterone.

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