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CONSTANT RELEASE RATE FROM INERT, HETEROGENEOUS MATRIXES BY MEANS OF POSITION-DEPENDENT LOADING

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ABSTRACT

Approximately zero-order release of ephedrine hydrochloride and procaine hydrochloride was obtained from multiple-layered matrixes of hydrogenated castor oil containing various concentrations of the medicinal compound in each layer. For the examples presented, an apparent zero-order release was observed for the release of 50-90% of the medicinal compound.

INTRODUCTION

In the search for sustained-release products numerous investigators (1-12) have explored dosage forms that deliver the medicinal compound in a zero-order pattern. One concept is the

use of an inert matrix from which the medicinal compound slowly diffuses. As the solvent front recedes into an inert matrix, the diffusional pathlength is increased, and the amount of medicinal compound released progressively diminishes. The amount of medicinal compound released from an inert, heterogeneous matrix has a square-root-of-time dependency (13-19). Some investigators (11, 12, 20, 21) have used matrixes with position-dependent drug loading that provides an approximately zero-order release.

The purpose of this study was to utilize matrixes of two or three layers that contained different concentrations of the medicinal compound in an effort to obtain a constant rate of release.

EXPERIMENTAL

The method of preparing matrixes of ephedrine hydrochloride or procaine hydrochloride and hydrogenated castor oil (HCO) by compression of a physical mixture and by compression of a congealed and milled melt has been described (22). The same method was used to prepare bilayered and trilayered matrixes. The desired weight of material was placed in the die and gently pressed with a flat-faced punch. The punch was removed, the desired weight of material of the next layer was placed on the initial layer and leveled, and then compressed into a bilayered matrix at 35 MPa. For a trilayered matrix a third layer of material was added, and then compressed into a trilayered matrix.

The layered matrix was embedded in paraffin so that only the surface of the outer layer was exposed to the dissolution medium.

The release of ephedrine hydrochloride and procaine hydrochloride from this planar surface of the matrix was conducted in a USP dissolution apparatus, and at appropriate intervals of time aliquots were removed by pipet and analyzed spectrophotometrically as previously described (22).

RESULTS AND DISCUSSION

Parameters affecting the planar release of ephedrine hydrochloride and procaine hydrochloride from hydrogenated castor oil (HCO) matrixes prepared by compression of a physical mixture and by compression of congealed and milled melt have been evaluated and reported (22). Having characterized these matrixes, it was thought that by position-loading of various concentration of the medicinal compound in multilayered compacts a useful technique of attaining a constant rate of release could be demonstrated.

Bilayered Matrixes. The initial compact consisted of a bilayered matrix of a physical mixture of ephedrine hydrochloride and HCO with 30 and 40% ephedrine hydrochloride in the outer and inner layer, respectively. Each layer was 1.7 mm thick and contained 1.0 g of ephedrine hydrochloride. The cumulative amount released per unit area at 25°C is plotted versus time in Figure 1a for the bilayered compact and for a matrix containing 30% ephedrine hydrochloride. For the initial 1.5 h the release from the two matrixes was the same. After 1.5 h the release from the 30% matrix progressively decreased, while the release from the bilayered compact continued unchanged.

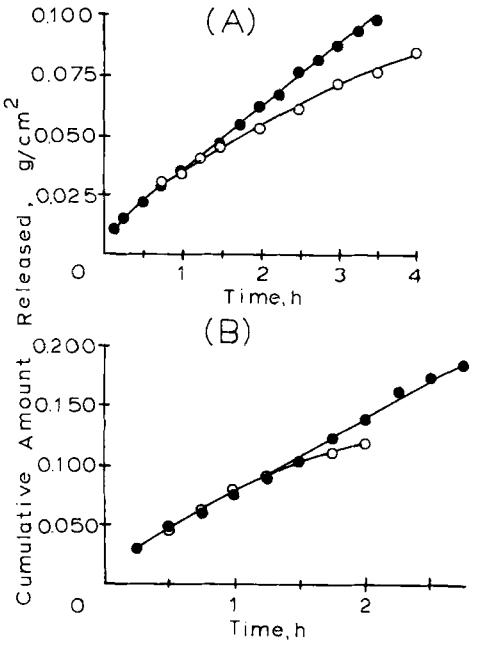

FIGURE 1

Release profile of ephedrine hydrochloride (a) from (○) 30% and (●) 30/40% bilayered matrix and (b) from (○) 40% and (●) 40/50% bilayered matrix.

A similar bilayered compact that contained 40 and 50% ephedrine hydrochloride in the outer and inner layer, respectively, was prepared. There were 2.0 g of the physical mixture in the outer layer that was approximately 3.2 mm thick, and 1.0 g of physical mixture in the inner layer that was 1.7 mm thick. The cumulative amount released at 25°C is plotted versus time in Figure 1b for the bilayered compact and for a matrix containing 40% ephedrine hydrochloride. After 1.5 h the drug loaded in the outer layer was released, and the solvent front

reached the 50% drug loaded region. The rate of release was essentially constant until observation was halted upon the release of 92% of the ephedrine hydrochloride.

The influence of drug loading is demonstrated in Figure 2 for a bilayered compact with 1.5 g of a physical mixture of 10% ephedrine hydrochloride with HCO in the outer layer and 1.5 g of various concentrations of ephedrine hydrochloride in the inner layer. The layers were approximately 2.5 mm thick. The data show that matrixes in which the inner layer was loaded with 30-50% ephedrine hydrochloride provided a fairly constant rate of release.

The influence of drug loading in the outer layer when the inner layer is composed solely of ephedrine hydrochloride is shown in Figure 3 and 4.

Bilayered matrixes produced by the melt process behaved similarly. Bilayered compacts containing 40% and 50% procaine hydrochloride or ephedrine hydrochloride in the outer and inner layer, respectively, were compressed of material prepared by the melt process. The release profiles are shown in Figure 5. The bilayered matrix continued to release procaine hydrochloride at a constant rate after 9 h, but the release from the 40% ephedrine hydrochloride matrix progressively diminished as shown in Figure 5a. For the matrix containing 40% ephedrine hydrochloride at approximately 37 h the ephedrine hydrochloride had been released, but the release from the bilayered matrix from 25 to 94 h was essentially constant as illustrated in Figure 5b.

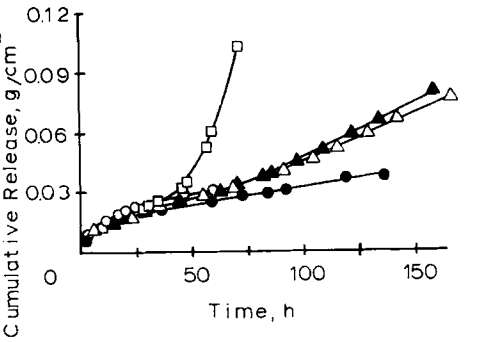

FIGURE 2

Influence of drug loading in a bilayered matrix with (○) 10% ephedrine hydrochloride in the outer layer and (●) 20; (△) 30; (▲) 50%; and (□) 100% in the inner layer.

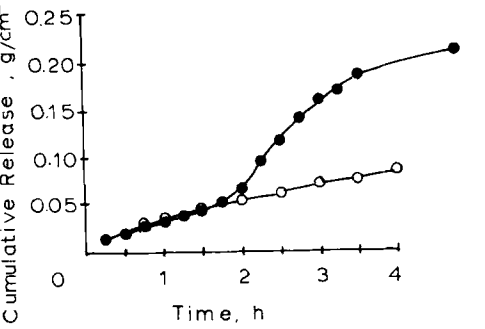

FIGURE 3

Release profile of ephedrine hydrochloride from (○) 30% matrix and (●) 30/100% bilayered matrix.

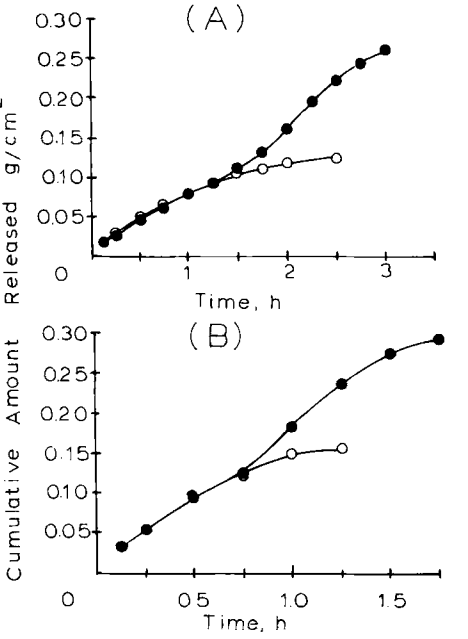

FIGURE 4

Release profiles of ephedrine hydrochloride (a) from (○) 40% matrix and (●) 40/100% bilayered matrix and (b) from (○) 50% matrix and (●) 50/100% bilayered matrix.

Trilayered Matrixes. The use of appropriate drug loading of a trilayered matrix may extend the time a dosage form would deliver a constant rate of release. A trilayered compact containing 75 mg in each layer having a thickness of 0.6 mm was prepared from physical mixtures having 30, 40 and 50% procaine hydrochloride for the outer, middle and inner layer, respectively. The release profile from this trilayered matrix is compared to the release profile from a matrix containing 30% procaine hydrochloride in Figure 6a. At a cumulative amount released of 0.018 g/cm², the

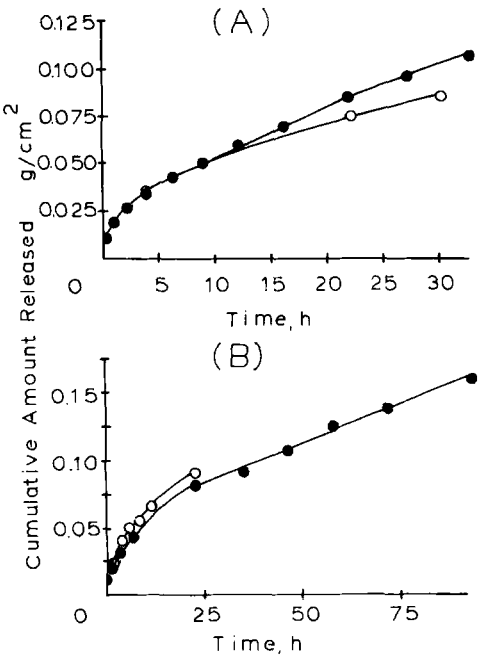

FIGURE 5

Release profiles from melt matrixes of (a) procaine hydrochloride from (○) 40% matrix and (●) 40/50% bilayered matrix and (b) ephedrine hydrochloride from (○) 40% matrix and (●) 40/50% bilayered matrix.

procaine hydrochloride from the outer layer had been dissolved. The procaine hydrochloride from the middle and inner layer was then released at a cumulative amount of 0.041 g/cm^2. Ninety-two percent of the total procaine hydrochloride was released at 49 h. The release for 60% of the delivery time (5 to 30 h) was apparent zero order.

Using the same drug loadings (30, 40, 50% in the outer, middle and inner layer, respectively) a trilayered matrix of

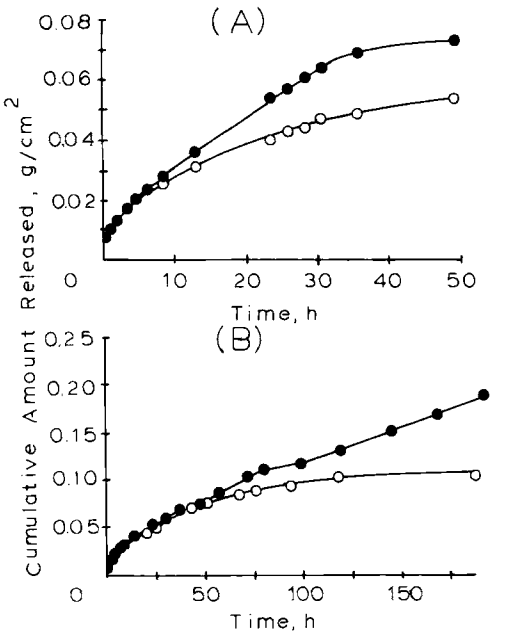

FIGURE 6

Release profiles from (○) 30% matrix and a (●) 30/40/50% trilayered matrix compressed of (a) physical mixture with procaine hydrochloride and (b) melt with ephedrine hydrochloride.

ephedrine hydrochloride was compressed of material produced by the melt process. Each layer weighed 1.0 g and was 1.6 mm thick. As shown in Figure 6b there is an apparent zero-order release for 94% of the delivery period (12 to 192 h).

To illustrate the release from a trilayered compact prepared by compression of a physical mixture with a delivery period similar to traditional administration, a matrix with 30, 40 and 50% procaine hydrochloride in the outer, middle and inner layers, respectively, was studied. Each layer contained 75 mg of mixture

and was 0.6 mm thick. The release profile of the trilayered matrix and a 30% matrix are compared in Figure 7. An apparent zero-order release is seen until 87% of the procaine hydrochloride has been released at 7.5 h.

A similar trilayered matrix in which 20, 30 and 40% ephedrine hydrochloride were incorporated in the outer, middle and inner layers, respectively, was prepared. Each layer weighed 150 mg and was 1.2 mm thick. As shown in Figure 8 an apparent zero-order release is obtained for 100 h.

Model for Multilayered Matrixes. Paul (12) suggested a model to describe the release from an inert, bilayered homogeneous matrix. The release from the outer layer of a homogeneous matrix is:

$$\frac{d(Q_t/C_m 1)}{d\theta} = \frac{1}{1_1}\left(\frac{\theta_1}{\theta}\right)^{\frac{1}{2}} \qquad \text{(Eq. 1)}$$

in which

$$\theta_1 = \frac{D_m t_1}{d\theta} = 0.5\left(\frac{1_1}{1}\right)^2\left(\frac{A_1}{C_m} - 0.5\right) \qquad \text{(Eq. 2)}$$

where $d(Q_t/C_m 1)/d\theta$ is a dimensionless release rate (see Appendix). When the medicinal compound is being released from the inner layer through the outer layer into the dissolution medium, and the undissolved solute has not been exhausted, the release rate is:

$$\frac{d(Q_t/C_m 1)}{d\theta} = \frac{1}{\left[\left(1 - \left(\frac{1_1}{1}\right)^2\right)\left(\frac{\theta - \theta_1}{\theta_2 - \theta_1}\right) + \left(\frac{1_1}{1_1}\right)^2\right]^{\frac{1}{2}}} \qquad \text{(Eq. 3)}$$

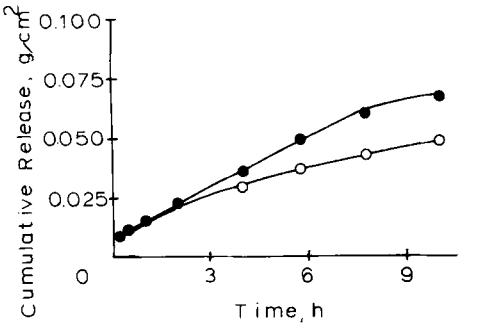

FIGURE 7

Release profile of procaine hydrochloride from (◯) 30% matrix and from (●) a 30/40/50% matrix compressed of a physical mixture.

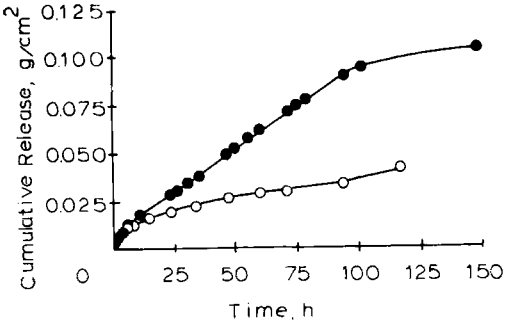

FIGURE 8

Release profile of ephedrine hydrochloride from (◯) a 20% matrix and from (●) a 20/30/40% matrix compressed of a physical mixture.

in which (see Appendix)

$$\theta_2 = \theta_1 + 0.5\left(1 - \left(\frac{l_1}{l}\right)^2\right)\left(\frac{A_1}{C_m} - 0.5\right) \qquad \text{(Eq. 4)}$$

The preceding equations may be modified to describe the release form a heterogeneous matrix by incorporating porosity, ε, and tortuosity, τ, terms. In the bilayered matrixes studied the layers were of the same thickness so that $l_1/l = 0.5$ and $l_1/l_2 = 1$. Introducing these modifications and integrating Eq. 1 yields:

$$Q_t = 4\varepsilon C_s \left(\frac{D}{\tau}\theta_1 t\right)^{\frac{1}{2}} \qquad \text{(Eq. 5)}$$

in which

$$\theta_1 = 0.125\left(\frac{A_1}{\varepsilon C_s} - 0.5\right) \qquad \text{(Eq. 6)}$$

Equation 5 describes the release of the medicinal compound from the outer layer of a bilayered, heterogeneous matrix.

Using the same modifications and integrating Eq. 3 yields:

$$Q_t = 2.67\varepsilon C_s l \left\{\left[0.75\left(\frac{(Dt/\tau l) - \theta_1}{\theta_2 - \theta_1}\right) + 1\right]^{\frac{1}{2}} - \left[0.75\left(\frac{-\theta_1}{\theta_2 - \theta_1}\right) + 1\right]^{\frac{1}{2}}\right. \qquad \text{(Eq. 7)}$$

in which

$$\theta_2 = \theta_1 + 0.375\left(\frac{A_2}{\varepsilon_2 C_s} - 0.5\right) \qquad \text{(Eq. 8)}$$

Equation 7 describes the release from the bilayered matrix after the solvent front has penetrated the inner layer.

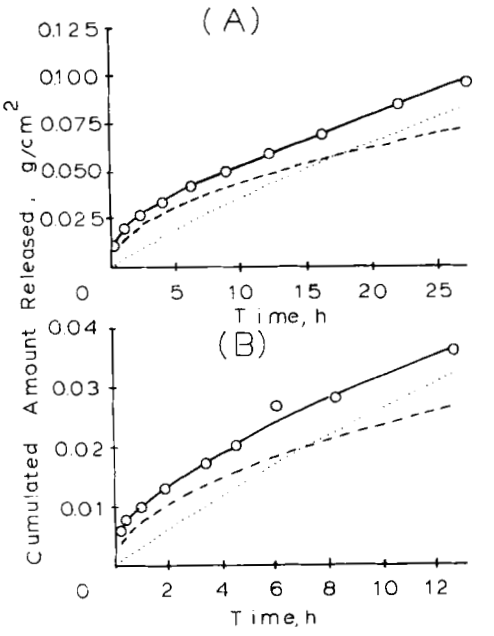

FIGURE 9

The release profiles of procaine hydrochloride calculated (- - -) by Eq. 5 and (• • •) by Eq. 7 and the (◯) observed release from (a) 40/50% bilayered matrix and (b) 30/40/50% trilayered matrix prepared by the melt process.

As an example a bilayered compact containing 40 and 50% procaine hydrochloride in the outer and inner layer, respectively, was examined to determine if Eq. 5 and 7 were applicable. The calculated and observed release profiles are shown in Figure 9a. The cumulative release according to Eq. 5 has a typical square-root-of-time dependency. The release according to Eq. 7 is apparently zero order and has a slope similar to the observed slope.

An attempt was made to apply the Paul equation to the outer and middle layer of a trilayered matrix containing 75 mg of

procaine hydrochloride in melts containing 30, 40 and 50% procaine hydrochloride in the outer, middle and inner layer, respectively. The calculated and observed cumulative release profiles are shown in Figure 9b before the solvent front reached the inner layer.

CONCLUSION

Apparent zero-order release of highly water-soluble medicinal compounds may be obtained by means of position-dependent loading in two and three layered, heterogeneous matrixes of hydrogenated castor oil.

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APPENDIX: GLOSSARY

A_1 = drug loading in outer layer, g/mL

A_2 = drug loading in inner layer, g/mL

C_m = solubility in matrix, g/mL

C_s = solubility in dissolution medium, g/mL

D_m = diffusivity in matrix, cm^2/s

D = diffusivity in dissolution medium, cm^2/s

ε = porosity

l = thickness of bilayered compact, cm

l_1 = thickness of outer layer, cm

l_2 = thickness of inner layer, cm

$\theta = D_m t/l^2$, dimensionless time

θ_1 = dimensionless time when solvent front reaches inner layer

θ_2 = dimensionless time when solvent front has penetrated completely through the inner layer

t_1 = time solvent front reaches inner layer

τ = tortuosity