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The release mechanism of drugs from polyurethane transdermal delivery systems

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Summary

Polyurethane sheets—Synthaderm—have been used as carriers for iodine delivery. The release profiles of iodine in vitro have been found to be highly sensitive to changes in the device rotational speed: at high rpm the matrix diffusion mechanism controlled the system while at lower rpm the drug was released following a zero-order process. At low rotation conditions the major barrier for drug release, was found to reside in a boundary diffusion layer. Thus for transdermal delivery systems, devices applied to the skin in non-stirred environments and designed as solvated matrices, a boundary solvent layer formed at the device–skin interface may provide zero-order release patterns.

Introduction

The design of controlled-release dosage forms for transdermal drug administration is now a subject of considerable interest. However, only a few quantitative studies have been done on such systems. Two basic physical models have been used to estimate drug release mechanisms: the membrane permeation-controlled and the matrix diffusion-controlled (or the monolithic system) release (Good, 1983). Nevertheless, no attention has been paid to the contribution to the drug-delivery pattern of the diffusion layer, formed at the device–skin interface. This is investigated in the present work using a hydrophilic polyurethane membrane—Synthaderm—as matrix and iodine, a relatively hydrophobic molecule as a model drug.

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Materials and Methods

A promising approach for the development of new transdermal systems is the use of polyurethane materials as drug delivery matrices (Touitou and Friedman, 1984). Therefore polyurethane sheets—Synthaderm (Armour Pharmaceuticals, U.K.)—have been chosen as hydrophilic carriers for iodine devices

Iodine (J.T. Baker Chemicals, Phillipsburg, NJ, U.S.A.), KI (Merck, F.R.G.) and NaCl (Frutarum, Israel) were analytical grade. Starch (B & A, New York) and sodium thiosulphate (BDH Chemicals, Poole, U.K.) were analytical reagents.

Various iodine-loaded devices have been obtained by equilibrating polyurethane patches with an initial weight of 110 ± 2 mg in iodine aqueous solutions and drying under controlled conditions (Touitou and Friedman, 1982). The iodine loading dose is expressed by the degree of iodination and defined by the expression:

$$H_I = \frac{W_{SI} - W_S}{W_S} \times 100 \qquad (1)$$

where W_S is the initial weight of the dry Synthaderm patch and W_{SI} is the weight of the iodinated device.

Determination of iodine release rates

The iodine devices tested were round patches with a diameter of 1 cm, thickness of 0.9 ± 0.03 mm and of various weights.

Iodine release from one surface area of the device was determined in a well-closed system using a modified rotating disk apparatus. The schematic diagram of the apparatus is presented in Fig. 1. The device was attached to the glass vessel by means of silicone rubber adhesive.

The experiments were carried out in standard work conditions at 37°C in a constant temperature bath (± 0.5°C), using 500 ml of physiological saline exchanged with fresh media every hour for maintaining sink conditions; conditions have been changed only where specified for testing the influence of any parameter. The disk was rotated at selected rpm by means of a constant rate adjustable stirrer (Fisher Stedi-Speed Stirrer).

The concentration of iodine released in the testing medium was measured titrimetrically using the assay for available iodine described in USP XX.

A cumulative correction was made for determining the total amount of iodine released from the polyurethane device. Experiments have been at least duplicated.

Measurements of degree of hydration

Samples of determined weights of polyurethane carriers (Synthaderm) have been shaken for 24 h in 100 ml water at 6 different temperatures in the range of 20–55°C. The surface excess of water was wiped carefully and the patches weighed. The degree

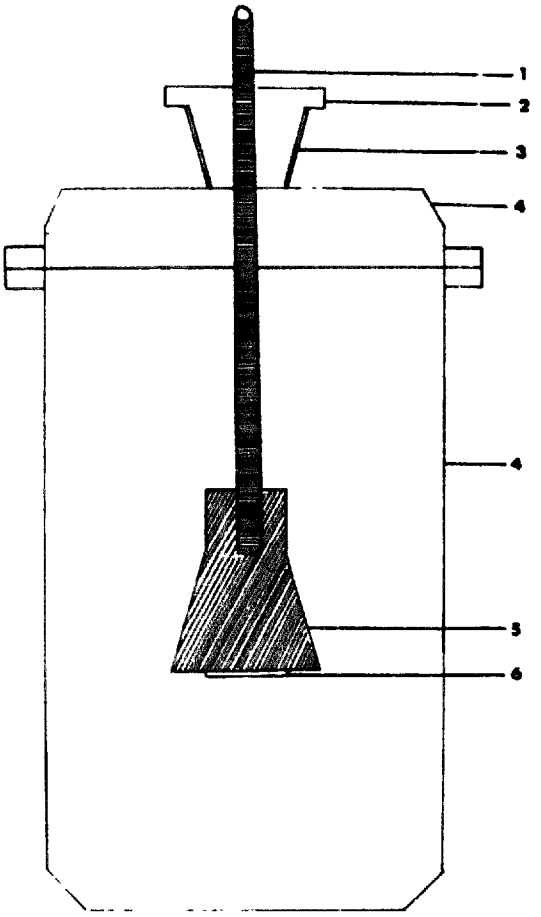

Fig. 1. Apparatus used for release rate measurements. 1, rotating metallic shaft; 2, teflon cork; 3, ground cone, 4, glass vessel; 5, removable device assembly; 6, device.

of hydration was calculated using the following relationship:

$$H\% = \frac{W_H - W_S}{W_S} \times 100 \quad (2)$$

where W_H is the weight of the sample after 24 h and W_S is the initial weight of the dry sample.

An additional experiment was undertaken to test the influence of iodine loading dose in the device on the degree of hydration. This was performed by shaking preweighed devices ranging from 10% to 90% degree of iodination (H_I) (for H_I-definition see above) for 1 h (required for equilibration) in 100 ml of 0.9% saline solution at 21°C and 37°C. The hydrated samples were weighed and the degree of hydration was calculated using Eqn. 2. The results are presented in Fig. 2.

Partition coefficient determination

Synthaderm patches of determined weights and diameters were shaken for 24 h in 100 ml physiological saline saturated with iodine. The period of 24 h was found to

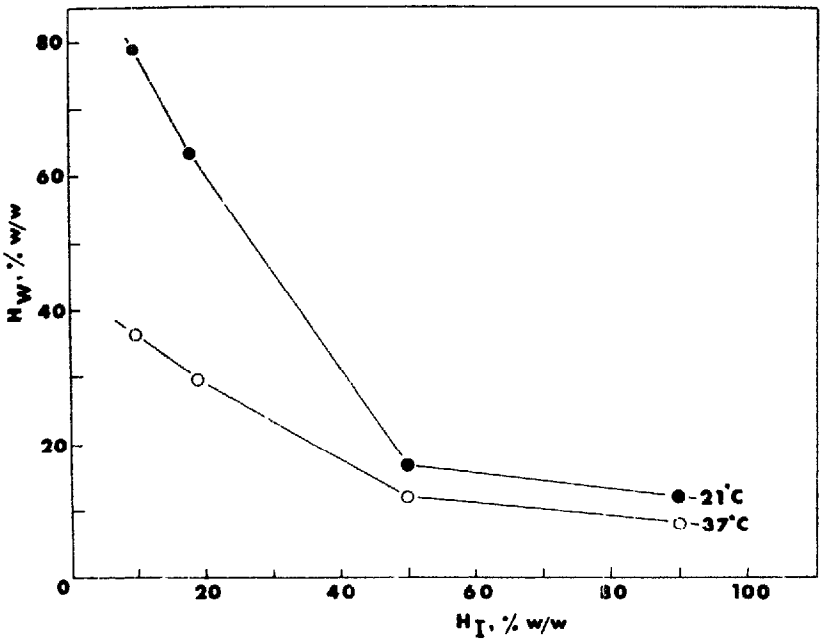

Fig. 2. Effect of the degree of iodination on the hydration of iodinated devices in normal saline at 21°C and 37°C; the degrees of hydration of the matrix 'per se' were 230 and 170 at 21°C and 37°C, respectively.

allow system equilibration. The patches were removed at the end of the experiments and the solution was assayed for the remaining iodine.

The partition coefficient K_m (aqueous solution/polyurethane) was calculated by means of Eqn. 3 (Hunke and Matheson, 1981):

$$K_m = \frac{I_s/V}{C_0} \tag{3}$$

where I_s is the quantity of iodine uptake by the polyurethane patch, V is the volume of the hydrated matrix and C_0 is the iodine concentration of the saline solution at

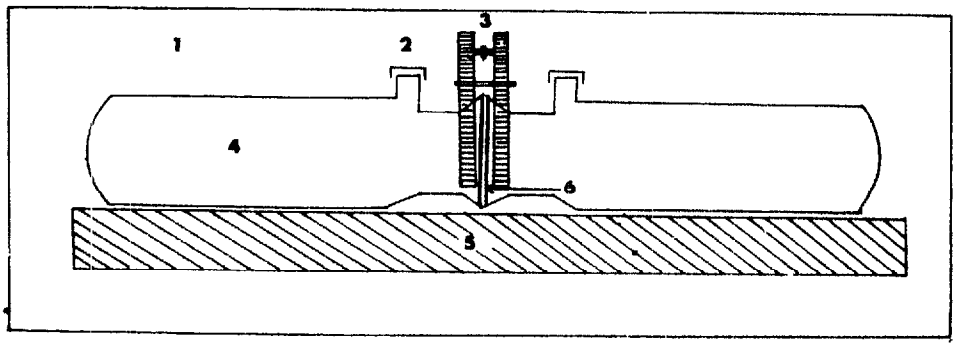

Fig. 3. Assembled diffusion cell. 1, steady temperature room; 2, sampling ports; 3, locking clipper; 4, diffusion cell compartments; 5, stedi-speed rotating table; 6, device.

equilibrium. A high value of 3475 was obtained, which tells us that Synthaderm has a great affinity to iodine.

Apparent permeability coefficient measurement

The permeability of Synthaderm to iodine was determined using a glass diffusion cell (Fig. 3) with a capacity of 250 ml for each compartment. The relative high volume is necessary to maintain sink conditions in the receiver compartment. Saturated devices (90% iodination) were clamped between the two compartments; the donor was filled up with a saturated iodine in physiological saline solution and the receiver with physiological saline. The cell was rotated at 200 rpm at 37°C in a thermostated room. Every hour during the experiment, the solution from the receiver compartment was exchanged with the same volume of saline solution. The samples were assayed for iodine concentration.

The apparent permeability coefficient P′ was calculated using the expression:

$$P' = \frac{(dQ/dt)h}{C_d} \tag{4}$$

where dQ/dt is the flow of iodine through Synthaderm in a steady-state regime and is obtained from the slope of the linear regression plot of the amount of iodine released per unit area verus the time of release; h is the matrix thickness and C_d is the initial donor concentration.

Results and Discussion

Preliminary work with this system showed that the 'simple' models of diffusion through a matrix do not describe the drug release rate determining process (Touitou and Friedman, 1984).

The contribution of a boundary diffusion layer to the mechanism of release and, as an immediate consequence, to the rate of release was investigated.

In a pure diffusion boundary layer-controlled system the amount of drug transported across the layer per unit time per unit area (dQ/dt) is defined by Eqn. 5 (Roseman and Higuchi, 1970):

$$\frac{dQ}{dt} = \frac{D_a}{h_a} \cdot \Delta C_a \tag{5}$$

where D_a is the diffusion coefficient in the aqueous medium, h_a is the boundary layer thickness and ΔC_a is the concentration gradient in the layer.

According to Nernst diffusion layer theory (Nernst and Brunner, 1904), an increase in the rate of stirring of the release medium should reduce h_a and increase the release rate. Therefore, the initial release rates of iodine from the polyurethane devices were tested in two stirring regimes—at high rotational speed, 325 rpm; and at a lower rotational speed, 80 rpm. Fig. 4 presents the two profiles obtained. As can

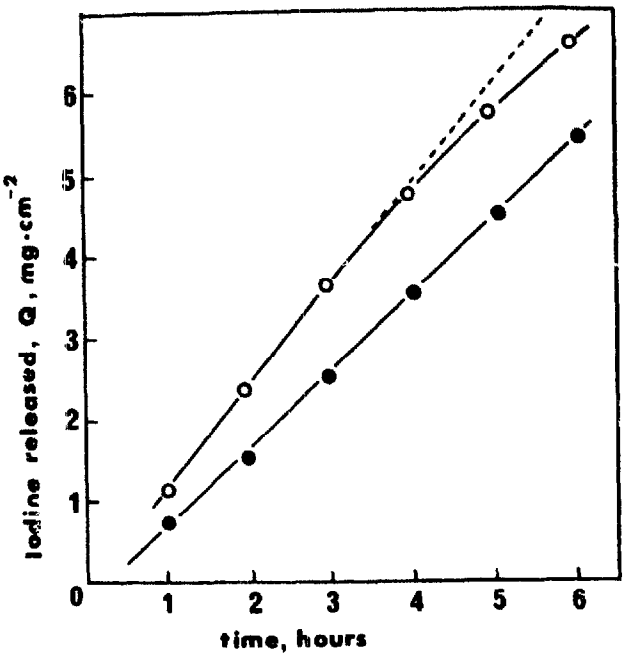

Fig. 4. Profiles of cumulative amounts of iodine released from iodinated Synthaderm devices (H_t-90%) as a function of time at 37 °C and at two rotation speeds: 325 rpm, ○; 80 rpm, ●.

be seen, the amount of iodine released per unit area at 325 rpm is much higher than at 80 rpm. Moreover, different time dependence release patterns are exhibited: the experimental release rate obtained as slope of the plot of the amount of iodine released against the time was constant over the whole period of testing (6 h) at 80 rpm, but decreased with time at 325 rpm. The rpm dependence indicates the formation of a diffusion boundary layer at the device interface. However, the change in the release pattern points to a double-barrier mechanism; the existence of an intermediate type mechanism was tested.

In order to better characterize the mechanism governing the release of iodine from Synthaderm, the effect of rpm on the initial drug release rates was further studied for a wide range of rotational speeds (65–400). It was shown (Mitchell and Saville, 1969; Touitou and Donbrow, 1981) that system agitation rate changes may be used as a tool for revealing intermediate type dissolution of drugs in which the following relation exists:

$$K_{obs} = \frac{K_i K_t}{K_i + K_t} \tag{6}$$

where K_i and K_t are the interfacial and the transport rate constants, respectively, and K_{obs} is the experimental dissolution rate constant. By increasing the agitation rate, the transport rate constant, K_t is increased and the observed rate shifts into the interfacial regime.

The logarithmic plot of dQ/dt versus rpm (Fig. 5) indicates that the release rates are highly sensitive to the increase in the rotational speed between 65 and 200 rpm;

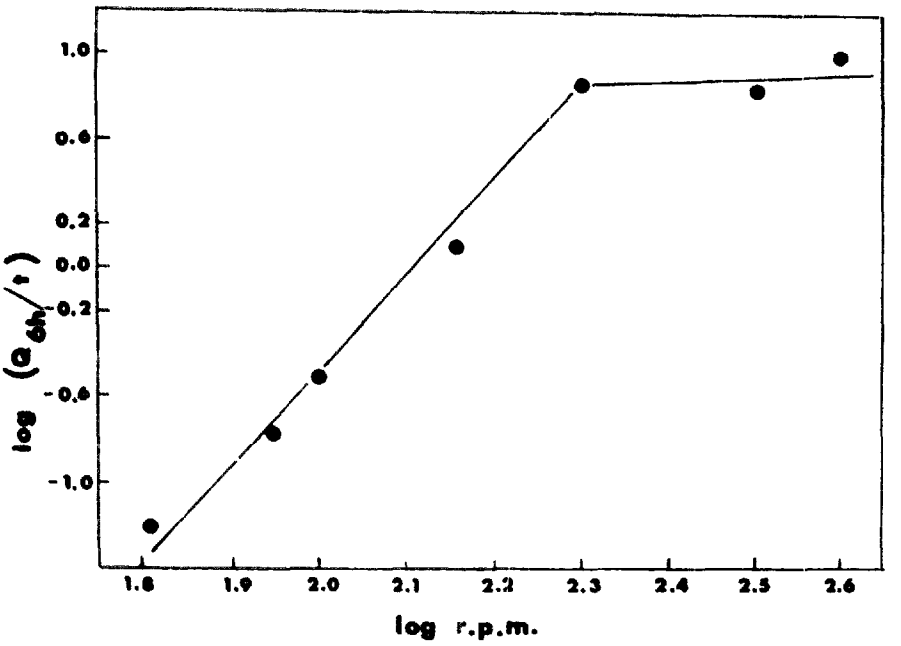

Fig. 5. Effect of rotation speed on the release rate of iodine from 90% iodinated devices at 37°C.

after this the rates remain unaffected. These results suggested that at higher rpm an interfacial barrier, the diffusion through the matrix, becomes the rate determining step. This assumption is supported by the data presented in Figs. 5–7 which demonstrate that at 325 rpm the system behaves as a monolithic matrix, from which iodine is released by diffusion according to Eqn. 7 (Higuchi, 1962):

$$Q = 2C_0 \cdot \left(\frac{Dt}{\pi}\right)^{1/2} \tag{7}$$

where Q is the amount of drug released per unit area, D is the diffusion coefficient

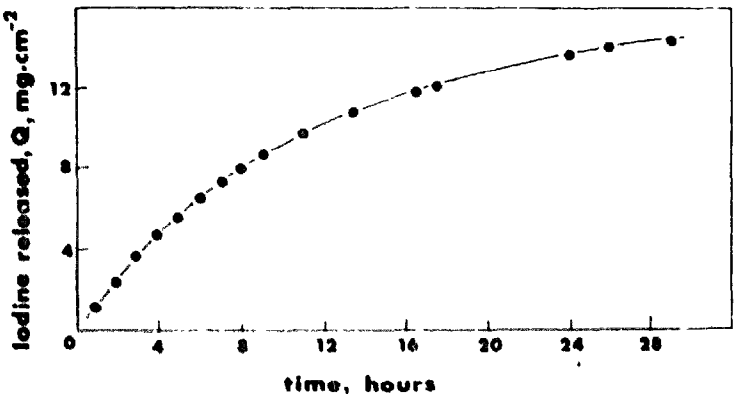

Fig. 6. Profile of the cumulative amount of iodine released from a 80% iodinated Synthaderm device at 37°C and 325 rpm tested during 30 h.

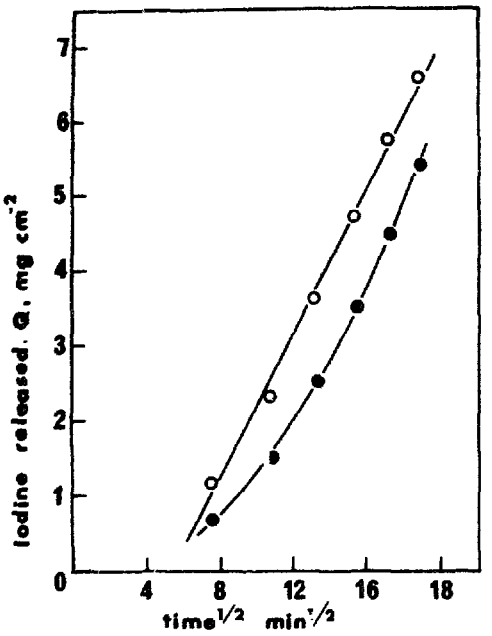

Fig. 7. Release profiles for iodine from 90% iodinated devices plotted using Higuchi equation: 325 rpm, ○; 80 rpm, ●.

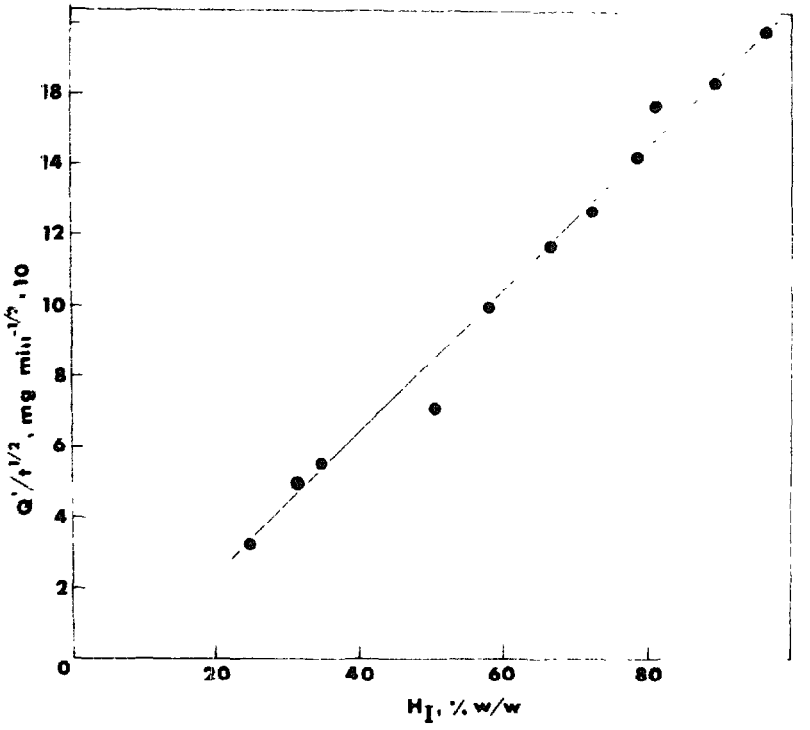

Fig. 8. Rates ($Q'/t^{1/2}$) as a function of the initial degree of iodination.

in the matrix, C_0 is the drug concentration in the device and t the time.

Fig. 6 shows the profile of iodine release from an 80% iodinated device rotated at 325 rpm at 37°C in physiological saline solution. The 30 h release curve exhibits the typical pattern for drug release from a monolithic system. The rate of release decreases with time.

By replotting the Q vs t profiles (Fig. 3) as Q vs $t^{1/2}$ (Fig. 7), according to Higuchi's model, the expected linear relationship for matrix diffusion control is obtained for the higher rotational speed—325 rpm. Furthermore, the Q vs $t^{1/2}$ slopes are linearly dependent upon C_0 (Fig. 8), indicating that Eqn. 7 is obeyed and the matrix controls is operative in this system.

The iodine apparent permeability coefficient through Synthaderm, obtained by the method described in the previous section, has a value of 7.5×10^{-7} $cm^2 \cdot s^{-1}$ which corresponds well with values previously reported for a number of drugs permeating polyurethane membranes (Hunke and Matheson, 1981). Schematically, the behavior of iodinated Synthaderm under various agitation conditions is drawn in Fig. 9. Under low rpm conditions the major barrier to release resides in the diffusion boundary layer; the drug is released by a zero-order release process where the cumulative amount is linearly related to time and the rate is independent of time. In a high rpm regime the mechanism is matrix-controlled, the cumulative amount of drug is linearly related to $t^{1/2}$ and the rate decreases with the time.

In order to realize the full potential of the skin route of administration one must be able to design systems to deliver the drug at 'a priori' estimated rate. For the polymeric transdermal devices it has generally been assumed that drug diffusion through the device is the principal rate-controlling process and that any boundary layer formed is relatively unimportant.

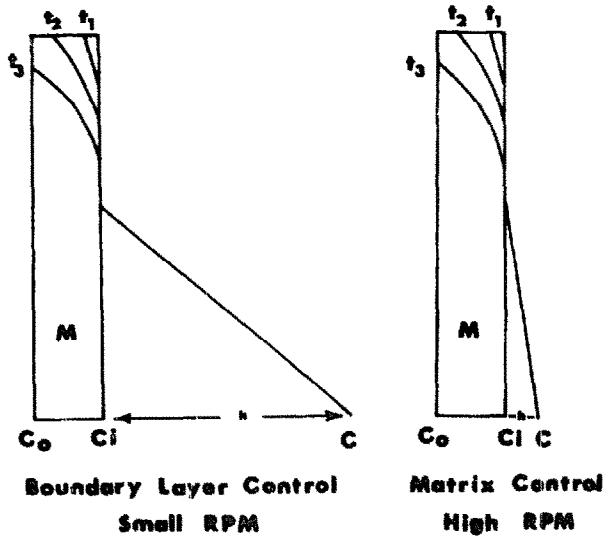

Fig. 9. Schematic representation for the intermediate type release model in which a matrix diffusion barrier and a boundary diffusion layer are involved. C_0 = initial concentration; C_i = interfacial concentration; C = bulk concentration; M = matrix; and t = time.

The results obtained in the present work show that when hydrated transdermal devices are applied to the skin, a milieu where the agitation is almost zero, the release of the drug is significantly controlled by a boundary layer existing between the device and the skin. Moreover, the concept offers an approach of zero-order drug release for a matrix-designed device.

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