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Principles of the Design and Operation of Generic Osmotic Pumps for the Delivery of Semisolid or Liquid Drug Formulations

F. THEEUWES AND S. I. YUM

ALZA Research, Palo Alto, California 94304

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Miniature osmotic delivery systems were constructed and tested in various environments according to the design criteria described in the present paper. These devices, when activated by water, can deliver a variety of solutions or suspensions at zero-order rates for periods of hours up to several weeks. The osmotic pumps consist of a cylindrical reservoir for the fluid, surrounded by a layer of an osmotic driving agent which, in turn, is encapsulated by a semipermeable membrane. The reservoir material is chemically inert to most aqueous drug formulations, dilute acids, bases, and alcohols. The outer housing of the pump, which is the membrane, is highly compatible with tissues when the pumps are implanted in animals. Typically, the miniature pumps have a total volume of approximately 0.6 ml, and an internal effective volume of approximately 0.2 ml. The delivery rate can be varied from 0.1 to 3 μl/hr. Devices of this type have been tested successfully as implants in mice for anticancer drug research, in endocrine studies, and in narcotic-drug evaluations. The time course of the pumping rate *in vivo* is accurately specified by the *in vitro* pumping rate under conditions that are isotonic and isothermal to extracellular fluid.

1. INTRODUCTION

Various forms of stored energy can be harnessed to provide continuous pumping by a portable device, e.g., electrical, electrochemical, mechanical, and chemical energy. If transduction is required, it usually entails a relatively large mass and volume in relation to deliverable volumes. Hence, there is an inherent economy in utilizing purely chemical forces. Osmosis offers several attractive features as a chemical pumping principle: it is controllable by membrane characteristics and utilizes the flow of water, which is incompressible, as a driving force.

Several osmotic devices have been described in the literature (Rose and Nelson, 1955; Stolzenberg, 1971; Theeuwes, 1973; Higuchi *et al.*, 1973). The present paper describes the principle of operation, the design criteria which are basic to developing systems of constant pumping rates, and the delivery rate and drug loading in relation to the characteristics of the membrane and the osmotic driving agent. These principles allow the reliable construction of miniature osmotic pumps, less than 1 ml total volume, suitable for implantation in small laboratory animals. The functional characteristics of such a pump are described. The system described here can be used as a dosage form or as a research tool. It lends itself particularly well to this last application, allowing definition of optimum drug regimen.

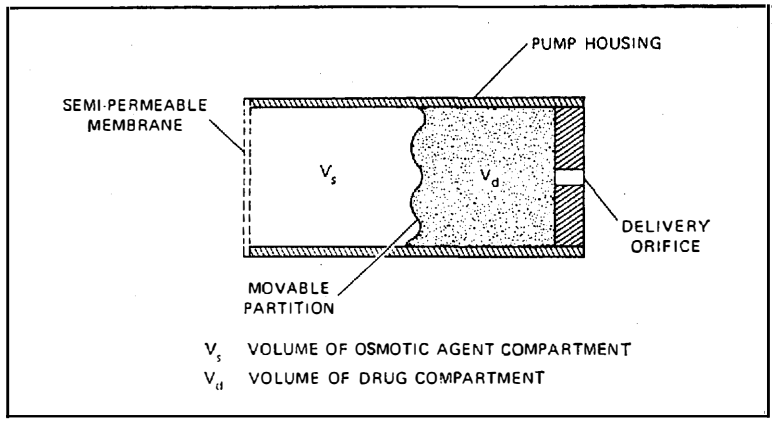

FIG. 1. Schematic representation of an osmotic pump.

2. THEORY

A. Principle of Operation

A schematic diagram of the most general form of an osmotic pump is given in Fig. 1. The active drug, prepared in a homogeneous solution, stable suspension, or emulsion, is contained in the drug reservoir of volume V_d, and a delivery orifice. A collapsible partition such as a diaphragm or bag separates the drug formulation from the osmotic driving agent that provides the osmotic driving force. The osmotic driving agent is isolated from the outside environment by a membrane that is permeable to water, but not to the osmotic driving agent. The volume of the chamber containing the osmotic driving agent is denoted V_s in the figure.

When the osmotic pump is placed in an aqueous medium, there is a net flux of water across the membrane into the compartment that contains the osmotic driving agent. The rate of flux is controlled by the water permeable membrane; pressure is exerted on the collapsible partition, and the contents of the drug compartment are displaced through the delivery orifice. The outside walls of the pump, including the membrane, are rigid and nondeformable, and so, by virtue of the incompressibility of water, the volume of water entering the system is equal to the volume of drug solution that is pumped out.

Equation (1) describes the rate of water flow across the semipermeable membrane caused by the osmotic pressure gradient. The discussion of the pump delivery rate will be analogous to the treatment given for the elementary osmotic pump (Theeuwes, 1975). When a single solute is used as the osmotic driving agent, the water flow can be written as

$$J = K \cdot A \cdot (\sigma \Delta \pi - \Delta P). \tag{1}$$

Here K is the permeability of the membrane to water, J is the volume of water transported per unit time, A is the effective surface area of the membrane, σ is the osmotic reflection coefficient of the membrane, and $\Delta\pi$ and ΔP are, respectively, the differences in osmotic and hydrostatic pressure between the compartment containing the osmotic driving agent and the outside of the device.

If the internal components and the drug solution are incompressible, the volume delivery rate from the osmotic pump is the same as the rate of water transfer across the membrane as given by Eq. (1). When the pump operates in an environment with an osmotic pressure, π_e, $\Delta\pi$ is given by

$$\Delta\pi = \pi_s - \pi_e, \tag{2}$$

where π_s is the osmotic pressure of the water solution of the osmotic driving agent consisting of a single solute. The hydrostatic pressure difference, ΔP, can be expressed as

$$\Delta P = \Delta P_d + \Delta P_c, \tag{3}$$

where ΔP_d is the elevation of internal pressure associated with the flow of the drug solutions through the outlet, and ΔP_c is the pressure necessary to deform the drug reservoir inward.

B. Design Criteria for Constant Delivery Rate

As can be seen from Eq. (1), a zero-order rate of delivery can be obtained if the following condition is satisfied:

$$\sigma\Delta\pi - \Delta P = \text{constant}. \tag{4}$$

The above condition can be achieved when both terms on the left-hand side of Eq. (4) are constants, i.e.,

$$\sigma(\pi_s - \pi_e) = \text{constant} \tag{5}$$

and

$$\Delta P_d + \Delta P_c = \text{constant}. \tag{6}$$

The requirement of a constant net osmotic force [Eq. (5)] can be met if the following are satisfied: (1) the amount of the osmotic driving agent is sufficient to maintain a saturation in its water solution; (2) the environmental osmotic activity is either constant or negligible; and (3) the osmotic reflection coefficient is constant and close to unity. The theoretical amount of the osmotic driving agent needed to keep the compartment occupied by the osmotic driving agent at saturation is

$$M_s = V_d \cdot \frac{S}{1 - (S/\rho_s)}, \tag{7}$$

where M_s is the mass of the osmotic driving agent, S is the solubility of the agent per volume of solution in water, ρ_s is the density of the osmotic driving agent, and V_d, here, is the initial internal volume of the drug compartment.

The values of ΔP in Eq. (6) can be reduced to approximately zero by selecting a sufficiently large orifice and by choosing a highly deformable partition. These will result in $\Delta P_d = \Delta P_c \simeq 0$, and even in the actual situation, one obtains $\Delta\pi \gg \Delta P$ when the low molecular weight salts are used as the osmotic driving agent. Therefore, under the preceding design criteria, Eq. (1) becomes

$$J = K \cdot A \cdot (\pi_s - \pi_e). \tag{8}$$

Here, π_s is the osmotic pressure of the saturated salt solution in the pump, and π_e is the constant environmental osmotic activity. The ideal membrane, which is selectively permeable to water but not to the osmotic driving agent, commonly called a semipermeable membrane, has a σ value of unity.

C. Membrane and Osmotic Agent Selection

As can be seen in Eq. (8), for a particular design, the pumping rate is directly proportional to the product of the membrane permeability to water and the net osmotic pressure, $K \cdot (\pi_s - \pi_e)$. The direct proportionality holds only if the membrane area stays constant and the osmotic reflection coefficient is unity.

The most important properties of the membrane are the water permeability, selectivity to water ($\sigma \simeq 1$), and a good wet strength. With decreasing selectivity or diminishing σ, the osmotic driving agent permeates through the membrane into the surrounding environment. The loss of osmotic driving agent poses an engineering problem, since an excess amount must be incorporated in order to maintain constant osmotic pressure. Moreover, when the pumps are implanted in animals, the excessive loss of the driving agent from the osmotic systems may cause a toxicity problem to the neighboring tissues. The general trend is such that the membranes that are more permeable to solvent (water) are also more permeable to solute (osmotic driving agent) (Lonsdale *et al.*, 1965) and, in designing osmotic pumps, high delivery rates must be compromised by greater loss of driving agent. The loss of osmotic driving agent from the osmotic pump is

$$m/t = \frac{P}{h} \cdot A \cdot S, \tag{9}$$

where P is the permeability coefficient of the membrane to osmotic driving agent, A is the membrane area, h is the membrane thickness, and S is the osmotic driving agent solubility.

For the osmotic driving agents, two most critical properties are the osmotic activity and the solubility in water. Equations (10) and (11) show the theoretical effects of the solubility on the osmotic force within the pumps and the volume of the osmotic driving agent the systems must contain:

$$\pi_s = S \cdot i \cdot RT, \tag{10}$$

$$V_s/V_d = S/(\rho_s - S). \tag{11}$$

Here in Eq. (10), i is the number of ions or particles per mole in solution, R is the ideal gas constant, and T is the absolute temperature. ρ_s in Eq. (11) is the density of the osmotic driving agent.

Equations (10) and (11) indicate that the use of highly soluble salts increases the system's pumping rate. As the solubility of the osmotic driving agent is increased for a pump of overall constant volume, the useful available volume, V_d, for the drug formulation is reduced. Therefore, it is not desirable to increase the solubility of the osmotic driving agent and/or the osmotic pressure, particularly when the pumps are small and the drug volume to overall pump volume ratio of 0.3 or larger is desired.

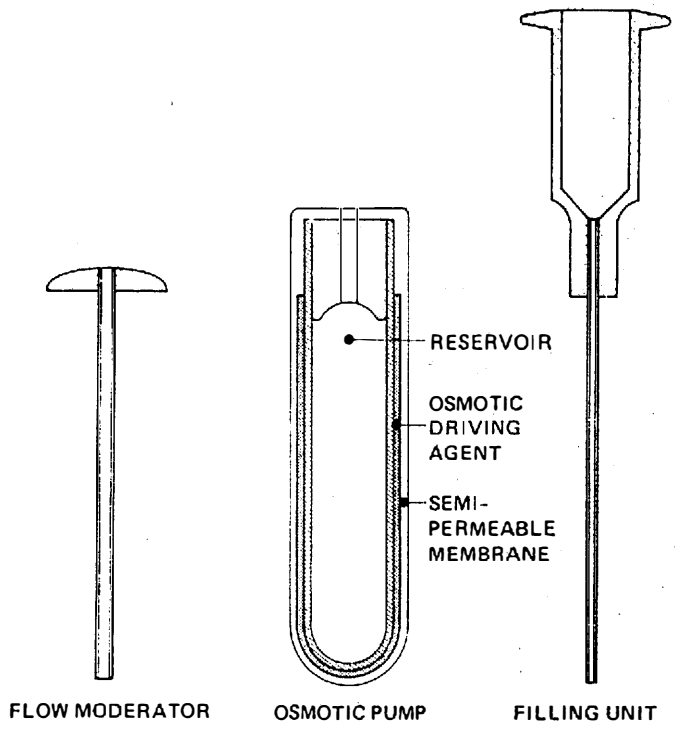

FIG. 2. Osmotic pump and components.

3. EXPERIMENTAL

A. Membrane Preparation for Permeability Measurements

Cellulose acetate grades of four different percentage acetyl contents (39.8, 39.4, 38.3, and 32.0%) were commercially[1] obtained, and dissolved in the following solvents, respectively: acetone, dioxane, dioxane and dimethylformamide. Solutions ranged from 10 to 20% of polymer by weight, and were cast on glass plates at room temperature with a Gardner knife to a dry thickness ranging from 3.8×10^{-3} to 10^{-2} cm. Clear films were obtained and dried in the oven at 50°C for at least 72 hr prior to permeation experiments.

B. Permeability Measurements

The permeability coefficient P, and the normalized volume flux of water $J \cdot h/A$, were determined in osmosis experiments. The membrane with area, A, and thickness, h, was placed in a diffusion cell (Lakshiminarayanaiah, 1969) separating water from the stirred saturated osmotic driving agent (salt) solutions. The diffusion cell was submersed in a water bath at 37°C. The permeability coefficient, P, was calculated from Eq. (9) by measuring the salt transported across the membrane by electrical conductance. The volume flow, J, was measured by the displacement of the meniscus of saturated solution in a graduated cylinder mounted on the half-cell containing the saturated solution during a time interval, Δt, measured with a stopwatch. The volume flow was measured approximately 30 min after initiation of the experiment.

[1] Eastman Chemical.

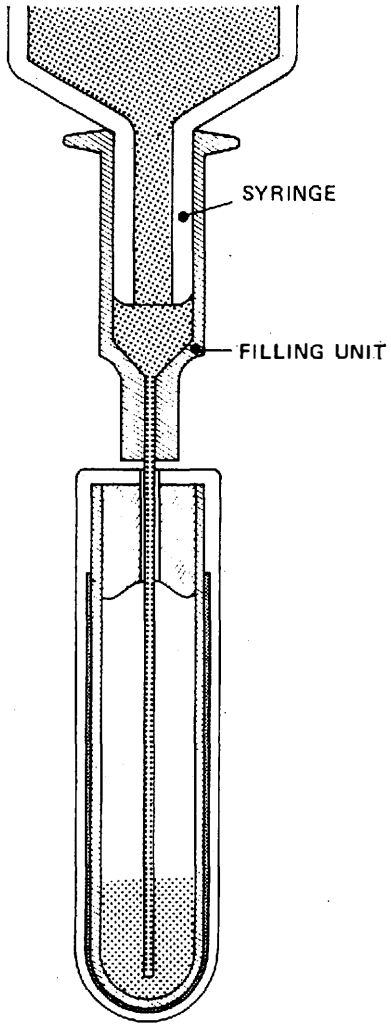

FIG. 3. Filling the osmotic pump.

C. Design and Fabrication of Osmotic Pump

Figure 2 shows schematic diagrams of the osmotic pump and ancillary components designed and manufactured for the present study.

The osmotic pump is cylindrical in shape and consists of a collapsible reservoir surrounded by a sealed layer of osmotic driving agent. The osmotic driving agent serving as the energy source is, in turn, contained by a rate controlling semipermeable membrane, as shown in Fig. 2. A miniaturized version of the osmotic pump used in this study contained approximately 0.155 ml of solution. The external dimensions were 0.65 cm in diameter and 2.5 cm in length.

The reservoirs were produced by injection molding a synthetic elastomer. To ensure the complete collapse of the reservoir and, hence, total delivery of the reservoir contents, the wall thickness of the reservoir was made very thin (0.3 mm).

The osmotic driving agent was applied to the outside surfaces of the reservoir by dipping into a stable suspension of salt and subsequent drying at 50°C. The process was repeated until, according to Eq. (7), the required amount of the

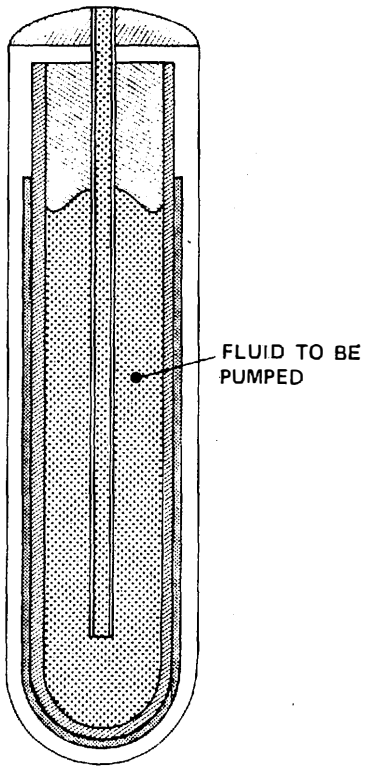

FIG. 4. Osmotic pump filled and assembled.

osmotic driving agent was coated on the reservoir. The semipermeable membrane was also put on by dipping the osmotic driving agent coated reservoir into a homogeneous solution consisting of appropriate cellulose ester and organic solvent. The solvent was driven off by drying at 50°C for 3 to 7 days, depending on the thickness of the membrane.

Figure 3 illustrates how the osmotic pump is filled by using a filling unit and a syringe. The tip of the filling unit is automatically placed close to the bottom of the reservoir and air is removed from the reservoir through the annular gap between the filling unit and the outlet hole of the pump. Note that the filling unit has a blunt tip to prevent accidental puncturing of the reservoir walls. The size of the tube in the filling unit is equivalent to about 25 gauge needle and is made of stainless steel 316.

Figure 4 is a schematic diagram of the osmotic pump filled and assembled for use. As can be seen from the figure, a flow moderator is inserted into the filled osmotic pump.

The flow moderator was designed and fabricated specifically for this study. Its functions are:

(1) to minimize the diffusion of active agent from the pump to the environment;

(2) to prevent accidental spill of the pump's contents;

(3) to minimize the effects of accidentally entrapped air bubbles during filling on the delivery rate of the pump.

For the miniaturized osmotic pumps used in this study, the flow moderators

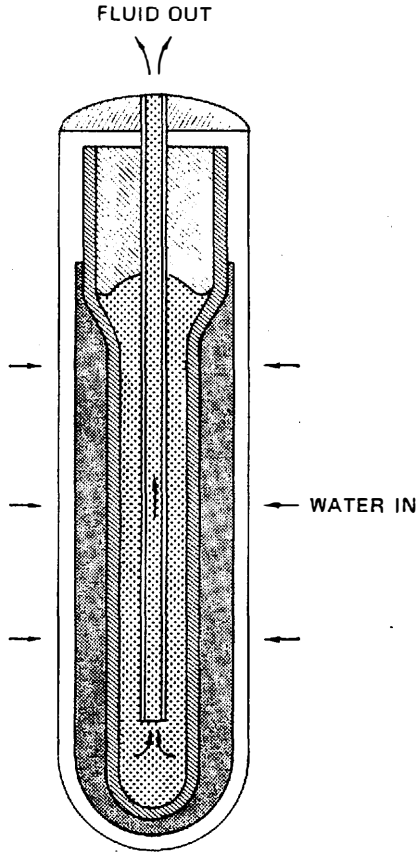

FIG. 5. Osmotic pump in use.

had about 0.05 cm inside diameter and 2.0 cm length. The flow moderators were made of stainless steel 316 for both cap and tube.

Figure 5 illustrates the operation of these miniaturized osmotic pumps in actual use. That is, when a filled pump is exposed to an aqueous environment, the osmotic driving agent beneath the membrane imbibes water at a controlled rate. The imbibed water generates hydrostatic pressure on the reservoir, which collapses and pumps the contents through the flow moderator.

D. Measurement of Pumping Rate from Osmotic Pump in Various Media

The osmotic pumps were filled with a solution of blue dye[2] in normal saline. The filled pumps were then placed in test environments. For *in vitro* pumping tests, the normal saline at 37°C was used as a medium, and for *in vivo* tests the pumps were implanted in subcutaneous sites of mice and rats by means of a simple surgical procedure. The miniature osmotic pumps used in this work were designed such that one can implant several pumps, even in a 20 g mouse, without causing any significant physiological changes in the animal.

The pumping rates were calculated in two ways, depending on the experimental design. The cumulative pumping rate was determined from the initial loading in the pump, the residual volume, and the total elapsed time since time zero. All the *in vivo*, and a part of the *in vitro* tests, were performed in this manner.

[2] FD&C Blue Dve No. 1.

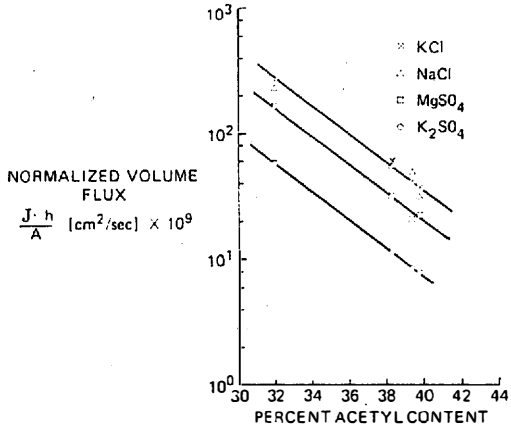

FIG. 6. Normalized volume flux of water through cellulose acetate membranes.

The instantaneous rate was determined by measuring the actual amount of the contents delivered in a time interval. The volume of the contents either pumped out or left within the reservoir was determined by measuring the amount of blue dye in solutions colorimetrically at 630 nm.

4. RESULTS

A. Permeability Measurements

The normalized volume flux of water, $J \cdot h/A$ and the salt permeability coefficient of cellulose acetate membranes were determined as functions of the membrane acetyl content, as shown in Figs. 6 and 7. The percentages of acetyl content were specified by the manufacturer as 32.0, 38.3, 39.4, and 39.8%, respectively. The water and salt permeability experiments were carried out in osmosis experiments driven by each of the four salts indicated: potassium chloride, sodium chloride, magnesium sulfate, and potassium sulfate. Both the water and osmotic driving agent permeabilities increase with decreasing acetyl content (Lonsdale, 1965). In Fig. 6, at each acetyl content the ratios of the fluxes are approximately equal to the ratio of the osmotic pressures of the salts. As can be seen from Fig. 7,

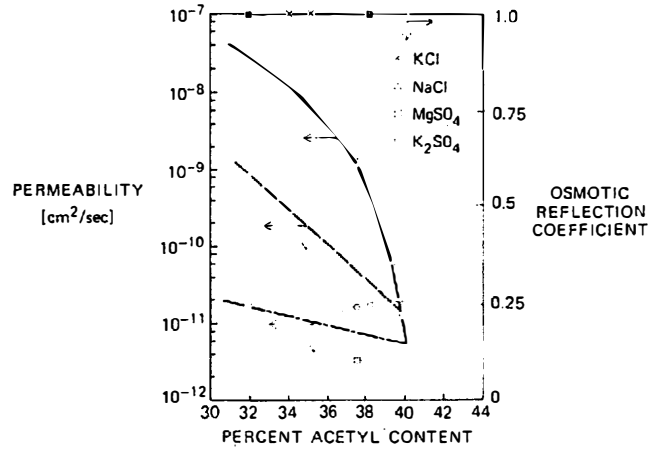

FIG. 7. Salt permeability through cellulose acetate membrane as a function of acetyl content.

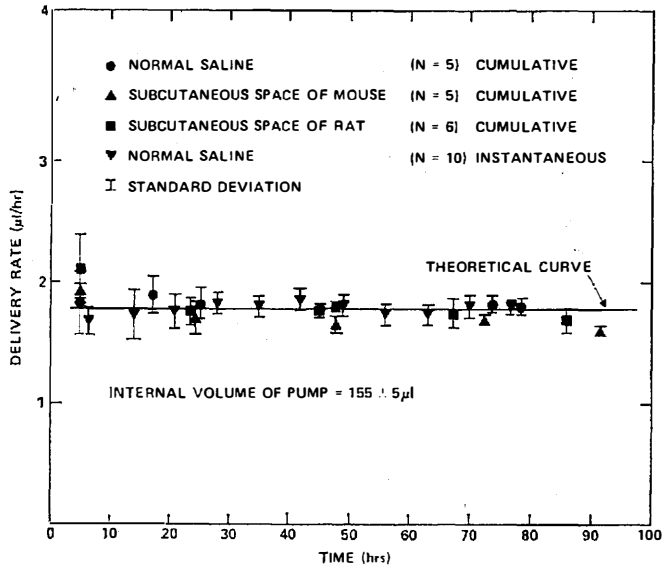

FIG. 8. Delivery rate from miniaturized osmotic pump as a function of time (Batch No. 728-78-13W).

the permeability of the salts through the same membrane material is small. For small values of P, σ is approximately equal to $(1 - P \cdot A/J \cdot h)$ (Katchalsky and Curran, 1967). In Fig. 7, σ is plotted against the acetyl contents of the cellulose acetate materials and for different osmotic driving agents. The value of the reflection coefficient, σ, is approximately unity for these salts and membrane combinations, indicating that the membranes are highly selective or nearly semipermeable.

B. Delivery Rate from Miniaturized Osmotic Pumps

It is possible to embody these principles in a miniaturized pump (Theeuwes, 1973; Higuchi and Leeper, 1973). Optimization of space is achieved by con-

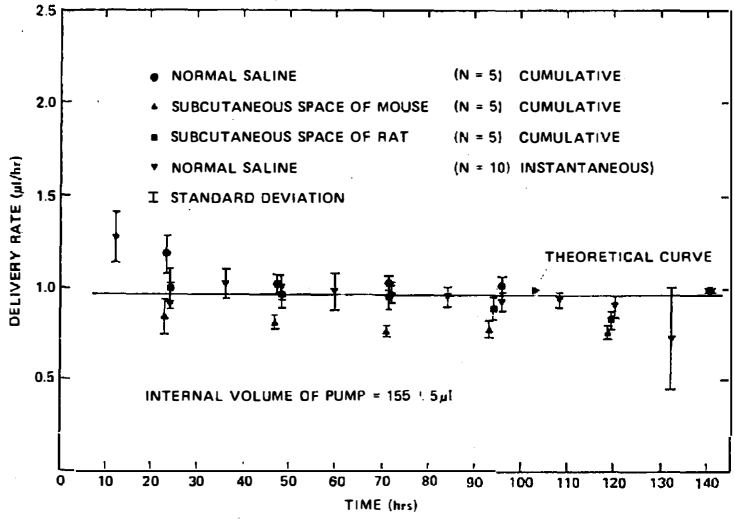

FIG. 9. Delivery rate from miniaturized osmotic pump as a function of time (Batch No. 728-110-16W).

centrically coating the salt layers onto the reservoir, followed by a final membrane coating. Devices of this type have been tested successfully in small experimental animals for anticancer drug research, endocrine studies, and narcotic-drug investigations. Figures 8 and 9 are delivery rate profiles of two of the typical miniaturized osmotic pumps. The pumps contained 155 μl of the blue-dye solution in normal saline. The overall volume of each device was about 0.6 ml. The filled systems were tested in normal saline at 37°C, and in the subcutaneous space of mixed-breed mice and albino rats. The cumulative pumping rate was determined by measuring the contents still remaining in the devices after the preset residence time. The instantaneous delivery rate was determined by measuring the volume of the dye solution released to the environment in a given time interval.

The miniaturized pumps achieve a steady-state delivery rate usually within 5 hr, and maintain constant rates during the remaining period. During the initial start-up period, several factors go through transient phenomena: time lag for water permeation through the membrane, equilibration of the system's temperature and osmotic pressure, and thermomechanical relaxation of the membrane.

As can be seen from Figs. 8 and 9, the delivery rates *in vitro* and *in vivo* are approximately the same within experimental error. This indicates that the normal saline at 37°C appears to be a good *in vitro* medium for predicting the *in vivo* pumping rate.

Therefore, it can be concluded that the osmotic pumps, when miniaturized, can be used to present biologically active agents to experimental animals. The system may be surgically implanted in mice or larger animals subcutaneously, intraperitoneally, or intramuscularly in order to administer agents continuously with minimal intervention.

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