Elementary Osmotic Pump

FELIX THEEUWES

Abstract □ The elementary osmotic pump is a new delivery system for drugs or other active agents; it delivers the agent by an osmotic process at a controlled rate. Control resides in the: (*a*) water permeation characteristics of a semipermeable membrane surrounding the formulated agent, and (*b*) osmotic properties of the formulation. In its simplest embodiment, the system is constructed by coating an osmotically active solid agent with the rate-controlling, semipermeable membrane. This membrane contains an orifice of critical size through which solubilized agent is dispensed. The system can contain the agent in solid form at loadings higher than 90% of the total volume, and the agent can be delivered at rates several orders of magnitude higher than can be achieved by solution diffusion through polymeric membranes. The delivery rate, the fraction of total content delivered at zero order, and the system's delivery portal size have been calculated for delivery of a single compound. Experimental work verified the theory. The release rate from the system was found to be independent of outside agitation when the system is not deformed by shaking action, the pH of the environment, and delivery portal size for sizes within a specified range. The delivery rate from this system *in vitro* and in the GI tract of dogs was found to be equal.

Keyphrases □ Delivery systems, drug—elementary osmotic pump, controlled delivery rate, release characteristics, equations □ Drug delivery systems—elementary osmotic pump, controlled delivery, release rates, equations □ Osmotic pump—osmotic process, controlled rate drug delivery system, release rates, equations □ Membrane permeation—osmotic process, controlled rate drug delivery system

To achieve controlled administration of active agents, delivery mechanisms that can provide desired temporal patterns of the delivery rate have attracted great interest. The mechanism of delivering the active species by solution diffusion through a rate-controlling barrier has been found to be flexible and dependable (1) but limited in magnitude [maximum on the order of 0.2 μg/(cm hr)] unless microporous barriers are used. To overcome these low rates and to permit the delivery of water-soluble species, an osmotic system was developed which delivers at membrane-controlled rates that can be several orders of magnitude higher than the drug diffusional rates. This new system is called the elementary osmotic pump (2). This paper describes such systems and gives examples of their characteristics for single-compound delivery.

The principles discussed here are applicable to systems using water or other solvents, but the reported work involved only water.

The elementary osmotic pump consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. A cross section of the system is shown in Fig. 1.

When exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. For a system at a constant internal volume, the device delivers, in any time interval, a volume of saturated solution equal to the volume of solvent uptake. The rate of solute delivery by the system is constant as long as excess solid is present inside the device, but the rate declines parabolically toward zero once the concentration falls below saturation. The solution volume and mass solute delivery rate from the elementary osmotic pump can be predicted from the physicochemical parameters defining the system, as will be discussed. A typical release rate obtained from this system is illustrated in Fig. 2.

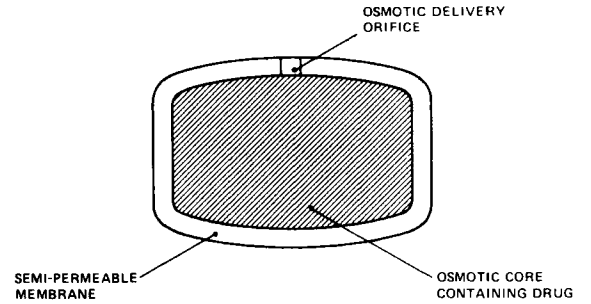

Figure 1—*Elementary osmotic pump cross section.*

THEORETICAL

Delivery Rate—The delivery of agent from the system is controlled by the solvent influx across the semipermeable membrane, which in turn carries the agent to the outside (Fig. 1). Liquid transport by osmosis was qualitatively discussed by Starling (3), who identified the osmotic and hydrostatic pressure differences across capillary membranes as important factors governing transcapillary fluid transport. The process was rigorously treated in the field of nonequilibrium thermodynamics; Eq. 1, which describes the volume flux, dV/dt, across semipermeable membranes has been basic to the field of reverse osmosis (4):

$$\frac{dV}{dt} = \frac{A}{h} L_p(\sigma \Delta\pi - \Delta P) \qquad \text{(Eq. 1)}$$

where $\Delta\pi$ and ΔP are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system; L_p is the mechanical permeability; σ is the reflection coefficient; A is the membrane area; and h is the membrane thickness.

Equation 1 also describes the water flux into the elementary os-

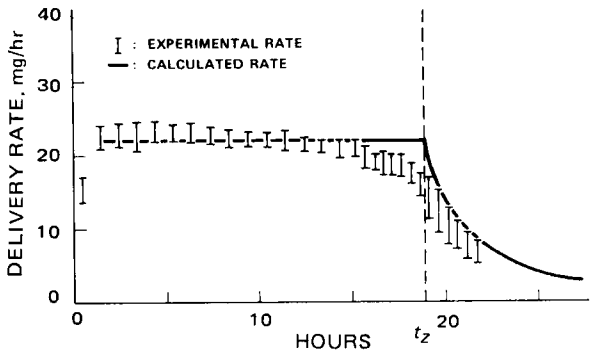

Figure 2—In vitro *release rate of potassium chloride from elementary osmotic pumps in water at 37°. Key:* I, *range of experimental data obtained from five systems; and* —, *calculated release rate.*

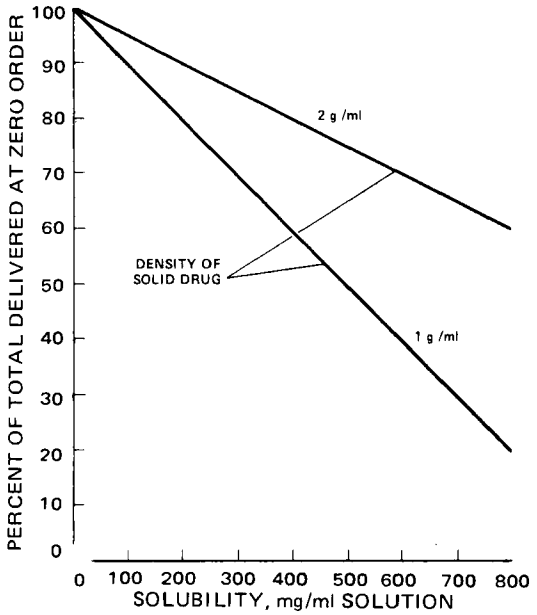

Figure 3—*Fraction of drug content delivered from the elementary osmotic pump at constant rate.*

motic pump (Fig. 1). The general expression for the solute delivery rate, dm/dt, obtained by pumping through the orifice is described by:

$$\frac{dm}{dt} = \frac{dV}{dt} C \qquad \text{(Eq. 2)}$$

where C is the concentration of compound in the dispensed fluid expressed per unit volume of solution.

Substituting Eq. 1 into Eq. 2 results in Eq. 3, which most broadly describes the solute delivery rate:

$$\frac{dm}{dt} = \frac{A}{h} L_p(\sigma \Delta\pi - \Delta P)C \qquad \text{(Eq. 3)}$$

As the delivery orifice increases, hydrostatic pressure inside the system is minimized as expressed by the condition $\Delta\pi \gg \Delta P$.

When the osmotic pressure of the formulation (π) is large compared to the osmotic pressure of the environment, π can be substituted for $\Delta\pi$. Equation 3 then reduces to a much simpler expression in which the constant k replaces the product $L_p\sigma$:

$$\frac{dm}{dt} = \frac{A}{h} k\pi C \qquad \text{(Eq. 4)}$$

Zero-Order Delivery Rate—The release rate from the elementary osmotic pump is zero order from $t = 0$ until a time t_z, at which time all of the solid in the core has dissolved and is described by:

$$\left(\frac{dm}{dt}\right)_z = \frac{A}{h} k\pi_s S \qquad \text{(Eq. 5)}$$

where S is the solubility, and π_s is the osmotic pressure at saturation.

The rate of dissolution of a single compound within the system is much larger than the rate of pumping as given by Eq. 5. For this reason, the concentration, C, can be replaced by the component solubility, S, from time $t = 0$ to $t = t_z$.

Nonzero-Order Release Rate—The nonzero-order release rate from the system (Eq. 4) is obtained by describing the concentration, C, as a function of time. For simplicity, the volume flux into the system is replaced by the symbol F:

$$F = \frac{A}{h} k\pi \qquad \text{(Eq. 6)}$$

and F_s represents the flux during the zero-order time and is related to F by:

$$\frac{F_s}{F} = \frac{\pi_s}{\pi} = \frac{S}{C} \qquad \text{(Eq. 7)}$$

By substituting Eq. 7 into Eq. 4, the nonzero-order release rate as a function of concentration is given by:

$$\frac{dm}{dt} = \frac{F_s}{S} C^2 \qquad \text{(Eq. 8)}$$

Beyond t_z, the mass, m, of component dissolved into the elementary pump volume, V, is given by:

$$m = CV \qquad \text{(Eq. 9)}$$

The change in mass at constant volume, V, causes a concentration change, dC/dt, given by:

$$\frac{dm}{dt} = -V\frac{dC}{dt} \qquad \text{(Eq. 10)}$$

The delivery rate, dm/dt, can be eliminated between Eqs. 8 and 10 as shown by:

$$-\frac{dC}{dt} = \frac{F_s}{VS} C^2 \qquad \text{(Eq. 11)}$$

The concentration, C, inside the system is obtained by integrating Eq. 11 from time t_z to t, when the concentration changes from S to C:

$$-\int_S^C \frac{dC}{C^2} = \frac{F_s}{VS}\int_{t_z}^t dt \qquad \text{(Eq. 12)}$$

Solving Eq. 12 and rearranging terms result in an expression for the concentration as a function of time:

$$C = \frac{VS}{V + F_s(t - t_z)} \qquad \text{(Eq. 13)}$$

Substituting Eq. 13 into Eq. 8 gives the release rate as a function of time, indicating the parabolic decline:

$$\frac{dm}{dt} = \frac{F_s S}{\left[1 + \frac{F_s}{V}(t - t_z)\right]^2} \qquad \text{(Eq. 14)}$$

The nonzero-order release rate can also be expressed as a fraction of the zero-order rate:

$$\frac{dm}{dt} = \frac{(dm/dt)_z}{\left[1 + \frac{1}{SV}\left(\frac{dm}{dt}\right)_z (t - t_z)\right]^2} \qquad \text{(Eq. 15)}$$

The delivery rate discussed in this section is the rate from the elementary osmotic pump when most of the contents are delivered by pumping. When the membrane is not ideally semipermeable, a fraction of the agent is delivered by diffusion through the membrane. The case involving both pumping and diffusion is treated in the *Appendix*.

Mass Delivered at Zero Order, m_z, and Zero-Order Delivery Time, t_z—For a total mass, m_t, contained in the core of the elementary osmotic pump, only an amount m_z is delivered at zero order, and an amount m_{NZ} is delivered at a parabolically declining rate given by Eq. 14. The amount m_{NZ} is the mass that just fills the internal volume of the system with a saturated solution, as shown by:

$$m_{NZ} = SV \qquad \text{(Eq. 16)}$$

The internal volume, V, of the system containing a pure component is related to the total mass, m_t, by the density, ρ, of the core by:

$$m_t = \rho V \qquad \text{(Eq. 17)}$$

The fraction not delivered at zero order is obtained from Eqs. 16 and 17 and given by:

$$\frac{m_{NZ}}{m_t} = \frac{S}{\rho} \qquad \text{(Eq. 18)}$$

Since the sum of m_{NZ} and m_z is equal to m_t, the fraction of the total mass delivered at zero order is given by:

$$\frac{m_z}{m_t} = 1 - \frac{S}{\rho} \qquad \text{(Eq. 19)}$$

The fraction of total device content expressed in percent calculated from Eq. 19 is shown in Fig. 3 for two different compound densities as a function of compound solubility.

The time t_z at which the mass m_z is delivered for an ideal system, with zero startup time, is obtained from:

$$\frac{m_z}{t_z} = \left(\frac{dm}{dt}\right)_z \qquad \text{(Eq. 20)}$$

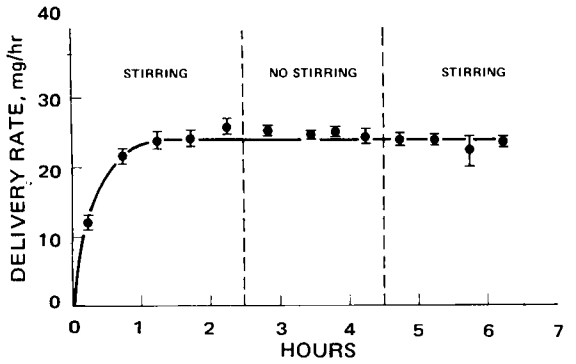

Figure 4—In vitro *release rate of potassium chloride from elementary osmotic pumps in water at 37°. The vertical dashed lines indicate the time at which the systems were transferred from a stirred to a stagnant medium and back to a stirred medium.* ⧳ *represents the range of experimental data obtained from five systems.*

Combining Eqs. 19 and 20 gives:

$$t_z = m_t \left(1 - \frac{S}{\rho}\right) \frac{1}{(dm/dt)_z} \qquad \text{(Eq. 21)}$$

Size of Delivery Orifice—The size of the delivery orifice must satisfy two conditions:

1. It must be smaller than a maximum size, A_{max}, to minimize the contribution to the delivery rate made by solute diffusion through the orifice.

2. It must be sufficiently large, above a minimum size, A_{min}, to minimize hydrostatic pressure inside the system that would affect the zero-order release rate in the following ways. Hydrostatic pressure within the system not only decreases the osmotic influx as seen from Eq. 1, but also it can increase the volume of the system. During the time that the system volume is increasing, the outflow would be smaller than the inflow, resulting in a depressed delivery rate.

Mathematically, these two conditions can be expressed by $A_{min} \leq A_0 \leq A_{max}$, where the cross-sectional area of the orifice, A_0, is larger than or equal to a minimum value and smaller than or equal to a maximum value.

The minimum cross-sectional area can be estimated from Poiseuille's law (4):

$$A_{min} = 5 \left(l \frac{dV}{dt} \frac{\eta}{\Delta P_{max}}\right)^{1/2} \qquad \text{(Eq. 22)}$$

where dV/dt is the volume flux through the orifice, l is the length of the orifice, η is the viscosity of the dispensed solution, and ΔP_{max} is the maximum hydrostatic tolerated pressure difference between the inside and outside of the device. The ΔP_{max} is the pressure at which deformation of the membrane housing occurs or that is significant with respect to the osmotic driving pressure, whichever is smallest.

The maximum cross-sectional area allowed, A_{max}, is obtained by imposing the condition that the diffusional contribution to the release rate must be a factor, F, smaller than the zero-order pumping rate as defined by Eq. 5. This condition is expressed by:

$$A_{max} = \frac{l}{F} \left(\frac{dm}{dt}\right)_z \frac{1}{DS} \qquad \text{(Eq. 23)}$$

in which D is the diffusion coefficient of the compound being delivered in the solvent within the orifice.

In practice, perfect membrane-controlled osmotic delivery has been obtained when $F \geq 40$, as will be discussed.

EXPERIMENTAL

Potassium Chloride Elementary Osmotic Pump Fabrication—Systems were prepared containing 500 mg of potassium chloride each, described by the following parameters: $V = 0.25$ cm^3, $h = 0.025$ cm, $A = 2.2$ cm^2, $k\pi_s = 0.686 \times 10^{-3}$ cm^2/hr, $P = 0.122 \times 10^{-3}$ cm^2/hr, $S = 330$ mg/ml, and $\rho = 2$ g/ml.

The total mass was compressed in a hard tablet and the volume, V, was calculated assuming the density, ρ (5). The area, A, was calculated from the tablet geometry, and the membrane thickness

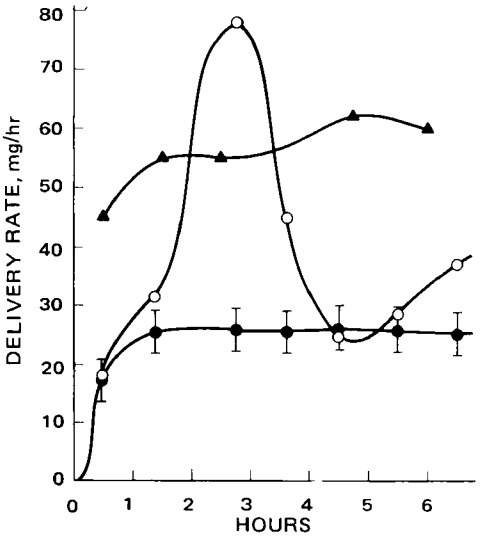

Figure 5—In vitro *release rate of potassium chloride from elementary osmotic pump systems in water at 37°. Key:* ⧳, *range of experimental data obtained from systems with cylindrical orifices of diameters 75, 128, 190, and 274 μm;* ○, *system with 435-μm orifice diameter; and* ▲, *system with 368-μm orifice diameter.*

was measured using a standard thickness gauge. The solubility, S, at 37° was determined by electrical conductance measurements after dilution of the filtered saturated solution into the concentration range where a calibration curve was constructed.

The permeability coefficient, P, and the product, $k\pi_s$, were determined in a permeation experiment (4) where the membrane was placed in a diffusion cell separating water from the stirred saturated solution of potassium chloride. The permeability coefficient, P, was calculated, by measuring the salt transported across the membrane by electrical conductance, from an equation of the form of the second term of Eq. A3. The product, $k\pi_s$, was calculated from Eq. 6, where the volume flow was determined by the displacement of the meniscus of the saturated solution in a graduated cylinder mounted on the cell half containing the saturated solution during a time interval, Δt, measured with a stopwatch.

***In Vitro* Delivery Rate Measurements**—The release rate from the systems was obtained by transferring each at regular, usually hourly, intervals from one test tube to the following and measuring the amount released in each test tube. All experiments were carried out at 37° in the fluids indicated on the figures. The potassium chloride systems were agitated with a stroke of 2.5 cm at a frequency of 0.5 stroke/sec for the experiments shown in Figs. 2, 4, 5, and 6. The larger phenobarbital sodium elementary osmotic pumps referred to in Fig. 7 were manually transferred to sequential flasks in which the liquid was stirred constantly.

Potassium chloride concentrations were measured by electrical conductance. Phenobarbital sodium concentrations were measured spectrophotometrically.

***In Vivo* Delivery Rate Measurements**—Color-coded 500-mg

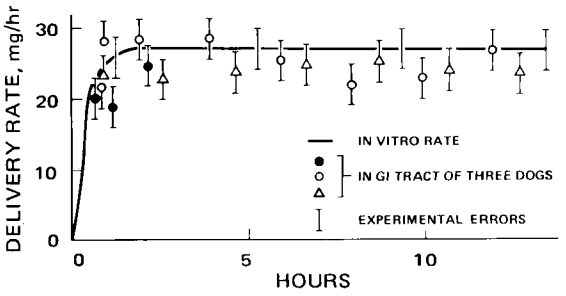

Figure 6—In vitro *and* in vivo *release rate of potassium chloride from elementary osmotic pumps. Key:* —, *average* in vitro *rate from systems of the same batch; and* △, ○, ●, *average release rate of one system in the GI tract of Dogs 1, 2, and 3, plotted at the total time period each system resided in the dog.*

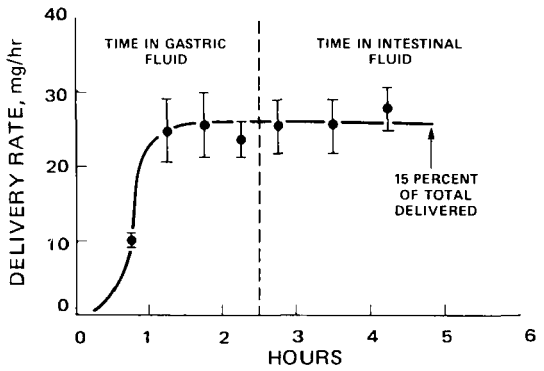

Figure 7—In vitro *release rate of phenobarbital sodium from elementary osmotic pump systems in gastric and intestinal fluid USP without enzymes. The vertical dashed line indicates the time at which the systems were transferred from gastric to intestinal fluid.* ⧳ *represents the range of experimental data obtained from three systems.*

potassium chloride elementary osmotic pump systems were administered to three dogs at recorded time intervals. The dogs were sacrificed, the devices were retrieved, and the *in vivo* rates were determined gravimetrically from the initial and final dry weights of each individual system.

RESULTS AND DISCUSSION

Predictability of Delivery Rate—For elementary osmotic pump systems containing 500 mg of potassium chloride and prepared as already described, the predicted pumping rate, as calculated from Eq. 5, was 20 mg/hr. By correcting for the 20% diffusional contribution, as shown by Eq. A4 (*Appendix*), the release rate was found to be 24 mg/hr.

When assuming one adjustable parameter, $(dm/dt)_z$ = 22 mg/hr, as the observed experimental rate, the zero-order time, t_z = 19 hr, was calculated from Eq. 21. When using the experimental zero-order rate, the nonzero-order tail was calculated from Eq. 15 (solid line in Fig. 2). An identical curve was obtained by accounting for the diffusional contribution (treated in *Appendix*) by calculating the nonzero-order rate from Eqs. A5 and A13. The data are represented within the limits of experimental error by these equations. For simplicity, the system is well described by the equations applying to pumping when the diffusional contribution is not more than 20%.

Because of its osmotic action, the system exhibits two important characteristics which are described in the next two subsections.

Delivery Rate Is Independent of Outside Agitation—The release rates of five similar potassium chloride systems were measured sequentially in (*a*) stirred, (*b*) stagnant (no stirring), and (*c*) stirred media. The release rate was measured by the mass delivered during about 30-min intervals (Fig. 4). During stirring, the systems were moved up and down with a stroke of 2.5 cm and a frequency of 0.5 stroke/sec in water at 37°. The devices were kept immobile during the stagnant period. As can be seen in Fig. 4, the release rate under both conditions was identical.

Delivery Rate Is Independent of pH—Because of the semipermeable characteristics of the membrane, ions are not readily exchanged across it and the formulation contained within the device can be programmed at a pH independent from its environment. A compound with a solubility that is highly pH dependent can be incorporated in the water-soluble salt form. During operation, the internal core of the elementary pump keeps the pH created by this salt form as its *in situ* created formulation. The delivery rate from the system, as explained previously, is governed by the osmotic pressure of the formulation and the water permeability of the membrane and is therefore independent of the pH of the environment.

As an example, the average release rate from three elementary osmotic pump systems delivering phenobarbital sodium in artificial gastric (pH 2) and intestinal fluid (pH 7.5) (without enzymes) is shown in Fig. 7. The release rate was independent of the pH of the delivery medium.

Delivery Rate Is Independent of Delivery Port Sizes within Predictable Limits—According to $A_{min} \leq A_0 \leq A_{max}$, the delivery rate should be independent of the delivery orifice size for sizes within the range expressed by Eqs. 22 and 23. For pharmaceutical dosage forms where the orifice length is on the order of the membrane thickness, $l = h \simeq 25 \times 10^{-4}$ cm, η = 1 cps, $(dV/dt) \simeq 0.1$ ml/hr, and $\Delta P \simeq 1$ atm, the minimum orifice area calculated from Eq. 22 is on the order of $A_{min} \simeq 13 \times 10^{-8}$ cm^2. For a cylindrical hole, the diameter is then 4×10^{-4} cm—difficult or impossible to be drilled.

To find an operational delivery orifice, it is of practical importance to calculate only the upper size, A_{max}, as defined by Eq. 23. The sizing factor, F, has been experimentally determined by measuring the release rate as a function of the hole size. In Fig. 5, the release rate from 500-mg potassium chloride elementary osmotic pumps is plotted for various hole sizes. Complete membrane-controlled delivery was observed for all hole diameters, 75, 128, 190, and 274×10^{-4} cm. At 368×10^{-4} cm and above, control over the delivery rate was lost. The transition from membrane control to the occurrence of diffusion and probably convection within the orifice was dramatic. No systematic trend in delivery was observed within the hole size range from 75 to 274 μm.

The sizing factor, F, was calculated from Eq. 23 assuming A_{max} as the orifice area corresponding to the 274-μm diameter hole. The length of the passageway through the membrane was $l = 25 \times 10^{-4}$ cm; $(dm/dt)_z$ = 25 mg/hr, as seen from Fig. 5; S = 330 mg/ml; and diffusion coefficient $D = 2 \times 10^{-5}$ cm^2/sec (5). The sizing factor was found to be F = 40.

Delivery Rate in GI Tract Is Equal to *In Vitro* Rate—The elementary pump system can be broadly applied to controlled delivery. A number of pharmaceutical applications such as implants, inserts in body cavities, or oral delivery come to mind, since all of these applications provide an environment of constant water activity.

The system is of special interest in oral application because high, predictable delivery rates can be obtained independent of GI motility and the pH of luminal fluids. An additional benefit is the system's delivery of the drug in solution ready for absorption. Thus, the elementary osmotic pump is an *in situ* prepared liquid dosage form.

In the example shown in Fig. 6, the *in vivo* functionality of the system is demonstrated in the GI tract of dogs. Each experimental point represents the average *in vivo* release rate from each system during its total residence time in the GI tract. The data points are plotted at the total residence time observed for the device. The solid line is the *in vitro* release rate.

The *in vitro* delivery profile was measured for systems of the same batch in water at 37°. The average *in vivo* delivery rate was found to be systematically lower by about 10%. The *in vivo* data agree with the *in vitro* data within the combined experimental error of 20% (6).

CONCLUSIONS

1. The mode of operation of the elementary pump is well understood, and the *in vitro* delivery rate from the system can be accurately predicted.
2. The fraction of drug delivered at zero order can be predicted from the compound solubility and core density.
3. The delivery rate is independent of: (*a*) the pH of the environment, (*b*) the agitation of the environment, and (*c*) the size of the orifice for orifices within the predictable range.
4. The *in vivo* delivery rate from the system is essentially equal to the predictable *in vitro* delivery rate.

APPENDIX

The release rate from the elementary osmotic pump is the total mass delivered per unit time from this system. In practice, three mechanisms contribute to the delivery: (*a*) delivery by pumping, $(dm/dt)_P$, which was described previously; (*b*) delivery by diffusion through the orifice, $(dm/dt)_{DO}$; and (*c*) delivery by diffusion through the membrane, $(dm/dt)_{DM}$. The total delivery rate is then given by:

$$\left(\frac{dm}{dt}\right)_t = \left(\frac{dm}{dt}\right)_P + \left(\frac{dm}{dt}\right)_{DO} + \left(\frac{dm}{dt}\right)_{DM} \qquad \text{(Eq. A1)}$$

By design of the system, the diffusion through the orifice was selected to be negligible, as expressed by $A_{min} \leq A_0 \leq A_{max}$, and Eq. A1 reduces to:

$$\left(\frac{dm}{dt}\right)_t = \left(\frac{dm}{dt}\right)_P + \left(\frac{dm}{dt}\right)_{DM} \quad \text{(Eq. A2)}$$

For most agents that have a high molecular weight and/or are ionic, the membrane will appear as ideally semipermeable and a negligible amount of agent will be delivered by diffusion through it.

When delivering low molecular weight substances and when the membrane is sufficiently solvated, the second term in Eq. A2 can become important. The total release rate (Eq. A2) is controlled by the same membrane and, as before, a zero-order and nonzero-order pattern will be observed.

Zero-Order Delivery by Pumping and Diffusion—The total zero-order rate is given by the sum of two terms: the pumping rate expressed by Eq. 5 and the diffusional term expressed by Fick's law:

$$\left(\frac{dm}{dt}\right)_{t,z} = \frac{A}{h} k\pi_s S + \frac{A}{h} PS \quad \text{(Eq. A3)}$$

where P is the permeability coefficient. Equation A3 reduces to:

$$\left(\frac{dm}{dt}\right)_{t,z} = \frac{A}{h} S(k\pi_s + P) \quad \text{(Eq. A4)}$$

which is of the same form as Eq. 5 for the ideal case.

In practice, the zero-order rate can be calculated from Eq. A4 or 5 after defining an effective $k\pi_s$ or solubility number.

Nonzero-Order Delivery by Pumping and Diffusion—The nonzero-order delivery rate is given by the sum of the pumping rate, Eq. 8, and the diffusional term:

$$\frac{dm}{dt} = \frac{F_s}{S} C^2 + \frac{A}{h} PC \quad \text{(Eq. A5)}$$

To express dm/dt as a function of time, the concentration, C, inside the system must be expressed as a function of time. This can be done by solving the differential Eq. A6 derived from Eq. A5 by substituting again Eq. 10 for dm/dt:

$$-\frac{dC}{dt} = \frac{F_s}{VS} C^2 + \frac{AP}{Vh} C \quad \text{(Eq. A6)}$$

Then substituting:

$$R = \frac{F_s}{VS} \quad \text{(Eq. A7}a\text{)}$$

$$Q = \frac{AP}{Vh} \quad \text{(Eq. A7}b\text{)}$$

into Eq. A6 results in:

$$\frac{dC}{C(RC + Q)} = -dt \quad \text{(Eq. A8)}$$

Equation A8 can be integrated by fractions after identifying the coefficients α and β as shown in:

$$\frac{1}{C(RC + Q)} = \frac{\alpha}{C} + \frac{\beta}{RC + Q} \quad \text{(Eq. A9)}$$

Equalizing the coefficients of equal powers of C results in:

$$\alpha = \frac{1}{Q} \quad \text{(Eq. A10)}$$

$$\beta = -\frac{R}{Q} \quad \text{(Eq. A11)}$$

Substituting Eqs. A10 and A11 into Eq. A9 and substituting Eq. A9 into Eq. A8 result in:

$$\frac{dC}{QC} - \frac{R}{Q}\frac{dC}{(RC + Q)} = -dt \quad \text{(Eq. A12)}$$

Equation A12 can be integrated from time t_z to t when the concentration changes from S to C. Also, replacing R and Q by their values given in Eq. A7 results in:

$$t - t_z = \frac{Vh}{AP} \ln \frac{\left(F_s \frac{C}{S} + \frac{AP}{h}\right)}{\left(F_s + \frac{AP}{h}\right)\frac{C}{S}} \quad \text{(Eq. A13)}$$

Equation A13 does not give the concentration, C, as an explicit function of time for substitution into Eq. A5. From Eq. A13, C and C^2 can be tabulated as a function of time, and from these values the rate can be calculated using Eq. A5.

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