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DRUG DELIVERY AND THERAPEUTIC SYSTEMS

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I. INTRODUCTION

Since ancient times, compounds of medicinal agents have been administered in dosage forms. Until recently, these dosage forms remained relatively unchanged: the pill, described in Eber's Papyrus 1500 BC; the coated pill, according to Rhazes about AD 900; the tablet, introduced by Al Zahrawi during the latter part of the 10th Century; and the capsule, introduced by Mothes in France, 1833.

During the last 20 years, however, a significant shift has been taking place. Heretofore pharmaceutical companies concentrated primarily on developing new drugs, through discovery of new chemical entities, and formulating aids that allow high-speed production of unit doses. Now, in addition to this approach, they are investing considerable energy in optimizing the pharmacodynamics of medications through dosage-form design. These new dosage forms can be called "therapeutic systems" as they employ technology to optimize the value of the medication delivered, either by delivering drug to the appropriate target area or controlling drug concentration in the body over a convenient dosing interval.

The systems approach used in the design of these new dosage forms draws on the fields of pharmacokinetics and pharmacodynamics. Pharmacokinetics deals with the distribution and elimination of drug and allows the definition of concentration as a function of time; pharmacodynamics deals with the definition of therapeutic and side effects as a function of delivery rate or concentration of drug in the body.

The ideal delivery rate for a therapeutic system is a priori unknown for a given drug substance and should follow from well designed pharmacodynamic studies. The classical view in pharmacodynamics is that there exists a well-defined concentration-effect relationship between drug concentration at the receptor site and pharmacological response. Thus the expectation is that maintaining drug concentration at an optimum level through constant (zero-order) drug administration will result in optimum therapy. This expectation can be realized in such a model when the desired effect is achieved at concentrations low enough to prevent side effects.

However, it has become clear that zero-order or constant drug delivery is not optimum for all drugs. The therapeutic value of some chemical entities is improved by patterned administration. For example, with some drugs, tolerance can sometimes be forestalled when drug delivery is patterned for an "off" period. Moreover, a number of conditions, among them gastric ulcers, asthma, and cardiovascular problems, show a circadian variation throughout the day, which rhythm also may be better served by patterned drug administration. For drugs with a significant nonlinear first-pass effect, pulsatile delivery to

the gastrointestinal tract can enhance drug absorption. Needless to say, technologies that allow such versatility are eagerly awaited.

In this chapter, we focus on a number of drug-delivery devices and therapeutic systems introduced since the early 70s or presently in development, including oral, transdermal, implantable, and intravenous systems. We describe their theory and mode of operation, and their delivery rates *in vitro* and *in vivo*. A number of these systems provide zero-order delivery.

II. ORAL DRUG DELIVERY

Compliance with a drug regimen depends, among other things, on the route and frequency of administration, the type of medication, and the condition being treated. Drugs are most commonly administered orally, and patients often forget to take their medication, especially when frequent dosing is required. For example, in a survey of 86 patients on mixed treatment for one to four weeks, Gatley (1) found that the percentage taking 95 to 105% of the full number of tablets was 67, 50, 44, and 22% respectively, for once, twice, thrice, and four times daily, demonstrating that fewer doses resulted in greater compliance.

A new technology called MEMS™ (Medication Event Monitoring System) allows physicians to monitor patient compliance throughout clinical trials. The device resembles an ordinary amber medication vial but contains a microprocessor that records, as presumptive medication times, the time and date of each opening and closing of the container (2). Such event monitoring and, ultimately, reminding systems aim at improving therapeutic outcome.

Controlled drug-delivery systems have the same aim. They offer the convenience of twice- or once-a-day regimens based on constant drug delivery for a period of 8 to 20 hours. Following absorption, the intention is to achieve a concentration in blood that is high enough to be effective but low enough to prevent toxicity. Sometimes more efficient drug delivery also results in a reduced dose.

The delivery of drug from a therapeutic system can be treated as a macroscopi transfer process based on a phenomenological approach, in which the rate of transfer (flux) is driven by a force (potential gradient). The linear proportionality constant between the flux and the gradient is the inverse of resistance of the delivery system.

Technologies underlying controlled-release oral dosage forms can be classifie according to two characteristics, namely delivery mechanism and structure of the system. The mechanism refers to the physical-chemical principles involved: dissolution, diffusion, erosion, ion exchange, and osmosis. The structure of a controlled-release oral dosage form allows the unique exploitation of any of the mechanisms to yield the drug-delivery rate. In physical terms, structure defines the boundary conditions for the delivery process.

A. Dissolution, Diffusion, and Matrix Systems

The rate-limiting step for dissolution of drug is the diffusion across an aqueous boundary layer, the driving force is the solubility of the active agent in the gastrointestinal fluid, and the resistance is the stagnant-fluid

diffusional boundary-layer thickness (h) surrounding the dosage form, usually about 0.2 mm thick. The diffusivity (D) of an active substance in water at 37°C having a molecular weight about 300 Da is $7(10)^{-6}$ cm^2/sec. Therefore, the aqueous boundary-layer resistance is h/D. For drugs with low solubilities the dissolution process can be maintained for hours; however, the release profile tends to decrease with time because the surface area for dissolution diminishes as the drug particles dwindle.

The rate of dissolution $(dm/dt)_d$ can in first approximation be expressed by Equation 1:

$$\left(\frac{dm}{dt}\right)_d = \frac{ADS}{h} \quad , \qquad (1)$$

where S is the aqueous solubility of the drug and A is the surface area of the dissolving particle or tablet. The solubility of many drugs is often highly dependent on the pH of the surrounding medium. As tablets traverse environments ranging from a pH of 1.2 in the stomach to 7.5 in the intestine, their rate of dissolution can change drastically.

The Adalat Retard® tablet (nifedipine, Bayer) is an example of dissolution control. Figure 1 shows the release-rate profile of the tablet, which disintegrates rapidly at 10 minutes, while the relatively insoluble drug particles dissolve slowly over 3 hours.

Matrix systems rely on dissolution and diffusion. Matrix systems for controlled release are made by tableting drugs uniformly mixed through conventional granulating processes with excipients of hydrophobic polymers (e.g., wax, polyethylene, polypropylene, ethyl cellulose) and/or hydrophilic polymers (e.g., hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, sodium carboxymethylcellulose). The water-insoluble matrix system, which is suitable for the formulation of water-soluble drugs, retains most of its dimensions as the system travels through the gastrointestinal tract. As the drug dissolves and diffuses through the matrix, it is depleted from the matrix surface toward the core. The diffusional path lengthens and the area of dissolution decreases, rendering an ever-declining release profile.

Drug release from a water-insoluble matrix can be described by an equation derived by Higuchi (3). When a loading of drug per unit volume (C_0) in the matrix exceeds its solubility (C_s) in the matrix through which it is uniformly dispersed, the drug-release rate (dm/dt) is controlled by diffusion of dissolved drug through the matrix, as given by Equation 2:

$$\frac{dm}{dt} = A\left[\frac{(C_0 - \tfrac{1}{2}C_s)C_sD}{2t}\right]^{\frac{1}{2}}, \qquad (2)$$

where D is the diffusion coefficient of drug in the matrix, t is time, and A is the area of the drug-releasing matrix. Equation 2 gives the classic square root of the time kinetics for drug release. A simpler form of Equation 2 can be derived if $C_0 >> C_s$. That is, Equation 2 becomes

$$\frac{dm}{dt} = A\left[\frac{DC_sC_0}{2t}\right]^{\frac{1}{2}} \qquad (3)$$

When water-soluble drug is in an insoluble matrix, drug will diffuse only through porous channels. Then D can be replaced with D_e, the effective diffusivity:

$$D_e = \frac{\epsilon D}{\tau} \quad , \qquad (4)$$

where ϵ is the porosity of the matrix, τ the tortuosity, and D the diffusivity of the drug in the release medium (4).

With the water-insoluble matrix system the release rate is usually correlated linearly with $t^{-1/2}$. Figure 2 depicts a release profile for a noneroding wax matrix of potassium chloride (Slow-K®, Ciba). The release kinetics follow the prediction of Equations 3 and 4.

A hydrophilic polymer matrix can, in many instances, give a pseudo-zero-order release profile. The release mechanism of the soluble matrix is a combination of matrix erosion and diffusion (i.e., water and drug migration in and out of the matrix). Upon exposure to an aqueous solution, a gel layer is formed on the surface of the system, followed by water penetration, thickening of the gel layer, and a gradual erosion of the outermost gel layer under excessive swelling pressure. The size and shape of the system vary with time, depending on the prevailing mechanism. Both soluble and insoluble drugs can be incorporated into a hydrophilic polymer matrix; with insoluble drugs, erosion

accounts for most of the release. However, erosion of the polymer matrix is affected strongly by the hydrodynamic conditions surrounding the system, a fact that remains an obstacle to consistent in vivo performance.

Simplicity of formulation makes the erodible matrix one of the most commonly used for sustained drug release. Methods for formulation have been extensively reviewed (5)(6)(7). Factors affecting the release rates are hydration rate, particle size, molecular weight of the matrix polymer, and drug concentration. The kinetics of release have been reviewed for pure erodible systems without diffusion (8)(9) and for erosion and diffusion combined (10)(11)(12)(13).

Isoptin® SR (240 mg verapamil HCl, Knoll, the same product as Calan® SR, Searle) is an example of an erosion-matrix delivery system. Figure 3 shows the release profiles of the system in simulated gastric and intestinal fluids (both without enzymes). Figure 4 shows a steady-state plasma concentration of verapamil following once-daily administration of Calan SR (240 mg). The plasma concentrations achieved appear to be consistent with the 8-hour delivery period in vitro.

B. Ion-Exchange Systems

In ion-exchange formulations, an ionizable drug is held in storage in opposite charge to the fixed charge of the ion-exchange resin. The resin, in bead or tablet form, can be overcoated with a porous membrane. The resin can either be of the cation-exchange type, in which the fixed charges in the resir are negatively charged, such as in phenolic, carboxylic, or sulfonic groups;

or of the anion-exchange type, in which the fixed charges are positive, such as in amino or quaternary ammonium groups. When the device is exposed to the gastrointestinal tract, external ions will migrate into the resin, thereby displacing drug molecules, which diffuse into the lumen of the gastrointestinal tract.

Delsym® (dextromethorphan, Pennwalt), a 12-hour cough medication taken as a liquid suspension, is an example of this type of dosage form. Figure 5 gives the in vitro release profiles of the Delsym suspension in artificial intestinal and gastric fluids. The top part of the figure shows roughly a 1-hour burst associated with the uncoated dextromethorphan-polymer complex, and then the remainder, or sustained-release portion, from the coated-drug complex, which releases its contents slowly. The lower part of Figure 5 indicates that release is still incomplete at 10 hours. In Figure 6, an in vivo profile shows plasma concentrations extending over a 12-hour period (14).

C. Osmotic Systems

Osmotic drug-delivery systems consist of a core structure containing drug (with or without osmotic driving agents) and a semipermeable membrane. The membrane is generally constructed with cellulosic polymers that are permeable to water. Orifices formed by drilling, erosion, or leaching in the membrane serve as drug-delivery pathways. The system absorbs water by osmosis, driven by the difference in water activity within and outside the membrane. The content in the drug core is thus displaced and delivered through the orifices by the pumping action of water continuously in flux. If the core and membrane

are properly formulated, the delivery process is independent of external pH and stirring conditions.

There are various types of osmotic systems. The elementary osmotic pump (EOP) tablet (15)(16), shown in Figure 7, is the simplest. The drug, with or without an osmotic driving agent, is surrounded by a semipermeable membrane with a delivery orifice. Water from the environment is absorbed through the membrane to dissolve the drug, which is pumped out in solution through the orifice. The release rate from these systems is predictable, as shown by Equations 5 and 6:

$$\frac{dm}{dt} = C \frac{dV}{dt} \tag{5}$$

$$\frac{dV}{dt} = \frac{AL_p[\sigma\Delta\pi - \Delta P]}{h} . \tag{6}$$

Mass release rate (dm/dt) is given by volumetric pumping rate (dV/dt) and concentration of drug in solution (C). Volumetric rate in turn can be calculated from the hydraulic permeability coefficient L_p of the membrane and the driving force. This force is the difference between the osmotic pressure ($\Delta\pi$) and the back pressure (ΔP) generated by the flow of liquid from inside to outside, and σ is the reflection coefficient. The orifice can be designed so that this pressure (ΔP) is negligible, which results in a very simple expression for the zero-order rate:

$$Z = \frac{Ak\pi S}{h} \quad , \tag{7}$$

where A is membrane area, h membrane thickness, k osmotic membrane permeability, π osmotic pressure of the core formulation, and S drug solubility. The system delivers at a zero-order rate until a time t_z when all solid drug inside the system is dissolved. From that time on, the drug concentration and osmotic pressure inside the system decline and the delivery rate declines in non-zero-order fashion. The non-zero-order rate is also predictable, but it is less important because the non-zero-order fraction is usually small. Equation 8 contains the internal volume of the system (V) and the time when the zero-order period ends (t_z):

$$\frac{dm}{dt} = \frac{Z}{[1 + (Z/SV)(t - t_z)]^2} \tag{8}$$

Acutrim® (75 mg phenylpropanolamine, CIBA), a onee-a-day appetite suppressant, is an example of a zero-order EOP system. The system includes an immediate-release dose of 20 mg overcoated on an elementary osmotic pump, which delivers its content at a constant rate for 16 hours. Figure 8(a) shows the solubility-pH profiles of phenylpropanolamine HCl and indicates a significant pH-dependent solubility for this drug; Figure 8(b) shows the cumulative amount released from the osmotic system (Acutrim) at two extremely different pH values. The release of phenylpropanolamine is unaffected by the pH of the media for the rated period in spite of the indicated solubility profile (17). The release profile of Acutrim is also unaffected by stirring (Figure 9).

Figure 10 shows the plasma concentration profile of phenylpropanolamine in 12 human subjects following administration of the Acutrim system, Dexatrim® (a sustained-release "tiny time pill"), and drug in solution. The profile for Acutrim is consistent with the in vitro release rate of the system, showing an immediate appearance of phenylpropanolamine in plasma following the loading dose and maintenance of concentration for 16 hours.

The push-pull osmotic pump is designed to deliver drugs of any solubility (18)(19)(20). The technology is especially useful for delivering insoluble and very soluble drugs; such delivery can be done but may be difficult for the elementary osmotic pump to perform adequately. The push-pull osmotic pump can be designed to deliver almost all its content at a zero-order rate.

The push-pull osmotic pump system is constructed with a bilayer tablet core containing drug in the top layer and polymeric osmotic-driving agent in the lower. It is coated with a semipermeable membrane that has one or more orifices drilled or leached on the drug side to allow delivery of the drug formulation. Figure 11 shows the construction of the system. The tablet typically contains 20-40% solid osmotic-driving formulation and 60-80% solid drug formulation that consists of drug, osmotic (optional), and suspending agents.

When the pump is in operation, both drug and osmotic layers osmotically imbibe water across the membrane ("pull"), swelling the osmotic layer and simultaneously formulating a suspension in the drug layer. The swelling of the osmotic layer "pushes" against the drug compartment, causing drug solution

or suspension to flow out the orifice at a controlled rate (Figure 11, right side). This mechanism of operation allows for the delivery of insoluble drugs (e.g., nifedipine) in suspension in a finely divided form ready for dissolution and absorption.

The drug delivery rate from the push-pull dosage form, dm/dt, can be written by Equation 9, where dV/dt is the total volume flow from the dosage form and C_d is the concentration of drug in suspension in the dispensed formulation:

$$\frac{dm}{dt} = C_d \frac{dV}{dt} \quad . \tag{9}$$

The volume of osmotic flow into the osmotic compartment is defined as Q and the volume of osmotic flow into the drug compartment is defined as F, such that dV/dt from Equation 9 is as given in Equation 10:

$$\frac{dV}{dt} = F + Q \quad . \tag{10}$$

If C_c is the concentration of all solids dispensed from the dosage form and f is the fraction of drug formulated in the drug compartment, then

$$C_d = fC_c \quad . \tag{11}$$

Equation 11 implies that the formulated drug fraction in the drug compartment is a constant and is equal to the fraction of drug dispensed in the drug formulation. Physically this makes sense: the water imbibed does not alter

the ratio of drug to total solid in the formulation so long as a uniform suspension is formed. A uniform suspension results from selecting the proper suspending agents to prevent separation between the different formulation materials during storage or operation. By substituting the values for Q, F, and C_d from Equations 10 and 11, we have Equation 12, the expression for the drug-delivery rate:

$$\frac{dm}{dt} = (Q + F)fC_c \quad . \tag{12}$$

The values of osmotic flows Q and F can in turn be written explicitly, as indicated in Equations 13 and 14, where k is the permeability coefficient of the osmotic membrane, h the membrane thickness, A_p the area of the push compartment, π_p the imbibition osmotic pressure of the push compartment, A the total area of the dosage form, π_D the imbibition osmotic pressure in the drug compartment, and H the degree of hydration:

$$Q = \frac{KA_p(H)\pi_p(H)}{h} \tag{13}$$

$$F = \frac{K[A - A_p(H)]\pi_p(H)}{h} \quad . \tag{14}$$

Equations 9, 12, 13, and 14 underlie the operation of the push-pull osmotic pump for the delivery of water-soluble compounds, wherein both the drug and the push compartment contain solutes with constant osmotic pressures. For the

delivery of an insoluble drug, however, both the drug and the push compartments are formulated with polymers characterized by imbibition pressures that are not constant, but rather are a function of the degree of hydration H, as defined in Equation 15. Here, W_H is the weight of the water imbibed per weight of dry polymer (W_p):

$$H = \frac{W_H}{W_p} \quad . \tag{15}$$

During pump operation, the area of the push compartment expands (Figure 11), indicating that A_p is also a function of the degree of hydration.

The push-pull system can be programmed for various delivery-rate profiles, by controlling the parameters defining the total drug delivery rate in Equation 12. This delivery rate can be programmed for the maximum fraction of drug content delivered at a constant rate by selecting the maximum flow (Q) such that the delivery rate can be written by Equation 16, where ρ is the density of the drug compartment:

$$\frac{dm}{dt} = Q\rho f \quad . \tag{16}$$

This expression implies that the dosage form dispenses drug from the drug layer at a rate equal to the speed at which the drug is formulated as a suspension by imbibed water. By comparing Equations 12 and 16, we can derive the condition for the concentration of solids dispensed from the dosage form:

$$C_c = \frac{Q\rho}{F + Q} . \qquad (17)$$

It is interesting to note from Equation 16, and from the expression for Q in Equation 13, that zero-order delivery rate must be programmed on the basis of a constant product of the area times the imbibition pressure (π_p) in the push compartment.

Figure 12 shows the average zero-order release rate and cumulative amount released from a once-daily, push-pull osmotic formulation of nifedipine, an insoluble, short-acting calcium channel-blocker. These systems have been fed to dogs, whose intestinal tracts are a fair replica of those in humans for both pH and motility. Figure 13 shows the cumulative amount of nifedipine release in the gastrointestinal tract of dogs as a function of time compared with the amount released in vitro. As can be seen, the gastrointestinal environment, with its variable pH and motility, had no influence on the performance of the dosage form. The in vitro versus in vivo predictability was demonstrated further in healthy volunteers, in whom steady-state plasma levels were maintained for 24 hours after once-daily administration; see Figure 14 (21).

D. Comparison and Conclusions

The conditions presented by the gastrointestinal tract challenge the ingenuity of dosage-form designers: in a 12- to 24-hour period, an oral dosage form traverses the stomach and small intestine, and resides in the

large intestine; throughout the intestinal tract, motility, pH, enzymatic activity, and ion content vary significantly. Thus dosage forms unaffected by these variables are most likely to achieve controlled, reproducible drug delivery.

Erodible matrix systems are cost effective and offer a moderate degree of versatility and control for handling different classes of drug. Systems based on ion exchange fill a unique niche, allowing the design of liquid dosage forms for controlled delivery of ionic drugs. However, osmotic drug-delivery systems provide both the greatest versatility and the highest degree of control among dosage forms designed for oral delivery.

III. TRANSDERMAL DRUG DELIVERY

Transdermal drug administration generally refers to the topical application of agents to healthy, intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Because of the rapid evolution in our basic understanding of the properties of skin and the mechanisms of skin permeation, modern therapeutics has advanced from the simple application of ointments to the sophisticated delivery of drugs through rate-controlled transdermal therapeutic systems.

Much of the continuing research on transdermal products is directed toward solving the problems of feasibility, efficacy, safety, and acceptability posed by the rate at which the agent applied is absorbed percutaneously. For example,

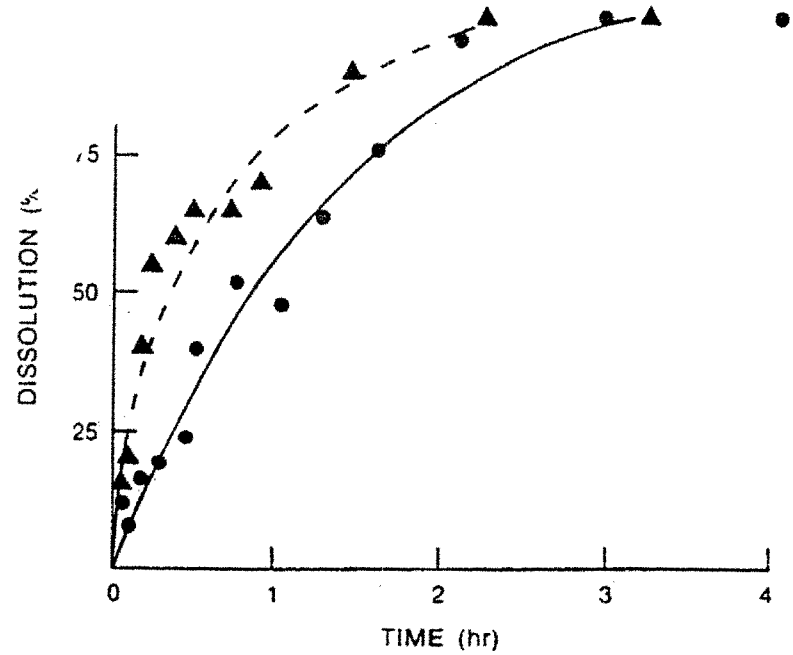


Figure 1

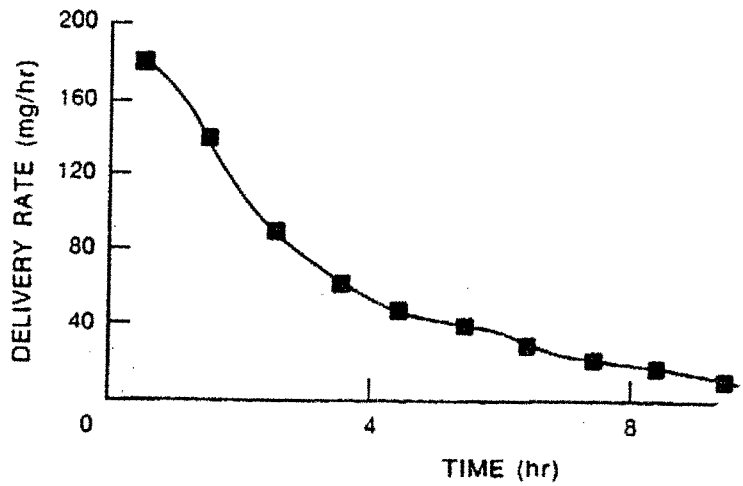


Figure 2

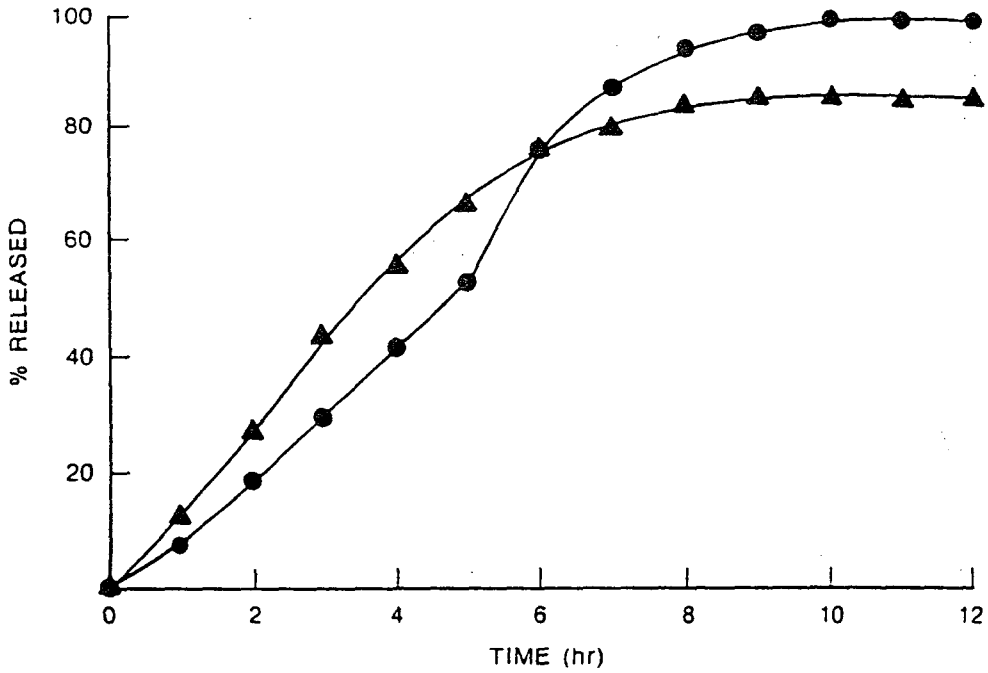


Figure 3

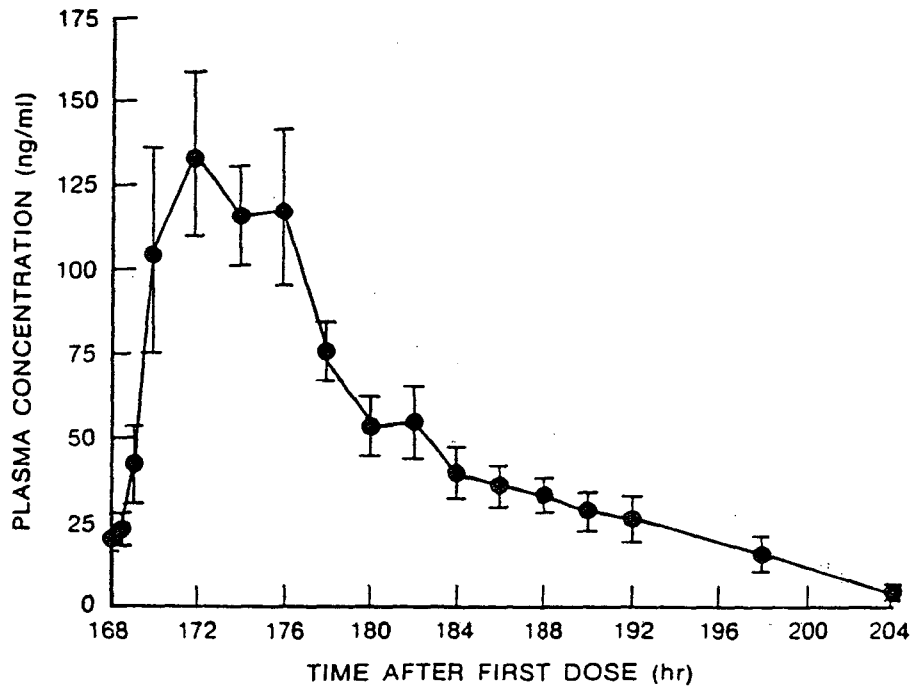


Figure 4

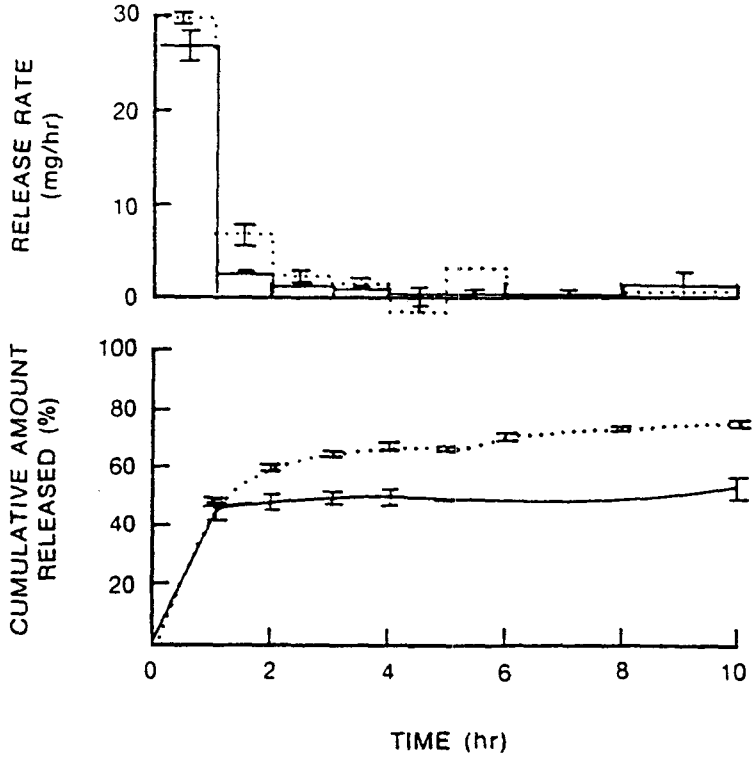


Figure 5

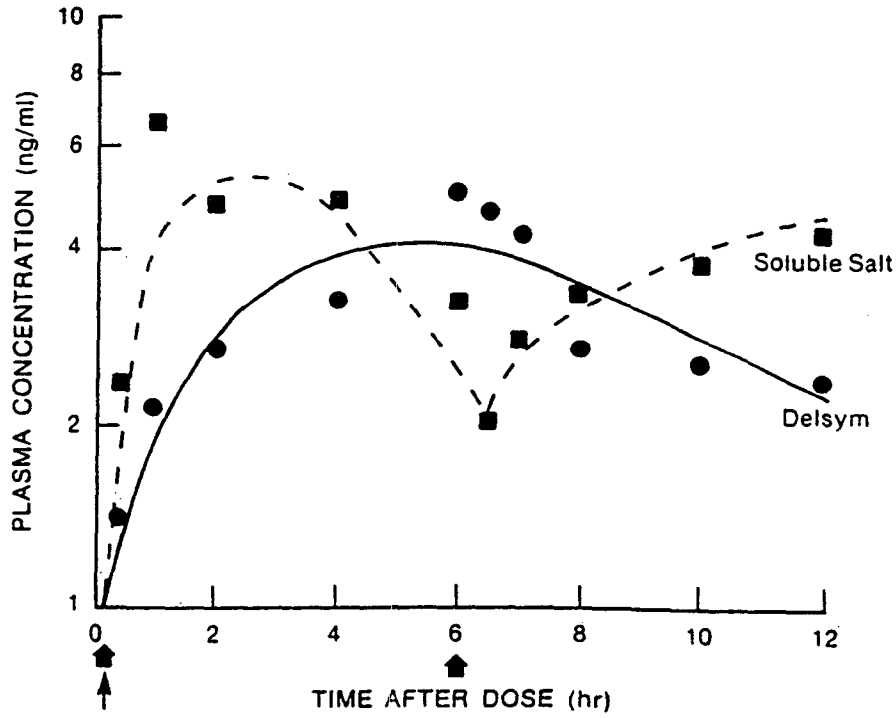


Figure 6

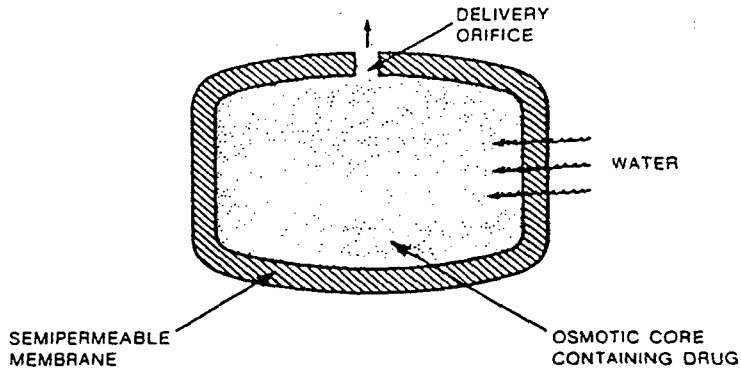


Figure 7

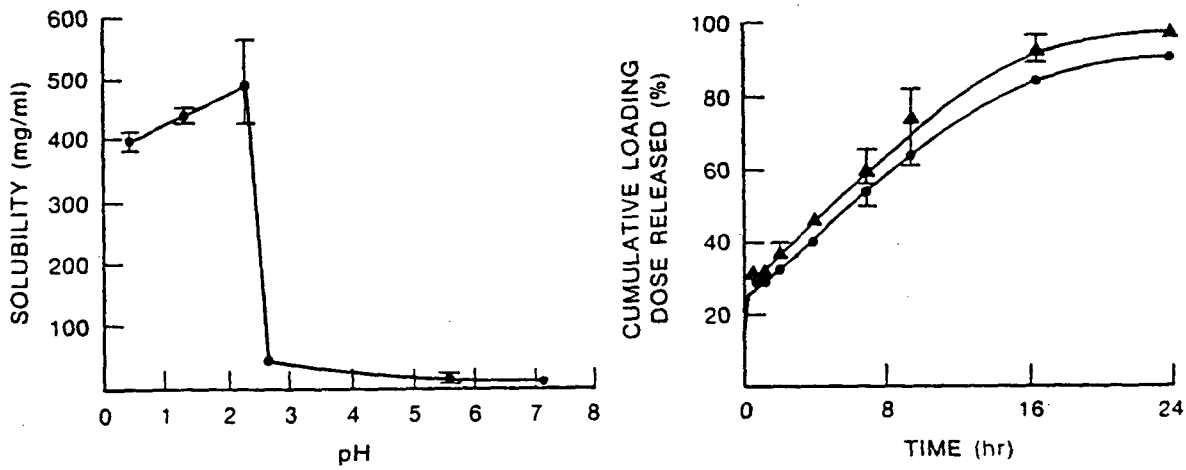


Figure 8

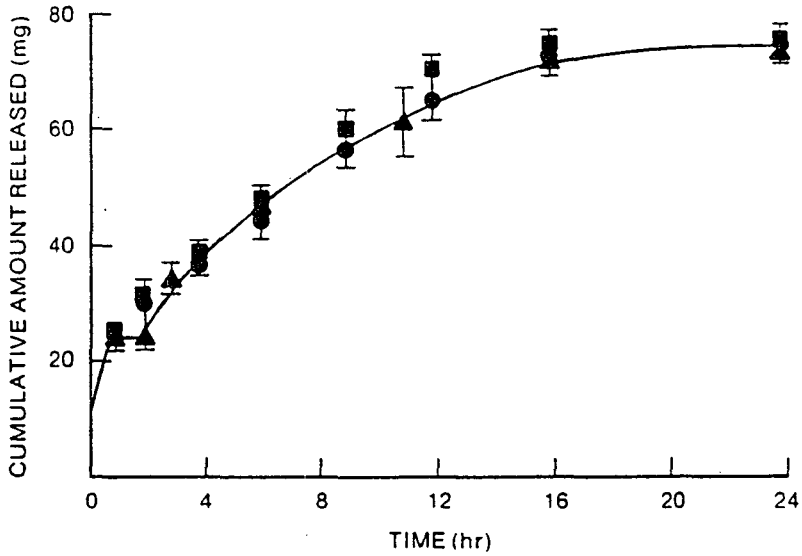


Figure 9

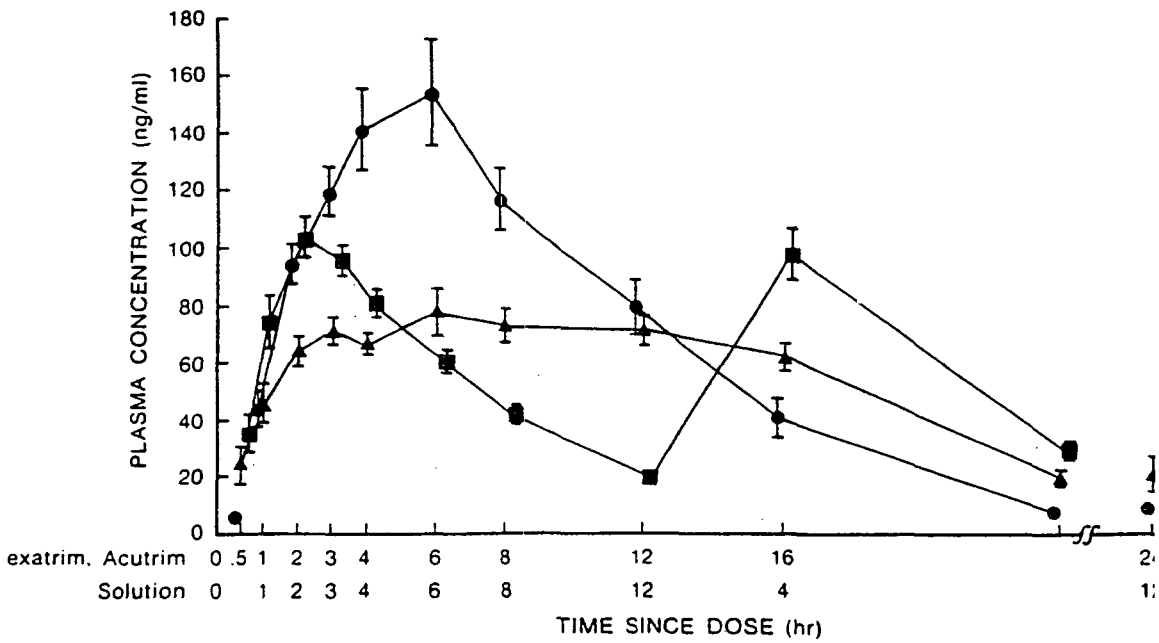


Figure 10

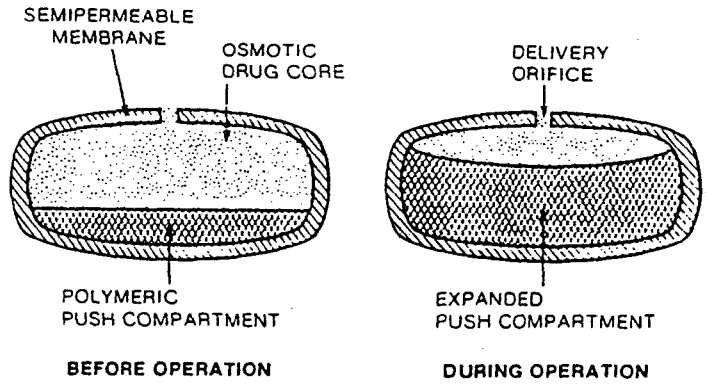
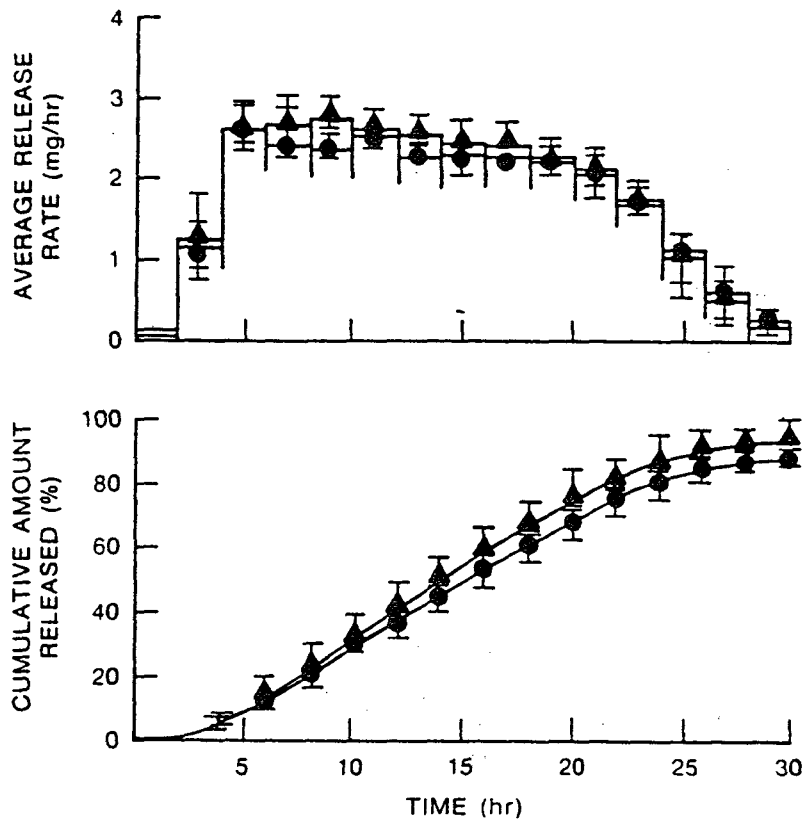


Figure 11



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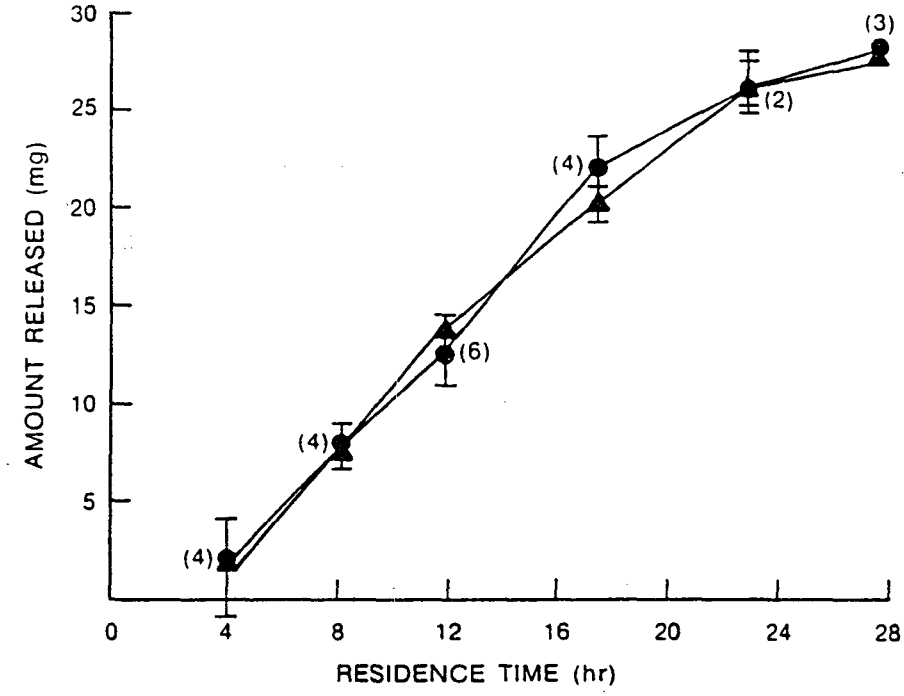

Figure 13

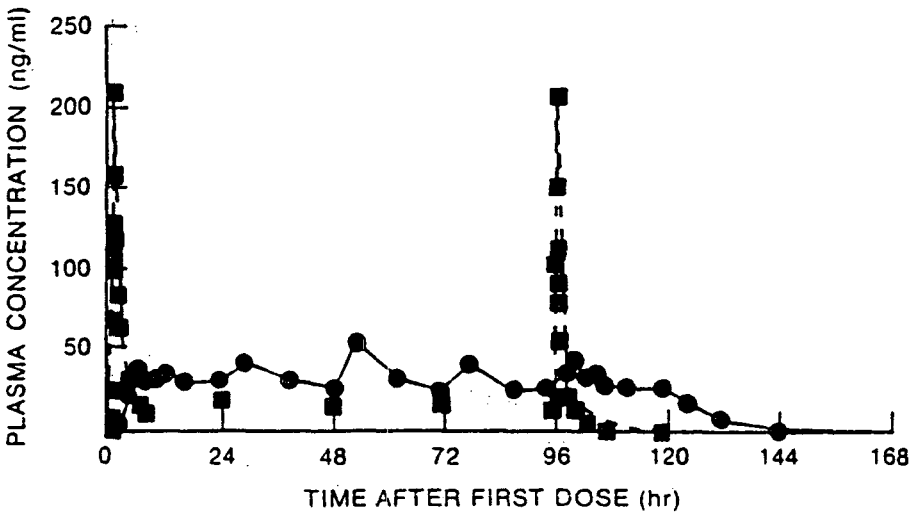

Figure 14

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