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REVIEW ARTICLE

Osmotically Controlled Oral Drug Delivery*

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ABSTRACT

It is advantageous to deliver some drugs with short half-life, and which are to be given frequently for chronic ailments, in the form of controlled-release (CR) formulations. The orally administered drugs, in the form of conventional matrix or reservoir type formulations, pose problems of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drug(s) from these systems is affected by the hydrodynamic conditions of the body. Osmotically controlled drug delivery systems utilize the principles of osmotic pressure for the controlled delivery of active agent(s). The release rate of drug(s) from these systems is independent of the physiological factors of the gastrointestinal (GI) tract to a large extent. In the present review, theory underlying the delivery of drugs from osmotic systems is presented. Different types of oral osmotic systems, their advantages over conventional matrix and reservoir types of systems, and their applications are also discussed. Finally, some of the limitations, adverse effects, and patent and market status of these systems are reviewed. These systems form a major segment of drug delivery products. Because of their advantages and strong market potential, it appears that the future of osmotic systems in rate-controlled oral drug delivery is promising.

Key Words: *Controlled drug delivery; Osmotic drug delivery; Osmotic pressure.*

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INTRODUCTION AND HISTORICAL BACKGROUND

Introduction

Oral ingestion is one of the oldest and most extensively used route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is little or no control over release of the drug, and effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. This kind of dosing pattern results in constantly changing, unpredictable, and often sub- or supratherapeutic plasma concentrations, leading to marked side effects in some cases. Moreover, the rate and extent of absorption of drug from conventional formulations may vary greatly, depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal (GI) tract, GI motility, and so on (1). Uncontrolled rapid release of drug may also cause local GI or systemic toxicity. Better dosage design and delivery can minimize many of these problems. Ideal oral drug delivery systems should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled-release (CR) delivery systems provide a uniform concentration/amount of drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. However, drug release from oral CR dosage forms may be affected by pH, GI motility, and the presence of food in the GI tract (2). An appropriately designed osmotically controlled oral drug delivery system (OCODDS) can be a major advance toward overcoming some of these problems. Drug delivery from these systems is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form (3).

Historical Background

It was in 1955 that Rose and Nelson utilized the principles of osmotic pressure in drug delivery for the first time (4). They described two systems, one that delivered 0.02 ml/day for 100 days and another that delivered 0.5 ml/day for 4 days, both for use in pharmacological research. A schematic diagram of their prototype device is shown in Fig. 1a. The device consists of three chambers: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. A semipermeable membrane (SPM) separates the salt and water chambers. The difference in osmotic pressure between the two compartments moves water from the water chamber into the salt chamber, across the membrane. The volume of the salt chamber increases because of this water influx, distending the latex diaphragm (separating the salt and drug chambers) and thus pumping drug out of the device. In 1971, Stolzenberg designed another osmotic system that was operationally similar to that of Rose and Nelson's system (5). Although both systems are useful for conducting labora-

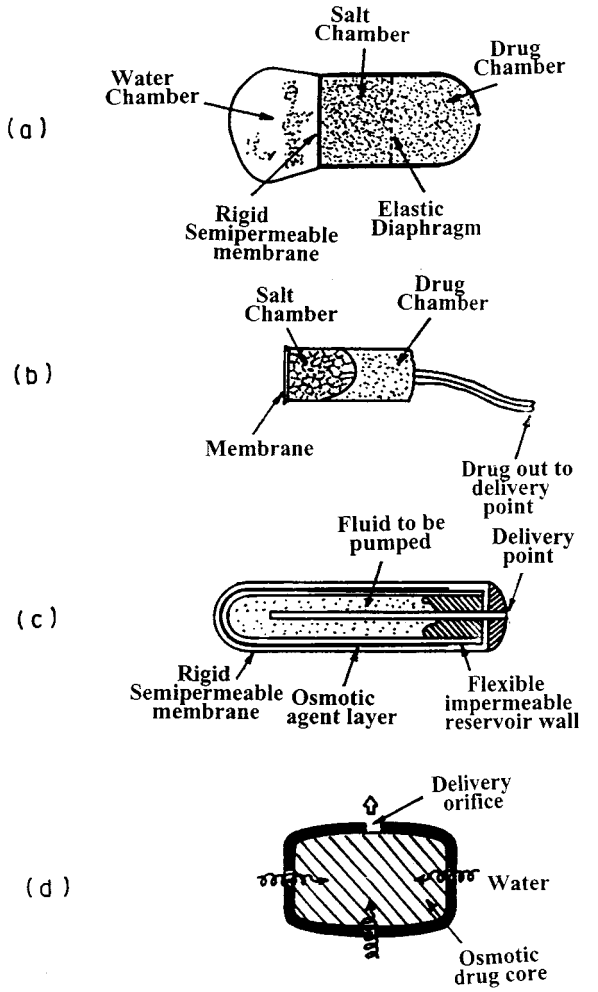

Figure 1. Cross-section of different osmotic dosage forms: (a) Rose-Nelson pump; (b) Higuchi-Leeper pump; (c) Theeuwes miniature osmotic pump; (d) elementary osmotic pump.

tory research, they have limited practical utility because of their complex design and difficulty in mass production.

In the 1970s, Higuchi and Leeper proposed a series of variations of the Rose-Nelson pump (6–8). One form of these types of pumps is illustrated in Fig. 1b. This device has no water chamber and is activated by water imbibed from the surrounding environment. Theeuwes further modified the Rose-Nelson pump (9) and developed a system shown schematically in Fig. 1c. In this system also, imbibition of the water from the surrounding environment activates the device. In the device of Theeuwes, the membrane forms the outer rigid casing. The device is loaded with the desired agent immediately prior to use. Small osmotic pumps of these forms are sold under the trade name ALZET® (Alza Corp., CA). The device has a volume of approximately 170 μl, and the normal delivery rate is 1 μl/hr.

OSMOTICALLY CONTROLLED ORAL DRUG DELIVERY

The osmotic systems discussed above have been used in investigational research only as they are not amenable to mass production because of their complex designs. This fact led to the development of OCODDSs.

System Types

Elementary Osmotic Pump

In 1975, Theeuwes further simplified the Rose-Nelson pump (10) and developed a system known as the elementary osmotic pump (EOP), which is shown schematically in Fig. 1d. In this device, an active agent, having suitable osmotic pressure, is compressed in the form of a tablet, which is then coated with a SPM, and a small orifice is created in the membrane. When this tablet comes in contact with the aqueous environment of the GI tract, the agent inside the tablet draws water through the SPM because of the osmotic pressure gradient and forms a saturated solution inside the device. As the membrane is nonextensible, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved, and only a solution-filled coating membrane is left. This residual dissolved agent continues to be delivered at declining rate until the osmotic pressure inside and outside the tablet are equal. Normally, the EOP delivers 60–80% of its contents at a constant rate, and there is a short lag time of 30–60 min as the system hydrates before zero-order delivery from the EOP is obtained (5).

Theory

The general expression for the solute delivery rate dM/dt from an EOP can be described by the following equation (10):

$$dM/dt = (A/h)Lp(\sigma\Delta\pi - \Delta\rho) \cdot C \quad (1)$$

where A and h are the membrane area and membrane thickness, respectively; Lp is the mechanical permeability; σ is the reflection coefficient; $\Delta\pi$ and $\Delta\rho$ are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system; and C is the concentration (or solubility, when excess solid is present inside the core) of compound in the dispensed fluid. As the size of the delivery orifice increases, hydrostatic pressure inside the system is minimized ($\Delta\pi > \Delta p$). Also, when the osmotic pressure of the formulation is large compared to the osmotic pressure of the environment, π can be substituted for $\Delta\pi$. Equation 1 then reduces to a much simpler expression in which constant K replaces the product $Lp\sigma$. After simplification, the following equation is obtained:

$$dM/dt = (A/h)K\pi \cdot C \quad (2)$$

The release rate defined by Eq. 2 remains zero order as long as the terms in the equation remain constant. The first three terms on the right-hand side of Eq. 2 can be maintained constant through proper selection and optimization of the SPM. Therefore, a constant release of drug from the device is maintained as long as excess solid agent is present inside the device to maintain both π and C in Eq. 2 at constant levels.

Factors Affecting the Release Rate

The following factors should be considered while designing an EOP. The factors discussed below are applicable to other type of OCODDS as well: solubility, osmotic pressure, size of delivery orifice, and membrane type and characteristics.

Solubility. It can be seen from Eq. 2 that the delivery rate of a drug from an osmotic pump depends to a large extent on the solubility of drug at saturation. Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml (11). However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might oth-

erwise appear to be poor candidates for an OCODDS. Some of examples are co-compression of the drug with excipients, which modulate the solubility of the drug within the core (12,13); use of swellable polymers in the core, which swells after absorbing water and pushes the poorly water soluble drug from the orifice in the form of a finely divided suspension (14); use of effervescent mixtures to speed up the release of poorly soluble drug from the orifice (15); use of various cyclodextrin derivatives to solubilize poorly water soluble drug (16,17); and so on. For ionic drugs, an alternative salt form can be used, as reported for oxprenolol (3). It was found that the hydrochloride salt of oxprenolol was too soluble to maintain a saturated solution and hence zero-order delivery for the anticipated delivery life of the dosage form. Subsequently, the succinate salt form was found to have the optimum solubility, and osmotic pumps were formulated with this salt form that gave extended release up to 24 hr.

Osmotic pressure. The next release-controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. For zero-order release, the π term in Eq. 2 must attain a constant value. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment (5). If a saturated solution of the drug does not possess sufficient osmotic pressure, an additional osmotic agent must be added to the core formulation. The osmotic pressure of soluble solutes is extremely high, as is evident from Table 1, which shows osmotic pressure of the commonly used solutes in CR formulations (18). In addition to these, potassium bicarbonate (19) and sodium bicarbonate (3) have also been used as osmotic agents. The addition of carbonate or bicarbonate salt to the drug chamber offers an advantage since the effervescent action prevents the precipitated drug from blocking the delivery orifice in the tablet (20).

Size of delivery orifice. Some of the methods to create a delivery orifice in the osmotic tablet coating are use of a mechanical drill (21), laser drilling (22), use of an apparatus with slidable punches (23), indentation that is not covered during the coating process (20), and use of leachable substances in the coating (24). The size of the delivery orifice must be smaller than the maximum size A_{max} to minimize the solute diffusion through the orifice. Also, 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. Large hydrostatic pressure can also lead to the deformation of the device, thereby resulting in unpredictable drug delivery.

Table 1

Osmotic Pressure of Saturated Solutions of Common Pharmaceutical Solutes

Compound or Mixture	Osmotic Pressure (atm)
Lactose-fructose	500
Dextrose-fructose	450
Sucrose-fructose	430
Mannitol-fructose	415
Sodium chloride	356
Fructose	335
Lactose-sucrose	250
Potassium chloride	245
Lactose-dextrose	225
Mannitol-dextrose	225
Dextrose-sucrose	190
Mannitol-sucrose	170
Sucrose	150
Mannitol-lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic · 12 H_2O	36
Sodium phosphate dibasic · 7 H_2O	31
Sodium phosphate dibasic · 12 H_2O	31
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic · H_2O	28

Source: From Ref. 18.

Mathematically, these two conditions can be expressed by $A_{min} \leq A_o \leq A_{max}$, where the cross-sectional area of the orifice A_o is larger than or equal to a minimum size and smaller than or equal to a maximum size. There are equations that can be used for estimating minimum cross-sectional area and maximum cross-sectional area (10).

Membrane type and characteristics. Recalling Eq. 2, which describes the volume flow, one can easily recognize the importance of the SPM in controlling release of the drug. The membrane must possess certain performance criteria (5), such as sufficient wet strength and water permeability. Moreover, it should be selectively permeable to water and should be biocompatible. The unique feature of the SPM utilized for an osmotic pump is that it permits only the passage of water into the unit, thereby effectively isolating the dissolution process from the gut environment. The in vivo release rate of the system is therefore independent of its position in the GI tract (3). Also, because of the semipermeable characteristics of the membrane, ions are not readily exchanged across it; therefore, the release of the drug from these systems is independent of pH of the surrounding environment (10).

Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. Examples include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and others (18). Among cellulosic polymers, cellulose acetate membranes are mostly used in this application because their water permeability is relatively high, and it can be adjusted easily by varying the degree of acetylation of the polymer (25). The permeability of these membranes can be increased further by adding plasticizers to the polymer, which increases the water diffusion coefficient, or by adding hydrophilic flux enhancers, which increase the water sorption of the membrane. A few examples of hydrophilic flux enhancers used are polyethylene glycols 300, 400, 600, 1500, 4000, and 6000 (18).

Other polymers that have been used are ethylcellulose (26) and Eudragits (27). The water permeability of pure ethylcellulose membrane is very low, only about 1/10th of the values obtained from the cellulose acetate films, which may explain the limited use of ethylcellulose for coating osmotic formulations (28). Lindstet and coworkers (29,30) added hydroxypropylmethylcellulose (HPMC) to the film composition to improve the permeability of the ethylcellulose membranes. They coated the cores of potassium chloride with a mixture of ethylcellulose and up to 24% HPMC and showed that the tablets released their content mainly through osmotic pumping.

Generally, in osmotic pumps, the SPM must be 200–300 μm thick to withstand the pressure within the device (20). This can result in slow release in the case of drugs exhibiting low osmotic pressure. This problem can be overcome by using coating materials with high water permeabilities. Another approach that can be explored is to use a multilayer composite coating around the tablet. The first layer is a thick microporous film that provides the strength required to withstand the internal pressure, while the second layer is a relatively thin SPM that produces the osmotic flux (31). Another variation in the membrane includes the use of biodegradable hydrophobic substances as the wall materials (32).

A new coating has been developed for osmotic drug delivery that offers significant advantages over the membrane coatings used in conventional osmotic tablets (33). These new coatings have an asymmetric structure, and the coating consists of a porous substrate with several unique characteristics. High water fluxes can be achieved, facilitating osmotic delivery of drugs with low solubility and making a higher release rate possible. In one study, capsules having asymmetric structures were developed for osmotic delivery of drugs having moderate to high aqueous solubility (34). The capsule wall was made by a phase inversion process in which the membrane structure was precipitated on stainless steel mold pins by a dip-coating process. The resulting wall of the capsule was composed of a thin, dense region supported on a thicker porous region. In vitro release of the model drugs from these types of systems was found to be dependent on capsule shell composition and the core formulation (35).

Multichamber Osmotic Pumps

The EOP is simple to design and is well suited for formulation and delivery of drugs with intermediate water solubility (5). However, there are many drugs with either poor or high water solubility. This problem led to the development of mutichamber osmotic pumps. These multichamber osmotic pumps can be further divided into two main categories depending on whether one of the chambers expands into the other (push-pull osmotic pump, PPOP) or whether the chambers are rigid and maintain their volume throughout the operational life of the device.

Push-Pull Osmotic Pump

The PPOP, which was developed by Alza Corporation (36), is shown schematically in Fig. 2a. The system con-

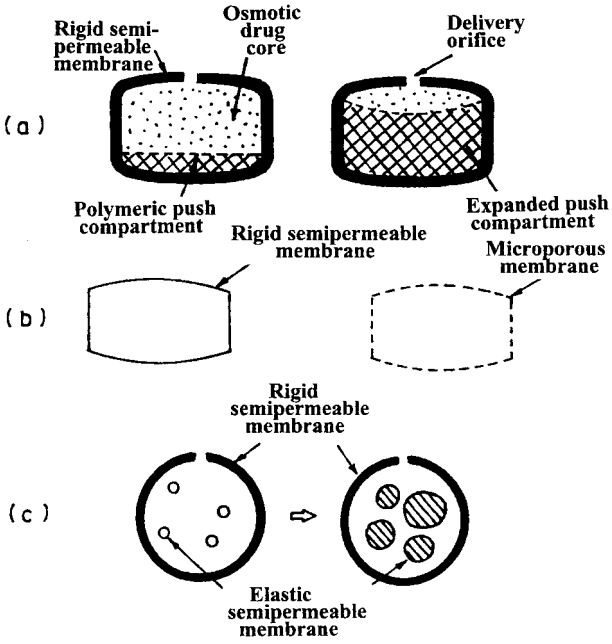

Figure 2. Modifications of elementary osmotic pump before operation and during operation: (a) push-pull osmotic pump; (b) controlled-porosity osmotic pump; (c) modified osmotic pump for delivering insoluble drugs.

sists of two compartments separated by an elastic diaphragm (optional). The upper compartment contains the drug and is connected to the outside environment via a small delivery orifice. A polymeric osmotic agent is present in the lower compartment and has no delivery orifice. The drug layer accounts for 60–80% of the tablet weight, while the osmotic polymer layer accounts for 20–40% (37). When the device comes in contact with the aqueous environment, both the drug layer and the polymer layer imbibe water. As the lower compartment is devoid of any orifice, it expands and pushes the diaphragm into the upper chamber, thereby delivering the drug via the delivery orifice. The basic mass delivery rate expression can be defined by Eq. 2. Several other equations are also involved that govern the various parameters defining the total mass delivery rate (37).

Osmotic Pumps with Nonexpanding Second Chamber

The second group of multichamber osmotic pumps consists of systems containing a nonexpanding second chamber (20). This group can be divided further into two subgroups that depend on the functions of the second chamber. In one type, the drug solution gets diluted in the second chamber before leaving the device. This is particularly useful in cases in which a saturated solution of the drug may cause irritation of the GI tract. The second category consists of two separate EOP tablets formed into a single tablet. The device releases both the drugs simultaneously. In another example of this type of device, one chamber contains an osmotic agent, and the second chamber contains the drug. When the system comes in contact with the aqueous environment, both the chambers imbibe water through the SPM. The solution of the osmotic agent formed in the first chamber is delivered to the drug chamber via the connecting hole, where it mixes with the drug solution before coming out of the microporous membrane that forms the part of SPM surrounding the drug chamber. Relatively insoluble drugs can be delivered by formulating them in this type of device (20).

Miscellaneous Types of Osmotically Controlled Oral Drug Delivery Systems

Controlled Porosity Osmotic Pump

Recently, osmotic tablets have been developed in which the delivery orifice is formed by incorporation of a leachable water-soluble component in the coating material (11,13,18,24,26,38,39). Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, and an osmotic pumping system results, as shown in Fig. 2b. Subsequently, water diffuses into the core through the microporous membrane, setting up an osmotic gradient and thereby controlling the release of drug. Some of the pore-forming additives that can be used are sodium chloride, urea, and potassium chloride (18). The release rate from these types of systems has been reported to be dependent on the coating thickness, level of soluble components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane, but is independent of the pH and agitation of the release media (24).

Modified Osmotic Pump for Insoluble Drugs

In the modified osmotic pump for insoluble drugs (Fig. 2c), particles of osmotic agent are coated with an elastic semipermeable film. These particles are then mixed with the insoluble drug and compressed in the form of a tablet, which is then coated with an SPM, and an orifice is created in the membrane. After coming in contact with the aqueous environment, water is drawn through the two membranes into the osmotic agent particles, which swell and hydrostatically push the insoluble drug via the delivery orifice (40).

Multiparticulate Delayed-Release System

In the multiparticulate delayed-release system, pellets containing drug with or without osmotic agent are coated with an SPM-like cellulose acetate. On contact with an aqueous environment, water penetrates into the core and forms a saturated solution of soluble components. The osmotic pressure gradient induces a water influx, resulting in a rapid expansion of the membrane, leading to the formation of pores. The osmotic ingredient and the drug are released through these pores according to zero-order kinetics. In a study by Schultz and Kleinebudde (41), lag time and dissolution rates were found to be dependent on the coating level and osmotic properties of the dissolution medium. Furthermore, dissolution characteristics were found to be influenced by such membrane components as incorporation of plasticizer and its concentration and lipophilicity (42).

Monolithic Osmotic Systems

In the monolithic osmotic system, a simple dispersion of a water-soluble agent is made in a polymer matrix. When the system comes in contact with the aqueous environment, water imbibition by the active agent takes place

that ruptures the polymer matrix capsule surrounding the agent, thus liberating it to the outside environment. Initially, this process occurs at the outer environment of the polymer matrix, but it gradually proceeds toward the interior of the matrix in a serial fashion. However, this system fails if more than 20 to 30 vol% of the active agent is incorporated into the device because, above this level, significant contribution from the simple leaching of the substance takes place (43).

Evaluation

In Vitro Delivery Rate Measurements

The in vitro delivery rate of drug(s) from the OCODDS can be determined by a number of methods. In one of the methods, osmotic pumps are placed in loosely woven mesh bags of nylon or polyethylene, and the bags are attached to a rod, which in turn is attached to a horizontal transfer arm connected to a vertically reciprocating shaker. The arms containing several systems are then positioned over test tubes/containers containing a known amount of release media. The temperature of the medium is kept constant (37°C ± 0.5°C) by keeping the containers in a temperature-controlled water bath. When the shaker is started, the systems are immersed in the release media and stirred vertically at an amplitude of 2.5–3.0 cm at a frequency of 0.5 cycle/sec. After a fixed period (1–2 hr), the systems are removed from the first receptor container and moved (either manually or automatically) to a second receptor container, and the stirring is resumed. This procedure continues until the systems are tested for a fixed period (12–24 hr). Each receptor solution is then analyzed for the drug content. The release rate (mg/hr) is determined by dividing the amount of drug in each container by the time (in hours) of the test interval. The cumulative amount released is determined by adding the amounts from the various intervals. This is a method first used by Theeuwes to determine the differential release rates of potassium chloride and phenobarbital sodium from EOP (10), and it is still followed by a number of workers (3,5,37). The method can be used to compare different dissolution media, including simulated gastric fluid for 2 hr followed by simulated intestinal fluid for the remainder of the experiment. Thus, the effect of pH variation on the release rate can be determined.

Conventional USP dissolution apparatus 1 and 2 can also be employed to determine the release profile (3, 21,37). A flow-through apparatus has been utilized to study the release characteristics of nifedipine from osmotic pumps (44). In vitro release of phenylpropanolamine hydrochloride (PPA) from the oral osmotic pump system and a marketed long-acting product (spansules) was compared using a calibrated Ghannam-Chien diffusion system as the dissolution apparatus (45). Ramadan and Tawashi (46) conducted the studies to see the effects of hydrodynamic conditions and orifice delivery size on the drug release rate from an EOP of potassium chloride. Release characteristics were examined using the USP basket method at different rotation speeds and a Turbula shaker mixer® (Wiley A. Bachofen, Basel, Switzerland) with an equivalent volume of distilled water (200 ml) at 37°C. In this investigation, drug release was found to be dependent on the rotation speed of the particular apparatus. Moreover, the release rate was considerably higher under the turbulent conditions in the Turbula mixer. Orifice size was not a significant factor under laminar hydrodynamic conditions.

In Vivo Delivery Rate Measurements

As the environment in the intestinal tract of the dog is very similar to that of human beings in terms of both pH and motility, dogs have been used widely for in vivo delivery rate measurement of drug(s) from the OCODDS and also to establish in vitro/in vivo correlation (37). Gastrointestinal transit of an osmotic tablet was measured by radiolabeling an intact osmotic tablet (placebo osmosin tablets) and monitoring the movement of the unit in the GI tract of young and old healthy volunteers using gamma scintigraphy (47). The units were observed to move through the GI tract at about the same rate as the released contents, arriving at the cecum about 7 hr after dosing.

Advantages and Applications

Apart from the general advantages shared by conventional CR systems, OCODDSs have several other unique advantages, such as the following:

- Delivery of drug can be designed to follow zero-order kinetics; thus, better control over their in vivo performance is possible. As discussed, as long as the terms on the right-hand side of Eq. 2 are maintained constant, the release of the drug from the OCODDS is constant. Figure 3 shows the results of a study in which three different formulations of nifedipine (conventional, extended release, and an osmotic pump) were evaluated for their in vitro release profile using a flow-through dissolution apparatus (44). It was observed that the release from the osmotic system was constant and prolonged for up to 24 hr.
- The drug release from the OCODDS is independent of the gastric pH and hydrodynamic conditions,

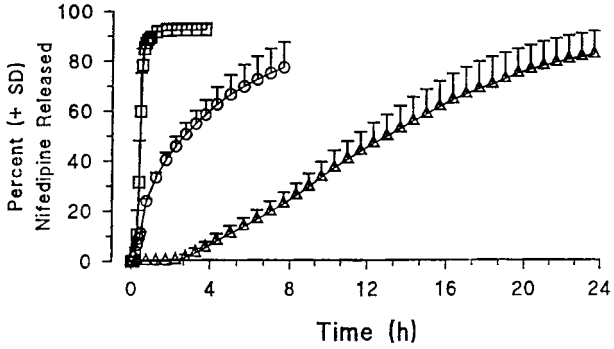

Figure 3. Cumulative percentage drug release profiles of three types of nifedipine formulations in 0.05 M phosphate buffer using flow-through dissolution apparatus: □, 10 mg conventional-release formulation; ○, 20 mg extended-release formulation; and △, 30 mg osmotic pump. (Reprinted from Ref. 44 by permission of Marcel Dekker, Inc., New York, NY.)

which is mainly attributed to the unique properties of the SPM employed in the coating of osmotic formulations (3,10). Figure 4 shows the nifedipine release from a PPOP in artificial gastric and intestinal fluid (37). The release profiles in both media are similar and are not affected by the pH.

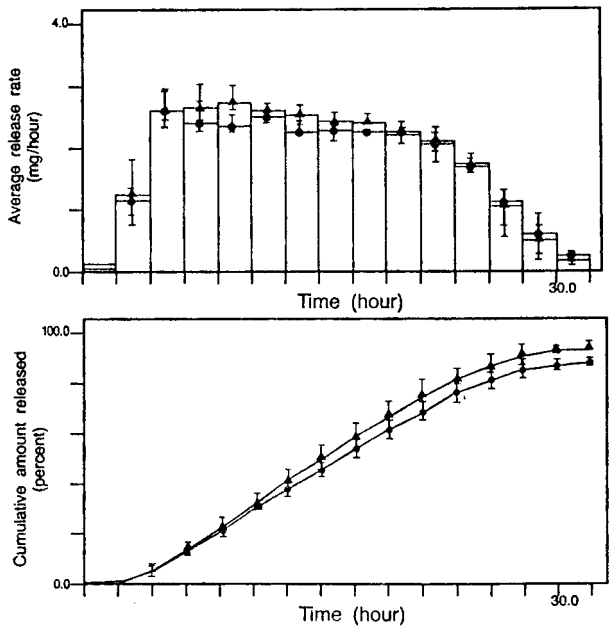

Figure 4. Average zero-order release rate and cumulative amount released for nifedipine GITS: ▲, artificial gastric fluid ($n = 5$); ●, artificial intestinal fluid ($n = 5$); I = range. (Reprinted from Ref. 37 by permission of Excerpta Medica, Inc.)

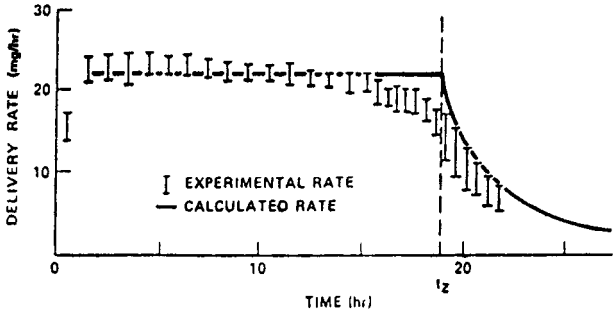

Figure 5. Comparison of experimental and calculated release rates of potassium chloride from elementary osmotic pumps in water. (Reprinted from Ref. 10 by permission of the American Chemical Society and American Pharmaceutical Association.)

It is possible to attain higher release rates than with conventional diffusion-based drug delivery systems (5).

The delivery rate of drug(s) from these systems is highly predictable and can be programmed by modulating the terms in Eq. 2. Figure 5 shows the experimental and calculated release rate of potassium chloride from an EOP in water (10,48). It is evident from the figure that the release rate from osmotic systems is programmable, and the experimental values are close to the calculated release rate.

Drug release from the OCODDS exhibits significant in vitro/in vivo correlation within specified limits. Figure 6 shows the cumulative amount of nifedipine released from a PPOP in vitro and in the GI tract of dogs as a function of time (37). The figure

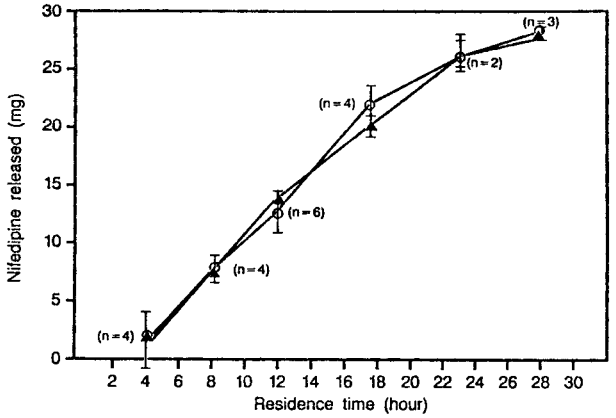

Figure 6. Comparison of in vivo and in vitro cumulative amount released for nifedipine GITS: ○, in vivo release, n as indicated; ▲, in vitro release, $n = 4$; I = standard deviation. (Reprinted from Ref. 37 by permission of Excerpta Medica, Inc.)

shows that the amounts released are almost identical; therefore, one can expect that the release behavior of the dosage form will be satisfactory in humans and can be correlated with the release behavior in vitro. In an another study, a significant in vitro/in vivo correlation was reported for a verapamil oral osmotic system (49).

Drug release from the osmotic systems is affected minimally by the presence of food. Figure 7 shows the fraction absorbed, in human volunteers, of pseudoephedrine from a GITS (Gastrointestinal Therapeutic System) formulation of pseudoephedrine and bromopheniramine under fed and fasted conditions (50). The fraction absorbed was nearly identical in both the conditions, demonstrating that the delivery and absorption of pseudoephedrine is not affected by food.

Several osmotic pumps for metoprolol have been developed that provide zero-order drug delivery for almost 24 hr (3). In a crossover double-blind study, a conventional sustained-release formulation of metoprolol was compared with an osmotic pump. The pharmacokinetic behavior of the osmotic pump system was found to be consistent with its in vitro release profile in that the formulation produced constant plasma levels over longer periods compared with the commercial slow-release formulation. It was also found that the osmotic formulation of metoprolol produced more uniform hemodynamic response compared to conventional slow-release tablets (51).

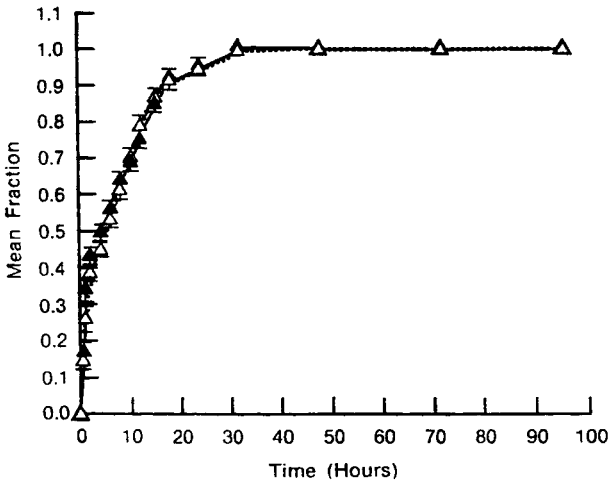

Figure 7. Fraction absorbed graph for pseudoephedrine from a GITS system under fed (▲) and fasted (△) conditions. (Reprinted from Ref. 50 by permission of the American Chemical Society and American Pharmaceutical Association.)

Oral osmotic systems have also been developed for oxprenolol (3). A multiple-dose comparative study was conducted to compare the pharmacokinetic and pharmacodynamic behavior of polymer-matrix and osmotic formulations of oxprenolol in healthy human volunteers. It was found that the osmotic systems considerably reduced the beta-adrenoceptor blockade and exercise heart rate when compared with the polymer matrix tablets (52).

Three PPOPs of nifedipine were developed that delivered drug for approximately 24 hr (37). When relative bioavailablity of nifedipine GITS was compared with conventional CR tablets (Adalat Retard), it was found that both products were bioequivalent with respect to the extent of absorption of nifedipine, but the GITS formulation was found to have better CR properties than the Adalat Retard product, making it suitable for once daily administration (53).

In another study, administration of an OROS formulation of amitriptyline hydrochloride resulted in much more consistent plasma concentrations of the drug and its metabolite compared to the immediate-release (IR) formulation (54).

Two osmotically driven CR systems of indomethacin were evaluated in 12 healthy subjects in a multiple-dose crossover study. Following equivalent daily doses, less frequent dosing of both CR forms was required, and the plasma concentration profile was more uniform than those following a conventional capsule regimen (55).

Prazosin GITS was found to give more sustained plasma levels, which were virtually constant for almost 24 hr, when compared with conventional IR and sustained-release formulations (56).

The steady-state pharmacokinetics of a salbutamol oral osmotic system (Volmax) was compared with a repeat action tablet. It was found that the drug release was more controlled from Volmax tablets compared to the repeat action tablets (57).

CR osmoregulatory sinosules of chlorpromazine hydrochloride (CPZ.OR.CR) were prepared that released the drug with zero-order kinetics. When tested for in vivo performance in Indian dogs and compared with the performance of conventional tablets, it was found that the CPZ.OR.CR maintained a uniform blood level around the peak level compared to the conventional tablet and resulted in significantly higher bioavailablity of chlorpromazine (58). Another GITS system capable of zero-order delivery of chlorpromazine hydrochloride was developed, and various parameters that affected the release rate were described (59).

The desirable release profile from osmotic systems helps to achieve better therapeutic control, as demon-

Table 2

Patents on Some Drugs Formulated in the Form of Elementary Osmotic Pumps

Year	U.S. Patent Number	Drugs
1981	4,265,874	Indomethacin formulation
1981	4,305,927	Acetazolamide formulation
1984	4,439,195	Theophylline formulation
1984	4,484,921	Theophylline formulation
1986	4,610,686	Haloperidol
1987	4,662,880	Pseudoephedrine and bromopheniramine
1988	4,732,915	Haloperidol
1988	4,751,071	Salbutamol formulation
1989	4,857,330	Chlorpheniramine
1991	4,986,987	Dimenhydrinate
1992	5,147,654	Buccal nicotine
1993	5,200,194	Mucosal delivery of antiplaque agents and nicotine
1998	5,776,493	Mucosal delivery of nystatin
1999	5,869,096	Covers mucosal osmotic device of levodopa

strated in a study in which it was found that the osmotic formulations of glipizide (glipizide GITS) were significantly more effective than the IR formulations in reducing fasting plasma glucose (FPG) levels. It was also suggested that glipizide GITS improves insulin sensitivity (60).

Ciprofloxacin hydrochloride was formulated in the form of an EOP, and the effects of various variables on the release rate were studied (61). The systems were found to release the drug in a controlled manner and were found to be appreciably stable when subjected to accelerated temperature studies.

Table 3

Patents of Some Drugs Formulated in the Form of Multichamber Osmotic Pumps

Year	U.S. Patent Number	Drugs
1986	4,612,008	Diclofenac sodium formulation
1988	4,765,989	Nifedipine and α blockers
1988	4,783,337	Calcium antagonists, ACE inhibitors
1989	4,812,263	Isradipine formulation
1989	4,837,111	Doxazosin formulation
1989	4,859,470	Diltiazem formulation
1990	4,904,474	Beclomethasone (colonic)
1990	4,948,593	Contraceptive steroids
1991	5,024,843	Glipizide formulation
1991	5,028,434	Nilvadipine
1992	5,160,744	Verapamil dosage form
1992	5,091,190	Glipizide dosage form
1993	5,185,158	Tandospirone
1993	5,190,763	Antiparkinson drugs
1993	5,192,550	Antiparkinson, antiepileptic drugs
1993	5,248,310	Beclomethasone (oral)
1996	5,545,413	Glipizide formulation
1997	5,591,454	Glipizide formulation

Table 4

Some Commercially Marketed Products

Product	Chemical	Developed by	Marketed by	Comments
Acutrim	Phenylpropanol-amine	Alza Corp.	Heritage Consumer Products	Introduced in September 1983 by Novartis Consumers Health, Inc. (NJ), as a 16-hr over-the-counter appetite suppressant. In August 1997, Novartis sold the rights to Heritage Consumer products.
Calan SR	Verapamil	Alza Corp.	G. D. Searle & Co., Skokie, IL	Used for the treatment of hypertension.
Ditropan XL	Oxybutynin chloride	Alza Corp.	Alza Corp. & UCB Pharma, Inc., Smyrna, GA	Approved for marketing in December 1998 for the treatment of overactive bladder.
Efidac/24	Pseudoephedrine	Alza Corp.	Novartis Consumers Health, Inc., NJ	Approved for sale in December 1992. It was the first over-the-counter 24-hr cold medication.
Efidac 24 Chlorpheniramine	Chlorpheniramine	Alza Corp.	Novartis Consumers Health, Inc., NJ	Cleared on November 18, 1994, and used for the treatment of allergies.
Efidac 24 Pseudoephedrine/ Brompheniramine	Pseudoephedrine and brompheniramine	Alza Corp.	Novartis Consumers Health, Inc., NJ	Approved in March 1996 and used as a once-a-day cold and allergy treatment.
Glucotrol XL	Glipizide	Alza Corp.	Pfizer, Inc., New York	Approved on April 26, 1994, for the treatment of non-insulin-dependent diabetes.
Minipress XL	Prazosin	Alza Corp.	Pfizer, Inc., New York	Approved for marketing in January 1992. In April 1989, the product was introduced in France by Pfizer as Alpress LP. In India, it is marketed by Pfizer, India, as Minipress XL.
Procardia XL	Nifedipine	Alza Corp.	Pfizer, Inc., New York	Approved in September 1989 and introduced on the market in October 1989.
Teczem	Enalapril and diltiazem	Merck & Co. Inc., NJ, and Hoechst Marion, Inc., MO	Hoechst Marion Roussel, Inc., MO	Approved on October 4, 1996. The product is a second-line hypertension therapy.
Tiamate	Diltiazem	Merck & Co., Inc., NJ	Hoechst Marion Roussel, Inc., MO	Approved on October 4, 1996, as a second-line hypertension therapy.
Volmax	Albuterol	Alza Corp.	Muro Pharmaceuticals, Inc., MA	Indicated for the relief of bronchospasm. Introduced overseas in 1987 by Glaxo Wellcome, Inc., NC. The product was granted U.S. marketing approval in December 1992. Licensed by Glaxo Wellcome to Muro Pharmaceuticals for U.S. promotion and marketed by that company since 1993.

A mucosal oral therapeutic system (MOTS), a CR osmotic system for oral cavity therapy, for nystatin was developed and was found to maintain a high salivary nystatin concentration throughout a 2-hr dosing interval when compared with a nystatin pastille (62).

Oral osmotic pumps for isosorbide dinitrate were developed and were found to release the drug at a relatively constant rate (63). Various factors, such as tablet weight, size of the delivery orifice, and thickness of the membrane, that influenced the drug release from these systems were also studied.

EOPs of nimesulide were prepared and compared for their in vitro release characteristics with conventional marketed tablets. It was found that the osmotic systems

Table 5

Products in Clinical Research

Product	Chemical	Developed by	Indication	Status
Cognex CR	Tacrine	Parke-Davis Research and Alza Corp.	Treatment of Alzheimer's disease	Phase III
OROS Hydromorphone	Hydromorphone	Knoll Pharmaceutical Co. and Alza Corp.	Treatment of chronic pain	Phase III
OROS Methylphenidate	Methylphenidate	Alza Corp.	Treatment of attention deficit–hyperactivity disorder in children	Phase II
Dilantin OROS	Phenytoin	Parke-Davis Research and Alza Corp.	Treatment of epileptic seizures	Phase I

gave prolonged and controlled release of nimesulide compared to the conventional tablets. The drug release from the osmotic systems was affected by the various formulation factors (64).

OCODDSs have been used successfully in veterinary medicine. Ivermectin was delivered to cattle at various controlled zero-order rates for 35 days via an orally administered, specially weighted osmotic pump (65).

Limitations and Adverse Effects

Osmotic delivery systems have yielded significant clinical benefits in a variety of therapeutic areas. Some systems have enhanced therapeutic efficacy due to increased convenience for users, while others have minimized the adverse effects of their active components. Still, some cases have been reported regarding the limitations and adverse effects of these types of systems.

During quality control of nifedipine GITS tablets, it was observed that several batches showed different release patterns of the drug. Magnetic resonance imaging (MRI) was used to evaluate the GITS tablets. It was found that nonuniform coating around the tablet produced different membrane thicknesses, which was responsible for differences in release patterns among different batches (66).

There have been some incidences of GI obstruction in patients with preexisting peptic ulcer disease and strictures who were receiving nifedipine GITS tablets for control of hypertension (67,68). It was postulated that the inert ingredient of the tablet, which remains intact during transit through the GI tract and normally is excreted in the feces, might be responsible for this adverse phenomenon.

Another case was reported for Osmosin® (indomethacin OROS), which was first introduced in the United Kingdom in early 1983. A few months after its introduction, frequent incidences of serious gastrointestinal reactions were observed by the Committee on the Safety of Medicines, and Osmosin was withdrawn in August 1983 (69). When the adverse reaction profile of Osmosin was compared with those of other indomethacin-containing products, it was found that serious GI reactions (hemorrhage and perforation) occurred more commonly with Osmosin than with other indomethacin-containing products. Various explanations were given for the apparent toxicity associated with Osmosin, including the effects of potassium chloride (osmotic agent) used in the formulation, the possibility of high local concentrations of indomethacin and potassium chloride released from the device in the guts of patients with GI stasis, the adhesive properties of the hydrophilic color coating, the mechanical effects of the device itself, or a combination of several such factors.

Patent and Market Status

There were 240 U.S. patents on osmotic drug delivery until December 1993, of which more than 50% were for oral systems (20). We recently completed a patent survey and found that most of the patents related to osmotic devices are assigned to Alza Corporation. Some of the other big companies active in this field are Pfizer, Merck, and Novartis.

Table 2 gives the list of patents related to specific drugs formulated in the form of EOPs. Table 3 gives a list of multichamber osmotic device patents related to specific drugs. Some of the products on the market and in various phases of clinical research are shown in Tables 4 and 5, respectively (70,71).

CONCLUSIONS

Drug delivery using principles of osmotic pressure is a versatile technology that can be used as an experimental

tool to determine important pharmacokinetic parameters of drugs. The data from these experiments can be used in the development of optimized drug delivery systems. At the same time, controlled and constant oral delivery of drugs can be achieved using these systems as drug delivery tools. Various types of oral osmotic systems and their advantages over conventional CR systems were reviewed briefly here. The release of drug(s) from these types of systems is governed by factors such as solubility and osmotic pressure of the core component(s), membrane nature, and size of the delivery orifice. By judicious choice of formulation and processing factors, these systems are amenable to deliver drugs of diversified nature at a preprogrammed rate. A survey of patent and marketed formulations revealed that these systems form a major segment of drug delivery products. In the present, when development of a NDDS is looked on as a fruitful business, the development of OCODDSs has a strong market potential, as shown by the number of marketed products and number of patents granted in the last few years.

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