

An Update on Osmotic Drug Delivery Patents

Aditya M. Kaushal and Sanjay Garg*

Patents contain a large part of what scientists know about osmotic drug delivery. Because patents are difficult to read, understand, and analyze, they are often neglected as a stimulus to creativity and a source of information. The objective of this article is to review the patent literature about the various types of osmotic drug delivery systems with an emphasis on their structural design and technology. The use of specialized coatings and processing improvement techniques also is discussed.

Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed. Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reach its site of action—hence the role of drug delivery technologies. Scientists are pursuing the discovery and development of new molecules that have better absorptive and pharmacokinetic properties. Nevertheless, many existing and new molecules provide challenges of poor pharmacokinetics (e.g., short biological half life). Drug delivery systems such as oral controlled-release dosage forms, transdermal patches, and implants are used to overcome these chal-

lenges. Although the cost of these drug delivery technologies is considerable, it is substantially less than the cost of developing a new molecule. Hence, a continued interest exists in developing novel drug delivery systems for the temporal and spatial delivery of active agents.

Among the aforementioned technologies used to control the systemic delivery of drugs, osmotic drug delivery is one of the most interesting and widely applicable. Osmotic drug delivery uses the osmotic pressure of drugs or other solutes (called *osmagents*) for controlled delivery of drugs. Osmotic drug delivery has come a long way since Australian pharmacologists Rose and Nelson developed an implantable pump in 1955. This area of drug delivery has expanded into oral delivery and implants for humans and animals.

Most knowledge about osmotic drug delivery, however, is found only in patents. Patents are hard to read, analyze, and judge because of the peculiar style in which they are written, and as a result, they are an often-neglected stimulus of creativity and source of information (1). The objective of this article is to review the patent literature about osmotic drug delivery. Only US patents have been included, and the year of the patent's issue is in parentheses. The authors have attempted to include all areas of osmotic delivery; however, because of the lack of any one basis for classification, few of the classes overlap in terms of their design, use, or applicability.

Advantages of osmotic drug delivery

Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery (2). The following advantages have contributed to the popularity of osmotic drug delivery systems:

- The delivery rate of zero-order (which is most desirable) is achievable with osmotic systems. Both in vitro and in vivo experiments have established this fact.
- Delivery may be delayed or pulsed, if desired.

- For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
- A high degree of in vivo–in vitro correlation (IVIVC) is obtained in osmotic systems.
- The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract (GIT).

These advantages are attributed to the design of osmotic systems. Environmental contents (e.g., GIT fluids) do not gain access to the drug until the drug has been delivered out of the device. Osmotic systems have a high degree of IVIVC because the factors that are responsible for causing differences in release profiles in vivo and in vitro (e.g., variable pH, agitation) affect these systems to a much lesser extent.

Osmotic drug delivery devices

Osmotic delivery devices have changed considerably since Rose and Nelson developed the first osmotic pump for delivering drugs to animals. From complex implantable devices to simple tablets, the extent of simplification and miniaturization has been remarkable. The osmotic delivery devices of today not only deliver drugs with moderate solubility, but also are capable of delivering drugs with solubility extremes. Furthermore, devices that deliver drugs as liquids (to deliver insoluble drugs and to enhance permeability) and that dispense subsaturated solutions of drugs are noteworthy developments.

In the following text, osmotic systems have been classified on the basis of their structural design and function.

Pulsatile drug delivery. Delivering a drug in one or more pulses is sometimes beneficial, from the required pharmacological-action point of view. Mechanical and drug solubility-modifying techniques have been

Aditya M. Kaushal is a PhD scholar at the Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER). Sanjay Garg, PhD, is an associate professor at the School of Pharmacy, University of Auckland, Auckland, New Zealand, tel. +64 9 373 7599 ext. 82836, fax +64 9 367 7192, sgarg@auckland.ac.nz.

*To whom all correspondence should be addressed.

implemented to achieve the pulsed delivery of drugs with an osmotic system. Also, the pulsed delivery of agents for oral and implantable devices has been mentioned in patent literature.

Solubility modulation for pulsed release. A series of patents was issued to Alza Corporation (Palo Alto, CA) for pulsed delivery, whereby the solubility modulator was used to control the drug release of a variety of agents. Patents 4751071 (1988), 4777049 (1988), and 4851229 (1989) describe the pulsed delivery of salbutamol sulfate. The composition described in the patents comprised the drug (salbutamol sulfate) and modulating agent (sodium chloride). The amount of sodium chloride that was present in the composition was relative to the amount of salbutamol but was less than the amount needed for the sodium chloride to maintain saturation in a fluid that enters the osmotic device. The device is useful for dispensing salbutamol at a substantial zero-order rate with a pulsed release at the end of the delivery period.

Pulsed delivery is based on drug solubility. Salbutamol's solubility is 275 mg/mL in water and 16 mg/mL in a saturated solution of sodium chloride. Sodium chloride's solubility is 321 mg/mL in water and 320 mg/mL in a saturated solution. These values show that the solubility of the drug is a function of the modulator concentration, whereas the modulator's solubility is largely independent of the drug concentration.

The modulating agent in this case can be a solid organic acid, an inorganic salt, or an organic salt. The modulating agent: drug ratio may be varied to determine the period of zero-order release and the start of pulsed release. For example, altering the drug:modulator ratio from 1:5 to 1:9 changes the period of zero-order release from 7 to 16 h. After the period of zero-order release, the drug is delivered as one large pulse. Other drugs that were reported to have a similar delivery include terbutaline and oxyprenolol (Patent 4751071 [1988]). Figure 1 shows the release-rate pattern of salbutamol from a solubility-modulated osmotic pump.

Multiparticulate pulsatile drug delivery system. Pulsatile systems based on multiparticulates for oral administration are described in Patents 5508040 (1996) and 5260068 (1993) issued to Andrx Pharmaceuticals (Fort Lauderdale, FL). The delivery system can be a capsule or tablet composed of a large number of pellets consisting of two or more pellet or particle populations. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. A water-permeable, water-insoluble polymer film encloses each core. A hydrophobic water-insoluble agent that alters permeability (e.g., a fatty acid, wax, or a salt from a fatty acid) is incorporated into the polymer film. The rate at which

water passes through to the core and drug diffuses out of the core causes the film coating of each pellet population to differ from any other pellet coating in the dosage form. The osmotic agent dissolves in water, which causes the pellet to swell and thereby regulate the rate of diffusion of drug from the dosage form. The effect of each pellet population releasing its drug into the environment sequentially provides a series of pulsatile administrations of the drug from a single dosage form. Coating thickness may also vary among pellet populations.

Furthermore, in special cases, all of the therapeutic agent in the dosage form may be found in a single population to provide a single pulse, which can be delayed by the release-controlling coating. The delivery of diltiazem from such a system was reported in Patent 5508040.

Pulsatile delivery based on an expandable orifice. Patents 5318558 (1994) and 5221278 (1993) assigned to Alza claim the pulsatile delivery of agents from osmotic systems based on the technology of an expandable orifice. The system is in the form of a capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. The delivery orifice opens intermittently to achieve a pulsatile delivery effect. The orifice forms in the capsule wall, which is constructed of an elastic material. As the osmotic infusion progresses, pressure rises within the capsule, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of drug through the orifice essentially stops, but when the elastic wall is stretched beyond its threshold because of increased pressure, the orifice expands sufficiently to allow drug release at a required rate. Elastomers such as styrene-butadiene copolymer can be used. A capsule designed for implantation can deliver drug intermittently at intervals of 6 h for 2 days.

Pulsatile delivery by a series of stops. Patent 5209746 (1993) also assigned to Alza describes an implantable capsule for pulsatile delivery. The capsules contain a drug and a water-absorptive osmotic engine that are each placed in compartments separated by a movable partition. Pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placement of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. Reports document that porcine somatotropin has been delivered from such a system (Patent 5209746).

Delayed-delivery osmotic devices. Because of their semipermeable walls, osmotic devices inherently show a lag time before

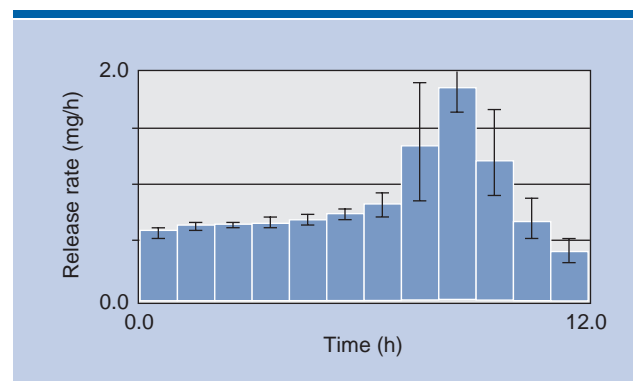


Figure 1: Release rate of salbutamol sulfate from a solubility-modulated osmotic device.

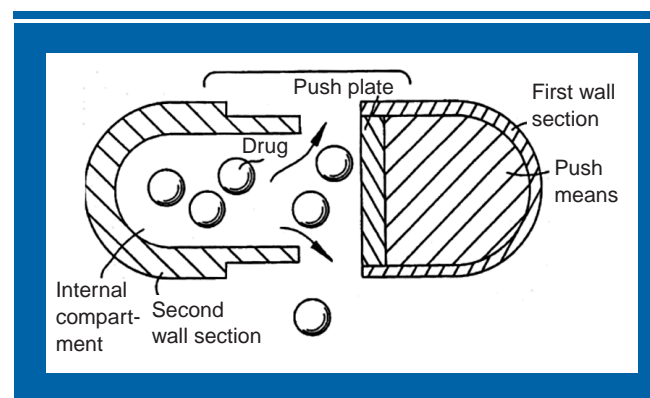


Figure 2: A delayed-release telescopic capsule releasing contents after expansion.

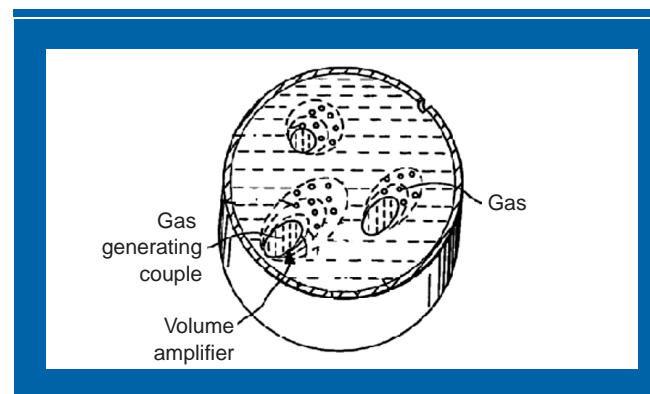


Figure 3: An osmotic delivery device with a volume amplifier.

drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drugs (e.g., drugs for early morning asthma or arthritis) may be beneficial. The following text describes other means to further delay drug release.

Telescopic capsules for delayed release. Patents 5531736 (1996), 5443459 (1993), 5498255 (1995), 5312390 (1994), 5312388 (1994), and 5223265 (1993) assigned to Alza describe fluid-imbibing dispensing devices for the immediate and extended delivery of an active agent during a prolonged period of time. The dispenser comprises a housing that has first- and second-wall sections in a slideable telescoping arrangement (see Figure 2). The housing maintains integrity in its environment of use. The device consists of two chambers; the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax-like material separates

the two sections. To assemble the delivery device, the desired active agent is placed into one of the sections by manual- or automated-fill mechanisms. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed into the closed end of the cap and the barrier layer exposed toward the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet, and vessel fit together tightly.

As fluid is imbibed through the housing of the dispensing device, the osmotic engine expands and exerts pressure on the slideable connected first and second wall sections. During the delay period, the volume of the reservoir containing the active agent is kept constant; therefore, a negligible pressure gradient exists between the environment of use and the interior of the reservoir. As a result, the net flow of en-

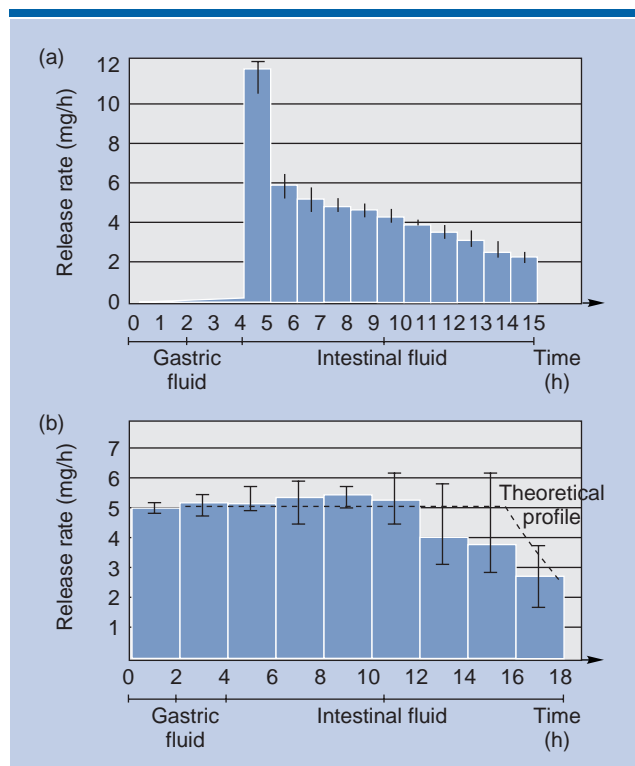


Figure 4: Release profile comparison of drug release from (a) a simple osmotic pump and (b) an effervescent osmotic pump.

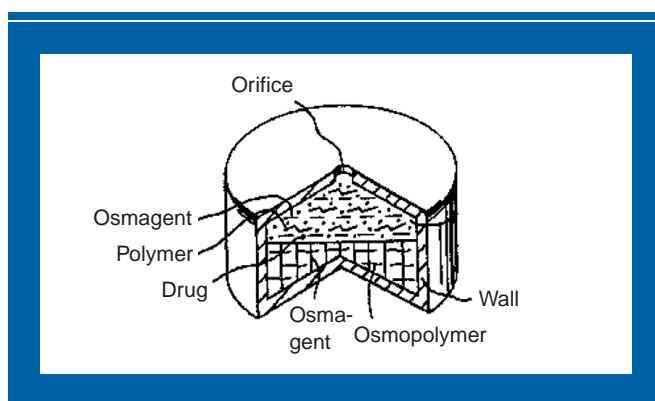


Figure 5: A push-pull osmotic pump in action.

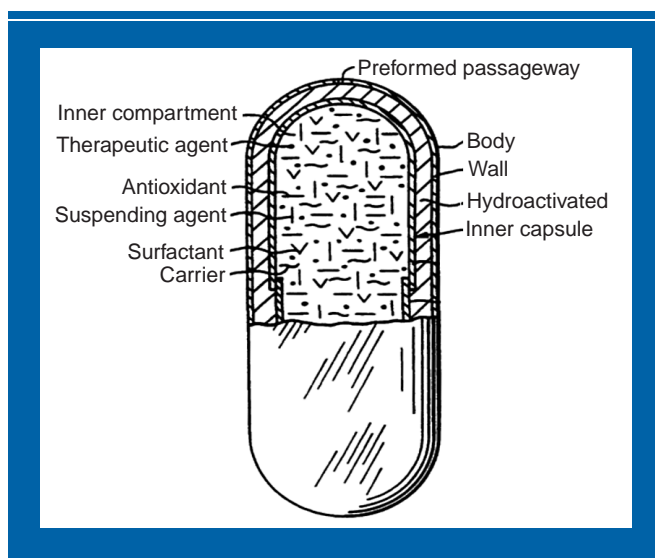


Figure 6: A hard capsule for delivery of liquids through osmotic pressure.

environmental fluid driven by the pressure to enter the reservoir is minimal, and consequently no agent is delivered for the period.

Delayed-release delivery based on multiple coatings. Patent 4976966 (1990) assigned to Alza describes an osmotic device that delivers fluid after a predetermined and con-

trollable time period. The osmotically driven pump can be miniaturized to a size suited for swallowing or implanting. The pump may be used to administer a drug in a fluid form after an initial activation period during which essentially no drug is administered. The basic components of the pump are a shaped semipermeable membrane (SPM) that encapsulates an osmotically effective solute and drug and a discharge port through which the drug is dispensed. A microporous outer cover surrounds the SPM and protects it from an external aqueous environment. A water-swallowable composition is positioned between the end of the SPM and the outer cover. As the pump is placed in an aqueous environment, water from the environment passes through the microporous portion of the outer cover into the water-swallowable composition. The water-swallowable composition absorbs water, expands, and in piston-like fashion displaces the outer cover, thereby exposing the SPM to the aqueous environment and activating the osmotic pump. The time required for the water-swallowable composition to absorb water, expand, and displace the outer cover provides an initial activation period during which essentially no drug is delivered by the pump. By suitably adjusting the membrane composition and structure, a predetermined activation period in the range of 3–18 h is achieved.

Enteric-coated and colon-targeted osmotic dosage forms. Patent 5536507 (1996) assigned to Bristol-Myers Squibb (New York, NY) describes a colon-targeted drug delivery system that is based on an osmotic mechanism. The three-component pharmaceutical formulation delivers more than 80% of the pharmacologically active substance to the large intestine. The first component includes the drug, microcrystalline cellulose, a pH-sensitive polymer (carboxymethyl cellulose, a sodium salt of a carboxymethyl cellulose), and an osmotic agent. The second component is a delayed-release coating that includes a water-insoluble polymer and a plasticizer. The third component is the enteric coating, which prevents drug release in the stomach, whereas the delayed-release coating, which is activated only upon the disruption of the enteric coating, does not allow any drug release in the small intestine.

Another patent issued to Alza, Patent 4705515 (1987), reports a dosage form that administers drug to the colon. The laminated wall of the device comprises three laminae: the first lamina consists of a composition that is permeable to fluid and essentially impermeable to drug; the second lamina is composed of the salt of a fatty acid and a polymer that is permeable to fluid; and the third lamina is an enteric coating. The device functions similarly to the one described previously.

Patents 5609590 (1997) and 5358502 (1994) issued to Pfizer Inc. (New York, NY) disclose the use of osmotic systems

for the pH-triggered burst of the active agent. The devices are designed for oral administration, either in the form of tablets or capsules. If used in tablets, the core consists of the drug, osmagent, diluents, and superdisintegrants. The tablets are coated first by SPM walls of insufficient thickness and then overcoated with the pH-triggered coating solution. The pH-triggered solution contains polymers such as cellulose acetate phthalate, pH-sensitive Eudragit grades, and insoluble polymers. The patent claims that using only pH-sensitive materials to achieve site-specific delivery is difficult because the drug often leaks out of the dosage form before it reaches the release site or desired delivery time. Typically 10–30% of the total beneficial agent is released prematurely. In addition, long time lags can be difficult to achieve before the release of the active ingredient after exposure to high pH because of rapid dissolution or degradation of the pH-sensitive materials.

Other benefits claimed by the invention include control of the break time with the thickness of the membrane and control of the tablet burst time by altering the ratio of pH-sensitive polymer to nondissolving material in the pH-triggered membrane coating. Another benefit is that, after the tablet is transferred into the intestinal buffer, the tablet burst time is independent of time spent in the gastric buffer. The device offers an advantage over conventional enteric coatings because it can control the tablet burst time after a change in the pH of the receptor solution, and it is more reliable in the high-pH conditions of the stomach. The delivery system also can be shaped in the form of a capsule, which can be made from materials similar to those used for the coating by filling the capsule with the desired active agents and then sealing it with the coating solution.

Volume amplifier delivery devices. One of the limitations of controlled-release devices, and especially with osmotic devices, is the incomplete release of the drug. The release rate decreases after ~80% of the drug has been delivered. The use of volume amplifiers to deliver the entire drug contained in the system is disclosed in Patents 4331728 (1982) and 4203439 (1980). The device consists of a core, an SPM, and a delivery orifice. In addition to the drug and the osmagent, the compartment contains a volume amplifier to increase the amount of agent delivered from the system (see Figure 3). The amplifier consists of a membrane surrounding a gas-generating couple with the membrane formed of an expandable material that is permeable to fluid and impermeable to the couple. In use, the active agent is delivered from the system through the passageway at a controlled rate because fluid is imbibed through the wall into the compartment to produce a solution-suspension of the drug. Simultaneously, the amplifier increases in volume (because

of the generation of the gas) and fills the compartment, forcing the desired agent to be released at a rate controlled by the permeability of the wall, the osmotic pressure gradient across the wall, and the rate of imbibition and increase in the amplifier's volume. The system completely delivers the drug at a nonfalling rate.

The gas-generation couple in a volume amplifier can be a mixture of an acid substance and a base substance. The volume amplifier membrane is free of passageways and contains an expansion agent that gives the membrane flexibility and expandability. Elastomeric materials used for this purpose include rubber, polyisoprene, polyisobutylene, polybutadiene, and ethylene-propylene copolymer.

Effervescent activity-based systems. Effervescent-based systems have been used throughout the years in mouth-dissolving and dispersible tablets. Patents 4265874 (1981) and 4344929 (1982) issued to Alza claim the use of effervescent activity for the delivery of drugs by osmotic systems. The major advantage of the disclosed method is the delivery of the drug, which is substantially free of rapid precipitation. The osmotic device comprises a semipermeable wall that surrounds a compartment housing a drug that exhibits limited solubility under neutral and acid conditions and a compound capable of releasing carbon dioxide in the presence of an acid. As fluid is imbibed through the wall into the compartment at a rate determined by the wall's permeability and the osmotic pressure gradient across the wall, a basic solution containing drug and compound is formed, which is delivered from the compartment through the passageway. The released compound reacts with the acid in the environment at the device-environment interface and evolves carbon dioxide, thereby providing an effervescent suspension that delivers the drug to the environment in a finely dispersed form over time. Thus the agent is delivered in a form that is rapidly absorbed and does not block the orifice of the delivery device. Drugs that can be delivered by such a system are those that exhibit a propensity for rapid precipitation in an environment that has a pH < 7 (e.g., the stomach). A few examples are the anti-inflammatory aryl-carboxylic acids such as indomethacin, aspirin, diclofenac, fenoprofen, flufenamic acid, and piroxicam.

Figure 4 shows the release of indomethacin from an osmotic device manufactured without a basic gas-generating compound and from a device manufactured with a basic gas-generating compound. The osmotic device without the compound releases the drug in the presence of an artificial gastric fluid containing hydrochloric acid; however, the drug precipitates onto the wall of the device and the exit port of the passageway and is

therefore not observed in the fluid of the environment. This problem is rectified with the use of an effervescent system.

Osmotic devices that use solubility modifiers. Several patents have been granted for modulating the solubility of drugs in osmotic systems. The solubility of the active agent within the device not only dictates the feasibility of making an osmotic system, but also determines the release rate and the percentage of the drug delivered in the desired zero-order fashion (3).

Patent 5284662 (1994) assigned to Ciba-Giegy Corporation (Ardsley, NY) describes the use of an oral osmotic system for a slightly soluble drug, carbamazepine. The system consists of a core that comprises the drug, a crystal habit modifier, and osmotic driving agents as well as lubricants, wetting agents, and carriers, which are optional. The wall is substantially impermeable to core components but is permeable to water and gastrointestinal fluids.

The crystal habit-modifying agent is necessary only when the active agent exists in more than one crystal form and when the desired form of administration is not the most stable form. Under these conditions, crystal modification and the resulting changes in solubility can be achieved. Even in such a case, the crystal habit-modifying agent is only necessary when the resultant property change is sufficiently large. The property that best indicates the need for a crystal habit-modifying agent is solubility.

Patent 4992278 (1991) also assigned to Ciba-Giegy describes a therapeutic system for sparingly soluble active agents. The core consists of an active ingredient that is sparingly soluble in water, a hydrophilic polymeric swelling agent composed of a mixture of a vinylpyrrolidone-vinyl acetate copolymer with an ethylene oxide homopolymer, and a water-soluble substance for inducing osmosis. The hydrophilic, polymeric swelling agent used in the system consists of a mixture of a vinylpyrrolidone-vinyl acetate copolymer and an ethylene oxide homopolymer. This mixture has the surprising advantage that pressure produced during swelling does not cause the system to rupture and that the swelling speed is uniform, which allows almost constant amounts of active ingredient to be released from the system. Theophylline, aspirin, carbamazepine, and nifedipine have been delivered by this system.

Patent 6110498 (2000) assigned to Shire Laboratories (Rockville, MD) describes an osmotic system for slightly soluble drugs. The core consists of a drug with limited solubility in water or physiological environments, a nonswelling solubilizing agent to enhance the solubility of the drug, and an osmagent. In addition, a nonswelling wicking agent is dispersed throughout the composition. A delivery

system for nifedipine used colloidal silicon dioxide, polyvinylpyrrolidone, and sodium lauryl sulfate as nonswelling wicking agents.

Patents also exist for systems that can regulate the release of the modulating agent. Patents 4755180 (1988) and 4610686 (1986) assigned to Alza disclose an osmotic dosage form comprising a polymeric olefin, vinyl, condensation polymer, additional polymer or silicon film surrounding a buffer, and an osmagent. The buffer or osmagent is released by the film to control drug solubility when external fluid is imbibed into the compartment.

Patent 4732915 (1988) assigned to Alza discloses a process for increasing drug solubility. The process consists of blending the drug (haloperidol) with acidifiers (maleic acid) and compressing them into a core, which allows the controlled delivery of a therapeutically effective amount of haloperidol. Similarly, Patents 4484921 (1984) and 4439196 (1984) claim the solubility modification of theophylline using a variety of agents, making delivery by an osmotic device a feasible option.

Patent 5891845 (1999) assigned to Fuisz Technologies Ltd. (Chantilly, VA) reports the use of drug delivery systems that use liquid-crystal structures. The patent discloses Vitamin E tocopheryl polyethylene glycol succinate (TPGS)-drug compositions to obviate the need for surfactants or nonevaporated cosolvents. The advantage of using a TPGS-drug solid solution is that insoluble drugs can be considered soluble for the purpose of getting the drug out of the osmotic device. In the controlled-release preparations, osmotic compounds such as sodium chloride, carbohydrates, or polyethylene glycol can be added as well as the binders and fillers required to form a tablet. Cyclosporine has been cited as an example in this patent.

Patent 5840335 (1998) assigned to Dr. Wenzel of Halle/Salle, Delaware, describes a system for the controlled release of drugs. The shell of the osmotic system comprises a wall formed of SPM, a core that has a water-soluble active agent, and a soluble polymeric adjuvant capable of unlimited swelling. The water-soluble polyvinyl alcohol polymeric adjuvant has less ability to dissolve in water than the active agent when the external fluid permeates through the shell. If a deviation occurs whereby the active agent's release rate is higher than the predetermined zero-order release rate, an additional amount of polymeric adjuvant is dissolved and delivered to the shell to decrease the shell's permeability, thereby eliminating the deviation. Conversely, if the active agent's release rate is lower than the predetermined zero-order release rate, an additional amount of the active agent is dissolved to increase hydrostatic pressure above the predetermined hydrostatic pressure to increase the shell's permeability.

Controlled-porosity osmotic pumps. Patents 4886668 (1989), 4968507 (1990), 4851228 (1989), and 4880631 (1989) assigned to Merck & Company (Whitehouse Station, NJ) describe controlled-porosity osmotic pumps. The pumps can be made with single or multiparticulate dosage forms. In either form, the delivery system comprises a core with the drug (diltiazem) and an effective buffering amount of sodium bitartrate. The core is surrounded by a rate-controlling water-insoluble wall made from a polymer that is permeable to water but impermeable to solute and a pH-insensitive pore-forming additive dispersed throughout the wall.

When the system comes in contact with a gastrointestinal aqueous environment, the coat's water-soluble component dissolves, leaving pores in the membrane. Water diffuses into the core through the microporous membrane and establishes an osmotic gradient that controls drug release. Substances such as sodium chloride, urea, and potassium chloride have been used as water-leachable components in the coating. The factors that control the release rate in these systems are coating thickness, the level of water-leachable component in the coating, solubility of the drug, and the osmotic gradient across the coating.

Push-pull osmotic pumps. Many general and product-specific patents exist for push-pull osmotic pumps (PPOPs). Patents 4327725 (1982), 4765989 (1988), and 4783337 (1988) assigned to Alza are a few examples of the general PPOP patents. These pumps are in the form of a two-layer tablet with a drug and push layer (see Figure 5). The drug layer comprises the diluents and low molecular weight polymers in addition to the drug. The push layer is constructed of a higher molecular weight osmopolymer and an osmagent. Polymers that can be used include sodium carboxymethyl cellulose, polyoxyethylene, and hydroxypropyl methylcellulose.

When the system comes in contact with an aqueous environment, both layers absorb water. The lower compartment, which does not have an orifice, swells and pushes against the diaphragm. Consequently, the upper chamber contracts, thereby delivering the drug through the orifice as a solution or a suspension. The drug layer in this device constitutes 60–80% of the tablet weight, and the osmotic polymeric layer constitutes 20–40%. The devices are capable of delivering drugs with solubility extremes.

Osmotic devices for use in the oral cavity. Patents have been issued to Alza for osmotic devices that can be used in the oral cavity based on elementary and PPOP technology. Patents 5021053 (1991), 5053032 (1991), and 5248310 (1993) describe oral controlled-release drug delivery systems. One device consists of a wall

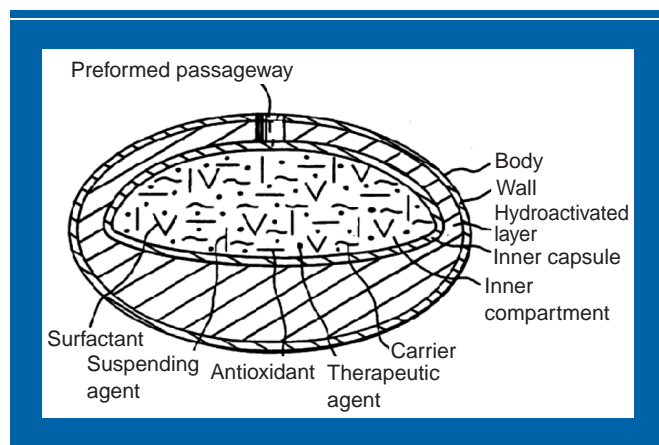


Figure 7: A soft-capsule osmotic device for the delivery of liquids.

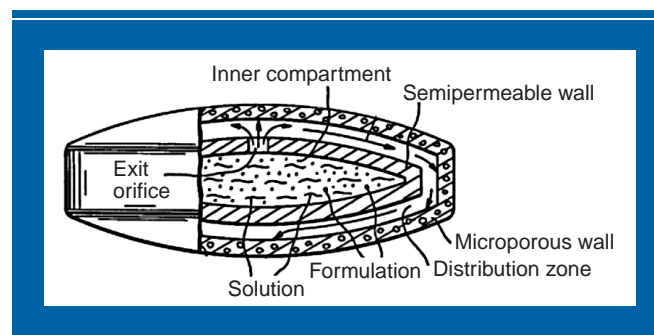


Figure 10: An osmotic device with a distribution zone to decrease the concentration of a dispensed drug.

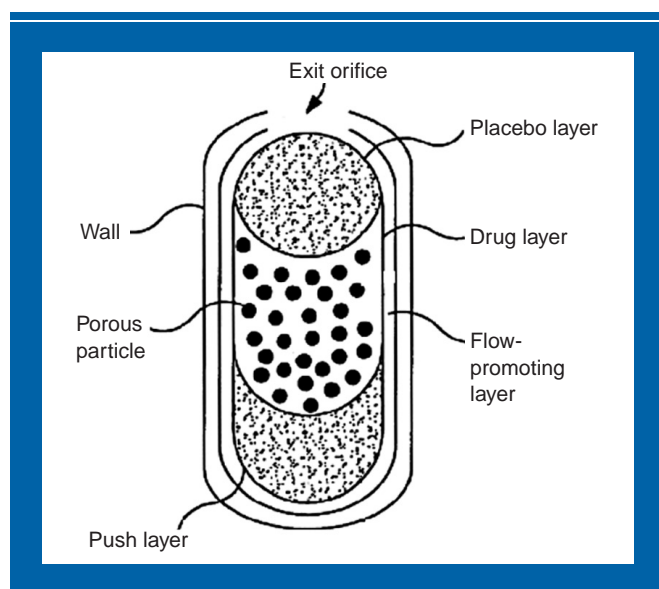


Figure 8: A hard capsule for the delivery of liquids adsorbed on particles.

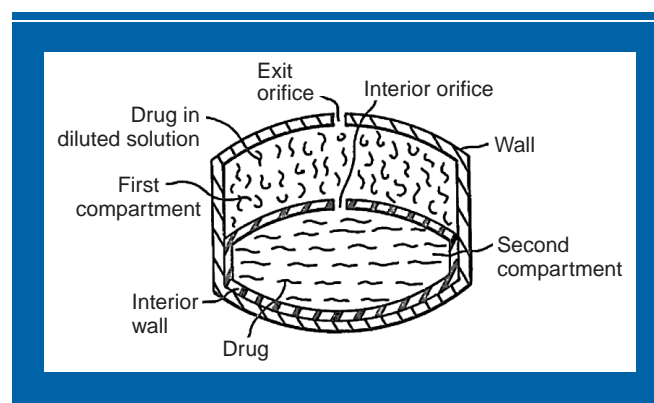


Figure 11: An osmotic pump with two compartments for the dilution of a dispensed drug.

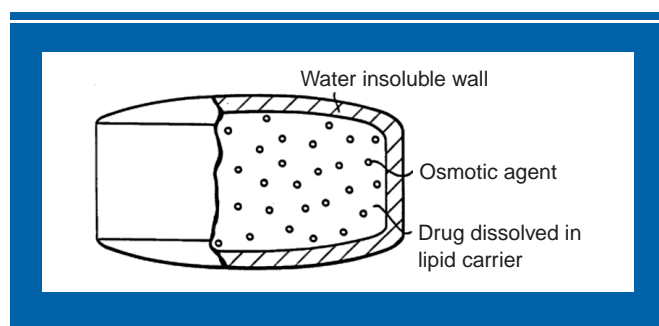


Figure 9: Cross-section of a lipid osmotic pump.

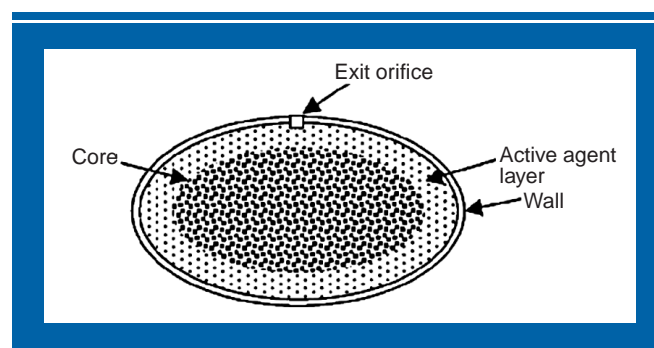


Figure 12: An osmotic device with a distribution zone to decrease the concentration of a dispensed drug.

surrounding a compartment that contains a layer of drug and a gelling agent and another layer that contains a hydrophilic polymer and a passageway through the semipermeable wall to the layer of drug, which also contains an osmogen and a gelling agent (e.g., κ -carrageenan).

One advantage of this delivery device is its precisely controlled delivery, which is not possible with other systems used for oral local delivery. Sprays used for this purpose have a very short exposure time, whereas tapes and other bioadhesion-based systems release the drug over a very localized area and consequently have a higher potential for toxicity or irritation. The advantage of decreased systemic toxicity is obvious. In addition, the system may have a means to decrease or mask the

unpleasant taste of the drugs delivered. An overcoat of the drug may be provided for immediate action.

Alza's Patent 5200194 (1993) mentions the use of fibrous support material composed of hydrophilic water-insoluble fibers (e.g., microcrystalline cellulose, cellulose ester, low-substituted hydroxypropyl cellulose, or seaweed fibers) in oral osmotic delivery systems. The fibrous support material, once hydrated, provides a rigid support (~5 to 70%) for the thin semipermeable wall and prevents the device from prematurely releasing the active agent even if the patient sucks on the device.

Few patents for oral osmotic devices report a method to determine the amount of agent delivered (Patent 5512299 [1996], Alza). The system consists of a relatively

translucent wall so that two layers of different colors can be seen easily. The color of the layers may differ because of the color of the agent itself or added color. The device has marks indicating when a predetermined percentage of the drug dose has been delivered into the oral cavity by comparing the location of the interface with the mark. The types of agents that can be delivered by this system include antifungal, antiviral, antimicrobial, antibiotic, nonsteroidal anti-inflammatory, anti-dental caries, saliva-enhancing, and smoking cessation agents.

Patent 5147654 (1992) issued to Alza claims the unique advantage of nicotine delivery by an oral osmotic device. The system consists of a nicotine salt and an optional alkaline salt, which is capable of

reacting with the nicotine salt in the presence of water to form a nicotine base. The conversion of nicotine salt to a nicotine base may take place within or outside the device and in the patient's mouth. The nicotine base or salt is delivered from the compartment through a passageway in the wall. The advantage is that nicotine salt exhibits good stability and a long shelf life, and the nicotine base exhibits excellent absorption through oral mucosal membranes.

Liquid drug delivery. Osmotic drug delivery was conventionally possible for solid drugs. However, during the past few years, Alza has developed osmotic systems to deliver liquids. This technology allows the delivery of insoluble drugs in aqueous fluids and is reported to increase the permeability of the drugs. Osmotic liquid drug delivery can be divided into the following sections.

Use of liquid carriers. Patents 5413572 (1995) and 5324280 (1994) assigned to Alza report osmotic drug delivery systems that use a liquid carrier. The osmotic system comprises a gelatin capsule (soft or hard) to provide an internal lumen, the dose of the liquid drug formulation in the lumen, an osmogen layer on the outside wall of the capsule, an SPM surrounding the osmogen, and an orifice to deliver the drug.

The orifice may be formed in situ or may be preformed. Examples of drugs that can be delivered by this system include steroids, polypeptides, enalapril, and diltiazem. Liquid carriers include vegetable oil, animal oil, monoglyceride, monoglyceride water-in-oil emulsion, and partially hydrogenated oils.

In the aqueous environment, fluid is imbibed through the semipermeable wall into the osmotic layer at a rate determined by the permeability of the semipermeable wall and the osmotic pressure gradient across the wall. The osmotic layer then swells and pushes against the capsule, causing the capsule to dynamically pump drug from the lumen. Both soft and hard capsules can be used for liquid delivery. These osmotic systems operate successfully and can deliver many drugs that are usually difficult to deliver. For example, a beneficial liquid-drug formulation such as a lipophilic drug formulation that is difficult to deliver can be delivered with this osmotic system. Furthermore, the lipophilic liquid formulation is essentially free from direct contact with a hydroactivated expansion composition and can be delivered at a controlled rate over a prolonged period of time. Figures 6 and 7 show the device in the form of a hard capsule and a soft capsule, respectively.

Use of porous particles. Patent 6342249 (2002) assigned to Alza claims a controlled-release formulation that can deliver a liquid active agent. The controlled release of liquid active agent formulations is provided by dispersing porous particles that

contain the liquid active agent formulation in osmotic push-layer dosage forms. The dosage forms can provide the continuous or pulsatile delivery of active agents. The porous particles are formed by spray-drying a calcium hydrogen phosphate with a high specific-surface area. The liquid active agent formulations may be absorbed into the interior pores of the material in significant amounts and delivered to the site of administration in the liquid state. It has been discovered that porous particles with liquid active agent formulations absorbed into the particles could be fabricated into controlled-release dosage forms without exuding the liquid active agent formulation during the manufacturing process. This discovery has led to the fabrication of controlled-release dosage forms that deliver the active agent in the liquid state. This type of drug delivery offers a minimal delay of the desired beneficial effect of the active agent because the active agent does not have to be initially dissolved or dispersed in the form of microparticles at the site of action. Furthermore, such dosage forms may permit large concentration gradients of active agent in solution and optional delivery of absorption enhancers. Microcrystalline cellulose, porous sodium carboxymethyl cellulose, porous soya bean fiber, and silicon dioxide—all of which have high surface area and good absorption properties—may also be used in the dosage forms described herein.

Structurally, the dosage form comprises an exit orifice and an SPM wall that defines a cavity (see Figure 8). An expandable layer is located within the cavity away from the exit orifice. The drug layer comprises a liquid active agent formulation absorbed in porous particles. In addition, the dosage form may have an optional placebo layer between the exit orifice and the drug layer.

Lipid osmotic pump. Patent 4685918 (1987) assigned to Merck describes an osmotic pump for lipid delivery (see Figure 9). The device concerns an osmotically activated system for dispensing beneficial active agents that have poor solubility in water. The core of the system comprises a beneficial amount of a substantially water-insoluble active agent, which is lipid-soluble or lipid-wettable; a sufficient amount of a water-immiscible lipid carrier, which is liquid at the temperature of use to dissolve or suspend the drug; and finally a sufficient amount of an osmotic agent to ensure the release of the lipid carrier from the pump. The water-insoluble wall is microporous and is wetted by the lipid carrier. The device is prepared by first dissolving the drug of interest in the lipid vehicle. The osmagent (e.g., sodium chloride) is dispersed in the melted lipid and is then quench-cooled to form lumps that are broken and made into tablets. The microporous membrane is coated at a moderate flow of unheated ambient air.

Osmotic devices that deliver drug below saturation. Osmotic systems mostly have a single port of drug delivery through which a concentrated (saturated) solution of the agent is dispensed. Hence, systems have been developed that can deliver a drug as a subsaturated or diluted solution. These types of delivery devices are useful for dispensing drugs that are irritants to mucosal and GIT tissue such as potassium chloride, aspirin, and indomethacin.

Patents 4285987 (1981) and 4200098 (1980) assigned to Alza describe the use of a dispersion or distribution zone to decrease the concentration of the active agent delivered by the system. The system comprises a first wall of a semipermeable material that surrounds a compartment containing a drug formulation and has a passageway through the wall for releasing agent from the compartment. A second wall is positioned away from the first wall and is constructed of a microporous or hydrogel material. Because of the distance between the two walls, a distribution zone interposed between the first and second walls exists (see Figure 10). In operation, drug is dispensed from the system by fluid passing through the second wall into the distribution zone, from which fluid is further imbibed through the first wall into the compartment and forms a solution that is released through the passageway and then through the second wall to the exterior of the system. Hence, the system can produce a drug distribution profile in time and space and can dilute and disperse the agent. Another invention is a solid dosage osmotic system, which in actual operation has a softness produced by a liquid cushion in the system.

Patent 4298003 (1981) assigned to Alza uses insoluble components in the core of the device. A compartment surrounded by an SPM contains a layer of compound that is insoluble in an exterior fluid and is juxtaposed with a layer of an active agent that is soluble in fluid. A delivery orifice through the wall connects the exterior of the system with the interface between the wall and the insoluble compound (e.g., calcium carbonate). In operation, the agent is delivered from the system when the agent imbibes fluid into the compartment to form a saturated solution of the agent, which is moved along the interface between the wall and the insoluble compound toward the passageway. The saturated solution is moved continuously by the corresponding imbibition of fluid, and as the solution moves along the interface, it imbibes fluid, is diluted, and is delivered below a saturated concentration to the exterior of the system.

Yet another system described in the osmotic patent literature for subsaturation drug delivery is the use of a two-compartment system (see Figure 11). Patent 4210139 (1980) assigned to Alza describes a device comprising an exterior

wall surrounding a first and second compartment. The first compartment is in contact with the exterior wall, and an interior wall that is in contact with the exterior wall surrounds the second compartment. A passageway exists through the exterior wall that connects the first compartment with the exterior of the device. Another passageway exists through the interior wall connecting the second with the first compartment. The first compartment contains an osmotic solute that exhibits an osmotic pressure gradient across the wall against an external fluid, and the second compartment contains a drug that exhibits an osmotic pressure gradient across the wall. The exterior and the interior walls are permeable to the passage of the fluid, and they are impermeable to the passage of solute and drug. However, these are designed so that the rate of fluid permeability is greater through the exterior wall than through the interior wall. In operation, fluid is imbibed through the walls into the compartments and is imbibed at a greater rate into the first compartment, thereby forming a more diluted solution than the drug solution formed in the second compartment. Hence, the drug solution is diluted before it exits the device.

Miscellaneous devices. Patent 6352721 (2002) assigned to Osmotica Corporation (Tortola, British Virgin Islands) reports a combined diffusion-osmotic pump drug delivery system (see Figure 12). The device has a centrally located expandable core that is completely surrounded by an active substance-containing layer, which is completely surrounded by a membrane. The core consists of an expandable hydrophilic polymer and an optional osmagent. The composition immediately surrounding the core comprises an active substance, an osmagent, and an osmopolymer. The membrane is microporous in nature and may have a delivery orifice. The device is capable of delivering insoluble, slightly soluble, sparingly soluble, and very soluble active substances to the environment.

Patent 5543155 (1996) assigned to Egis Gyogyszergy Rt. (Budapest, Hungary) describes a controlled-release system that is based on the combination of diffusion and osmotic mechanisms. The delivery system is a one-layer tablet core that includes a polymeric film coat, a therapeutically active agent, and a hydrophilic polymer. Ammonium methacrylate copolymer is used as the coating material, and hydroxypropyl methylcellulose is used as the hydrophilic polymer. The patent claims that the device solves many of the drawbacks of two-layered devices. Among the advantages of the single-layer tablet are the aqueous-based coating systems and no need to drill an orifice.

Specialized coatings. Patent 5827638 (1998) assigned to Alza claims use of vapor-permeable coatings. The wall in this

case is formed of a semipermeable hydrophobic membrane that has pores in the wall. The pores are substantially filled with a gas phase. The hydrophobic membrane is permeable to water in the vapor phase and is impermeable to an aqueous medium at pressures <100 Pa. The drug is released by osmotic pumping or osmotic bursting upon the imbibition of sufficient water vapor into the device core. These devices minimize incompatibilities between the drug and the ions (such as hydrogen or hydroxyl) or other dissolved or suspended materials in the aqueous medium because contact between the drug and the aqueous medium does not occur until after the drug is released, which results from the SPM's selective permeability for water vapor. In addition, the high water fluxes associated with these vapor-permeable membranes facilitate the delivery of beneficial agents that have low solubility and the delivery of high dosages of beneficial agents. Polymers used to make such coatings include polyvinylidene fluoride.

Patent 5126146 (1992) issued to Merck describes a specific coating of cellulose material that is applicable to controlled-porosity osmotic pumps. The microporous coating composition comprises synthetic latex formed by emulsification of cellulosic polymers that are stabilized by surfactants containing a water-soluble pore-forming agent and a plasticizer. The pore-forming agent dissolves when the coating comes in contact with water and is eluted, leaving a water-insoluble microporous cellulosic coating.

Patent 6245357 (2001) describes an osmotic device with two distinct wall layers. The interior wall comprises a hydrophobic substance and a hydrophilic substance, and the exterior wall is semipermeable. The patent reports a method that can increase the rate of drug released from a dosage form. The drug layer is covered with a wall comprising a passage former that, in the presence of fluid, leaves the wall and lets more fluid into the dosage form to increase drug release over a period of time.

Another patent claim is a device with a wall that provides support to the dosage form. The device maintains an extended, linear, nondeclining release drug profile from a dosage form by coating it with a composition that comprises a passage former that leaves the composition when in the presence of fluid and correspondingly increases the passages, which increases the fluid flow into the dosage form over time.

Processing and performance improvement. Patent 4892739 (1990) assigned to Ciba-Giegy describes a method for improving core membrane-adhesion properties. The tablet core containing the drug and other required components is evenly coated with a discrete layer of a water-soluble (or

Continued on page 97

Continued from page 44

water-dispersible) and water-permeable nonosmotically active solid polymeric binder to a level of $\leq 10\%$. The SPM is then coated on the tablet.

Many solid pharmaceutical active agents and conventional osmotically active driving solutes possess few or no inherent binding capabilities to SPM films, which may lead to poor adhesion between the core and the SPM. This problem can be aggravated if the core tablet picks up a static charge during coating. High amounts of conventional polymeric binders used to solve this problem can interfere with the desired continuous-release profile of the active agent in the core by excessively retarding the dissolution and release of the active agent in the GIT or by clogging the one or more passageways. The active agent containing the core may be evenly coated with a thin discrete layer of a water-soluble (or water-dispersible) and water-permeable nonosmotically active solid polymeric binder. This treated core can thereafter be coated with SPM material that adhesively binds to the binding layer to form a stable, laminated, osmotically activated device that is essentially free from defects.

Patent 6132420 (2000) assigned to Alza claims a method for enhancing the start-up and performance of osmotic delivery systems. The osmotic delivery system includes a liquid or gel additive that surrounds the osmotic agent to enhance start-up and lubricate the osmotic agent. The liquid or gel additive is an incompressible lubricating fluid that fills any air gaps between the osmotic agent and the walls of a chamber and substantially reduces start-up delays. The presence of air-filled gaps causes water to be drawn into the osmotic tablet. The osmotic tablet expands into the surrounding air space, and the beneficial agent delivery start-up is delayed. During this time, the osmotic tablet expands to fill the air spaces within the chamber. The start-up may be delayed for several days or weeks depending on the size of the air gaps and the flow rate of the system. Delayed start-up of the agent delivery is a significant problem in osmotic delivery systems. Hence, a fluid additive that is not significantly absorbed by the osmotic agent (e.g., polyethylene glycol [PEG] 400, PEG 1000, Tween 80, prostoglandin, or peanut oil) may be used. This method is applicable to implantable systems.

Conclusions

Osmotic drug delivery has come a long way since the discovery of the first osmotic device. Present-day osmotic delivery devices not only seek to deliver a variety of agents (i.e., high, moderate, or low solubility substances and liquid formulations), but also are capable of modulating drug release. Thus a delayed, pulsatile, or pH-triggered release is possible with these sys-

tems. Modifications implemented over time and many more possibilities for these systems indicate that, in spite of being used for drug delivery for nearly 30 years, osmotic drug delivery holds promise for the future.

References

1. G. Santus and R.W. Baker, "Osmotic Drug Delivery: A Review of the Patent Literature," *J. Controlled Release* **35**, 1–21 (1995).
2. R.K. Verma, B. Mishra, and S. Garg, "Osmotically Controlled Oral Drug Delivery," *Drug Dev. Ind. Pharm.* **26** (7), 695–708 (2000).
3. F. Theeuwes, "Elementary Osmotic Pump," *J. Pharm. Sci.* **64** (12), 1987–1991 (1975). **PT**