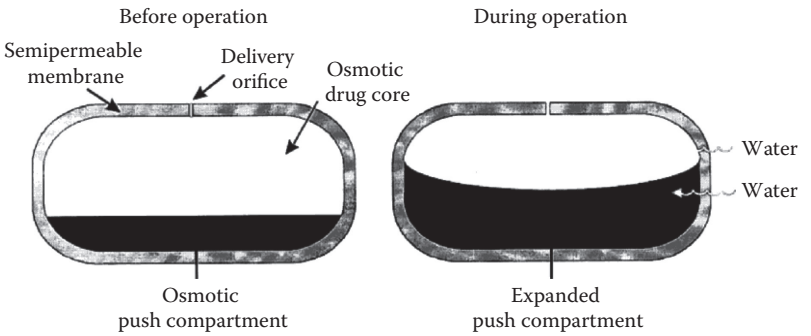

FIGURE 22.9 A cross-section of an OROS® Push-Pull™ bilayer system before and during operation.

OROS® Push-Pull™ Drug Delivery System

Delivery systems that use a multicompartment core can theoretically deliver drugs of any solubility (Wong et al. 1986; Theeuwes et al. 1991). A basic Push-Pull™ system consists of two layers: the first contains the drug, osmotically active hydrophilic polymer(s), and other pharmaceutical excipients; the second layer, often called the *push layer*, contains a hydrophilic expansion polymer, other osmotically active agents, and the excipients, as shown in Figure 22.9. Poorly water-soluble compounds can be delivered using an OROS Push-Pull delivery system by incorporating drug as a micronized form, or as a hot-melt material suspended in a polymer matrix.

The OROS Push-Pull delivery technology was used for successful controlled release of nifedipine, a poorly water-soluble calcium channel blocker. Procardia XL® tablets is a once-daily nifedipine product developed by ALZA Corporation (Mountain View, CA) and marketed by Pfizer (New York City) (Wong et al. 1988, 2003) as an antihypertensive agent. Nifedipine has an elimination half-life of approximately 2 h, and oral absorption is known to be proportional to the dose. Owing to its poor aqueous solubility and the BCS Class II drug characteristics, the compound is usually micronized to increase the specific surface area for an enhanced dissolution rate enabling drug absorption. The controlled-release osmotic pump system for nifedipine consists of an osmotically active drug core tablet surrounded by a semipermeable membrane. The core itself is divided into two layers: (1) an active drug layer comprising 20 wt% nifedipine, 71 wt% poly(ethylene oxide) with a molecular weight of 200,000, 2 wt% potassium chloride, 5 wt% hydroxypropyl methylcellulose, and 2 wt% magnesium stearate; and (2) an osmotic push layer consisting of 68.7 wt% poly(ethylene oxide) with a molecular weight of 5,000,000, 29.3 wt% sodium chloride, and 2% w/w magnesium stearate. The wet granulation method is used to prepare drug layer and push layer granules. The compressed bilayer core is then coated with a semipermeable membrane containing 95 wt% cellulose acetate (CA) with an acetyl content of 39.8% and 5 wt% poly(ethylene glycol) 4000 as a permeation enhancer. An exit orifice on the drug layer side is formed by laser drilling through the semipermeable membrane with an opening of 0.26 mm in diameter. The Procardia XL tablet was designed to release drug at a constant rate over 24 h as shown in Figure 22.10.

Clinical study demonstrated a steady plasma level throughout the day after dosing of a single 60-mg dose with elimination of the rapid rise in plasma concentration seen with IR dosing (20 mg nifedipine administered three times a day) as shown in Figure 22.11. The study also showed that the product was well tolerated with an improved safety profile.

OROS Push-Stick™ Drug Delivery System

The OROS Push-Stick technology is designed to deliver high doses of poorly water-soluble or slowly dissolving drugs at a controlled rate (Wong et al. 2003; Cruz et al. 2005). The basic system consists