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# Osmotic micropumps for drug delivery ☆

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ABSTRACT

This paper reviews miniaturized drug delivery systems applying osmotic principles for pumping. Osmotic micropumps require no electrical energy and consequently enable drug delivery systems of smallest size for a broad field of new applications. In contrast to common tablets, these pumps provide constant (zero-order) drug release rates. This facilitates systems for long term use not limited by gastrointestinal transit time and first-pass metabolism. The review focuses on parenteral routes of administration targeting drug delivery either in a site-specific or systemic way. Osmotic pumps consist of three building blocks: osmotic agent, solvent, and drug. This is used to categorize pumps into (i) single compartment systems using water from body fluids as solvent and the drug itself as the osmotic agent, (ii) two compartment systems employing a separate osmotic agent, and (iii) multi-compartment architectures employing solvent, drug and osmotic agent separately. In parallel to the micropumps, relevant applications and therapies are discussed.



**Contents**



## 1. Introduction

Besides the drug itself, the right dosage over time is crucial for an effective therapy. Rate-controlled release systems allow maintaining the drug concentration within the body at an optimum level. This minimizes the risk of disadvantageous side effects, poor therapeutic

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activity, or even adverse effects. Over the years, a multitude of different technological approaches addressing this goal have been developed. However, only few of them succeeded in becoming cutting edge technologies applied to versatile therapeutic applications. A very successful approach for rate controlled drug delivery is represented by osmotic micropumps. This might be related to the bionic concept applying one of the most fundamental principles of biology, osmosis, in a technical device.

Osmotic pumps belong to the class of rate-controlled systems providing continuous delivery and offer a set of distinct advantages. First and foremost this includes the simple principle of operation requiring no electric energy. Hence, pump designs can be kept simple resulting in increased robustness as well as high potential for miniaturization.

Within osmotic pumps, drugs can be stored in liquid or solid form. In the latter, the drug is efficiently stored in concentrated manner requiring a minimum of space. It is then dissolved by water used as solvent and delivered as a liquid solution. Hence, osmotic systems can be considered to be one of the most space-saving drug delivery technologies. Considering that water is available in all body fluids, extremely miniaturized implantable devices for use in body parts that are not accessible in other ways can be developed. Furthermore, the efficient drug storage enables implantable devices providing constant drug release over a prolonged duration.

Orally administered drugs suffer often from poor pharmacokinetics, e.g. too slow or too fast absorption in the gastrointestinal tract. Osmotic technologies can be used to improve the pharmacokinetic properties of drugs by better adjustment of the release rate with respect to conventional tablets or pills. Therefore, in the past a lot of effort was dedicated to the development of osmotic pumps for oral drug delivery. The historical evolvement of these devices was summarized in multiple literature reviews [1–6].

Currently, the patent protection of the early osmotic drug delivery devices is already expiring [7,8] making the technologies available to all interested parties. In parallel, pharmaceutical companies that have closely expiring patents on their drugs are interested in combining the drugs with new routes of administration to regain patent protection for this combination and to extend by this way the life cycles of their drugs. In this respect, osmotic pumps offer a convenient way to increase the performance of drugs already on the market without addressing completely new drug development.

Although the first osmotic pumps were developed more than 50 years ago [9], the technology has continued to progress. Especially the fabrication technologies developed for microengineering and microelectromechanical systems (MEMS) during the last decades opened completely new perspectives with respect to device miniaturization and system integration. This enabled new osmotic devices specifically addressing parenteral routes of administration which nevertheless enable drug delivery either in a site-specific or systemic way. The following review concentrates on these emerging osmotic micropumps being already commercially available or currently under active development.

## 2. Fundamentals

Osmosis is one of the fundamental phenomena in biology enabling for instance cells and plants to adjust water balance. An osmotic flow is generated when two solutions of different solute concentrations are separated by a semi-permeable membrane rejecting the solute on the one hand but allowing passage of the solvent molecules on the other hand, as illustrated in Fig. 1A1. The osmotic flow across the semi-permeable membrane is directed to compensate differences in solute concentrations. This leads to a flow of solvent from the region of low solute concentration (high chemical potential) to the region of higher solute concentration (low chemical potential). As a consequence it results in a hydrostatic pressure difference across the semi-permeable membrane causing in turn an oppositely directed flow of solvent as illustrated in Fig. 1A2. In equilibrium, the flow due to the hydrostatic pressure difference balances the osmotic flow. The pressure difference required to generate this balancing flow is equivalent to the difference of the osmotic pressures of the two solutions.

There are several theories to predict the osmotic pressure of a solution. However, the Van't Hoff equation (Eq. (1)) applicable to ideal diluted mixtures is the most commonly accepted and best known theory [10]. According to the Van't Hoff equation, the osmotic pressure of a solution is proportional to solute concentration and temperature. By knowing these parameters, the osmotic pressure $\pi$ can be easily calculated:

$$\pi = i \cdot \frac{n}{V} \cdot R \cdot T = i \cdot C \cdot R \cdot T \tag{1}$$

where $n$ is the number of moles of solute (mol), $V$ is the volume of solution (L), $C$ stands for the corresponding solute concentration (mol/L), $R$ is the molar gas constant (8314 J $mol^{-1}$ $K^{-1}$), and $T$ the absolute temperature (K). The Van't Hoff factor $i$ represents the number of moles of solute actually dissolved in a solution per mole of added solid solute, i.e. $i$ equals one if the solute does not dissociate (e.g. non-electrolytes in water) or becomes larger than one in case dissociation occurs. In the latter, the number of solute molecules increases, as it is the case for most ionic compounds. With $\alpha$ being the degree of dissociation and $\upsilon$ the number of ions, a solute can dissociate into $i$ molecules according to the following equation:

$$i = 1 + \alpha \cdot (\upsilon - 1). \tag{2}$$

In most cases, water is used as solvent. Different osmotic pump principles for drug delivery are depicted in (Fig. 1B–D). All pumps exploit the solvent flow across the semi-permeable membrane for actuation. In single compartment systems, the solvent inflow through the membrane into the device dissolves the drug which is used as an osmotic agent and displaces the saturated drug solution through an outlet (Fig. 1B). In two compartment systems, the solvent dissolves an osmotic agent stored in a separate confinement from the drug. The compartment of the osmotic agent expands and accordingly displaces the liquid drug in a neighboring compartment (Fig. 1C–D). In general, the net flow rate of solvent can be described by the following equation:

$$\frac{dV}{dt} = K \cdot A \cdot (\sigma \cdot \Delta\pi - \Delta P) \tag{3}$$

where $dV/dt$ stands for the volumetric net flow rate of solvent across the semi-permeable membrane, $K$ is the permeability of the semi-permeable membrane with respect to the solvent, $A$ is the surface area of the semi-permeable membrane, and $\sigma$ is its osmotic reflection coefficient. The osmotic pressure difference across the semi-permeable membrane is $\Delta\pi$. $\Delta P$ stands for the hydrostatic pressure difference between the two sites of the semi-permeable membrane. Theoretically, in the case of an osmotic agent in a sealed container, a hydrostatic pressure equivalent to the osmotic pressure can build up over time. In applications for drug release, an open release port is necessary which limits the hydrostatic pressure due to the continuous drug flow through the release port. Consequently, the hydrostatic pressure difference between the osmotic agent compartment and the outlet area is defined by the flow resistance of the release port times the net flow of solvent across the semi-permeable membrane.

The effective drug release rate, i.e. the mass of drug molecules released over time through the outlet orifice of osmotic pumps $dm/dt$, can be derived from the volume flow rate of liquid drug solution $dV/dt$ as:

$$\frac{dm}{dt} = \frac{dV}{dt} \cdot C \tag{4}$$

where $C$ stands for the drug concentration of the dispensed solution.

The reflection coefficient $\sigma$ describes the leakage of solute through semi-permeable membranes and is ideally equal to one. For commonly used membranes, this parameter is close to one. Typically, $\Delta P$ is

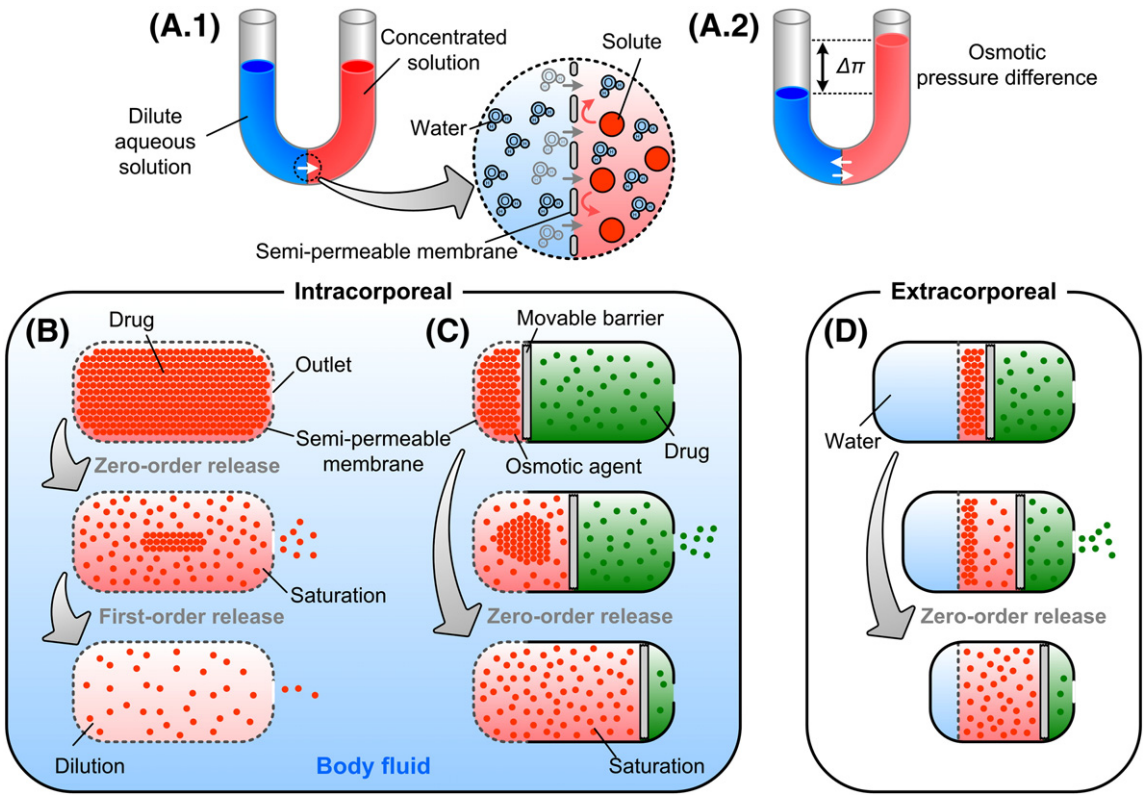


**Fig. 1.** (A) Osmotic principle: (B) Operation principle of a single compartment pump. Constant (zero-order) release is maintained as long as the drug solution is saturated. (C) Operation principle of a two compartment pump. The constant (zero-order) release can be maintained for the entire period of operation. (D) Operation principle of a multi compartment pump being similar to a two-compartment pump. While (B) and (C) make use of body fluids as solvents and consequently are applied inside of the body, (D) is designed for extracorporeal use and requires an additional compartment that supplies the solvent.

negligibly small compared to $\Delta\pi$. Additionally, the osmotic pressure of the osmotic agent is several orders of magnitude larger than that of the surrounding medium. Therefore, the term $(\sigma\cdot\Delta\pi-\Delta P)$ of Eq. (3) can be substituted by the osmotic pressure $\pi$ of the osmotic agent. After substitution of the resulting expression into Eq. (4), the following relationship is obtained:

$$\frac{dm}{dt} = K\cdot A\cdot\pi\cdot C. \tag{5}$$

This fundamental equation applies to all osmotically driven pumps illustrated in Fig. 1B–D.

Osmotic pumps consist of three building blocks: osmotic agent, solvent, and drug. This can be used to categorize osmotic pumps into three different groups. Single compartment pumps (Fig. 1B) define a first category. The drug itself is employed as osmotic agent and accordingly only one compartment separating the drug from the solvent is required. Consequently, the concentration $C$ of the dissolved drug equals the concentration of the osmotic agent. Thereby, the solubility of the drug itself is one of the most important parameters affecting the release rate. This pump type was first described by Theeuwes in 1975 as the elementary osmotic pump [11].

Constant zero-order release kinetics can be maintained as long as the drug solution in the compartment remains saturated. When the solid drug is completely dissolved, the release rate is determined by the depleting concentration of the solution and declines parabolic in time. The amount of drug $m_{zero}$ which can be released with zero order kinetics from the total stored amount of drug $m_{total}$ can be determined as [11]:

$$m_{zero} = \left(1-\frac{S_{drug}}{\rho_{drug}}\right)\cdot m_{total} \tag{6}$$

The total amount of drug $m_{zero}$ released at a constant rate increases with decreasing drug solubility $S_{drug}$ according to Eq. (6). The osmotic pressure decreases for decreasing solubility and in consequence the release rate is slowed down. Hence, single compartment pumps depend on the physical properties of the drug. This is a major limitation if the systems are planned to be used with different drugs. However, there are several strategies to modulate drug solubility, e.g. the use of solubilizers described in detail elsewhere [2].

Two compartment osmotic pumps (Fig. 1C) store drug formulation and osmotic agent in two separate compartments. During operation, the expansion of the agent compartment displaces the content of the drug compartment. This class of osmotic pumps was described for the first time by Theeuwes and Yum in 1976 [12]. Due to the separation of osmotic agent and drug, the special feature of those pumps is a drug release rate independent of the osmotic pressure of the drug. Thus, any drug solution or suspension, aqueous or non-aqueous in nature, contained in the drug compartment can be released. In addition, the stability of the drug solution can be tailored by selecting the optimal solvent independent of the osmotic agent. This is specifically important for implantable systems, where the drug formulation must not degrade at body temperature during long-term applications lasting up to years, e.g. for protein or peptide delivery. Suspensions of drug solids and non-aqueous solvents are less prone to hydrolytic degradation reactions because of the absence of water. However, the solvent is also released to the body and has to be considered, even if the amounts are small. A list of investigated non-aqueous drug solvents for osmotic pumps is provided in [13].

The main drawbacks of the two compartment approaches are the reduced drug storage capacity per volume compared to single compartment pumps as well as the more complicated technological design. In order to achieve a constant release rate with this type of pump, the osmotic agent solution must remain in a saturated state

during the entire operational time. Consequently, the stored amount of solid agent $m_{osm}$ should not be completely dissolved before the volume of the drug compartment $V_{drug}$ is completely displaced and end of operation is reached. This can be expressed by the following two relations before (Eq. (7)) and after operation (Eq. (8)):

$$m_{osm} = \rho_{osm} \cdot V_{osm} \tag{7}$$

$$m_{osm} = S_{osm} \cdot \left(V_{osm} + V_{drug}\right) \tag{8}$$

where $\rho_{osm}$ is the density of the osmotic driving agent and $V_{osm}$ is its initial compartment volume. To ensure constant release rate, the critical volume ratio of both compartments can be derived by combining Eqs. (7) and (8) which results in

$$\frac{V_{osm}}{V_{drug}} = \frac{S_{osm}}{(\rho_{osm} - S_{osm})}. \tag{9}$$

Consequently, the critical mass of osmotic agent $m_{osm}$ required to entirely dispense the volume $V_{drug}$ is given by

$$m_{osm} = V_{drug} \cdot \frac{S_{osm}}{1 - (S_{osm}/\rho_{osm})}. \tag{10}$$

According to Eqs. (9) and (10), the osmotic actuator unit can be properly designed in terms of volume and loading of the osmotic agent chamber. To build pumps of small size or to load pumps of similar size with more drug solutes, a low ratio $V_{osm}/V_{drug}$ is advantageous. For example, sodium chloride (NaCl) and fructose generate similar osmotic pressures which are about 36 MPa. Nevertheless, using NaCl as osmotic agent requires only a fifth of the osmotic agent volume compared to fructose. This is because (i) the solubility of NaCl is lower than that of fructose ($S_{NaCl} = 36.1$ g/100 g $H_2O$ vs. $S_{fructose} = 79.0$ g/100 g $H_2O$) and (ii) the density of NaCl is higher than that of fructose ($\rho_{NaCl} = 2.17$ g/cm$^3$ vs. $\rho_{fructose} = 1.59$ g/cm$^3$). Therefore, the ratio $V_{osm}/V_{drug}$ is lower in case of NaCl requiring less volume $V_{osm}$ of osmotic agent needed to displace a given volume $V_{drug}$ of the drug chamber. Generally, salts are preferred as osmotic agents in two-compartment systems instead of non-electrolytic compounds.

While single and two compartment pumps are driven by water from body fluids used as solvent, multi-compartment systems have at least one additional enclosed water compartment separated from the osmotic agent by the semi-permeable membrane. Since a dedicated liquid environment is not required, such pumps can be operated under "dry" conditions, e.g. as part of extracorporeal systems.

The Rose–Nelson pump [9] featuring three compartments was developed in 1955 for pharmaceutical research and is generally recognized as the pioneering device of this most sophisticated osmotic pump type. As multi compartment pumps differ in the attached water compartment from two compartment pumps, the general operation principles apply also to this pump type.

## 3. Osmotic matrix systems/monolithic systems

A very special sub-category of single compartment osmotic pumps is known as "osmotic matrix systems" or "monolithic systems". These systems require no separate semi-permeable membrane. Instead, uniformly dispersed particles of drug used as osmotic agent are directly embedded within a biocompatible polymer matrix serving as the semi-permeable membrane. The particles, often smaller than 40 μm, form a multiplicity of microcapsules throughout the matrix which are initially not connected to each other. This concept was first introduced by Gale et al. [14].

The osmotically driven drug release mechanism is considered to occur as follows [15–19]: Water from the surrounding aqueous medium diffuses into the polymer matrix where it encounters and dissolves the polymer-encapsulated drug particles (Fig. 2A). The osmotic flux of water across the matrix walls aims to dilute the drug solution inside the microcapsules resulting in swelling, microcracks, and finally rupture of the microcapsules. The hydrostatic pressure is building up in each microcapsule as long as the matrix walls resist crack formation. When cracks are formed, drug solution leaks through them and interconnects microcapsules that have been already ruptured. The mechanism is affected by several parameters [16] including osmotic activity, saturation concentration as well as density of the incorporated agent [20], and also elastic modulus, tensile strength, and hydraulic permeability of the polymer. In addition, dissolution and diffusion of compounds, exposed on the matrix surfaces and immediately released, need to be considered.

Hence, osmotic matrix systems can be considered as a multitude of single compartment pumps featuring staggered release in time. The non-diffusive mechanism is restricted to water-soluble drugs in hydrophobic matrices resulting in constant drug release kinetics. In the case of using lipophilic drugs, release would be diffusively controlled (Higuchi matrix mode [21]).

The release of different proteins was tested from different matrix materials, such as polydimethylsiloxane (PDMS) [22], poly(ethylene-co-vinyl acetate) [23], and photo-crosslinked polymers [24,25]. Drug delivery devices applying this release mechanism include steroid eluting rings attached to the lead electrodes of cardiac pacemakers. The rings shown in Fig. 2B are fabricated by microinjection molding of PDMS and are sleeved over the distal lead tips. Each ring contains a maximum of 1 mg of dexamethasone-21-dihydrogen phosphate which is eluted after exposure to body fluids during the first month of implantation. This steroid is known to suppress inflammatory tissue responses which are believed to cause increasing stimulation thresholds typically associated with implanted pacing electrodes [26,27]. Micrographs taken by a scanning electron microscope (SEM) of steroid eluting rings before and after a 30 days in vitro release period are shown in Fig. 2C. The empty microcapsules formed by elution can be clearly seen.

## 4. Single compartment drug delivery systems

### 4.1. LiRIS®

A small and flexible osmotic system that can move freely in the human bladder was introduced by Lee and Cima [28] from Massachusetts Institute of Technology (MIT). The LiRIS® – Lidocaine Releasing Intravesical System – (TARIS Biomedical, Inc., Lexington, MA, USA) is in Phase I clinical development for the site-specific treatment of interstitial cystitis and painful bladder syndrom (IC/PBS) [29]. A placebo device (i.e. containing no drug or drug surrogate) was already successfully assessed during a Phase 1 safety and tolerability study [30]. IC/PBS is a chronic urological malfunction and can provide serious disability associated with pain, urinary urgency as well as frequency. A recent study about the prevalence of IC/PBS indicates that symptoms affect more than 3.3 million people in the United States, the majority of them being women [31]. The standard treatment method is based on lidocaine solutions directly instilled into the bladder. However, the effect of the drug is limited by its short half-life (90 min) and urination [32]. In contrast, LiRIS® provides the drug over a time period of two weeks which is long enough to counteract flare-ups of the disease.

The device is based on a double lumen medical grade PDMS tube. One lumen is filled with lidocaine tablets whereas the other incorporates a shape-memory wire made of nitinol (see Fig. 3A). Insertion into and retrieval from the bladder is performed by standard non-surgical procedures (catheter or cystoscopy). Interstices, i.e. breaks between the lidocaine tablets, together with the superelastic effect of the wire allow the deformation of the system into a linear shape for insertion and return to its pretzel-like shape post insertion (see Fig. 3B). In its native shape, the system has the size of a paper clip

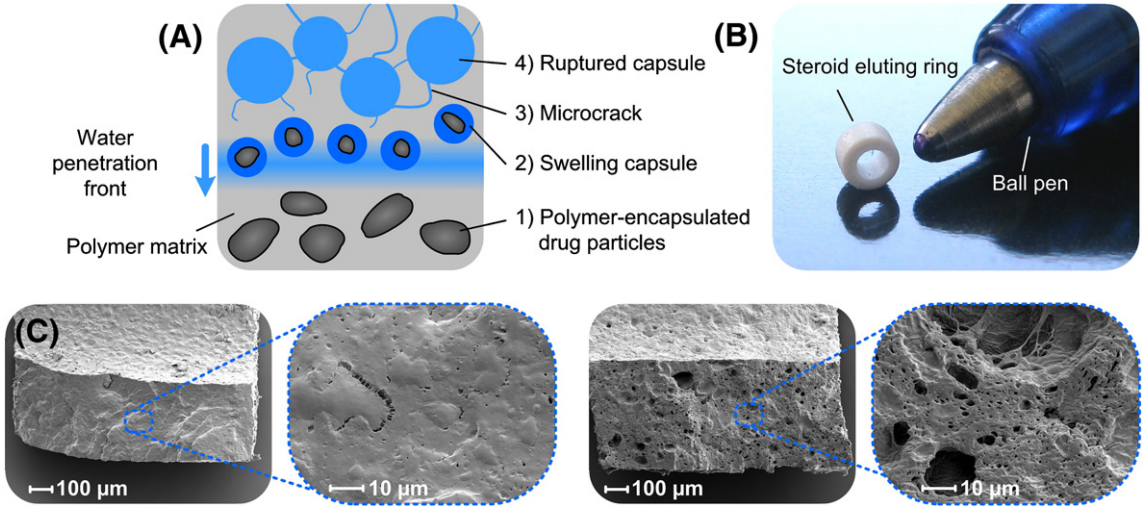


**Fig. 2.** Osmotic matrix systems: (A) Osmotic release mechanism adapted from [16]. (B) Photograph of a drug eluting steroid ring. (C) Series of SEM micrographs showing cross section of rings before and after a 30 days in vitro release period. Courtesy of Osypka AG, Rheinfelden, Germany.

preventing it from being expelled from the bladder during urination and having minimized risks of injury or inflammation.

Once inserted into the bladder, the whole silicone tube operates as the semi-permeable membrane and a small laser-drilled orifice within its wall acts as the lidocaine-release outlet. Besides interstitial cystitis, LiRIS® is also being considered to treat patients related to ureteral stent placement after suffering from kidney stones. Further prospects of the technology platform include applications like chemotherapy for bladder cancer, overactive bladder, and other bladder diseases (all pre-clinical status).

### 4.2. IntelliDrug

IntelliDrug is a highly integrated osmotic microdosage system designed to operate in the oral cavity and delivering the drug to the buccal mucosa. The system has the size of two mandibular molar teeth and was developed to circumvent drug absorption by the stomach and the associated disadvantages [34]. In particular, poor patient compliance, e.g. pills not taken as prescribed, poor bioavailability by hepatic first pass metabolism, and fluctuating drug plasma levels have been addressed.

Drug administration to the buccal mucosa is an advantageous route to the blood stream. A microsystem designed as a dental implant can easily be refilled by a physician without the need for surgery. The main challenges for such a system are the limited space and the harsh environment in the oral cavity including mechanical loads of up to 250 N. Moreover, the device has to withstand varying pH values, temperatures, saliva secretion, and the bacterial flora of the oral cavity.

The IntelliDrug system is shown in Fig. 4A. On the lingual side, water from saliva enters the system through a water-permeable membrane. The solid drug pill stored in the reservoir is dissolved and a hydrostatic pressure is built up by compression of a fluidic capacity implemented as a compressible polymer balloon filled with air (Fig. 4B). The pressurized drug solution can be released by opening a microvalve that is (i) designed to be normally-closed for medical safety reasons and (ii) based on an ionic electroactive polymer polypyrrole (PPy) actuator keeping the energy consumption as well as the actuation voltage on a minimum level [35,36]. Downstream of the microvalve, a flow sensor with integrated impedance measurement [37] is implemented to allow the metering of both, the flow rate and the concentration of the released drug solution. Multiplying the flow rate with the concentration of the solution allows to determine the drug release rate on the buccal side (refer to Eq. (4)) as well as the moment when the solid drug pill is fully dissolved and depletion starts.

The system was supposed to find application with Alzheimer's disease [38,39] and drug addiction [40,41] administering galantamine and naltrexone hydrochloride, respectively. However, the extreme

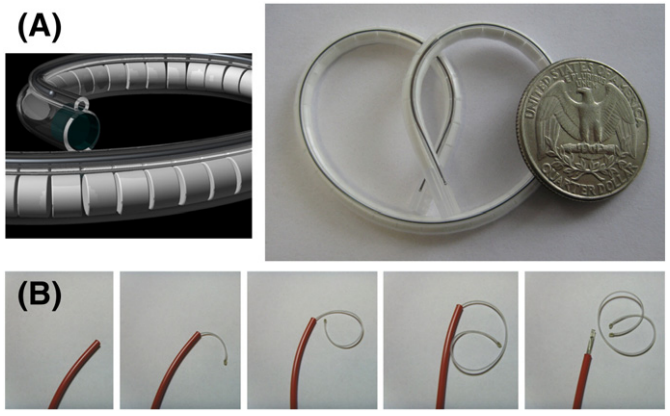


**Fig. 3.** (a) LiRIS® for sustained drug delivery to the bladder. (b) Deployment of the device via a catheter. Courtesy of TARIS Biomedical, Inc. [33].

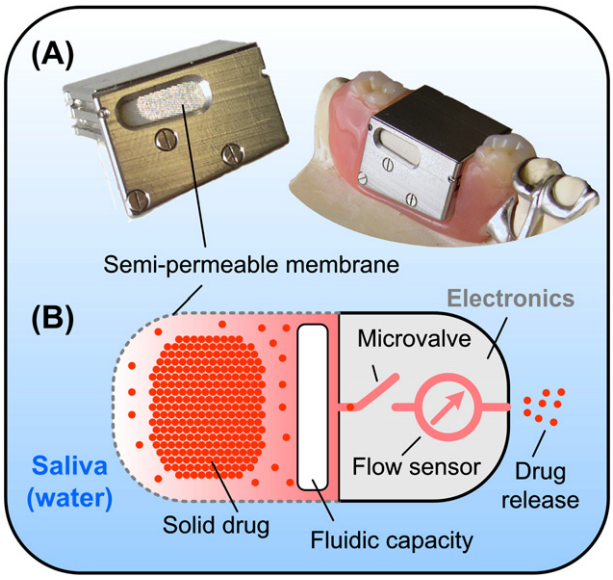


**Fig. 4.** Prototype and operation principle of the intraoral drug delivery system IntelliDrug.

system complexity delayed the development and did not allow demonstrating fully functional prototypes. Nevertheless, a first human in vivo trial was done for treating drug addiction. A simplified system without microvalve was mounted on a partial removable prosthesis and resulted in a 25-times increased bioavailability compared to the same drug load administered per-oral [42]. The IntelliDrug system requires sufficient saliva secretion flow to work properly. Because of this, the system might be contraindicated in individuals suffering from xerostomia or dry mouth. Hence, the patient's salivary gland function should be considered.

## 5. Biodegradable single compartment systems

The materials typically applied to drug delivery systems fabricated by MEMS technology demonstrated biocompatibility and reduced biofouling [43]. A major drawback of using materials that are not biodegradable is the requirement for an additional explantation procedure after depletion of the drug. This is particularly relevant for osmotic pumps, which can be generally regarded as single-use devices for which a refill is not feasible, at least during the implanted state. Therefore, increasing interests are assigned to biodegradable polymer materials for drug delivery devices [44,45].

Most often, the degradation of such devices relies on polymer erosion and is directly used to control the drug release. However, the degradation process is severely dependent on the polymer properties and can become ineffective if a more precise medication is required. One possible approach to resolve this issue includes the separation of the release mechanism (e.g. osmosis) and the biodegradable material used as structural support for the therapeutic duration. Hence, the degradation process can be tailored to primarily occur after complete depletion of the device, not affecting the release rate anymore.

For instance, Ryu et al. [46] used biodegradable materials in combination with a single compartment osmotic micropump for controlled long-term release of fibroblast growth factors. The device is fabricated by compression molding of 85/15 poly(L-lactide-co-glycolide) into 25 and 75 μm thick films as well as mirco-molding of the reservoir and the release channels into the thicker film. During operation, the biodegradable material serves as the device housing as well as the semi-permeable membrane. However, in case the material is selected to be partially permeable to the drug, i.e. the reflection coefficient is selected to be low, a device combining osmotic with diffusive release is obtained [47].

A biodegradable variant of the LiRIS® device described in Section 4.1 was developed by the same group [48]. The main advantage of this approach is obvious, since retrieval of the pump from the bladder has not necessarily to be performed anymore. During fabrication of the device, a structure with a hollow core is first made from biodegradable poly(glycerol-*co*-sebaic acid) (PGS). After cross-linking the pre-polymer with heat in vacuum, the core of the structure is filled with drug and sealed. Finally, a release orifice is drilled into the PGS.

In vitro release experiments performed with ciprofloxacin–HCl resulted in controlled zero-order release rates and PGS showed sufficiently high water permeability.

## 6. Two compartment drug delivery systems

### 6.1. ALZET®

The ALZET® osmotic pumps [49] were developed in the seventies [12] and are today probably the most prominent examples of miniature osmotic pumps. They were designed for research purposes and are commercially available by DURECT Corp., Cupertino, CA, USA. The ALZET® pumps can be implanted in multiple animal species as small as mice and in multiple anatomical sites. Providing researchers with a reliable method for continuous delivery of agents, novel therapies and therapeutic regimes being potentially applicable to human therapies is typically investigated.

ALZET® osmotic pumps are cylindrically shaped (see Fig. 5). They comprise a collapsible reservoir made of impermeable thermoplastic hydrocarbon elastomer which is surrounded by a coating layer of osmotic driving agent. The semi-permeable membrane is based on a cellulose ester blend that overcoats the osmotic layer and forms the outer surface of the pump. A cannula working as flow moderator is inserted after filling of the pump with drug. Its geometry minimizes diffusive release and prevents accidental spill of the pump's content. Furthermore, the flow resistance hinders the drug content to be accidentally spilled out. All this ensures constant delivery solely controlled by osmosis.

Water entering the osmotic layer generates a pressure inside the reservoir and displaces the stored drug volume. The drug release rate is defined by the volume of water penetrating the semi-permeable membrane multiplied with the concentration of the stored drug solution. The pumps are available with three different reservoir capacities of 100 μL, 200 μL, and 2 mL with delivery rates ranging from 0.11 μL/h to 10 μL/h. Depending on the chosen pump model and the delivery rate, the devices can be operated from 1 day to 6 weeks. In case a catheter is attached to the flow moderator of the ALZET® osmotic pump, substances can be delivered site-specifically directly into any organ or tissue, e.g. the brain. The catheter enables not only site-specific medication, but also time-programmed release patterns. For this purpose, the catheter is filled with drug segments separated by a non-miscible placebo compound which is also filled into the drug reservoir. Displacement of the liquid out of the catheter results in a transient drug release profile defined by the length of the different drug segments.

### 6.2. Ivomec SR® Bolus

Having a diameter of 20 to 30 mm and a length of about 100 mm, the Ivomec SR® Bolus pump (Merck & Co., Inc., Rahway, NJ, USA) is not as highly miniaturized as the previously described systems. However, the system for veterinary use is particularly noteworthy because of its system design and functionality. The osmotic pump is designed to administer ivermectin, an anthelmintic drug fighting parasitic worms directly in the rumen of cattles [50–52]. The device sediments in the rumen of the animal due to its higher density (up to 3.0 g/cm$^3$) and is permanently anchored by this. The osmotic agent compartment and the drug compartment of the device are separated by a wax-based piston. Typically, thermoresponsive drug formulations which melt at body temperature are released. As the piston pushes a melted substance, this technology was named Push-Melt™. Steady-state delivery of ivermectin can be maintained for 135 days with the pump. Afterwards, delivery ceases quickly.

### 6.3. DUROS®

The DUROS® system was developed by ALZA Corporation, Mountain View, CA, USA, which was acquired by Johnson and Johnson in 2001. Has the size of a matchstick and its cylindrical housing is made from titanium alloy (Fig. 6). One end of the cylinder incorporates a semi-permeable membrane material constructed from a polyurethane polymer whereas the other end features the drug outlet port. Next to the membrane, the housing contains the osmotic agent tablet consisting mainly of NaCl. A piston made from an elastomeric material separates the osmotic agent from the drug formulation. The drug outlet port has to be adapted to the rheological properties of the drug formulation. It can be implemented as simple as a straight channel or as a more sophisticated structure.

The device is activated when water from body fluids passes through the semi-permeable membrane into the compartment containing the osmotic agent. A pressure builds up and the compartment expands displacing the piston. This way the drug formulation is

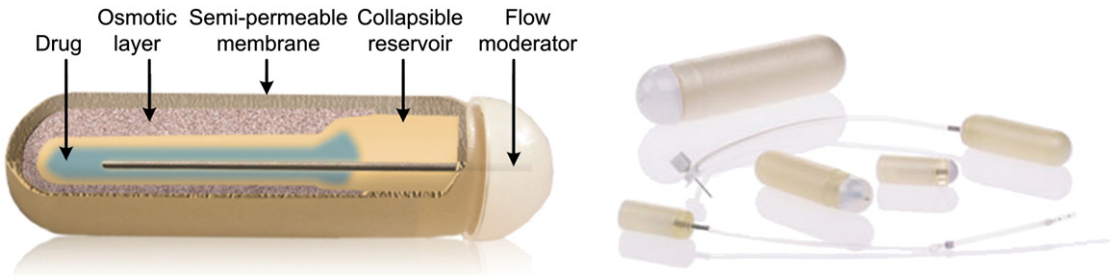


**Fig. 5.** ALZET® osmotic pumps are available in different sizes suitable for a multitude of systemic and site-specific (with catheter) drug delivery applications. Pictures with permission from Ref. [49].

displaced through the outlet at a constant rate. Depending on the composition of the semi-permeable membrane, the drug release can be maintained for a time period of 3 to 12 months. The device has an outside diameter of 4 mm, a length of 44 mm, and a drug reservoir capacity of 155 μL. It can be inserted subcutaneously beneath the skin at various locations on the arms and abdomen in a simple outpatient procedure. Being a non-biodegradable system, explantation has to be performed after drug depletion.

The first FDA-approved application incorporating the DUROS® technology was the palliative treatment of advanced prostate cancer with leuprolide acetate. The implant named Viadur® (Bayer AG, Leverkusen, Germany) delivered the drug over a period of 1 year. The behavior of the leuprolide acetate implant was extensively studied in several clinical long-term studies with focus on dose dependency [53,54], toxicity [55] as well as safety and efficacy [56,57]. Thereby, the revealed in vivo release rates were comparable to those observed under in vitro conditions [58] and were highly predicable [59].

The device was well accepted by patients [60,61]. However, the technical and pharmaceutical advantages of Viadur® failed to compensate the growing manufacturing costs and diminished market demand leading to the discontinuance of the product [62,63].

The DUROS® technology was also used in combination with the compound sufentanil intended for treatment of patients with opioid-responsive chronic conditions that result from a variety of causes. Sufentanil is 500 times more potent than morphine. Therefore, the Chronogesic™ (sufentanil) Pain Therapy System can cover a three-month-therapy at physician specified doses [64].

Further applications of the subcutaneous device are currently in the clinical development pipeline of Intarcia Therapeutics, Inc., Hayward, CA, USA. This includes active Phase III clinical development for type 2 diabetes mellitus treatment with exenatide for up to 1 year [65] as well as Phase I clinical evaluation for the treatment of obesity and chronic hepatitis C with weight regulating endocrine peptides (glucagon-like peptide-1) and type-1 interferons (omega interferon), respectively [66].

Besides the systemic applications mentioned above, DUROS® pumps can also be used for drug release to a specific target site. For this purpose, a catheter can be attached to the outlet port directing the drug release to the target organ or tissue. An adapted device with an increased outer diameter of 10 mm and a reservoir of 1080 μL is intended for intrathecal delivery of opioids such as morphine or hydromorphone for chronic pain and intratumoral chemotherapy of brain tumors, respectively [67].

**Fig. 6.** The DUROS® pump is subcutaneously inserted to deliver drugs for up to 1 year. Picture from Ref. [68].

### 6.4. BuccalDose

BuccalDose is a disposable intraoral drug delivery cartridge for the self-medicated treatment of Parkinson's disease (PD). Currently, advanced stages of this disorder are characterized by a narrowing therapeutic window. This requires either frequent per oral intake of tablets with short and strict time intervals or more invasive routes of administration, e.g. subcutaneous pumps or duodenal catheters with the preferred goal to reach constant drug plasma levels [69]. BuccalDose is aimed as a less invasive alternative compared to the latter approach. The system concept is based on a constant release of dopamine agonists to the buccal mucosa and subsequently to the bloodstream, thereby avoiding first-pass metabolism. The BuccalDose system is currently under preclinical development [70].

The disposable cartridge is magnetically attached into the receptacle of a partial removable prosthesis (Fig. 7A). By applying an assistive tool, the cartridge can be handled even by patients affected by motility disorders. The cartridge comprises further a RFID tag for identification purposes (e.g. sort of drug, adjusted release rate and operational time, expiration date, etc.). The RFID-tag and the filling level of the cartridge with drug can be read with an external base station. Hence, therapeutic relevant information like patient compliance, medication, and delivered amount of the cartridge can be determined before and after usage. By transmitting the data to a point of care unit, treatment is monitored and the patient is individually assisted in his home-based environment.

The cartridge is composed of the following components: (i) a micro injection molded housing made from a cyclic olefin copolymer (COC) with good barrier properties against water and high mechanical stiffness, (ii) a semi-permeable polyamide thin film composite membrane, (iii) a hyperelastic styrenic copolymer (SEBS) barrier membrane separating the osmotic agent from the drug, and (iv) fluidic capillaries for drug release. For attachment of the cartridge to the partial removable prosthesis, two neodymium cuboids ($1.6\times1.0\times0.5$ mm$^3$) are fixed on top of the main housing in addition to a RFID-tag of similar size. A laser-cut magnetizable stainless steel plate is located at the front side of the cartridge directly underneath the semi-permeable membrane. Due to the plate, the cartridge sticks to a magnetic assistive tool and can be handled this way during insertion and removal.

Similar to the intraoral IntelliDrug system, the degree of saliva secretion needs to be considered for proper opration.

### 6.5. Others

Of course, application of the osmotic principle is not only limited to drug delivery. It can also be employed to generate steady mechanical movements, forces, or pressures. Li and Su presented an osmotic-

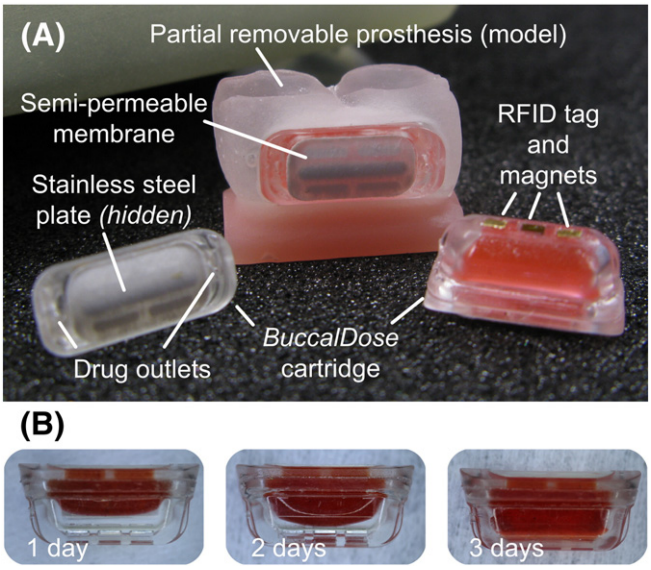


**Fig. 7.** (A) BuccalDose cartridge for intraoral osmotic drug delivery. The cartridge is insertable into a partial removable prosthesis. (B) Cross-sectional view of the cartridge after removal at day 1, day 2, and day 3 of use. The displacement of the hyperelastic membrane (SEBS) can be clearly detected and is used as a measure for the delivered drug volume.

powered system featuring a controlled linear displacement for bone distraction combined with the release of bone morphogenetic proteins [71]. Thereby, the main application area is seen in maxillofacial osteogenesis as illustrated in Fig. 8. The miniature device is composed of two 30 mm long cylindrically shaped polytetrafluoroethylene (PTFE) casings. The piston-type actuator used for distraction has an inner diameter of 500 µm whereas the diaphragm-type actuator used for drug release features an inner diameter of 250 µm. Thermoplastic polyurethane is used as the semi-permeable membrane material for both actuators. A maximum distraction force of 6 N was achieved at a linear displacement velocity of 32 µm/h over a time period of about one week. During this time, the second actuator released drug at a constant rate of 0.15 µL/h. The distraction microactuator can be tailored to realize optimal distraction rate, rhythm, and osteogenic activity.

A two compartment micropump driven by osmosis and entirely fabricated by MEMS technologies was presented by Su et al. [72]. The device comprises a system volume of $2.5\times2.5\times2.0\ mm^3$. Thereby, a liquid drug volume of 2 µL can be released at a constant delivery rate of 0.2 µL/h or lower. The system consists of a compartment made of PDMS which is fabricated by replica molding of epoxy-based SU-8 negative mold and is used as the drug reservoir as illustrated in Fig. 9. It further contains a delivery channel, a delivery port, and an osmotic microactuator unit used for squeezing out the drug reservoir [73]. The microactuator itself is composed of a cellulose acetate-based bottom layer serving as the semi-permeable membrane, a casted structural layer from the same material comprising an osmotic agent chamber, and a top layer of a flexible polyvinylidene chloride (PVDC) membrane with high barrier properties against water vapor transmission. The PVDC surface is then bonded to the PDMS cover with an intermediate layer of a styrenic copolymer (SIS) for system integration. Thereby, the liquid drug can be directly encapsulated during the bonding process. The delivery channel is 10 mm long with a cross-sectional area of $30\times100\ µm^2$. Consequently, the pressure drop remains moderate, while the diffusive outward flow of drug and the potential diffusive inward flow of contaminants are minimized.

## 7. Multi compartment drug delivery systems

Osmotic pumps with three or more compartments store the solvent in addition to the osmotic agent and the drug within the pump. Those

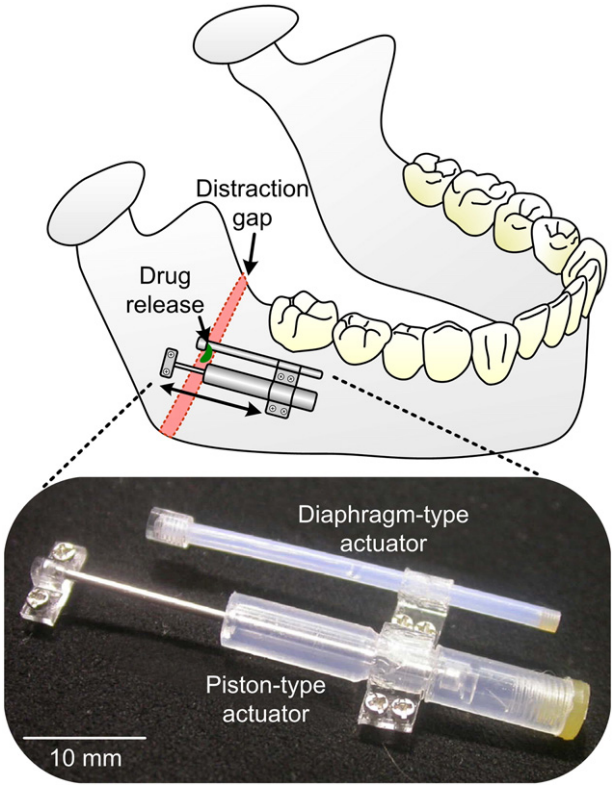


**Fig. 8.** Photograph of an assembly for distraction osteogenesis featuring a piston-type actuator for distraction and a diaphragm-type actuator for drug release. Adapted with permission from Ref. [71].

pumps are completely autonomous requiring neither external power nor any body fluids and can be applied to long-lasting and extreme conditions such as elevated temperatures or high pressures relevant for applications apart from medical purposes [74]. With respect to drug delivery, this kind of device architecture is especially beneficial if extracorporeal use is envisaged.

### 7.1. Acuros

An osmotic micropump employing the principle of osmoregulation is available by Acuros GmbH, a spin-off company of the Humboldt University Berlin, Germany [75]. Osmoregulation is a process known from phloem loading in plant leaves. The osmoregulatory micropump consists of a salt chamber (osmotic agent), a water chamber (solvent), and an extrusion chamber with a movable barrier displacing drug from the drug reservoir as illustrated in Fig. 10A. As a key feature, a semi-permeable hollow fiber meandering within the water chamber connects the salt chamber with the extrusion chamber. This enables water to penetrate into the fiber by osmosis and generates a convective flow inside the fiber towards the extrusion chamber. On its way towards the extrusion chamber, the diluted salt solution within the fiber passes the salt chamber containing higher concentrated solution. Therefore, a small fraction of water permeates back into the salt chamber. In turn, this leads to the displacement of salt solution at this dedicated location and generates a convective flow inside the osmotic agent chamber. Hence, a convective recirculation is established that supplies the fiber continuously with highly concentrated salt solution. Nevertheless, the majority of the diluted salt solution within the hollow fiber flows into the extrusion chamber and induces the outflow of the drug solution by displacing the moveable barrier into the liquid drug reservoir. The release rate of the system can be easily preset by adjusting the length of the extended fiber segment within the water chamber.

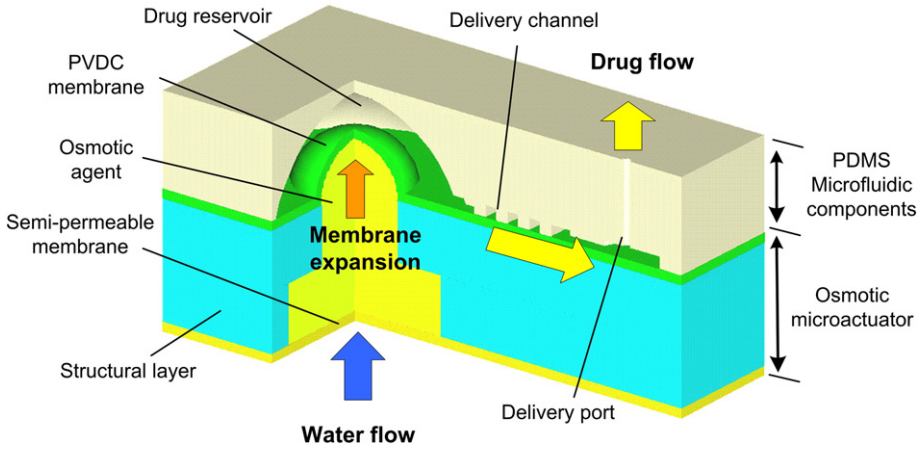


**Fig. 9.** Schematic diagram of the osmotic micropump entirely fabricated by MEMS technologies. Adapted with permission from Ref. [72].

The corresponding micropump (Fig. 10B) has the size of two matchboxes placed side by side and uses a standard 3.0 mL ready-to-fill or prefilled glass syringe as drug compartment. For each drug volume delivered from the syringe, the device consumes a certain volume of water and salt from the internal reservoirs. Thereby, the volume ratio between delivered liquid drug solution, consumed solvent (water), and consumed osmotic agent (salt) is 1:1:0.3. The solvent is supplied via a cartridge which is pressurized by a spring enabling easy start and stop of the pumping process. Furthermore, the selected materials are compatible with use during magnetic resonance imaging and the micropump is affordable enough to be disposed after single use. The preset flow rates range from 1.0 μL/h to 2.0 mL/h and are independent of backpressures up to 300 kPa. Hence, clogging of the micropump is very unlikely. Therefore, continuous intravenous or subcutaneous injections are independent of blood pressure and injection site.

### 7.2. Hydrogel pump

Smart polymers which are responsive to external stimuli, e.g. change in pH or temperature, can be applied to control drug release [76]. If the polymers are hygroscopic, i.e. liquid absorbing, they can additionally be used as osmotic agents. Possible examples include polymeric suspensions and swelling hydrogels. Micropumps utilizing this effect have been developed for applications such as microdispensing [77–80], fluid sampling [81], or lab-on-a-chip systems [82].

Chemical compounds maintain a solution with constant concentration in the osmotic compartment of a pump resulting in constant water flow across the semi-permeable membrane. In contrast, the concentration of polymeric suspensions is continuously lowered by the inflowing water and the water uptake of swelling polymers is depending on the particle size as well as the crosslinking density. Typically, this results in non-continuous and decreasing release rates. However, linearization of the release characteristics to almost zero-order release can be realized in case of hydrogels if the water supply is limited, i.e. the quantity of water provided is less than the hydrogel needs for swelling to equilibrium [83]. Generally, polymeric osmotic agents require not necessarily semi-permeable membranes due to their high molecular weight. Therefore, narrow microfluidic channels are often sufficient.

A pump introduced by Richter et al. [83] uses poly(N-isopropylacrylamide) (PNIPAAm) or other strong swelling superabsorbent polymers [84] as osmotic agents. The pump is activated by switching a trigger as shown in Fig. 11. After initialization, the reservoir opens and the liquid based swelling agent is provided to the hydrogel actuator. Since the reservoir is pressurized by a spring force, the supply with swelling agent is independent of the spatial orientation of the device. The swelling hydrogel has first to fill a predefined volume before it starts to displace the self-locking piston. Hence, the size of the

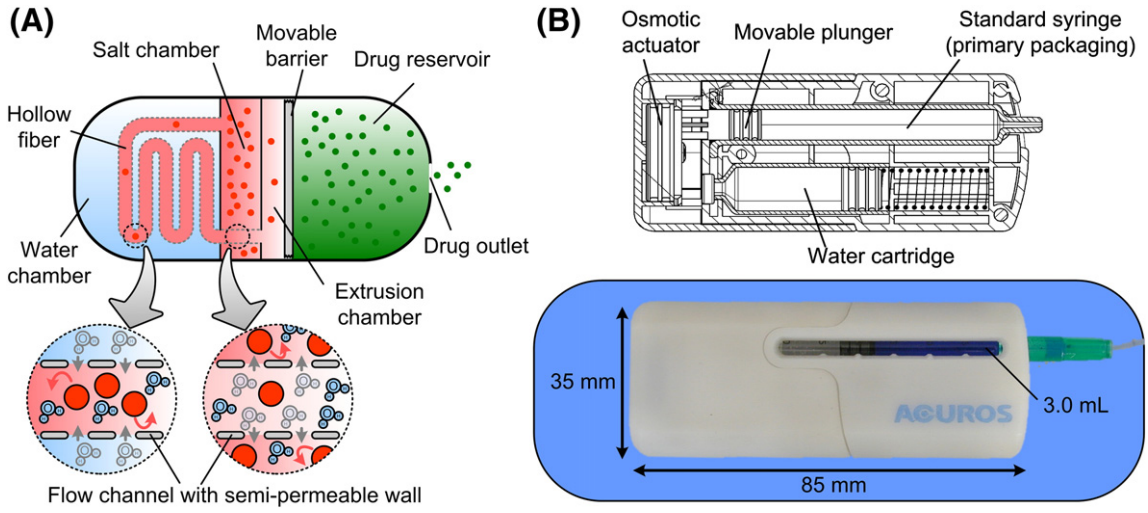


**Fig. 10.** Osmotic micropump utilizing the principle of osmoregulation: (A) Osmotic release mechanism adapted with permission from Ref. [75]; (B) Realization of the Auros micropump. Courtesy of Acuros GmbH.

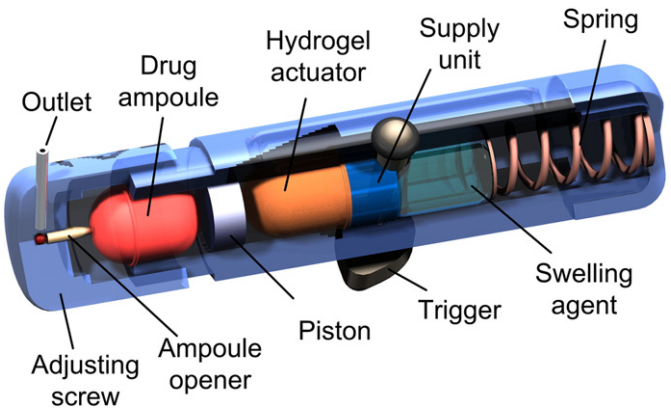


**Fig. 11.** Illustration of a hydrogel based osmotic micropump. Adapted with permission from Ref. [83].

volume determines a time delay which can be adjusted by an external screw enabling individual delays. Afterwards, the piston begins to move and presses a drug ampoule against an ampoule opener. Once the drug ampoule is crushed, delivery of drug through the outlet starts.

The pump was primarily developed for the chronotherapeutic treatment of the Dawn phenomenon of diabetes mellitus indicated by an increased blood sugar level in the morning. A patient suffering from this malfunction is required to trigger the device just before going to bed. If the time delay is properly adjusted, drug dosing starts then during the early morning period when the patient is still asleep. Consequently, medication is already realized at wake up.

## 8. Conclusions

Osmotic micropumps for drug delivery are applied to a broad range of different applications addressing multiple routes of administration. In general, three different operating principles of osmotic pumps having distinct advantages and disadvantages can be distinguished.

Single compartment pumps also including osmotic matrix systems feature simple and robust design and allow to store a maximum of drug in a given device volume. However, this device type is limited by the fact that the release rate depends on the drug itself. This requires the devices to be adapted to a specific drug. Single compartment pumps are predominantly applied when space for the device is limited.

Two compartment systems employ an osmotic agent different from the drug to be released resulting in a drug release rate independent of the drug properties. This increases the complexity of the device and less device volume is available for drug storage compared to single compartment pumps. All kind of liquid drugs can be delivered, including non-aqueous liquids and suspensions. Typically, this operation principle is predominantly applied to implantable pumps with a multitude of systemic and site-specific applications.

Requiring solvents for operation, osmotic pumps are predominantly used in liquid environments, e.g. body fluids. In order to be able to operate osmotic pumps in any environment, multicompartment architectures with an additional reservoir for solvents were developed. Although this increases further the device complexity, new fields of application such as the use as extracorporeal drug delivery systems can be addressed. However, until now only few approaches exist here.

In general, osmotic drug delivery systems provide distinct advantages compared to the standard therapies. Osmotic devices are especially beneficial for long-term applications eliminating the need for frequent intake of single doses as it is the case for tablets and injections. This can result in better patient compliance and adherence as well as a less strict therapy plan. Moreover, this makes them suitable for patients with substantial therapy adherence problems. Furthermore, by applying microengineering and new MEMS fabrication technologies, further miniaturization of the devices was enabled and resulted in new devices for body regions that were difficult to access so far.

Potential drawbacks of osmotic pumps include the temperature dependency of the principle. While this is mostly not an issue for intra-corporeal use, it could be of relevance for extracorporeal devices subjected to changing environmental conditions. Although the release rate of osmotic pumps is constant, the rate cannot be modified during operation with few exceptions. This requires knowledge on the optimum delivery rate already before operation. Additionally, refilling of the pumps is mostly not possible or complicated making osmotic pumps predominantly single-use devices. With respect to implantation, this resulted in a trend towards biodegradable materials requiring no explantation anymore.

By transforming ordinary drugs into better acting drugs, osmotic pumps offer pharmaceutical companies an accessible technology that can also manage the life cycle of drugs with closely expiring patents. However, many of the shown pumps which arrive now at the end of the technical development pipeline have still to prove their competitiveness on the medical markets.

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