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Review

Formulation aspects in the development of osmotically controlled oral drug delivery systems

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Abstract

Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug(s) from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane. By optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of diverse nature at a pre-programmed rate. In the present review, different types of oral osmotic systems, various aspects governing drug release from these systems, and critical formulation factors are discussed.

Keywords: Controlled drug delivery; Formulation factors; Osmotic drug delivery; Osmotic pumps; Targeted delivery

1. Introduction

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). The reason for this paradigm shift is relatively low development cost and time required for introducing a NDDS ($20–50 million and 3–4 years, respectively) as compared to a new chemical entity (approximately $500 million and 10–12 years, respectively). In the form of NDDS, an existing drug molecule can get a 'new life,' thereby, increasing its market value, competitiveness, and patent life. Among the various NDDS available in market, per oral controlled release (CR) systems hold the major market share because of their obvious advantages of ease of administration and better patient compliance [1]. CR delivery systems provide desired concentration of drug at the absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency. These products typically provide significant benefits over immediate-release formulations, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to a simplified dosing schedule.

A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral CR dosage forms fall in

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the category of matrix, reservoir, or osmotic systems. In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/coated by a rate controlling membrane. However, factors like pH, presence of food, and other physiological factors may affect drug release from conventional CR systems (matrix and reservoir). Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system [2]. Alza Corporation of the USA (now merged with Johnson & Johnson, USA) was first to develop an oral osmotic pump and today also, they are the leaders in this field with a technology named OROS™. The oral osmotic pumps have certainly come a long way and the available products based on this technology [1] and number of patents granted in the last few years [3] makes its presence felt in the market. They are also known as GITS (gastro-intestinal therapeutic system) and today, different types of osmotic pumps are available to meet variety of drug delivery demands (Table 1). Osmotic pumps can be used as experimental tools to determine important pharmacokinetic parameters of new or existing drugs. At the same time, they can also be utilized to deliver drugs at a controlled and predetermined rate. In an earlier review, different types of oral osmotic systems and factors affecting the drug release were discussed [4]. Present review is an update on the formulation aspects that are important in the development of oral osmotic systems.

2. Osmotically controlled oral drug delivery

Osmotic systems utilize osmotic pressure as driving force for controlled delivery of drugs. Fig. 1a shows schematic diagram of elementary osmotic pump (EOP), which in its simplest design, consists of an osmotic core (containing drug with or without an osmagent) coated with a semipermeable membrane (SPM). The dosage form, after coming in contact with the aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation [5]. This osmotic imbibition of water results in formation of a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane. Though 60–80% of drug is released at a constant rate from EOP, a lag time of 30–60 min is observed in most of the cases as the system hydrates before zero-order delivery from the system begins [6]. These systems are suitable for delivery of drugs having moderate water solubility.

Push–pull osmotic pump (PPOP) can be used for delivery of drugs having extremes of water solubility. As shown in Fig. 1b, it is a bilayer tablet coated with a SPM. Drug along with osmagents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents [7,8]. The drug compartment is connected to the outside environment via a delivery orifice. After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice [9]. A number of modifications are available for this type of system such as delayed push–pull system (as used in Covera HS, extended release formulation for verapamil), multi-layer push–pull system (for pulsatile or delayed drug delivery), and push–stick system (for delivery of insoluble drugs requiring high loading, with an optional delayed, patterned, or pulsatile release profile).

OROS-CT is used as a once- or twice-a-day formulation for targeted delivery of drugs to the colon [10]. The OROS-CT can be a single osmotic unit or it can comprise of as many as five to six push–pull osmotic units filled in a hard gelatin capsule (Fig. 2). After coming in contact with the gastrointestinal fluids, gelatin capsule dissolves and the enteric coating prevents entry of fluids from stomach to the system. As the system enters into the small intestine, the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time, flowable gel is formed in the drug compartment which is pushed out of the orifice at a rate which is precisely controlled by the rate of water transport across the SPM.

Table 1
Different types of commercially available osmotic systems[a]

(I) Osmotic pumps for experimental research	
ALZET (Durect Corp., USA)	Miniature, implantable osmotic pumps for laboratory animals. Commonly implanted subcutaneously or intraperitoneally but, with the help of a catheter, can be used for intracerebral, intravenous, and intraarterial infusion. Different models having delivery rates from 0.25 to 10 μl/h and durations from 1 day to 4 weeks available. Delivery profile independent of drug formulation.
OSMET (Durect Corp.)	Used as experimental tools for human pharmacological studies and can be used for oral, rectal, or vaginal administration. Delivery profile independent of drug formulation and it is available with release rates ranging from 8 to 120 μl/h
(II) Osmotic pumps for humans	
Oral	
Elementary osmotic pump (Alza Corp., USA)	Single layer tablet for delivery of drugs having moderate water solubility. Can be utilized for zero-order delivery as well as pulsed release.
Push–pull osmotic pump (Alza Corp.)	Bilayer tablet, used to deliver drugs having low to high water solubility. Products such as Ditropan XL (oxybutynin chloride), Procardia XL (nifedipine), and Glucotrol XL (glipizide) are based on this technology. Number of modifications available such as delayed push–pull system, multi-layer push–pull system, and push–stick system.
L-OROS (Alza Corp.)	Designed to deliver lipophilic liquid formulations and is suitable for delivery of insoluble drugs.
OROS-CT (Alza Corp.)	For targeted delivery to colon and can be used for local or systemic therapy.
Portab System (Andrx Pharmaceuticals, USA)	Tablet core consists of soluble agent, which expands and create microporous channels for drug release.
SCOT (single composition osmotic tablet, Andrx Pharmaceuticals)	Utilizes various osmotic modulating agents and polymer coatings to provide zero-order release.
ENSOTROL drug delivery system (Shire Labs. Inc., USA)	Utilizes various solubilizing and wicking agents for delivery of poorly water soluble drugs.
Zero-Os tablet technology (ADD Drug Delivery Technologies AG, Switzerland)	Specifically for delivery of lipophilic compounds. Consists of gel forming agents in the core that forms gel after coming in contact with water and drug is released as a fine dispersion.
Implantable	
DUROS (Durect Corp.)	Miniature (4×45 mm), implantable osmotic pumps for long-term, parenteral, zero-order delivery of potent therapeutic agents. Deliver drugs at a precisely controlled and constant rate within therapeutic range for long periods. Viadur (leuprolide acetate), a successful product in the market, delivers leuprolide continuously at a nominal rate of 125 μg/day over 1 year for palliative treatment of prostate cancer. DUROS sufentanil (3 months continuous delivery for treatment of chronic pain) and DUROS hydromorphone (for continuous delivery to the spine) are in various developmental phases.

Table 1. Continued

(III) Osmotic pumps for veterinary use	
VITS (veterinary implantable therapeutic system, Alza Corp.)	Designed to deliver drugs at a controlled rate in animals for a period of 1 day to 1 year and can be implanted subcutaneously or intraperitoneally in any ruminant, non ruminant, companion, or production animals. Available in various sizes (2–10 mm in diameter) and can be designed to give delivery rates from μg/day to mg/day. Drug is kept isolated from body fluids and thus, can be used to deliver water-labile compounds, e.g. proteins and peptides.
RUTS (ruminal therapeutic system, Alza Corp.)	For controlled delivery of drugs up to 1 year in the rumen of cattle and sheep. Up to 10 g of drug can be administered. Generally 2–3 cm in diameter and up to 10 cm in length but larger dimensions are possible depending upon application. Can be designed for zero-order delivery of up to g/day for durations ranging from 1 day to 1 year. Ivomec SR (ivermectin) and Dura SE (sodium selenite) available commercially.

[a] Compiled from Refs. [1,79–84].

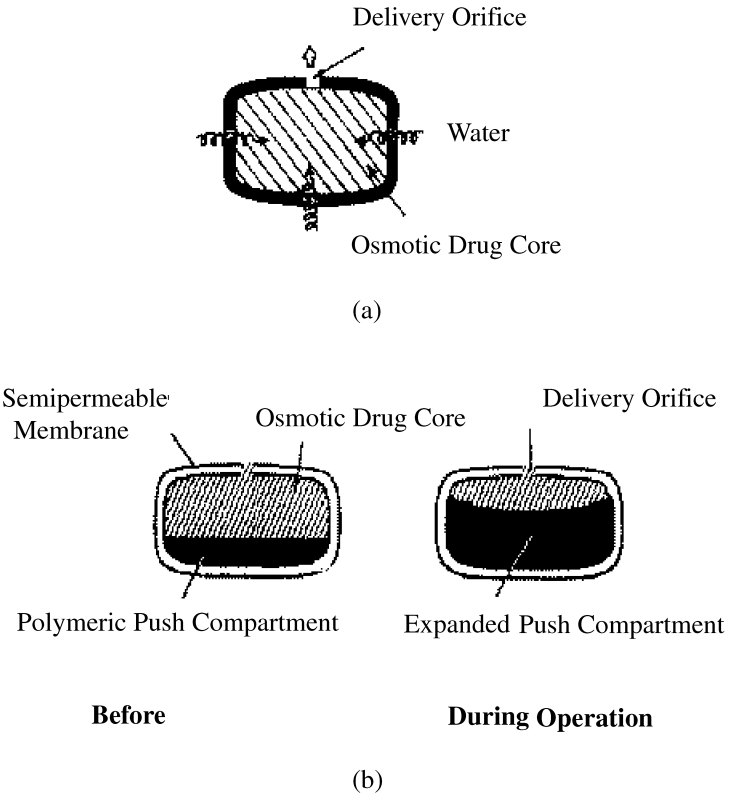

Fig. 1. Schematic diagram of an elementary osmotic pump (a) and a push–pull osmotic pump (b).

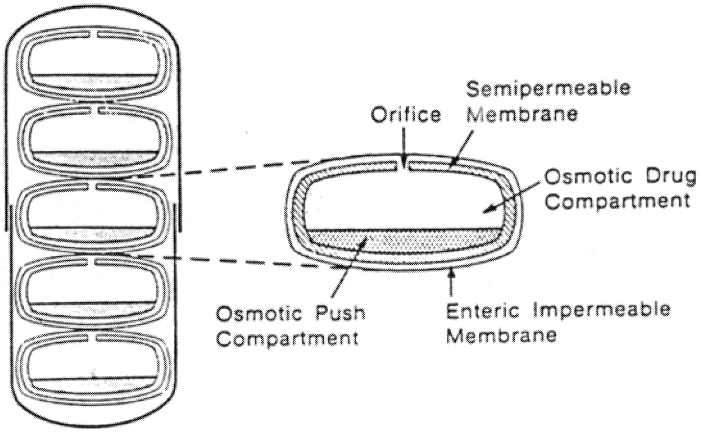

Fig. 2. Cross-sectional diagram of OROS CT delivery system. Reprinted from Ref. [10] by courtesy of Marcel Dekker, New York.

Liquid OROS controlled release systems are designed to deliver drugs as liquid formulations and combine the benefits of extended-release with high bioavailability [11]. Fig. 3 shows the cross-sectional diagram for L-OROS SOFTCAP delivery system before and during operation. These systems are suitable for controlled delivery of liquid drug formulations including lipophilic self-emulsifying formulations (SEF). The liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate-controlling membrane. A delivery orifice is formed through these three layers. When the system is in contact with the aqueous environment, water permeates across the rate controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice. The liquid drug formulation is pumped through the delivery orifice. L-OROS HARDCAP is similar to L-OROS SOFTCAP and consists of a liquid drug layer, a barrier layer, and an osmotic engine, all encased in a hard gelatin capsule and coated with a SPM [12]. A delivery orifice, drilled in the membrane at the end of the drug layer, provides an outlet for the drug suspension. After coming in contact with the aqueous environment, water is imbibed across the SPM, expanding the osmotic engine. The

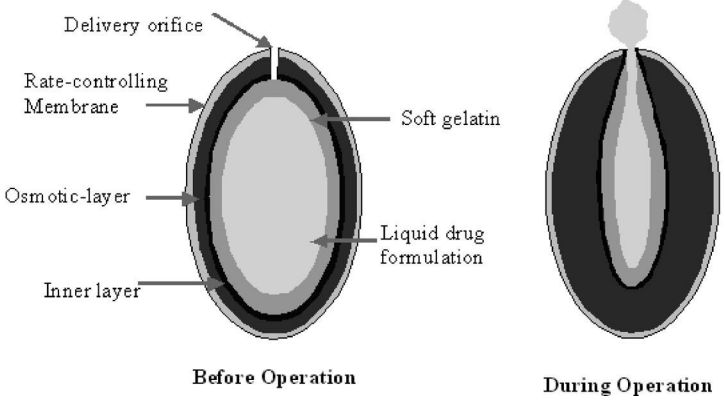

Fig. 3. Cross-sectional diagram of L-OROS delivery system before and during operation. Courtesy by Alza Corp., reprinted from Ref. [11] with permission of the Controlled Release Society 2000©.

osmotic engine pushes against the barrier, releasing drug through the delivery orifice.

In majority of cases, osmotic systems have a pre-formed passageway in the membrane from where the drug release takes place. Controlled porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in an in situ formation of a microporous membrane (Fig. 4). The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role [13–15].

Multi-particulate delayed release systems consist of pellets of drug (with or without osmagents) coated with a SPM. These pellets, after coming in contact with the aqueous environment, imbibe water osmotically, which results in a rapid expansion of the membrane leading to the formation of pores and drug release [16,17].

Use of asymmetric membranes in osmotic drug delivery that consist of very thin, dense skin structure supported by a thicker, porous substructural layer is also described in the literature [18–22]. These membranes have high flux characteristics and thus, higher release rates for poorly water-soluble drugs can be obtained. Moreover, the permeability of the membranes to water can be easily adjusted by controlling the membrane structure and porosity. The asymmetric membranes can be applied to tablets, capsules, or multi-particulate formulations.

In sandwiched osmotic tablet (SOTS), a tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM [23]. As seen in Fig. 5, both the drug layers are connected to the outside environment via two delivery orifices (one on each side). After coming in contact with the aqueous environment, the middle push layer containing swelling agents swells and the drug is released from the delivery orifices. The advantage with this type of system is that the drug is released from the two orifices situated on two opposite sides of the tablet and thus can be advantageous in case of drugs which are prone to cause local irritation of gastric mucosa.

3. Formulation aspects

Before discussing the formulation variables that affect the release of drugs from oral osmotic systems, it will be prudent to deal with some of the theoretical aspects. The delivery of agent from oral osmotic systems is controlled by the influx of solvent across the SPM, which in turn carries the agent to the outside environment. Water influx into EOP can be described by the following equation [5]:

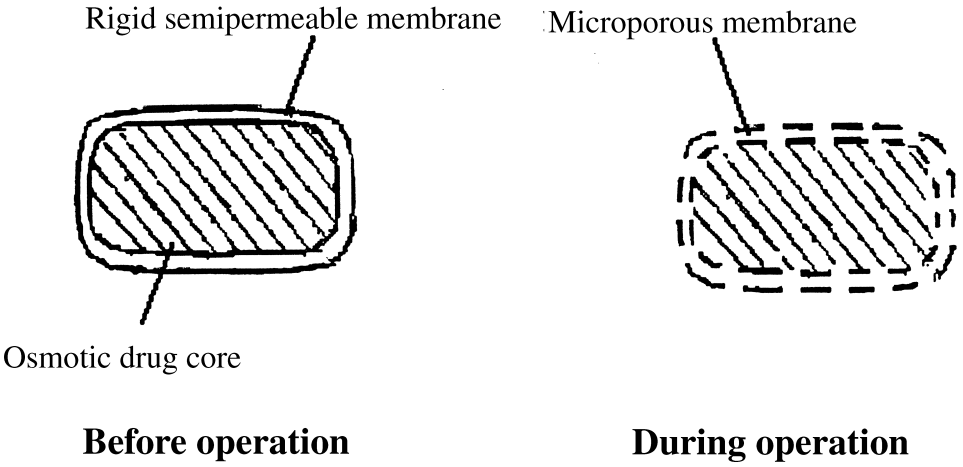

Fig. 4. Schematic diagram of controlled porosity osmotic pump before and during operation.

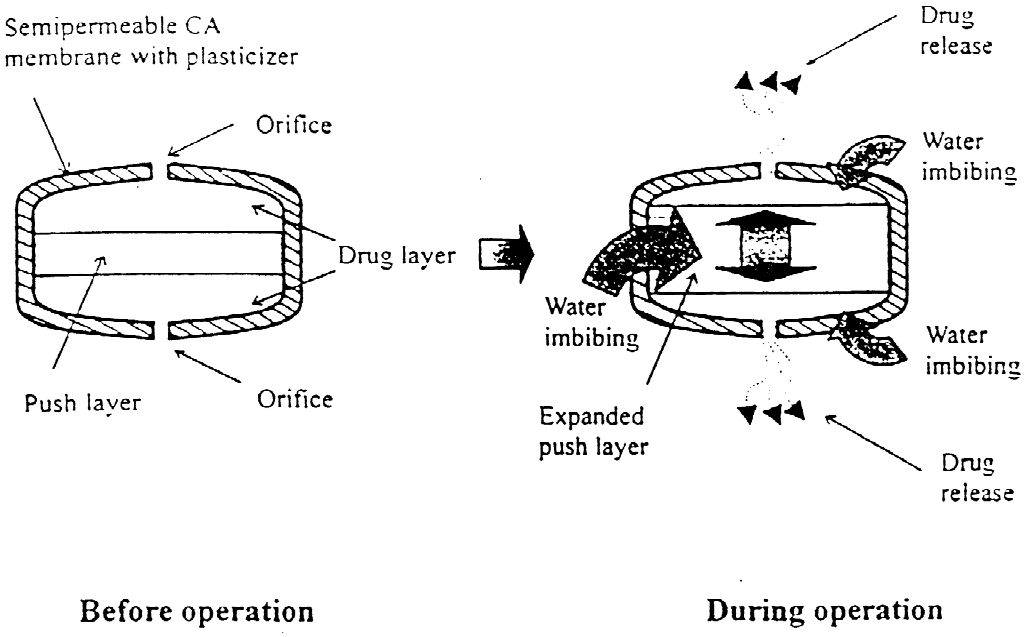

Fig. 5. Schematic diagram of sandwiched osmotic tablet before and during operation. Reprinted from Ref. [23] with permission from Excerpta Medica, Amsterdam.

$$\frac{dv}{dt} = \frac{A}{h} Lp(\sigma\Delta\pi - \Delta p) \quad (1)$$

where dv/dt is water influx, A and h are the membrane area and membrane thickness, respectively; Lp is mechanical permeability; σ is the reflection coefficient; and $\Delta\pi$ and Δp are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system. The general expression for the solute delivery rate, dM/dt, obtained by pumping through the orifice is given by:

$$\frac{dM}{dt} = \frac{dv}{dt} \cdot C \quad (2)$$

where C is the concentration of compound in the dispensed fluid.

Reflection coefficient takes into account the leakage of solute through the membrane. A perfectly SPM is selectively permeable to water only and does not allow solute to pass through it. Thus, in case of a perfectly semipermeable membrane, σ is close to unity. As size of the delivery orifice increases, hydrostatic pressure inside the system is minimized and $\Delta\pi \gg \Delta p$. Since, osmotic pressure of the gastrointestinal fluids is negligible as compared to that of core, π can be safely substituted for $\Delta\pi$. By replacing the product $Lp\sigma$, in Eq. (1), by a constant K and substituting Eq. (1) in Eq. (2), the following equation is obtained:

$$\frac{dM}{dt} = \frac{A}{h} K\pi C \quad (3)$$

The best possible way to achieve a constant release from osmotic systems is through proper selection and optimization of the SPM (to maintain the first three terms on the right hand side of the equation constant) and maintaining a saturated solution of drug within the core. As long as excess solid agent is present inside the system, both π and C in Eq. (3) can be maintained at constant levels. Therefore, it is possible to obtain constant zero-order release rates from osmotic system by maintaining the terms in Eq. (3) constant.

Other equations dealing with theoretical aspects of drug release from PPOP and CPOP are discussed

elsewhere [9,13,14]. Various factors that affect the drug release from osmotic pumps and should be considered in the formulation development are listed in Table 2 and discussed below

3.1. Solubility

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation [24,25]:

$$F(z) = 1 - \frac{S}{\rho} \quad (4)$$

where $F(z)$ is the fraction released by zero-order kinetics, S is the drug's solubility (g/cm^3), and ρ is the density (g/cm^3) of the core tablet. Drugs with a solubility of ≤ 0.05 g/cm^3 would be released with $\geq 95\%$ zero-order kinetics according to Eq. (4). However, the zero-order release rate would be slow according to Eq. (3), due to the small osmotic pressure gradient. Conversely, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core, and thus, extend this technology for delivery of drugs that might otherwise have been poor candidates for osmotic delivery. Some of the approaches that have been used to deliver drugs having extremes of solubility are:

3.1.1. Co-compression of drug with excipients

Incorporation of excipients that modulate the solubility of drug within the core can be one approach to control the release of drugs from the osmotic systems.

McClelland and coworkers [24,25] reported CPOP of a highly water-soluble drug, diltiazem hydrochloride (solubility more than 590 mg/ml at 37 °C). Because of very high water-solubility, the majority of the drug fraction was released predominantly at a first-order rather than the desired zero-order rate. The solubility of diltiazem hydrochloride was reduced to 155 mg/ml by incorporation of sodium chloride (at 1 M concentration) into the core tablet formulation. The modification resulted in more than 75% of the

Table 2
Formulation factors affecting drug release from oral osmotic pumps

Drug solubility	Release rate directly proportional to the solubility of drug within the core. Both highly and poorly water soluble drugs, per se, are not good candidates for osmotic delivery. Number of approaches available to deliver drugs having extremes of solubility.
Osmotic pressure	Release rate directly proportional to the osmotic pressure of the core formulation. Additional osmagent required if drug does not possess suitable osmotic pressure.
Delivery orifice	Should be within the desired range to control the drug release. Number of approaches available to create orifice within the membrane.
Coating membrane	Release rate affected by the type and nature of membrane-forming polymer, thickness of the membrane, and presence of other additives (type and nature of plasticizer, flux additives, etc.). Membrane permeability can be increased or decreased by proper choice of membrane-forming polymers and other additives.

drug to be released by zero-order kinetics over a 14–16-h period.

Controlled porosity solubility modulated osmotic pumps for delivery of drugs having low water solubility are described in US patent nos. 4,946,686 and 4,994,273 [26,27]. The composition described consists of controlled release solubility modulating agents, which are either surfactants (e.g. sodium dodecyl sulfate) or complexing agents (e.g. sodium salicylate). In order to prolong the availability of these excipients within the device, they were either surrounded by a rate controlling membrane or dispersed in a matrix. In the examples, tablet cores of two different drugs, namely, simvastatin and lovastatin, along with the solubility modulating agents were prepared and coated with a microporous membrane. The release of drug from the systems was controlled for an extended period of 4–24 h.

Herbig et al. [20] reported osmotic delivery of doxazosin, which has pH-dependent solubility. Tablet cores containing drug, along with organic acids (succinic and adipic acid) to increase the solubility of doxazosin within the core, were prepared and coated with asymmetric membranes. The solubility of doxazosin was improved in the presence of organic acids and pH-independent release patterns were obtained.

Use of polymer coated buffer components to modulate the drug solubility within the core is described in US patent no. 4,755,180 [28]. Solubility of a weakly acidic drug, acetyl salicylic acid, was modified by a basic excipient, which maintains alkaline pH within the device. The drug and the solubility modifying agent (sodium acetate) were coated separately by a rate controlling film of hydroxypropyl methyl cellulose (HPMC), mixed, and compressed in the form of a tablet. The tablet cores were coated and a hole drilled in the membrane wall. Coating of sodium acetate ensures its availability within the device for prolonged period and thus solubility of the drug is controlled through out the operational life span of the device. The drug was released in predominantly zero-order fashion for the desired period of time.

Use of buffers, which react with the drug to produce a new compound having thermodynamic properties different from the parent drug, is described in US patent no. 4,326,525 [29]. Theophylline, along with L-tartaric acid and polyvinyl pyrrolidone (PVP), was formulated in the form of EOP. Theophylline, in presence of tartaric acid, is converted to theophylline tartarate. Theophylline free-base had a solubility of 10 mg/ml and theophylline tartarate had a solubility of 220 mg/ml in water at 37 °C. Drug release from the systems was found to be constant over a period of 7 h.

In another study [30], solubility of a weakly acidic drug, nimesulide, was improved by using alkalinizing agents like disodium hydrogen phosphate and sodium bicarbonate. Nimesulide, along with different alkalinizing agents, was formulated in the form of EOP and release profile compared with immediate-release tablets. It was found that release of nimesulide from the osmotic pumps was relatively slow and prolonged for 12 h.

Co-compression of drugs along with solubility modulating agents can also be utilized for pulsatile delivery of drugs. This was demonstrated in the case of salbutamol [31–33], a highly water-soluble drug (270 mg/ml in pure water). Solubility of salbutamol was reduced by the addition of sodium chloride in the tablet core (11 mg/ml in a saturated salt solution). Salbutamol, along with sodium chloride was formulated in the form of osmotic pumps, which after coming in contact with the aqueous environment, initially imbibes water at a rate controlled by the osmotic pressure of the core formulation. Due to the presence of excess of salbutamol within the tablets, sodium chloride is depleted first from the device. This results in decrease of osmotic pressure of the solution inside the tablets and thus the rate of water flow into the tablet decreases. However, the solubility of salbutamol is increased due to a fall in sodium chloride concentration and its delivery to the body actually increases. The net result is a tablet formulation that initially delivers salbutamol at a relatively constant rate, until sodium chloride gets exhausted. After this, the remaining drug is delivered as a large pulse. Using this approach, zero-order release was achieved for about 7 h, followed by a pulsatile release of 7–9 h.

3.1.2. Use of encapsulated excipients

Thombre and coworkers [34,35] described a capsule device coated with asymmetric membranes to deliver drugs having poor water-solubility (Fig. 6). In the examples, solubility of a poorly water-soluble

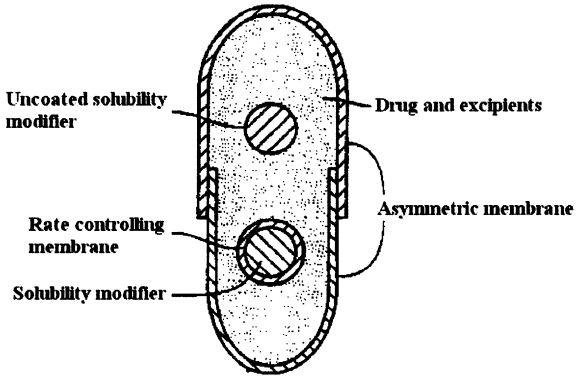

Fig. 6. Schematic view of delivery system having encapsulated excipients (from US patent no. 5,697,922).

drug, glipizide, was improved by incorporation of encapsulated excipients (pH-controlling excipients) within the capsule device. The solubility modifier (meglumine), in the form of mini-tablets, was coated with a rate controlling membrane to prolong its availability within the core. Thus, the solubility of glipizide was improved leading to its prolonged release from the device.

3.1.3. Use of swellable polymers

Swellable polymers can be utilized for osmotic delivery of drugs having poor aqueous solubility. Examples using this approach are reported in US patent no. 4,992,278 [36] for carbamazepine, theophylline, acetylsalicylic acid, and nifedipine. The formulation mainly consists of a compartment, containing the drug, swelling agents, and osmagents, coated with a rate controlling membrane. Vinylpyrrolidone/vinyl acetate copolymer (Kollidon® VA 64, BASF) and polyethylene oxide (MW: 5×10^6, Polyox®-coagulant, Union Carbide) were used as swelling agents. Uniform rate of swelling of these polymers ensures that the drug is released at a relatively constant rate. Also, the pressure produced during swelling does not lead to rupture of the system.

In addition, PPOP can also be utilized for delivery of drugs having either high, e.g. oxybutynin chloride [37], or low water solubility, e.g. glipizide [38–41]. Drug is released from the delivery orifice in the form of a very fine dispersion ready for dissolution and absorption.

Sandwiched osmotic tablets (SOTS) have also been utilized for osmotic delivery of water insoluble drugs, such as nifedipine [23]. The release profile from the tablets was found to be comparable with the commercially available push–pull osmotic system of the drug.

3.1.4. Use of effervescent mixtures

Use of effervescent mixture, can be another approach to deliver poorly water-soluble drugs from osmotic dosage forms. After administration, the effervescent mixture containing the drug is delivered under pressure through the delivery orifice in the membrane. This method of enhancing release of poorly water-soluble drug is reported in US patent no. 4,036,228 [42]. In one of the examples, citric acid and sodium bicarbonate were used as the effervescent couple for the delivery of acetyl salicylic acid. The formulation imbibes aqueous fluids across the membrane causing the couple to generate an effervescent solution that dispenses the drug in a suspension form.

3.1.5. Use of cyclodextrin derivatives

Incorporation of the cyclodextrin–drug complex has also been used as an approach for delivery of poorly water-soluble drugs from the osmotic systems. A CPOP has been described for testosterone (having a solubility of 0.039 mg/ml at 37 °C), solubility of which was improved to 76.5 mg/ml through complexation with sulfobutyl ether-β-cyclodextrin sodium salt, (SBE)-$_{7m}$-β-CD [43]. In a comparative study with hydroxypropyl-β-cyclodextrin (HP-β-CD) and a sugar mixture, it was found that testosterone release from the device in the presence of (SBE)-$_{7m}$-β-CD was mainly due to osmotic pumping while for HP-β-CD, the major contribution was due to diffusion. In case of the sugar mixture, the drug was poorly released due to the absence of solubilizer. Similar results were obtained with prednisolone [44] and chlorpromazine [45]. It was reported that (SBE)-$_{7m}$-β-CD could serve both as a solubilizer and osmotic agent.

3.1.6. Resin modulation approach

Release of a highly water-soluble drug, diltiazem hydrochloride from a CPOP was modulated effectively using positively charged anion-exchange resin,

poly (4-vinyl pyridine) [25]. Pentaerythritol was used as osmotic agent and citric and adipic acids were added to maintain a low core pH to assure that both the drug and resin carry a positive charge. The solubility of diltiazem hydrochloride was reduced for an extended period and pH-independent zero-order release was obtained.

3.1.7. Use of alternative salt form

For an ionic drug, an alternative salt form can also be used as reported for metoprolol and oxprenolol [2]. Hydrochloride salt used in commercial formulations of oxprenolol was found to have high water solubility (70% w/v) making it difficult to achieve extended zero-order delivery from osmotic systems. The authors replaced it by the less soluble succinate salt. In case of metoprolol, they used fumarate salt form as drug and osmotic driving agent, instead of tartrate salt. These salt forms were found to have optimum solubility and provided extended release up to 24 h.

3.1.8. Use of crystal habit modifiers

If the drug exists in more than one crystal form, each having different aqueous solubility, it is beneficial to include a crystal modifying agents. One such example is reported in US patent no. 5,284,662 [46], wherein a slightly soluble drug, carbamazepine, along with crystal modifying agents (combination of hydroxymethyl cellulose and hydroxyethyl cellulose) and other excipients was formulated in the form of osmotic pumps that were able to provide approximately zero-order release for the desired period of time.

3.1.9. Use of lyotropic crystals

Use of lyotropic liquid crystals, to assist osmotic delivery of poorly water soluble drugs, is also reported in the literature [47,48]. The lyotropic liquid crystals are non-polymeric compounds, generally in the molecular weight range of 200–1500. Also known as amphipathic compounds, these form mesophases and swell in presence of water. Compounds that can be used as lyotropic liquid crystals include natural phosphatides such as phosphatidylcholine (lecithin), phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, and the like. Few examples using this approach are mentioned in US patent no. 5,108,756 and 5,030,452. In these examples, Alcolec lecithin (American Lecithin Co., Atlanta, GA) and mixture of soybean phospholipids was utilized for osmotic delivery of two insoluble drugs, namely, glipizide and prazosin. The inventors claimed that the extended drug release up to 24 h was achieved.

3.1.10. Use of wicking agents

Inclusion of wicking agents in the osmotic formulations has also been reported as an approach for poorly water-soluble drugs [49]. A wicking agent is dispersed throughout the composition that enhances the contact surface area of drug with the incoming aqueous fluids. Thus, the drug is released predominantly in a soluble form through the delivery orifice in the membrane. The authors delivered nifedipine using this approach and some of the reported wicking agents are colloidal silicon dioxide, PVP, sodium lauryl sulfate, etc.

3.2. Osmotic pressure

Osmotic pressure, like vapor pressure and boiling point, is a colligative property of a solution in which a nonvolatile solute is dissolved in a volatile solvent. Osmotic pressure of a solution is dependent on the number of discrete entities of solute present in the solution. From Eq. (3), it is evident that the release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation. For controlling the drug release from these systems, it is important to optimize the osmotic pressure gradient between inside compartment and the external environment. It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment [6]. If a drug does not possess sufficient osmotic pressure, an osmagent can be added in the formulation. Some of the compounds that can be used as osmagents are listed in Table 3.

Polymeric osmagents are mainly used in the fabrication of PPOPs and other modified devices for controlled release of drugs with poor water solubility. These are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state. These polymers have a

Table 3
Compounds that can be used as osmagents

Category	Examples
Water-soluble salts of inorganic acids	Magnesium chloride or sulfate; lithium, sodium, or potassium chloride; lithium, sodium, or potassium sulfate; sodium or potassium hydrogen phosphate, etc.
Water-soluble salts of organic acids	Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate, etc.
Carbohydrates	Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc.
Water-soluble amino acids	Glycine, leucine, alanine, methionine, etc.
Organic polymeric osmagents	Sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linked PVP, polyethylene oxide, carbopols, polyacrylamides, etc.

capacity to retain a significant portion of the imbibed water within the polymer structure [8].

It is possible to confirm the contribution of osmotic pressure in drug release from osmotic systems by conducting the release studies in media of different osmotic pressure. The release rates obtained can be plotted against the osmotic pressure difference across the device wall. Using this approach, release of potassium chloride from CPOP was studied in aqueous media of different osmotic pressure and as seen from Fig. 7, an inverse relationship was found between the two [13,14]. A linear relationship was obtained confirming osmotic release from the system.

3.3. Delivery orifice

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of delivery orifice must be optimized in order to control the drug release from osmotic systems. If the size of delivery orifice is too small, zero-order delivery will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery. On the other hand, size of delivery orifice should not also be too large otherwise; solute diffusion from the orifice may take place. There are mathematical calculations that can be used to calculate the optimum size of the delivery orifice [5]. Drug release from osmotic systems is not affected by the size of the delivery orifice within certain limits as reported in the following examples

Drug release from osmotic pumps of nifedipine was studied as a function of orifice diameter and no significant differences were found in the release profiles for orifice diameter ranging from 0.25 to 1.41 mm [50]. Drug release was somewhat rapid with an orifice diameter of 2.0 mm possibly because

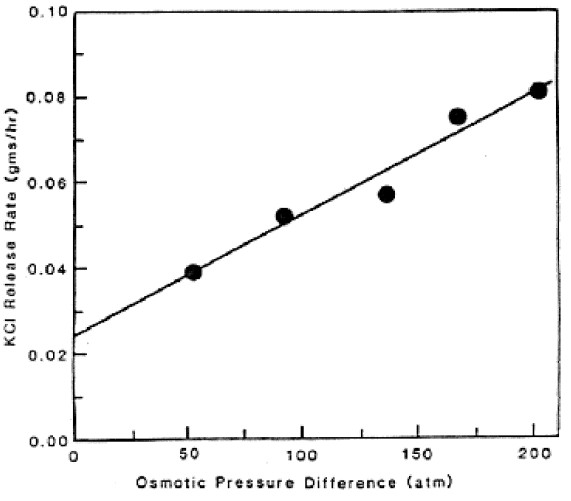

Fig. 7. Dependence of release rate from controlled porosity osmotic pumps of potassium chloride as a function of osmotic pressure difference across the device wall. Reprinted from Ref. [13] with permission from Elsevier, Amsterdam.

of significant diffusion. On the other hand, a longer lag time and unpredictable and slower release rates were obtained from the systems without any orifice.

In a study by Theeuwes [5], a complete membrane controlled delivery of potassium chloride was obtained with orifice diameter in the range of 0.075–0.274 mm. At orifice size of 0.368 mm and above, control over the delivery rate was lost because of significant contribution from diffusion and possibly convection. However, no systematic trends were observed within the orifice diameter between 0.075 and 0.274 mm.

Delivery orifices in the osmotic systems can be created with the help of a mechanical drill [30,51–56], but for commercial production scale, tablets need to be produced using a continuous process. Some of the reported processes to create delivery orifices in the osmotic systems are

3.3.1. Laser drilling

Laser drilling is one of the most commonly used techniques to create delivery orifice in the osmotic tablets. The top view of the portion of the apparatus used to drill hole in the osmotic tablets is shown in Fig. 8a [57]. In simple words, the tablets in which holes are to be formed are charged in the hopper. The tablets drop by gravity into the slots of the rotating feed wheel and are carried at a predetermined velocity to the passageway forming station. At the passageway forming station, each tablet is tracked by an optical tracking system. If the speed of the moving tablets increases, the hole may become elliptical because of movement of tablets during the laser firing time. To avoid this problem, tracking velocity is synchronized with the velocity at which the tablets are moving. As shown in Fig. 8b, the tracking is accomplished by the rotational oscillation of the mount and tracking mirror of the optical tracking system. During tracking, laser beam is fired in a pulse mode fashion and the beam is transmitted by the optical tracking mechanism onto the surface of the moving tablets and moves with the moving tablets as the mirror oscillates clockwise. The walls of the tablet absorb the energy of the beam and gets heated ultimately causing piercing of the wall and, thus forming passageway. After completion, the tracking mirror oscillates counterclockwise back to its starting position to track the next tablet. It is possible to control the size of the passageway by varying the laser power, firing duration (pulse time), thickness of the wall, and the dimensions of the beam at the wall.

3.3.2. Systems with passageway formed in situ

Oral osmotic systems in which delivery passageway is formed in situ are described in US patent no. 5,736,159 [58]. The system described consists of a tablet core of the drug along with water-swellable polymers and osmotic agents, which is surrounded by a rate-controlling membrane. In contact with the aqueous environment, water is imbibed osmotically at a controlled rate and water swellable polymer expands as the osmotic agents dissolves and increases the osmotic pressure inside the tablet. This results in a rate-controlled slight expansion of the partially hydrated core. The expansion of core causes a small opening to form at the edge of the tablet (weakest point in the membrane) from where the contents of the formulation are released (Fig. 9). In the working examples, core tablets of nifedipine were prepared using polyethylene oxide as a water swellable agent and coated with a rate controlling membrane. The osmotic system was able to maintain plasma concentration of the drug within the therapeutic range for 24 h.

3.3.3. Use of modified punches

Use of modified punches for producing a delivery orifice in osmotic dosage forms has also been described in the literature [59]. The working of this apparatus is shown schematically in Fig. 10. The dosage form is pierced using a piercing device that is biased in a sheathed position and unsheathed upon application of compression force. The coating powder to be compressed is charged to the die mold and an unpierced tablet core is placed upon it. Additional quantity of coating powder is added to the die mold, subsequent to which both compression and piercing are done simultaneously.

Another process for forming a passageway in osmotic system consists of charging the drug into round molds having a concave lower surface and compressing it with a plunger having a convex surface [60]. After removing the plunger from the mold, a second plunger equipped with a funnel shaped cone is pressed into the compressed drug,

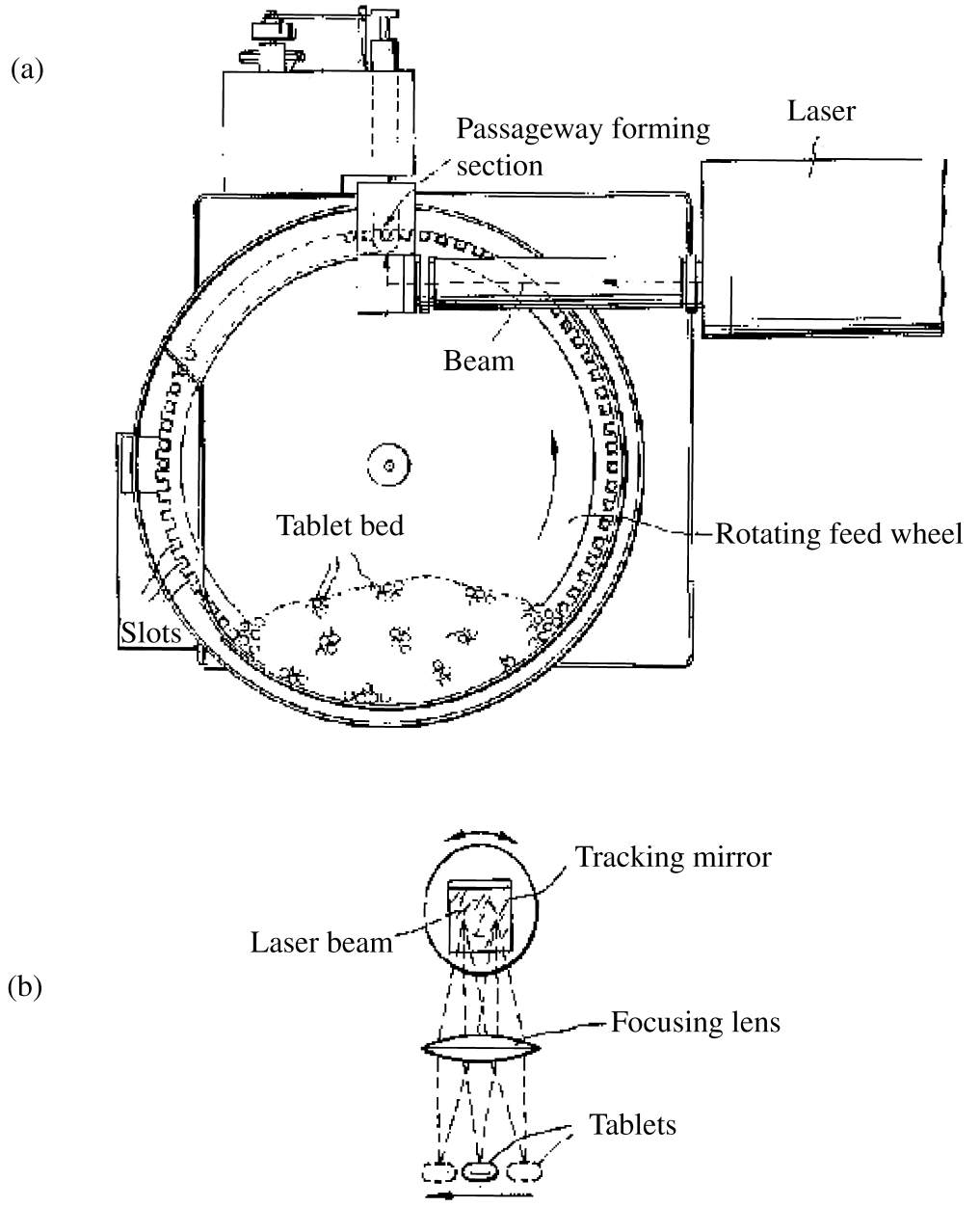

Fig. 8. Top view of the laser hole-drilling system for osmotic dosage forms (a) and the pill tracking means (b) (from US patent no. 4,088,864).

thereby creating a small indention in the tablet core. Alternatively, compression can be performed using a plunger with a V-shaped indenture die integrally formed as part of the plunger. Thereafter, the tablets are coated and the passageway is formed automatically during the coating. The depression formed is of sufficient width and depth to remain at least partly uncoated by the wall so that the drug is released in a controlled manner throughout the operational life of the system.

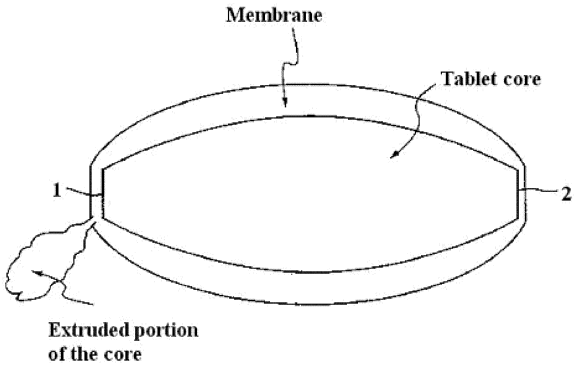

Fig. 9. Oral osmotic system showing in situ passageway formation (from US patent no. 5,736,159). The relatively thin membrane at edges 1 and 2 is also shown in the cross section.

3.3.4. Use of pore formers

CPOP are extension of EOPs and are essentially similar, except that there is no need to create a delivery orifice. Drug release from these types of system takes place through controlled porosity pores formed in situ. Incorporation of water-soluble additives in the membrane wall is the most widely reported method for the formation of pores in CPOP [15,61]. These water-soluble additives dissolve on coming in contact with water, leaving behind pores in the membrane through which drug release takes place. Drug release from these types of system is independent of pH and has been shown to follow zero-order kinetics [13,14]. Water-soluble additives that can be used for this purpose consist of dimethyl sulfone, nicotinamide, saccharides, amino acids, sorbitol, pentaerythritol, mannitol, organic aliphatic and aromatic acids, including diols and polyols, and other water-soluble polymeric materials [15]. Erodible materials, such as poly(glycolic), poly(lactic) acid, or their combinations can also be used for the purpose of formation of pores in the membrane. These erodible or leachable materials produce one or more passageways with different geometrical shapes. The pores may also be formed in the wall prior to the operation of the system by gas formation within curing polymer solutions, resulting in voids and pores in the final form of the membrane. The pores may also be formed in the walls by the volatilization of components in the polymer solution or by chemical reactions in the polymer solution leading to evolution of gases prior to application or during application of the solution to the core tablets resulting in the creation of the polymer foams serving as the porous wall from where the drug release can take place [15].

Zentner and coworkers [13,14] studied drug release from CPOP as a function of water-soluble additive (sorbitol) in the coating membrane and reported that the release rates increased as the

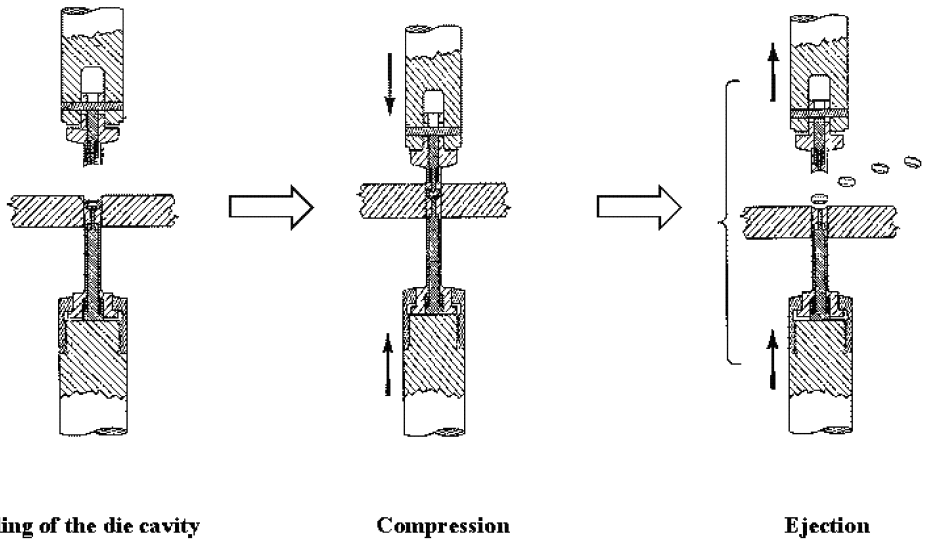

Fig. 10. Flow diagram showing the formation of passageway in the osmotic device using slidable punches (from US patent no. 5,071,607).

sorbitol content in the wall increased from 10 to 50% w/w of cellulose acetate (CA).

In a similar study by Appel and Zentner [62], potassium chloride release from CPOP was found to increase with increasing pore-former (urea) concentration in the membrane. There was also a critical point (50% urea) above which there was a near-linear dependence of release rate on urea content. In devices with less than 50% urea, swelling of the devices was observed where as devices with more than 50% urea retained their characteristic tablet shape. It was suggested that at lower urea concentration, the pores were not continuous and at higher concentrations greater fraction of the pores were continuous.

In another study [63], propranolol HCl tablets were coated with CA latex plasticized with either triethyl citrate (TEC) or triacetin (TA). Membrane permeability to the drug was increased by the addition of HPMC or sucrose. In case of TA plasticized films (at 150% w/w level), tablets with 15% w/w of HPMC had a tendency to swell and the film to rupture, showing insufficient porosity and/or film strength. Sucrose containing films showed a decrease in lag time with an increase in sucrose content. However, higher levels of sucrose (20% w/w and higher) caused rupturing of CA films. In case of TEC plasticized films (at 120% w/w level), higher levels of sucrose (50% w/w and higher) caused rupturing of CA films in the dissolution medium. In this study, the authors concluded that the film plasticized with TEC and containing 40% sucrose and 10% PEG 8000 were found to provide the best release characteristics in terms of small lag time and extended drug release profile for over 12 h. When sucrose was added to TA and TEC plasticized films, a macroporous membrane was created during exposure to the dissolution fluid because of release of sucrose from the film. The mechanism of drug release was mainly a combination of molecular diffusion and osmosis.

3.4. Membrane types and characteristics

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. From Eq. (3), the importance of rate-controlling membrane in the drug release can be easily recognized. Drug release from osmotic systems is independent of the pH and agitational intensity of the GI tract to a large extent. This is because of selectively water permeable membrane and effective isolation of dissolution process from the gut environment [2,5]. To ensure that the coating is able to resist the pressure within the device, thickness of membrane is usually kept between 200 and 300 μm [3]. However, this may be problematic in cases where the drug is having low osmotic pressure because of which incomplete/slow drug release may take place. Selecting membranes that are having high water permeabilities can be a solution to this problem. One approach that can be utilized is by using composite walls [64]. The tablet cores are coated with a membrane that has a passageway through the wall for releasing the agent. The wall is formed of a multiplicity of materials comprising a material permeable to an external fluid and substantially impermeable to agent (like CA) and at least one additional material selected from a group of materials that imparts stability to the wall and enhances the permeability of the wall to fluids (like HPMC or hydroxybutyl methylcellulose). Another approach that can be explored is to use a multilayer composite coating around the tablet [65]. The first layer is a thick microporous film that provides the strength required to withstand the internal pressure, while the second layer is a relatively thin SPM that produces the osmotic flux. Hence, high delivery rates can be obtained even for drugs with poor water solubility.

Some of the membrane variables that are important in the design of oral osmotic systems are;

3.4.1. Type and nature of polymer

Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, etc. [66]; cellulose ethers like ethyl cellulose [67]; and eudragits [68].

Cellulose acetate (CA) has been widely used to form rate-controlling membranes for osmotic systems. CA films are insoluble, yet semipermeable to

allow water to pass through the tablet coating. The water permeability of CA membrane is relatively high and can be easily adjusted by varying the degree of acetylation. As the acetyl content in the CA increases, the CA film permeability decreases, and solvent resistance increases. The permeabilities of these films can be further increased by the addition of hydrophilic flux enhancers. Incorporation of plasticizer in CA coating formulation generally lowers the glass transition temperature, increases the polymer-chain mobility, enhances the flexibility, and affects the permeability of the film [69].

Ethyl cellulose is also widely used in the formation of membranes for oral osmotic systems. However, the water permeability of pure ethyl cellulose membrane is very low that may result in slow release of drugs [70]. Nevertheless, drug release from osmotic systems coated with ethyl cellulose membrane can be enhanced by incorporation of water-soluble additives. Addition of HPMC in the coating composition improves the permeability of ethyl cellulose membranes. Tablet cores of potassium chloride coated with a mixture of ethyl cellulose and up to 24% of HPMC, were shown to release the contents mainly through osmotic mechanism [70,71]. In another study [62], urea was added to commercially available ethyl cellulose aqueous dispersion (Aquacoat) in an attempt to increase the release rates of potassium chloride and diltiazem chloride from osmotic tablets. It was found that the drug release from these systems is affected by coating thickness, plasticizer type and concentration, and pore-former level.

The use of eudragit acrylic latexes as membrane formers for osmotic systems has also been reported in the literature [68]. Potassium chloride tablets were coated with mixtures of eudragit RS30D and RL30D containing triethyl citrate or acetyl tributyl citrate as plasticizers and urea as a pore-forming agent. The release rate was most affected by the ratio of RS30D to RL30D and the level of urea was found to have effect on lag time and burst strength. The type of plasticizer and amount of pore former were also found to be critical for the desired release rates. The mechanism of release from the formulations containing acetyl tributyl citrate as plasticizer and 100% urea level (of total polymer solids) was found to be primarily osmotic and these formulations exhibited similar release rates in water and phosphate buffer saline pH 7.4.

3.4.2. Membrane thickness

Thickness of the membrane has a profound effect on the drug release from osmotic systems. It can be seen from Eq. (3) that release rate from osmotic systems is inversely proportional to membrane thickness. Pellets of phenylpropanolamine coated with an aqueous ethyl cellulose based films were found to release the drug mainly through the mechanisms of osmotic pumping and diffusion [72]. On studying the release as a function of coating thickness, it was found that as the coating thickness increased from 9 to 50 μm, the drug release decreased in an inversely proportional manner. In case of monolithic osmotic tablets of nifedipine, release rates were found to decrease with increase in membrane thickness from 85 to 340 μm [50]. An increased resistance of the membrane to water diffusion resulted in this effect.

On the other hand, thickness of the membrane in case of asymmetric coating was found to have insignificant effect on drug release. In a study by Herbig et al. [20], release rates were found to be virtually unaffected by the overall membrane thickness in the range of 95–150 μm. The possible reason for this may be the unique structure of the asymmetric membrane coatings in which the porous substrate consists of open pores (void volume between 60 and 90%). Since most of resistance to the transport is the skin structure rather than the porous substrate of the asymmetric membranes, the thickness of the porous substrate had only a slight effect on the release kinetics.

3.4.3. Type and amount of plasticizer

In pharmaceutical coatings, plasticizers or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films.

The effect of different types of plasticizers (TA and polyethylene glycols) on the water permeation

and mechanical properties of CA was reported by Guo [73]. The water permeability of CA films was found to decrease with increasing plasticizer concentration to a minimum and then increases with higher concentration of plasticizer. Low plasticizer concentrations were found to decrease water permeability by their antiplasticization effect. This antiplasticization effect could be because of interaction between the polymer and the plasticizer molecules that decreased the molecular mobility of the polymer. In a similar study [74], Guo investigated the effect of PEG-600 on the sucrose permeability, void volume, and morphology of CA films. The sucrose permeability was found to decrease with increasing PEG-600 concentration and increase dramatically when they were plasticized by over 30% (w/w). The decrease in sucrose permeability at lower plasticizer concentration was attributed to the antiplasticization effect. The increase in sucrose permeability at higher plasticizer concentration was because of formation of plasticizer channels, results of which were confirmed by the void volume and scanning electron microscopic studies.

Liu et al. [75] studied the influence of nature and amount of plasticizers on the properties of CA membrane including drug release profile, thermal properties, microporosity, and mechanical properties. Hydrophilic plasticizer (PEG-200) was found to increase the drug release, whereas hydrophobic plasticizer (TA) was found to decrease the drug release from osmotic pumps of nifedipine. Films plasticized with PEG developed completely porous structure after 24 h leaching, whereas films plasticized with TA retained their dense structure and porosity was observed only on the surface. At low plasticizer levels (0–5% w/w), it was found that both the ultimate tensile strength (σ_u) and elastic modulus (E) of dry membranes increased as the plasticizer level increased and there was no significant difference because of the nature of plasticizer. However, at higher plasticizer levels (5–40% w/w), both σ_u and E of membranes decreased as plasticizer levels increased.

Drug release from potassium chloride tablets coated with microporous membrane was found to decrease with increasing plasticizer concentrations from 24 to 48% w/w [62]. Higher release rates were observed with TEC as compared to dibutyl sebacate (DBS) at equal concentrations. These results can be attributed to differences in aqueous solubilities of plasticizers. Since DBS is more hydrophobic than TEC, it decreases the water permeability of the membrane and hence the drug release.

In another study by Okimoto et al. [76], chlorpromazine (CLP) release from controlled porosity osmotic tablets was found to increase with decreasing amounts of TEC. Drug release was also found to be much faster in formulations containing PEG-400 as a plasticizer than with TEC and was similar to that obtained without a plasticizer. It was concluded that PEG-400 is not a very effective plasticizer.

Bindshaedler et al. [77] have described mechanically strong films produced from CA latexes. By proper choice of type of plasticizer and its content in the coating composition, membranes comparable with those obtained from organic solutions can be produced from CA latexes. Water-soluble plasticizers possessing some degree of volatility resulted in films that had high ultimate tensile strength and elasticity modulus. In the series of films prepared with cellulose latexes containing different types and amount of plasticizers, it was found that the films plasticized with volatile additives (ethylene glycol monoacetate and ethylene glycol diacetate) were nearly as strong as those resulting from evaporation of solution in acetone. The majority of volatile plasticizer evaporates during the processing of the film at 60 °C. On the other hand, more permanent plasticizers (triethyl phosphate and diethyl tartarate) are retained in the film and yield membranes that are weak and less resistant. Thus, by proper selection of these volatile plasticizers, it is possible to balance two contradictory requirements, i.e. high mechanical strength of films and initial high amounts of plasticizer. In a similar study by the same group of workers [78], very volatile plasticizers, such as ethylene glycol monoacetate and ethylene glycol diacetate, were used to produce films with low permeability. More permanent plasticizers, such as diethyl tartrate or diacetin, resulted in films that were much more permeable.

4. Conclusions

Osmotic systems utilize osmotic pressure as the energy source and can be used for controlled and

constant delivery of drugs. The first oral osmotic pump was developed 25 years ago and today there are number of modifications available to meet a variety of drug delivery demands. These systems hold a major market share in the drug delivery products as exemplified by the number of products in the market and patents granted in the last few years. The release of drug(s) from these types of systems is affected by various formulation factors such as solubility and osmotic pressure of the core component(s), membrane characteristics, and size of the delivery orifice. By modulating these formulation factors, it is possible to use these systems to deliver drugs of diversified nature at a pre-programmed rate.

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