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Review Article

Oral osmotic drug delivery system: An update

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ABSTRACT

It is advantageous to deliver some drugs with short half-life, and which are to be given frequently for chronic ailments, in the form of controlled-release (CR) formulations. The orally administered drugs, in the form of conventional matrix or reservoir type formulations, pose problems of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drug(s) from these systems is affected by the hydrodynamic conditions of the body. Osmotically controlled drug delivery systems utilize the principles of osmotic pressure for the controlled delivery of active agent(s). The release rate of drug(s) from these systems is independent of the physiological factors of the gastrointestinal (GI) tract to a large extent. The main clinical benefits of ODDS are their ability to improve treatment tolerability and patient compliance. 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 article deals with history, development, general considerations and key aspects for the formulation of oral osmotic drug delivery systems.

Keywords: Controlled drug delivery; General consideration; Key formulation aspects; Osmotic pumps.

INTRODUCTION

Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed. Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reach its site of action, hence the role of drug delivery technologies.

Scientists are pursuing the discovery and development of new molecules that have better absorptive and pharmacokinetic properties. Nevertheless, many existing and new molecules provide challenges of poor pharmacokinetics (e.g., short biological half life). Drug delivery systems such as oral controlled-release dosage forms, transdermal patches, and implants are used to overcome these challenges. Although the cost of these drug delivery technologies is considerable, it is substantially less than the cost of developing a new molecule. Hence, a continued interest exists in developing novel drug delivery systems for the temporal and spatial delivery of active agents. Among the aforementioned technologies used to control the systemic delivery of drugs, osmotic drug delivery is one of the most interesting and widely applicable. Osmotic drug delivery uses the osmotic pressure of drugs or other solutes (called *osmagents*) for controlled delivery of drugs. Osmotic drug delivery has come a long way since Australian pharmacologists Rose and Nelson developed an implantable pump in 1955. This area of drug delivery has expanded into oral delivery and implants for humans and animals (Santus G, 1995).

In the form of Novel drug delivery system (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 (Verma RK, 2001).

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.

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 the category of matrix, reservoir, or osmotic systems.

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

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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 (Theeuwes F et al., 1985).

Alza Corporation of the USA (now merged with Johnson & Johnson, USA) was first to develop an oral osmotic pump and today also, they are leaders in this field with a technology named OROS^{TM} (Verma RK, 2001).

Osmotic delivery devices have changed considerably since Rose and Nelson developed the first osmotic pump for delivering drugs to animals. From complex implantable devices to simple tablets, the extent of simplification and miniaturization has been remarkable. The osmotic delivery devices of today not only deliver drugs with moderate solubility, but also are capable of delivering drugs with solubility extremes. Furthermore, devices that deliver drugs as liquids (to deliver insoluble drugs and to enhance permeability) and that dispense subsaturated solutions of drugs are noteworthy developments (Kaushal AM, 2003).

ADVANTAGES OF OSMOTIC DRUG DELIVERY

Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery (Verma RK, 2000). The following advantages have contributed to the popularity of osmotic drug delivery systems:

- The delivery rate of zero-order (which is most desirable) is achievable with osmotic systems. Both in vitro and in vivo experiments have established this fact.
- Delivery may be delayed or pulsed, if desired.
- For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
- A high degree of in vivo–in vitro correlation (IVIVC) is obtained in osmotic systems.
- The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract (GIT).

These advantages are attributed to the design of osmotic systems. Osmotic systems have a high degree of IVIVC because the factors that are responsible for causing differences in release profiles in vivo and in vitro (e.g., variable pH, agitation) affect these systems to a much lesser extent.

Historical Background

It was in 1955 that Rose and Nelson utilized the principles of osmotic pressure in drug delivery for the first time (Rose S, 1955). They described two systems; one that delivered 0.02 ml/day for 100 days and another that delivered 0.5 ml/ day for 4 days, both for use in pharmacological research. A schematic diagram of their prototype device is shown in Fig. 1a. The device consists of three chambers: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. A semipermeable membrane (SPM) separates the salt and water chambers. The difference in osmotic pressure between the two compartments moves water from the water chamber into the salt chamber, across the membrane. The volume of the salt chamber increases because of this water influx, distending the latex diaphragm (separating the salt and drug chambers) and thus pumping drug out of the device. In 1971, Stolzenberg designed another osmotic system that was operationally similar to that of Rose and Nelson's system (Jerzewaski RL, 1992). Although both systems are useful for conducting laboratory research, they have limited practical utility because of their complex design and difficulty in mass production. In the 1970s, Higuchi and Leeper proposed a series of variations of the Rose-Nelson pump (Higuchi T, 1973, 1976). One form of these types of pumps is illustrated in Fig. 1b. This device has no water chamber and is activated by water imbibed from the surrounding environment. Theeuwes further modified the Rose-Nelson pump (Chandrasekaran SK et al., 1979) and developed a system shown schematically in Fig. 1c. In this system also, imbibition of the water from the surrounding environment activates the device. In the device of Theeuwes, the membrane forms the outer rigid casing. The device is loaded with the desired agent immediately prior to use. Small osmotic pumps of these forms are sold under the trade name ALZET® (Alza Corp., CA). The device has a volume of approximately 170 µl, and the normal delivery rate is 1 µl/hr.

Relatively complex and scalable with technical difficulties, a major milestone was achieved in 1974 with the description by Theeuwes and Alza's coworkers of a tablet design (Theeuwes F, 1974; Theeuwes F, 1975) composed of a compressed tablet-core surrounded by a semipermeable membrane with a single passageway (orifice), the so-called elementary osmotic pump (EOP). This design adaptation for human use was conveniently processable using standard tabletting and coating procedures and equipment (Verma RK et al., 2002). The first two products indomethacin, Osmosin® (Theeuwes F et al., 1983) and phenylpropanolamine, Acutrim TM (Weintraub M et al., 1986), were launched in the 1980s. In contrast to the originally anticipated business success (Heilmann K, 1982; Bertouch JV et al., 1983; Francis H et al., 1983), Osmosin® had to be withdrawn from the market due to severe side effects such as GI irritation and perforation

of the intestinal wall (Calin A, 1984; Donnelly P, 1980; Laidler P et al., 1985).

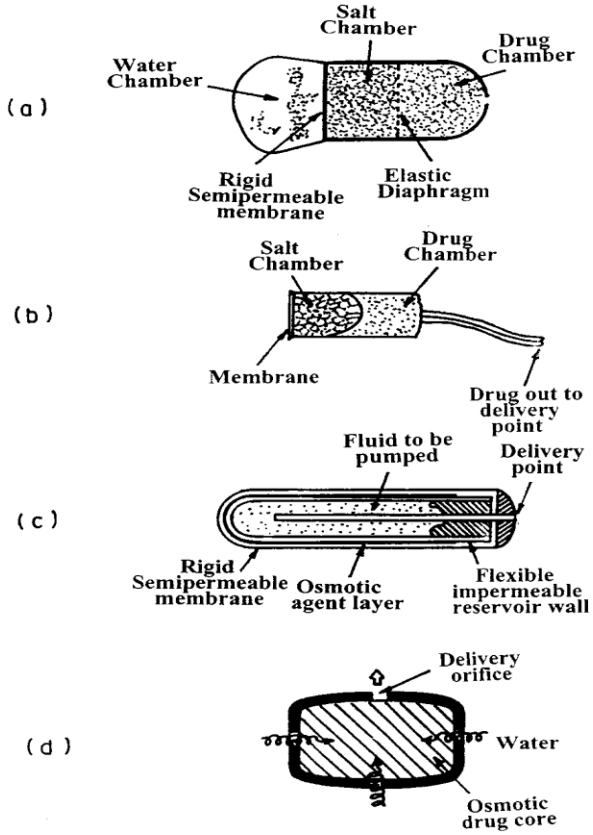

Figure 1: Cross-section of different osmotic dosage forms: (a) Rose-Nelson pump; (b) Higuchi-Leeper pump; (c) Theeuwes miniature osmotic pump; (d) elementary osmotic pump

Despite these events negatively affecting the reputation of these drug delivery systems, oral osmotic drug delivery system (OODS) development continued with two new OODS designs, the controlled-porosity osmotic pumps (CPOP) and the push–pull osmotic pumps (PPOP). The first of these was the CPOP, which was designed to decrease the risk of extremely localized drug-induced irritation at the site close to the orifice, as seen in the case of Osmosin (Weintraub M et al., 1990).

In the 2000s, a new drug product based on OODS technology was formulated to deliver methylphenidate to children (above the age of 6 years) with attention-deficit hyperactivity disorder (ADHD). These delivery systems were based on a new design, the push-stick osmotic pumps (PSOP), which combined immediate and sustained drug release phases (Coghill D, 2006).

The history of the OODS reflects the difficulty in developing an innovative technology in the pharmaceutical field. Currently, OODSs are becoming attractive technologies because of their abilities to enhance the clinical profile of certain therapeutic agents and to positively differentiate a drug product from others on the market.

PRINCIPLE OF OSMOSIS

Osmosis refers to the process of movement of solvent from lower concentration of solute towards higher concentration of solute across a semipermeable membrane. Abbe Nollet first reported osmotic effect in 1748, but Pfeffer (1877) had been pioneer of quantitative measurement of osmotic effect. He measured the effect in 1877 by utilizing a membrane, which is selectively permeable to water but impermeable to sugar. The membrane separated sugar solution from pure water. Pfeffer observed a flow of water into the sugar solution that was halted when a pressure P was applied to the sugar solution. Pfeffer postulated that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and absolute temperature. At equilibrium Van't Hoff established the analogy between the Pfeffer results and the ideal gas laws by the expression

$$\pi = n_2RT$$

Where n_2 represents the molar concentration of sugar (or other solute) in the solution, R depicts the gas constant, and T the absolute temperature.

Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment regulates the delivery of drug from the osmotic device. There are various factors that govern a particular pattern of drug delivery like nature of semipermeable membrane, diameter of delivery orifice, surface area of semipermeable membrane, pH, and electrolyte concentration in external fluid, nature and concentration of osmogen etc. (Vyas SP, 2004).

DEVELOPMENT OF OSMOTIC PUMP

Elementary osmotic pump

Rose Nelson pump was further simplified in the form of elementary osmotic pump, which made osmotic delivery as a major method of achieving controlled drug release. The device is formed by compressing a drug having a suitable osmotic pressure into a tablet using a tableting machine. The tablet is then coated with a semipermeable membrane, usually cellulose acetate, and a small hole is drilled through the membrane coating as shown in Figure 2.

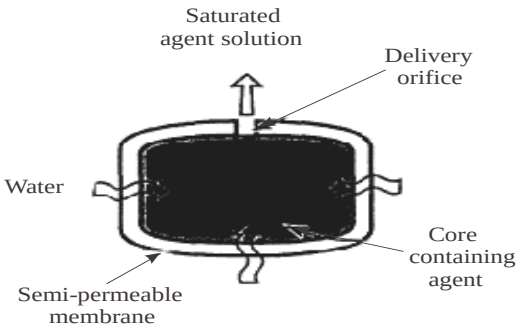

Figure 2: Elementary osmotic pump

When this tablet is placed in an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semipermeable coating, forming a saturated aqueous solution inside the device. The membrane is non-extensible, and the increase in volume caused by the imbibitions of water raises the hydrostatic pressure inside the tablet slightly. This pressure is relieved by a flow of saturated solution out of the device through the small orifice. Thus, the tablet acts as a small pump. This process continues at a constant rate until the entire solid drug inside the tablet has been dissolved and only a solution- filled shell remains. This residual dissolved drug continues to be delivered, but at a declining rate, until the osmotic pressures inside and outside the tablets are equal. The driving force to draw water into the device is the difference in osmotic pressure between the outside environment and a saturated drug solution. The osmotic pressure of the dissolved drug solution has, therefore, utilized for a number of drugs (Verma RK et al., 2002; Santus G, 1995; Theeuwes F, 1975; Kaushal AM, 2003; Schultz P, 1997).

Though 60 - 80% of drug is released at a constant rate from elementary osmotic pump, a lag time of 30 - 60 min is observed in most of the cases, as the system has to be hydrated before zero - order delivery from the system begins.

The elementary osmotic pump was developed by Alza under the name of OROS for controlled release oral drug delivery formulations. The conventional high-speed tableting machinery is utilized for producing the devices. The tablet is coated which is semipermeable and laser drilling system used for drilling small hole in the coated tablet (Verma RK et al., 2002).

Modifications in elementary osmotic pump

Modifications of elementary osmotic pumps are as explained below:

Use of multilayer composite coating around the tablet

The first layer of multilayer composite coating pump Figure 3 is made up of thick microporous film that provides the strength required to withstand the internal pressure, while second layer is composed of thin semipermeable membrane that produces the osmotic flux. The support layer is formed by various approaches; one novel approach is based on coating the tablets with a layer of cellulose acetate containing 40 to 60% of pore-forming agent such as sorbitol. This layer in turn is coated with the semipermeable layer. When contacted with water, the water soluble sorbitol leaches out from the membrane, leaving a microporous structure behind (Schultz P, 1997).

Method for delivering insoluble drugs

In this approach osmotic agent is coated with an elastic, semipermeable film. These particles are then mixed with the insoluble drug substance and the resultant mixture is coated with the rigid semipermeable membrane. Osmotic agent tends to draw water across two membranes, eventually swells and hydrostatic pressure forces the insoluble drug through the orifice made in the device (Santus G, 1995).

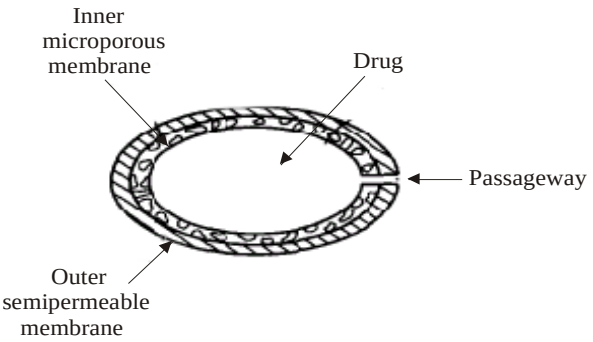

Figure 3: Multilayer composite coating pump design

Method for delivering liquid drugs

Liquid OROS controlled release systems are designed to deliver drugs from liquid formulations and yielded the benefits of extended-release with high bioavailability.

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, osmotic layer, and the 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 (Verma RK et al., 2002).

Multichamber osmotic pumps

Elementary osmotic pump is limited to the delivery of relatively soluble drugs, generally with solubilities more than 2 –5 w/w%. These multichamber tablets can be divided into two main categories, depending on whether one chamber expands into the other or whether the chambers are rigid, maintaining their volume throughout the period of operation**.**

Tablets with a second expandable osmotic chamber

Tablets with two chambers separated by an elastic or movable barrier are particularly interesting and valuable, because they allow delivery of drugs with limited solubility. In the tablets with a second expandable osmotic chamber, the water is drawn into both chambers in proportion to the osmotic gradient and the water drawn into the osmotic chamber causes the volume of this chamber to increase, forcing the

drug from the drug chamber. The mechanism of action of these devices is illustrated in Figure 4.

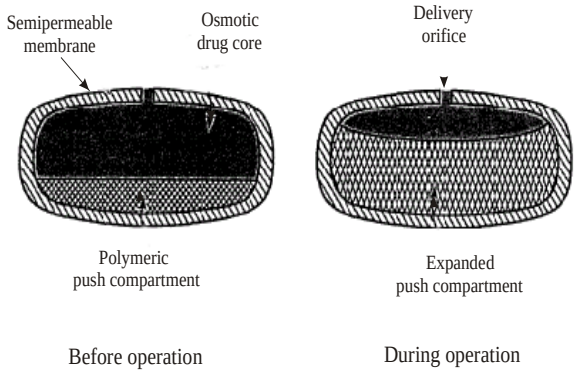

Figure 4: Drug delivery process of two- chamber osmotic tablets

It is a bilayer tablet coated with a semipermeable membrane. Drug along with osmogens is present in the upper compartment, whereas lower compartment consists of polymeric osmotic agents. 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 (Thombre AG et al., 2004).

Devices with a non-expanding second chamber

The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber.

In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk.

The devices consist of a normal drug-containing OROS® tablet from which drug is released as a saturated solution. However, before the drug can escape from the device, it must pass through a second chamber. Water is also drawn osmotically into this chamber either because of the osmotic pressure of the drug solution or because the second chamber contains a water-soluble diluents, such as sodium chloride.

Controlled porosity osmotic pump

Controlled porosity osmotic pump is simplest form of osmotic pumps, as shown in Figure 5.

These are not having any aperture to release the drugs. The drug release is achieved by the pores, which are formed in the semipermeable wall *in situ* after administration. The semipermeable coating membrane contains water-soluble pore forming agents. This membrane after formation of pores becomes permeable for both water and solutes (Zentner GM et al., 2002; 1991).

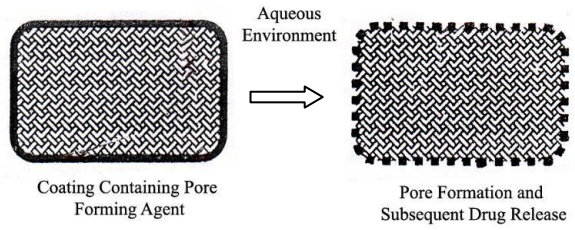

Figure 5: Working principle of controlled porosity osmotic pump

A controlled porosity wall can be described as having a sponge like appearance. The pores can be continuous that have an opening on both faces of a microporous lamina, interconnected through tortuous paths of regular and irregular shapes including curved, curve-linear, randomly oriented continuous and hindered connected. Generally, microporous lamina is defined by the pore size, number of pores, the tortuosity of the microporous path and the porosity, which relates to the size and number of pores. Generally, materials producing from 5 to 95% pores with a pore size from 10 – 100 µm can be used.

The release rate from these types of systems has been reported to be dependent on the coating thickness, level of soluble components in the coating, solubility of the drug in the core, and osmotic pressure difference across the membrane, but is independent of the pH and agitation of the release media. (Thombre AG et al., 1989).

Asymmetric- membrane coated tablets

A new type of membrane coating has been developed for osmotic drug delivery, which offers significant advantages over the membrane coatings used in the conventional osmotic tablets. The coatings have an asymmetric membrane made for reverse osmosis or ultrafiltration, in that the coating consists of a porous substrate with a thin outer skin (membrane) (Herbig SM et al., 1995).

Asymmetric tablet coating possesses some unique characteristics, which are more useful in the development of osmotic devices, as mentioned below:

- High water fluxes can be achieved, facilitating osmotic delivery of drugs with low solubilities and making possible higher release rates.
- The permeability of the coating layer to water can be adjusted by controlling the membrane structure, thereby allowing control of the release kinetics without altering the coating material agents or significantly varying the coating thickness.
- The porosity of the membrane can be controlled to minimize the lag time before drug delivery begins and allow the drug to be released from a large number of delivery ports.

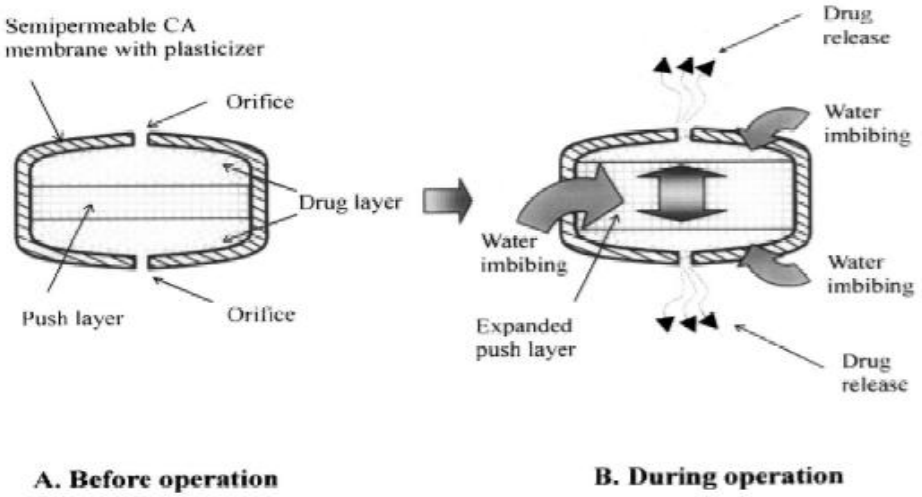

Figure 6: Schematic diagram of sandwich osmotic tablet

Table 1: Shows compounds that can be used as osmogents

Category	Examples
Water soluble salts of organic 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 inorganic 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 os-mogents	Sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linked PVP, polyethylene oxide, carbopols, polyacrylamides, etc.

Asymmetric- membrane coatings were made via a phase inversion process. Tablet cores were dip coated in a polymer solution and then immersed in a water quench bath, which allowed exchange of the polymer solvent (acetone or methylene chloride) with water, which is non-solvent for the polymer. This exchange of solvent with non-solvent causes the asymmetric membrane structure formation. The coating with 10% glycerol gives an appreciable surface porosity to the coating membrane. The osmotic release rate of a drug from an asymmetric membrane capsule is dependent on its solubility (Thombre AG et al., 1999).

Sandwich osmotic tablet

In sandwiched osmotic tablet (SOTS), a tablet middle push layer is sandwiched between two drug layers coated with a semipermeable membrane, as seen in Figure 6. 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 (Liu L et al., 2000).

GENERAL CONSIDERATIONAND MATERIAL USED

Osmotic pumps essentially contain a drug and semipermeable membrane. In this case, drug itself may act as osmogen and shows good aqueous solubility (e.g., potassium chloride pumps). If the drug does not possess any osmogenic property, the osmogenic salt and other sugars can be incorporated in the formulation. Osmogens are freely water soluble and capable of producing osmotic pressure. Single osmogen can be used for formulations and in some case combination of osmogens have been used.

Apart from these essential components, other materials such as hydrophilic and hydrophobic polymers and hydrogel (either swellable or non-swellable nature), wicking agent, solubilizing agents and surfactants have been used depending on type of formulations.

The semipermeable membrane usually contains a plasticizer and in some cases surfactant, fluxes regulating agents and pore forming agents.

Apart from the above materials, common tableting aids such as lubricants, binder, diluents, glidants, and

wetting agents can be incorporated for the development of osmotic systems.

The wall thickness is in between 1-1000µm, but 200-500µm is desirable. The percentage weight increase of tablets after coating should be around 10-15%.

Semipermeable membrane

Cellulose acetate is commonly employed semipermeable polymer for the preparation of osmotic pumps. It is available in different acetyl content grades. Particularly, acetyl content of 32% and 38% are widely used. Acetyl content is described by the degree of substitution (DS), i.e. the average number of hydroxyl groups on the anhydroglucose unit of the polymer replaced by substituting group. If the DS is up to 1, the acetyl content would be 21%. Cellulose diacetate is having a DS of 1-2 and an acetyl content of 21-35%. Cellulose triacetate is having a DS of 2-3 and an acetyl content of 35-44.8%.

Apart from cellulose derivatives, some other polymers such as agar acetate, amylase triacetate, betaglucan acetate, poly (vinylmethyl) ether copolymers, poly (orthoesters), poly acetals and selectively permeable poly (glycolic acid) and poly (lactic acid) derivative can be used as semipermeable film forming materials. The permeability is the important criteria for the selection of semipermeable polymers.

Hydrophilic and hydrophobic polymer

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The highly water soluble compounds can be co-entrapped in hydrophobic matrices and moderately water soluble compounds can be co-entrapped in hydrophilic matrices to obtain more controlled release.

Generally, mixtures of both hydrophilic polymers have been used in the development of osmotic pumps of water soluble drugs.

The selection is based on the solubility of drug as well as the amount and rate of drug to be released from the pump.

The polymers are of either swellable or non-swellable nature. Mostly, swellable polymers are used for the pumps containing moderately water-soluble drugs, since they increase the hydrostatic pressure inside the pump due to their swelling nature. The non-swellable polymers are used in case of highly water-soluble drugs.

Hydrophilic polymers such as hydroxyl ethyl cellulose, carboxy methylcellulose, hydroxyl propyl methylcellulose, high molecular weight poly (vinyl pyrrolidone) and hydrophobic polymers such as ethylcelluose and wax materials can be used for this purpose (Vyas SP, 2004).

Wicking Agents

Inclusion of wicking agents in the osmotic formulation has also been reported as an approach for poorly soluble drugs [(38)].

A wicking agent is defined as a material with the ability to draw into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature. They are characterized by having the ability to undergo physisorption with water.

The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area.

Material which suitably for act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly (vinyl pyrrolidone), m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene. SLS, colloidal silica and PVP are non-swellable wicking agent.

Osmogents

Osmogents are essential ingredient of the osmotic formulation (Verma RK et al., 2002).

Coating solvent

Solvent suitable for making polymeric solution that is used for manufacturing the wall of the osmotic devices include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials.

The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water, etc.

The mixture of solvent such as acetone-methanol (80:20), acetone-ethanol (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc can be used.

Plasticizer

Plasticizers increase the workability, flexibility and permeability of the fluids. Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated in to 100 parts of wall forming material.

Exemplary plasticizers included dialkyl phthalates and other phthalates, trioctyl phosphates and other phosphates, alkyl adiptes, triethyl citrate and other citrate, acetate, propionates, glycolates, glycerolates, myristates, benzoates, sulphonamides and halogenated phenyls.

Flux regulators

Flux regulating agent or flux enhancing agent or flux decreasing agents are added to the wall forming material; it assists in regulating the fluid permeability of flux through wall.

Table 2: Some 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.

Table 3: Leading articles focusing on OODS

Review on	Description	Ref.
Formulation	First article on the formulation of elementary osmotic pumps. Formulation strategy to design EOP. Review in the ODDS technologies. Review of formulation factor affecting the OODS drug delivery. Description of the OODS technologies and product.	(Theeuwes F, 1975) (Theeuwes F, 1983) (Verma RK, 2000) (Verma RK et al., 2002) (Verma RK et al., 2004)
Patents	Patent review of 240 patent dealing with osmotic system. Update on the OODS patent review up to 2003. Patent review up to 2006.	(Santus G, 1995) (Kaushal AM, 2003) (P. Kumar, 2007)
Clinics	Review of the OODS clinical use. Comparison of the Nifedipine controlled release formulation.	(Conley R et al., 2006) (Meredith PA, 2007)
Safety	Retrospective review on the gastrointestinal safety of OODS.	(Bass DM et al., 2002)

These agents can be pre-selected to increase or decrease the liquid flux.

Agent that produce a marked increase in permeability to fluid such as water are essentially hydrophilic, while those produce a marked decrease in permeability to fluids are essentially hydrophobic.

Poly hydric alcohols such as poly alkylene glycols and low molecular weight glycols such as poly propylene, poly butylenes and poly amylene etc. can be used as flux regulators. The amount of flux regulator added to material generally is an amount sufficient to produce the desired permeability, and it will vary according to the lamina forming materials.

Usually, from 0.001 parts to 50 parts or higher weight fraction of flux regulator can be used to achieve the desired results.

Pore forming agents

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These pore-forming agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore former by its leaching during the operation of the system.

The pore formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and diols and polyols such as poly hydric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

Pore former should be non-toxic and on their removal, channels should be formed. The channels become a transport path for fluid (Vyas SP, 2004).

FORMULATION ASPECTS

The formulation variables that affect the release of drug from oral osmotic system (Verma RK et al., 2002):

- Solubility
- Osmotic pressure
- Delivery orifice
- Membrane types and characteristics

PAST WORK DONE ON ODDS

McClelland and Co-workers (McClelland GA et al., 1991; Zentner GM et al., 1991) 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 drug to be released by zero-order kinetics over a 14–16-h period.

Use of polymer coated buffer components to modulate the drug solubility within the core is described in US patent no. 4,755,180 (Ayer AD, 1988). Solubility of a weakly acidic drug, acetyl salicylic acid, was modified by basic excipients, 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 de- scribed in US patent no. 4,326,525 (Swanson D, 1982). 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 8C. Drug release from the systems was found to be constant over a period of 7 h.

Rajan K. Verma *et al* (2002) studied the formulation aspects in the development of osmotically controlled oral drug delivery systems. In this review, different types of oral osmotic systems, various factors governing drug release from these systems and critical formulation factors were discussed.

Mahalaxmi.R *et al* (2009) developed the extended release controlled porosity osmotic pump formulations of model drug glipizide using a wicking agent and a solubilizing agent. The effect of different formulation variables like level of wicking agent, solubilizing agent, level of pore former and membrane weight gain on *in vitro* release were studied. Drug release was found to be affected by the level of wicking agent and solubilizing agent in the core. Glipizide release from controlled porosity osmotic pump was directly proportional to the level of pore former (sorbitol) and inversely proportional to membrane weight gain.

Hai Bang Lee *et al* (2000) studied the sandwiched osmotic tablet system (SOTS). A sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on the surfaces of both sides was successfully prepared for the purpose of delivering nifedipine. The appropriate orifice size was observed in the range of 0.50 – 1.41 mm. It was also found that the drug release rate of SOTS could be increased by incorporating hydrophilic plasticizer in the membrane, whereas it could be decreased by incorporating a hydrophobic plasticizer.

Toshiaki Nagakura *et al* (1996) designed an osmotic pump using a semipermeable membrane that changes its volume according to the concentration of the outside solution. By a mechanochemical actuator mechanism, an insulin pump works by changing the glucose concentration. It was found that this pump may possibly be used in the treatment of diabetes mellitus patients.

Herbig S. M. *et al* (1995) found a new type of asymmetric membrane tablet coatings offering significant advantages over conventional osmotic tablets. These asymmetric-membrane coatings can be used to make osmotic drug-delivery formulations with several unique characteristics. The permeability of the coating to water can be adjusted by controlling the membrane structure, thereby allowing the control of the release kinetics without altering the coating material or significantly varying its concentration. The use of asymmetric-membrane coatings on pharmaceutical tablets is described in this study; the coatings have also been applied to capsules and multi-particulate formulations.

Sanjay Garg *et al* (2003) studied the development and evaluation of extended release formulations of isosorbide mono nitrate (IMN) based on osmotic technology. The release from developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. Prediction of steady state levels, showed the plasma concentrations of IMN to be within the desired range.

Andrew Tasker *et al* (2000) studied the use of osmotic mini pumps as alternatives for injections for sustained drug delivery in adult rats. Sustained delivery rat pumps were assigned to control, mini-pump or sham surgery treatment. Based on the results the use of osmotic mini-pumps is a viable alternative to repeated injections for sustained delivery.

Roger A. Rajewski *et al* (2004) investigated the application of controlled-porosity osmotic pump tablet (OPT) utilizing (SBE)7m --CD both as a solubilizer and an osmotic agent for drugs with varying physical properties. OPTs utilizing (SBE) 7m --CD were prepared for five

Table 4: Some commercially marketed products

Product	Chemical	Developed by	Marketed by	Comments
Acutrim	Phenylpropanolamine (75mg)	Alza Corp.	Heritage consumer products	Introduced in September 1983 by Novartis Consumers Health, Inc. (NJ), as a 16-hr over-the-counter appetite suppressant. In August 1997, Novartis sold the rights to Heritage Consumer products.
Calan SR	Verapamil (120-240mg)	Alza Corp.	G.D. Searle & Co., Skokie, IL	Used for the treatment of hypertension
Ditropan XL	Oxybutynin chloride (5-10mg)	Alza Corp.	Alza Corp. & UCB Pharma, Inc., Smyrna, GA	Approved for marketing in December 1998 for the treatment of overactive bladder
Efidac/24	Pseudoephedrine (60mg IR, 180mg CR)	Alza Corp.	Novartis Consumers Health, Inc., NJ	Approved for sale in December 1992. It was the first over-the-counter 24-hr cold medication
Efidac 24 Chlorpheniramine	Chlorpheniramine (4mg IR, 12mg CR)	Alza Corp.	Novartis Consumers Health, Inc., NJ	Cleared on November 18, 1994, and used for the treatment of allergies
Efidac 24 Pseudoephedrine/ Brompheniramine	Pseudoephedrine (240mg) and brompheniramine (16mg)	Alza Corp.	Novartis Consumers Health, Inc., NJ	Approved in March 1996 and used as a once-a-daily clod and allergy treatment
Glucotrol XL	Glipizide (5-10mg)	Alza Corp.	Pfizer, Inc., NY	Approved on April 26, 1994 for the treatment of non-insuline-dependent diabetes.
Minipress XL	Prazosin (2.5-5mg)	Alza Corp.	Pfizer, Inc., NY	Approved for marketing in January 1992. In April 1989, the product was introduced in France by Pfizer as Alpress LP. In India, it is marketed by Pfizer, India, as Minipress XL
Procardia XL	Nifedipine (30-90mg)	Alza Corp.	Pfizer, Inc., NY	Approved in September 1989 and introduced on the market in October 1989.
Teczem	Enalapril (5mg) and diltiazem (180mg)	Merck & Co. inc., NJ and Hoechst Marion, Inc., MO	Hoechst Marion Roussel, Inc., MO	Approved on October 4, 1996. The product is a second-line hypertension therapy.
Tiamate	Diltiazem (120-240mg)	Merck & Co., Inc., NJ	Hoechst Marion Roussel, Inc., MO	Approved on October 4, 1996, as a second-line hypertension therapy.
Volmax	Albuterol (4-8mg)	Alza Corp.	Muro Pharmaceuticals, Inc., MA	Indicated for the relief of bronchospasm. Introduced overseas in 1987 By Glaxo Wellcome, Inc., NC. The product was granted U.S. marketing approval in December 1992. Licensed by Glaxo Wellcome to Muro Pharmaceuticals for U.S. promotion. and marketed by that company since 1993.

poorly soluble drugs such as prednisolone, estradiol, naproxen, indomethacin and chlorpromazine and for two highly water soluble drugs such as diltiazem hydrochloride and salbutamol sulfate. It was found that for the soluble drugs (SBE)7m --CD acts primarily as an osmotic and an OPT control agent. Significantly, (SBE) 7m --CD not only enhances the delivery of poorly soluble drugs from OPTs but acts as a controlling excipient for soluble drugs such that the release rate, corrected for tablet surface area, of both poorly soluble and soluble drugs are similar.

REFERENCES

Ayer AD, Wong PSL. Dosage form comprising solubility regulating member. US patent 4,755,180, July 5, 1988.

Bass DM, Prevo M, Waxman DS. Gastrointestinal safety of an extended release, nondeformable, oral dosage form (OROS(R)) – a retrospective study, Drug Saf. 2002; 25(14): 1021-1033.

Bertouch JV, Maycock S, Harrington B, Brooks PM. Pharmacokinetics of indomethacin gits (osmotically controlled drug delivery system). Aus Nz J Med. 1983; 13(2): 212.

Calin A. Intestinal perforation associated with osmotic slow release indomethacin capsules. Br Med J. 1984; 288(6412): 240-241.

Chandrasekaran SK, Theeuwes F, Yurn SI. The design of controlled drug delivery systems, in Drug Design, Vol 8 (E. J. Ariens Ed.) Academic, New York, 1979, pp. 134-165.

Coghill D, Seth S. osmotic controlled release methylphenidate for the treatment of ADHD. Expert Opin Pharmacother. 2006; 7(15): 2119-2138.

Conley R, Gupta SK, Sathyan G. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form. Curr. Med. Res. Opin 2006; 22(10): 1879-1892.

Donnelly P. indomethacin and perforated duodenal ulcer. Br Med J. 1980; 281(6234): 230.

Francis H, Corrigan AB, Hill W, Geddes R, Brooks P. The gastrointestinal therapeutic system (gits) for indomethacin to decrease side-effects. Aus Nz J Med. 1983; 13(2): 212.

Garg S, Verma RK, Kaushal AM. Development and evaluation of extended release formulations of Isosorbide mononitrate based on osmotic technology. Int. J. Pharm. 2003; 263: 9-24.

Heilmann K. Gits- A new medicine administration system, zeit. Rheum. 1982; 41(4): 137.

Herbig SM, Cardinal JR, Korsmeyar RW, Smith KL. Asymmetric-membrane tablet coatings for osmotic drug delivery. J Control Rel.1995; 35:127–36.

Higuchi T, Leeper HM. US Patents 3,760,804 (1973)

Higuchi T, Leeper HM. US Patents 3,995,631 (1976)

Higuchi T. US Patents 3,760,805 (1973)

Jerzewaski RL, Chien YW. Osmotic drug delivery, In Treatise on Controlled Drug Delivery. Fundamentals, Optimization, Applications (A Kydonleus, Ed.), Marcel Dakker, New York, 1992, pp. 225-253.

Kaushal AM, Garg S. An Update on Osmotic Drug Delivery Patents. Pharmaceutical technology. 2003; 38-44.

Kaushal AM, Garg S. An update on osmotic drug delivery patents. Pharm Tech. 2003; 23: 38-97.

Laidler P, Maslin SC, Gilhome RW. What's new in osmosin and intestinal perforation? Pathol Res Pract. 1985; 180(1): 74-76.

Lee HB, Liu L, Ku J, Khang G, Lee B, Rhee JM. Nifedipine controlled delivery sandwiched osmotic tablet system. J. Control. Rel. 2000; 68: 145-156.

Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB. Nifedipine controlled delivery by sandwiched osmotic tablet system. J Control Rel.2000; 68:145–56.

Mahalaxmi R, Phanidhar S, Kalra RA, Kanagale P, Narkhede. Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump Using a Wicking Agent and a Solubilizing Agent. Int. J. PharmTech Res. 2009; 1(3): 705-711.

McClelland GA, Sutton SC, Engle K, Zentner GM. The solubility modulated osmotic pump: In vitro/in vivo release of diltiazem hydrochloride. Pharm Res. 1991; 8: 88-92.

Meredith PA. The unique adalat story – nifedipine gastrointestinal therapeutic system, Eur. Cardiovasc. Dis. 2007; 1(1): 97–102.

Nagakura T, Ishihara K, Furukawa T, Masuda K, Tsuda T. Auto-regulated Osmotic pump for insulin therapy by sensing glucose concentration without energy supply. Sensors and Actuators B. 1996; 34: 229-233.

P. Kumar, B. Mishra, An overview of recent patents on oral osmotic drug delivery systems, Recent Patent Drug Del. Form. 1 (3) (2007) 236–255.

Rajewski RA, *et al.* Applicability of (SBE) $_{7m}$ β-CD in controlled-porosity osmotic pump tablets (OPTs). Int. J. Pharm. 2004; 286: 81-88.

Rose S, Nelson JF. Aus J Exp Biol Med Sci. 1955; 33: 415.

Rudnic EM, Burnside BA, Flanner HH, Wassink SE, Couch RA, Pinkett JE. Osmotic drug delivery system, US April 27, 1982. Patent 6,110,498, Aug. 29, 2000.

Santus G, Baker RW. Osmotic drug delivery: a review of the patent literature. J Control Rel. 1995; 35: 1– 21.

Santus G, Baker RW. Osmotic Drug Delivery: Review of the patent literature. J Controlled Release. 1995; 35: 1-21.

Schultz P, Kleinebudde P. A new multiparticulate delayed release system. Part I, Dissolution properties and release. J Control Rel.1997; 47: 181–9.

Swanson D, Edgren D. Osmotic device that improves delivery properties of agent in situ. US patent 4,326,525, April 27, 1982.

Tasker RA, Doucette TA, Ryan CL. Use of osmotic mini pumps for sustained drug delivery in rat pups: effects on physical and Neurobehavioral Development. Physiology & Behavior. 2000; 71: 207-212.

Theeuwes F, Higuchi T. Osmotic dispensing device for releasing beneficial agents, US Patents 3845,770. May 11, 1974.

Theeuwes F, Swanson D, Wong P, Bonsen P, Place V, Heimlich K, Kwan KC. Elementary osmotic pump for indomethacin. J Pharm Sci. 1983; 72(3): 253-258.

Theeuwes F, Swanson DR, Guittard, Ayer A, Khanna S. osmotic delivery system for the beta-adrenoceptor antagonists Metoprolol and Oxprenolol: design and evaluation of systems for once-daily administration, Br. J. Clin. Pharmacol. 1985; 19: 69S-76S.

Theeuwes F. Elementary osmotic pump. J Pharm Sci. (1975) 1987-1991; 64(12).

Theeuwes F. Elementary osmotic pump. J Pharm Sci. 1975; 64: 1987-1991.

Theeuwes F. Evolution and design of 'rate controlled osmotic forms. Curr. Med. Res. Opin. 1983; 8(S2): 20–27.

Thombre AG, Appel LE, Chidlaw MB, Daugherity PD, Dumont F, Evans LA, Sutton SC. Osmotic drug delivery using swellable-core technology. J Control Rel. 2004; 94; 75-89.

Thombre AG, Cardinal JR, DeNoto AR, Herbig, KL, Smith SM. Asymmetric membrane capsules for osmotic drug delivery: Development of a manufacturing process. J Control Rel.1999; 57:55–64.

Thombre AG, Zentner GM, Hammerstein KJ. Mechanism of water transport in controlled porosity osmotic devices. J Membrane Sci.1989; 40:279–310.

Verma RK, Arora S, Garg S. Osmotic pumps in drug delivery. Crit Rev. Ther. Drug Carrier Syst. 2004; 21(6): 477–520.

Verma RK, Garg S. Current status of drug delivery technologies and future directions. Pharm Technol.-online (http://www.pharmaportal.com) 2001; 25: 1-14.

Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Control Rel. 2002; 79(1-3): 7-27.

Verma RK, Mishra B, Garg S. Osmotically Controlled Drug Delivery. Drug Dev Ind Pharm. 2000; 26(7): 695-708.

Vyas SP, Khar RK. Targeted and controlled drug delivery novel carrier system. In: Osmotically regulated system. CBS Publisher and distributor. 2004, p. 479-482.

Weintraub M, Ginsberg G, Stein EC, Sundaresan PR, Schuster B, Connor PO, Byrne LM. Phenylpropanolamine OROS (Acutrim) vs. placebo in combination with caloric restriction and physician-managed behavior modification. Clin Pharmacol Ther. 1986: 39(5): 501-509.

Weintraub M, Horn JH, Krakoff L, Vetrovec G. P+T committee review of nifedipine gits- new modality for angina and hypertension. Hosp Form. 1990; 25: 10-14.

Zentner GM, McClelland GA, Sutton SC. Controlled porosity solubility- and resin-modulated drug delivery systems for release of diltiazem hydrochloride. J Control Rel.1991; 16:237– 44.

Zentner GM, McClelland GA, Sutton SC. Controlled porosity solubility- and resin- modulated osmotic drug delivery system for release of diltiazem hydrochloride. J Control Release. 1991; 16: 237-244.

Zentner GM, Rork GS, Hammerstein KJ. The controlled porosity osmotic pump. J Control Rel.2002; 4: 269–82.