A review on osmotically regulated devices

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Abstract
Osmosis is a physical phenomenon that has been extensively studied by scientist in various disciplines of science and engineering. Osmotic devices are the most promising strategy based system for controlled drug delivery. Convention drug delivery system has little control over their drug release and almost no control over the effective concentration at the targeted site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentration. Drug can be delivered in a controlled pattern over a long period of time by the process of osmosis. Osmotic pump offers many advantages over other controlled release devices i.e. they are easy to formulated and simple in operation, improve patient compliance with reduced dosing frequency and prolong therapeutic effect with uniform blood concentration. They are the most reliable controlled drug delivery system and could be employed as oral and implantable drug delivery system. Drug delivery from this system is not influenced by the different physiological factor with in the gut lumen and the release characteristics can be predicted easily from the known properties of drug and dosage form. In this paper, various types of osmotically controlled pump with basic component and factor affecting have been discussed briefly.

Keywords: Osmotic pump, Semipermeable membrane, Wicking agent, Osmogen, Leachable pore former.

Introduction
Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems1. Because of pharmaceutical agents can be delivered in a controlled pattern over a long period. Conventional oral drug delivery systems supply an instantaneous release of drug, which cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility etc.2. To overcome this limitation a number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral dosage form fall in the category of matrix, reservoir or osmotic system. Reservoir systems have a drug core surrounded/coated by the rate controlling membrane; there has been increasing interest in the development of osmotic devices over the past 2 decades. A detailed review of various types of osmotic pumps has been done by Santus and Baker3. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system4. Theeuwes introduced the elementary osmotic pump (EOP)5. The EOP consists of an osmotic core, with the drug surrounded by a semipermeable membrane with a delivery orifice. In operation, the osmotic core acts by imbibing water from the surrounding medium via the semipermeable membrane. Subsequently, drug solution is generated within the device and delivered out of the device via the orifice. Various attempts to increase the permeability of the semipermeable coating have been reported, such as incorporating water-soluble pore-forming additives in the coating6.
The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core and osmotic pressure difference across the membrane but is independent of the pH and agitation of the release media. It was observed that predominantly the drug was released through the pores at a constant rate. It was also observed that most of the core content released through pores at a constant rate, where the mechanism was primarily governed by osmosis with simple diffusion playing a minor role. 

Osmosis and its principle

Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Conventionally, osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane that allows passage of water but cast offs solute molecules or ions. The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

\[ \Pi = \mathcal{O} \cdot c \cdot RT \]

Where, \( \Pi \) = Osmotic pressure, \( \mathcal{O} \) = osmotic coefficient, \( c \) = molar concentration, \( R \) = gas constant, \( T \) = Absolute temperature

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug.

Types of Osmotic pump

They fall in two categories

1. Implantable

A. The Rose and Nelson Pump: About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems. The modified version of osmotic pump was introduced by rose and nelson as rose and nelson pump who were interested in the delivery of drug to the sheep and cattle gut. The pump is made up of three chambers, a drug chamber, a salt chamber and a water chamber. In which a salt chamber and water chamber are separated by a semipermeable membrane. The movement of water towards salt chamber is influenced by difference in osmotic pressure across the semipermeable membrane. The movement of water in salt chamber increases the volume of salt chamber due to which the latex diaphragm which divide the salt and water chamber moves and the drug is pumped out of the device. The kinetics of pumping from Rose and Nelson pump is given by equation:

\[ \frac{dM_t}{dt} = \frac{dv}{dt} C \]

Where, \( \frac{dM_t}{dt} \) is the drug release rate, \( \frac{dv}{dt} \) is the volume flow of water in to salt chamber, \( C \) is the concentration of drug in the drug chamber.

B. Higuchi Leeper Pump: A number of variations of Rose and Nelson pump have been proposed by higuchi and Leeper. In U.S patent these designs have been described. Alza Corporation represented the first series of Rose and Nelson pump. There is no water chamber in Higuchi Leeper pump and the device activate after penetration of water inside the device from surrounding environment. A new patented series of modified Higuchi Leeper pump has issued in 1991. Higuchi Leeper pump is widely used for veterinary use. This type of pump is either swallowed or implanted in the body of animal for delivery of antibiotic or growth hormones. Higuchi Leeper pump consist of rigid housing and semipermeable membrane. A layer of low melting waxy solid, such as microcrystalline paraffin wax is used in place of elastic diaphragm to separate the drug and osmotic chamber. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug.
C. Higuchi Theuwes pump: Early 1970s Higuchi and Theuwes developed a variant type of Rose and Nelson pump which is simpler than Higuchi Leeper pump. This device is illustrated in Fig. In this device the rigid housing is made up of a semipermeable membrane which is strong enough to withstand the pumping pressure developed inside the device due to permeation of water. The drug is loaded only to the prior of application of device. The release of drug from device can be controlled by the permeability characteristic of outer membrane and orifice. Osmotic pump of this form are available under trade name Alzet. A mixture of citric acid and sodium bicarbonate in salt chamber in presence of water generate carbon dioxide gas. Which exert a pressure on the elastic diaphragm, eventually delivers the drug from device.

D. Implantable Mini osmotic pump

2. Oral osmotic Pump

A. Single chamber osmotic pump

Elementary osmotic pump: Rose and nelson pump was further simplified in the form of elementary osmotic pump. In 1974 Theuwes invented elementary osmotic pump. Elementary osmotic pump was fabricated as a tablet containing an osmotic agent having suitable osmotic pressure coated with a semipermeable membrane. This membrane contains an orifice of critical size through which agent is delivered. This pump eliminates the separate salt chamber. When this coated tablet comes in contact with aqueous environment then water penetrates the semipermeable membrane and solution of osmogen creates a osmotic pressure inside the device due to which the flexible wall of collapsible material squeeze, eventually leading to the flow of saturated solution of active agent out of device through small orifice. This process of pumping continues at a constant rate till the entire solid drug inside the tablet is eliminated leaving only solution filled shell. Though 60 -80 percent of drug is released at a constant rate from the EOP, a lag time of 30-60 minute is observed in most of the cases as the system hydrates before zero order delivery from the system begins. These system are suitable or delivery of drugs having moderate water solubility.
Fig. 3 Elementary Osmotic Pump

B. Multi chamber osmotic pump

1. Push pull osmotic pump: Push pull osmotic pump is a modified EOP. Through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (depict as the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colorings agents, polymer and tablet excipients. This layer are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semipermeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the non-drug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of non drug layer pushes the drug suspension out of the delivery orifice\textsuperscript{25-26}.

Fig. 4 Push Pull Osmotic Pump

2. Osmotic pump with 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. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs\textsuperscript{27}.

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Miscellaneous

1. **Controlled porosity osmotic pump**: Controlled porosity pump is simplified form of osmotic pump. The delivery system comprises a core with the drug surrounded by a membrane. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. The drug release is achieved by the porous formed in semipermeable membrane. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall. When device is exposed to water, low levels of water-soluble additive are leached out from membrane that was permeable to water. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents. Rate of drug delivery depends upon the factors are water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating \(^{28,29}\). The rate of flow \(dv/dt\) of water into the device can be represented as:

\[
dv/dt = Ak/h (Dp - DR)
\]

Where, \(k\) = Membrane permeability, \(A\) = Area of the membrane, \(Dp\) = Osmotic pressure difference, \(DR\) = Hydrostatic pressure difference.

![Fig. 5 Controlled Porosity Osmotic Pump](image)

2. **Osmotic bursting osmotic pump**: This system is similar to an EOP expect delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsed release \(^{30}\).

3. **Effervescent activity-based osmotic systems**

4. **Lipid osmotic pump**

5. **Multiparticulate osmotic pump**

Advantages of osmotic drug delivery systems

Osmotic drug delivery systems for oral and implantable use propose individual and realistic advantages above additional controlled drug delivery system. The following advantages have contributed to the attractiveness of osmotic drug delivery systems \(^{31}\).

1. The zero-order drug release rate is attainable with osmotically controlled drug delivery system.
2. Delayed or pulsed delivery may be possible.
3. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
4. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
5. In oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
6. The presence of food in gastrointestinal tract minimally affects the release of drug from osmotic system.
7. A high extent of in vivo- in vitro correlation (IVIVC) is obtained in osmotic systems.

Disadvantage

1. High cost
2. If the coating process is not well controlled there is a risk of film defects, which results in dumping
3. Reduce potential for dose adjustments
4. Increased potential for first pass clearance
5. Poor systemic availability in general
6. Size hole is critical

**Basic components of osmotic systems**

**Drug**

All drugs are not suitable candidate for osmotic system as prolong action medication. Drug with biological half life > 12 hr eg: Diazepam and drug which have very short half life i.e <1 hr eg. Penicillin G, furosemide are not suitable candidate for osmotic controlled release. Drug which have biological half-life in between 1 – 6 hrs and which is used for prolonged cure of diseases are ideal applicant for osmotic systems. A variety of drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide etc. are formulated as osmotic delivery.

**Semi permeable membrane**

There are various types of polymers are used as semi permeable membrane. the selection of polymer is based on the solubility of drug as well as amount and rate of drug to be released from pump. Cellulose acetate is commonly used polymer for preparation of semi permeable for osmotic pump devices. Different grades of cellulose acetate with different acetyl content usually 32% and 38% are mostly used. A part from cellulose derivative, some other polymers such as poly(vinylmethy) ether copolymer, poly (orthoester), poly acetals and selectively permeable poly(glycolic acid) and poly(lactic acid) derivatives, Eudragits can be used as semi permeable film forming materials. The permeability is the most important criteria for the selection of semi permeable membrane. Therefore, the polymeric membrane selection is important to osmotic delivery formulation. The membrane must have certain performance criteria such as:

1. It should be adequately thick to withstand the pressure generated within the device.
2. It should have enough wet strength and water permeability
3. It should be biocompatible.
4. It should be rigid and non-swelling
5. The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity.

Unfortunately, polymer membranes that are more permeable to water are also, in general, more permeable to the osmotic agent.

**Plasticizers**

Plasticizers have a crucial role to play in the formation of a film coating and its ultimate structure. Plasticizers increases the workability, flexibility and permeability of fluids. Generally from 0.001 to 50 parts of plasticizer or a mixture of plasticizers are incorporated in to 100 part of wall forming material. They can change viscous-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Plasticizers can have a marked effect both quantitatively and qualitatively on the release of active materials from modified release dosage forms where they are incorporated into the rate-controlling membrane. Some of the plasticizers used are as below: Polyethylene glycols, Glycolate, Glycerolate, myristates, Ethylene glycol monoacetate; and diacetin for low permeability, Tri ethyl citrate, Diethyl tartarate or Diacetin for more permeable films.

**Osmotic agent**

Osmogen are essential ingredient of osmotic pump, usually is ionic compounds consisting of either inorganic salts or hydrophilic polymers and carbohydrates. Generally combination of osmogen is used to achieve desired osmotic pressure within the device. Some of the osmotic agents that can be used for such systems are classified below. Different type of osmogens can be used for such systems are categorized as

- Inorganic water-soluble osmogens
- Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride
- Sodium bicarbonate
- Organic polymer osmogens
- Sodium carboxymethyl cellulose, Hydroxypropylmethyl cellulose, Hydroxethylmethylcellulose, Methylcellulose, Polyethylene oxide, Polyvinyl pyrollidine.

**Wicking agent**

A wicking agent has ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non swellable in nature. The function of wicking agent is to carry water to surfaces inside the core of tablet, thereby creating channels or network of increased surface area. Material used for wicking agent...
includes colloidal silicon dioxide, kaolin, alumina, sodium laurel sulphate, low molecular weight poly (vinyl pyrrolidone), bentonite etc.

**Pore former**

These agents are particularly used in the development of pump for poorly water solubled drugs and in controlled porosity tablets. These agents cause the formation of micro porous membrane. The micro porous wall may be formed by the leaching of water soluble substrate from membrane leaving a micro porous structure. The pore former can be organic or inorganic and solid or liquid in nature. Some examples of pore former are given below.

Alkaline earth metal salts Sodium chloride, potassium chloride, sodium bromide, potassium phosphate.

Carbohydrate such as sucrose, lactose, glucose, mannitol, fructose etc is used as pore forming agent.

**Coating solvents**

The primary function of solvent system is to dissolved or dispersed the polymer and other additive and convey them to substrate surface. Solvent used to prepare polymeric solution include inert inorganic and organic solvents that do not adversely harm the core, wall and other material. The various types of solvents and their combinations are as follows:

Methylene chloride, methanol, isopropyl alcohol, di-chloromethane, ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc and the mixture of solvents such as acetone-methanol (80:20), methylene chloride- methanol (79:21), acetone-ethanol (80:20), methylene chloride-methanol-water (75:22:3).

- It should easily and completely dissolve the polymer.
- It should easily disperse other coating components into solvent system.
- It should not give extremely viscous solution with small concentration of polymer (2-10%) because it creates process problem.
- It should be odorless, colorless, tasteless, inexpensive, nontoxic and non-irritant.
- It should have rapid drying rate.

**Factors affecting drug release rate**

The drug release from osmotic device depends on many process and formulation variables, including plasticization, curing treatment, and properties of the core. Besides the water solubility of the drug, the solubility of the other core ingredients can also have a major impact on the drug release by creating an osmotic pressure gradient across the polymeric coating upon contact with dissolution medium. The rate of drug release from osmotic pumps is dependent on the total solubility and the osmotic pressure of the core. The poorly water-soluble drugs do not create sufficient osmotic pressure and are delivered at low rates. To overcome this problem, other types of osmotic pumps for poorly water-soluble drug have been designed which are very complicated in design and difficult to optimize.

In contrast, highly water-soluble drugs may create considerable osmotic pressures and may release the active drug at undesirable high rates. In some cases this problem may be solved by addition of a solubility modulating agent to the core.

Recently it has been reported that presence of swellable polymer within the core of EOP can modulate the drug release. Inclusion of swellable polymer is expected to cause significant swelling of the core compartment which creates significant internal pressure within the core compartment. This leads to decreased imbibitions of the membrane and thereby decreased release of drug from the EOP. In addition presence of PEO within the core may restrict or delay the contact of solvent molecules with drug and osmotic agent molecules. Which results in decreased osmotic pressure generation within the device consequently decreased release of the drug from EOP.

1. **Osmotic pressure**

Osmotic pressure is one of the most rate controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The rate of drug release is mainly depends upon the atmospheric pressure created by osmogen. The simplest and most predictable way to achieve a constant osmotic pressure for constant delivery of drug is to maintain a saturated solution of suitable osmotic agent in the compartment. Sometimes combination of osmotic agents is also used for desired osmotic pressure. The following table shows osmotic pressure of commonly used solutes in CR formulations.
### Table No.: 1 Osmotic pressure of saturated solution of commonly used osmogent

<table>
<thead>
<tr>
<th>Compound or mixture</th>
<th>Osmotic pump atmospheric pressure (atm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride</td>
<td>356</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>245</td>
</tr>
<tr>
<td>Fructose</td>
<td>355</td>
</tr>
<tr>
<td>Sucrose</td>
<td>150</td>
</tr>
<tr>
<td>Dextrose</td>
<td>82</td>
</tr>
<tr>
<td>Potassium sulphate</td>
<td>39</td>
</tr>
<tr>
<td>Mannitol</td>
<td>38</td>
</tr>
<tr>
<td>Lactose-fructose</td>
<td>500</td>
</tr>
<tr>
<td>Dextrose-fructose</td>
<td>450</td>
</tr>
<tr>
<td>Sucrose-fructose</td>
<td>430</td>
</tr>
<tr>
<td>Mannitol-fructose</td>
<td>415</td>
</tr>
<tr>
<td>Lactose-sucrose</td>
<td>250</td>
</tr>
<tr>
<td>Lactose-dextrose</td>
<td>225</td>
</tr>
<tr>
<td>Mannitol-dextrose</td>
<td>225</td>
</tr>
</tbody>
</table>

### 2. Size of delivery orifice

To achieve an optimal zero order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure build up in the system. The typical orifice size in osmotic pumps ranges from 600µ to 1 mm.

Methods to create a delivery orifice in the osmotic tablet coating are:

1. Mechanical drill
2. Laser drill: This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO₂ laser beam (with output wavelength of 10.6µ) is used for drilling purpose, which offers excellent reliability characteristics at low costs⁴⁹⁻⁵⁰.
3. Indentation that is not covered during the coating process⁵¹: Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.
4. Use of leachable substances in the semipermeable coating: e.g. controlled porosity osmotic pump

### 3. Solubility

Osmotic pumps are suitable for delivery of drugs having intermediate water solubility. It has been reported that in case of high water soluble drugs, meaningful release rates may not be obtained using elementary osmotic pump (EOP) or controlled-porosity osmotic pump (CPOP) ⁵². This is because the kinetics of osmotic drug release is directly related to solubility of drug within the core. APIs for osmotic delivery should have water solubility in the desired range to get optimize drug release. However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidate for osmotic delivery.

Solubility-modifying approaches:

1. Swellable polymers such as vinyl acetate copolymer, hydroxyl polymethyl cellulose have uniform swelling rate which causes drug release at constant rate⁵³.
2. Effervescent mixture of citric acid and sodium bicarbonate generate carbon di-oxide which creates pressures in the osmotic system and ultimately the release drug at a constant rate⁵⁴.
3. Cyclodextrin derivatives improve apparent drug solubility and dissolution through inclusion complexation or solid dispersion, by acting as hydrophilic carriers for drug with inadequate molecular characteristic for complexation, or as tablet dissolution enhancer for drug with high dose, with which use of a drug/cyclodextrin complex is difficult, eg, paracetamol. The same phenomenon can also be used for the osmotic systems.  
4. Salts have improved solubility and dissolution characteristics in comparison to the original drug. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water-soluble than the parent drug.  
5. Encapsulated excipients play a vital role as solubility modifier excipient, used in form of mini-tablet coated with rate controlling membrane. By using hydrophilic diluents such as PEG, PVP, dextrose, etc. which coat the surface of hydrophobic drug particles and render them hydrophilic.  
6. Ion-exchange resin methods are commonly used to modify the solubility of APIs. Some of the resins used in osmotic systems are Poly (4-vinyl pyridine), Pentacyrithitol, citric and adipic acids.  
7. Micronization process reduces the size of the solid drug particles to 1 to 10 microns by spray drying or by use of air attrition method.  
8. Use of surfactants promoting wetting and penetration of dissolution fluid into solid drug particles. Non-ionic surfactants like polysorbate are widely used.  
9. Use of metastable polymorphs is more soluble than the stable polymorph of a drug that exhibit polymorphism eg. B form of chloramphenicol palmitate is more water soluble than A and C forms.  
10. Use of crystal habit modifiers: Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate the solubility of poorly soluble drug.  
11. Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are organic acids, buffering agent, etc.  
12. Use of wicking agents: These agents may enhance the surface area of drug with the incoming aqueous fluids e.g., colloidal silicon dioxide, sodium lauryl sulfate, etc., Ensolot® technology uses the same principle to deliver drugs via osmotic mechanism.

References


