Controlled Porosity Osmotic Pump (Cpop)-An Advanced Delivery System For Cardio Selective β1 Blockers

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ABSTRACT
Conventional drug delivery systems have little control over their drug release and unpredictable plasma concentrations.Controlled drug delivery systems offer spatial control over the drug release.Osmotic pumps are most promising for controlled drug delivery, thus can be used for both oral and implantation. Controlled porosity osmotic pump(CPOP) tablets were designed to release the drug in controlled manner upto 12 hours. Mostly it is used to treat various chronic diseases like hypertension,heart diseases, diabetes and asthma.CPOP is based on the principle of osmosis which provides better release of drug that is independent of pH and agitation intensity. The controlled porosity osmotic pump tablet is spray coated or coated with semi permeable membrane(SPM) containing leachable pore forming agents. The drug release through pores which are formed in SPM. The release rate from these systems is dependent on coating thickness,solubility of drug in tablet core and osmotic pressure difference across membrane. It is also effective in multi drug therapy of hypertension by delivering both drugs in controlled manner.

Keywords: Controlled porosity osmotic pump(CPOP),controlled osmotic drug delivery.

INTRODUCTION
Hypertension is a common cause of cardiovascular disorder and is essentially associated with abnormal lipid and altered glucose metabolism .thus management of cardiovascular disease in particular hypertension becomes important to improve health care system. About 2.5million deaths in India in 1990 which have doubled by the year 2015, where hypertension alone contributes 57% of all stroke death and 24% of all coronary heart disease. The beta blockers are used individually or a combination therapy to treat hypertension. The development of oral osmotic systems has a strong market potential and is evident from the marketed products and number of patents granted in last few years. CPOP is simple and it is not necessary to consider complicated side drilling, compared to other osmotic pump systems less excipients is required. The coating composition of CPOP includes pore forming agents which generates pores in contact with aqueous media.it was observed that most of the core content releases through pores at constant rate where the release mechanism primarily is osmotic with simple diffusion playing a minor role. A zero order delivery pattern was designed to produce plasma levels within the desired range. Controlled release drug delivery systems provide desired concentration of drug at absorption site allowing maintenance of plasma concentrations within the therapeautic range and reducing the dosing frequency. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

BASIC COMPONENTS OF OSMOTICS SYSTEMS
The following are the materials used in formulation of osmotically regulated system.

1. Semipermeable Membrane
Since the membrane in osmotics systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can
beselected. Cellulose acetate is a 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% is widely used. Acetyl content is described by the degree of substitution (DS), that is, the average number of hydroxyl groups on the anhydroglucose unit of the polymer replaced by substituting groups. Some of the polymers that can be used for this purpose include cellulose esters such as cellulose acetate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose. Apart from cellulose derivatives, some other polymers such as agar, xanthan gum, and sodium alginate can be used for this purpose.

2. Hydrophilic and Hydrophobic Polymers
These polymers are used in the formulation development of osmotic systems for making drug containing matrix cores. The highly water-soluble compounds can be coentrapped in hydrophilic matrices and moderately water-soluble compounds can be coentrapped in hydrophilic matrices to obtain more controlled release. Generally, mixtures of both hydrophilic and hydrophobic polymers have been used in the development of osmotic pumps of water-soluble drugs. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump. The polymers are of either swellable or nonswellable 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 nonswellable polymers are used in case of highly water-soluble drugs. Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature. More precise controlled release of drugs can be achieved by incorporating these polymers into the formulations. Hydrophilic polymers such as hydroxy ethyl cellulose, carboxy methylcellulose, hydroxy propyl methylcellulose, high-molecular-weight poly(vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose.

3. Wicking Agents
A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent helps to enhance the rate of drug release from the orifice of the drug. A wicking agent is of either swellable or nonswellable nature [32]. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Van der Waals interactions between the surface of the wicking agent and the adsorbed molecule. 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. The examples are colloidal silicon dioxide, PVP and Sodium lauryl sulfate.

4. Solubilizing Agents
For osmotic drug delivery systems, highly water-soluble drugs would demonstrate a high release rate that would be of zero order. Thus, many drugs with low intrinsic water solubility are poor candidates for osmotic delivery. How ever is possible to modulate the solubility of drugs within the core. Addition of solubilising agents into the core tablet dramatically increases the drug solubility. Non swellable solubilising agents are classified into three groups,

(i) Agents that inhibit crystal formation of the drugs otherwise act by complexation with the drugs (e.g., PVP, poly(ethylene glycol) (PEG8000) and β- cyclodextrin),
(ii) Amicelle-forming surfactants with high HLB value, particularly non-ionic surfactants (e.g., Tween 20, 60, and 80, polyoxyethyleneoxyethylene containing surfactants and other long-chain anionic surfactants such as SLS)
(iii) Citrate esters (e.g., alkyl esters particularly triethyl citrate) and their combinations with anionic surfactants. The combinations of complexing agents such as polyvinylpyrrolidone (PVP) and poly(ethylene glycol) with anionic surfactants such as SLS are mostly preferred.
5. Osmogens
Osmogens are essential ingredients of the osmotic formulations. Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure build up inside the pump and pushes medicament outside the pump through delivery orifice. They include inorganic salts and carbohydrates. Mostly, potassium chloride, sodium chloride, and mannitol used as osmogens. Generally combinations of osmogens are used to achieve optimum osmotic pressure inside the system.

6. Surfactants
Surfactants are particularly useful when added to wall-forming material. They produce an integral composite that is useful for making the wall of the device operative. The surfactants act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. Typical surfactants such as poly oxyethylene glyceryl secioleate, polyoxyethylene castor oil having ethylene oxide, glycerides, and glycerol (sorbitonoleate, stearate, or laurate) are incorporated into the formulation.

7. Coating Solvents
Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, and water. The mixtures of solvents such as acetone-methanol (80 : 20), acetone-ethanol (80 : 20), acetone-water (90 : 10), methylene chloride-methanol (79 : 21), methylene chloride-methanol-water (75 : 22 : 3) can be used.

8. Plasticizers
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 visco elastic behaviour of polymers significantly. Plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. Plasticizers lower the temperature of the second order-phase transition of the wall or the elastic modules of the wall and also increase the workability, flexibility, and permeability of the coating solvents. Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated into 100 parts of coating materials. PEG-600, PEG-200, triacetin (TA), dibutyl sebacate, ethylene glycol monoacetate, ethylene glycol diacetate, triethyl phosphate, and diethyl tartrate used as plasticizer in formulation of semipermeable membrane.

9. Pore-Forming Agents
These agents are particularly used in the pumps developed for poorly water-soluble drugs and in the development of controlled porosity multiparticulate osmotic pumps. These pore-forming agents cause the formation of microporous membrane. The microporous wall may be formed insitubypore-former by its release during the operation of the system. The pore-formers can be inorganic or organic and solid or liquid in nature. Forexample, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate, and so forth, alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol, and diol and polyol such as polyhydric alcohols, polyethylene glycols, and polyvinylpyrrolidone can be used as pore-forming agents. Triethyl citrate (TEC) and triacetin (TA) are also used to create pore in the membrane. Membrane permeability to the drug is further increased by addition of HPMC or osmocure.

Advantages
a) The controlled porosity osmotic pump can be following zero order kinetics and thus better control over the drug’s bioavailability possible.
b) The drug release is independent of the gastric pH and hydrodynamic conditions.
c) The delivery rate of drug from the system is highly predictable and can be programmed by modulating the terms.
d) Drug release from the controlled porosity osmotic pump exhibits significant in vitro-in vivo correlation (IVIVC) within specific limits.
e) Noneedof drilling.
f) Therationale forthisapproachisthatthe presenceofwaterinGlTisrelativelyconstant, atleasntterms of the amount required for activationandcontrollingosmoticallybase technologies.
g) Production scales up is easy.

Disadvantages
a) Retrieval of therapy is not possible in the case of unexpected adverse events.
b) Drug release from the osmotic systems is affected to some extent by the presence of food.
c) If the coating process is not well controlled there isarisk of film defects, which results in dosedumping.

OSMOSIS
Process of movement of the solvent from the lower concentration of solution to the higher concentration of the solution through the semipermeable membrane. Osmosis is the process that can control the drug delivery system. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of the solute (osmogen).

Principles of Osmosis
The first report of osmotic effect datesto Abbenollet(1748). But Pfeffer obtained the first quantitativemeasurement in 1877.InPfefrer experimentamembrane permeable towatetbut impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until pressure is applied to the sugar solution. Pfefrer showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$$\pi = \Phi c r t$$

Where $\Phi$ is the osmotic coefficient of the solution, $c$ is the molar concentration of sugar in the solution, $r$ is the gas constant, $t$ is the absolute temperature.

Osmotic pressure for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high ranging from 8 atm for adipic acid up to 500 atm for lactose-fructose mixture. This high osmotic pressure can produce high water flow across semi permeable membrane. The osmotic water flow through membrane is given by the equation,

$$dv/dt = A Q \Delta l$$

Where $dv/dt$ is the water flow across the membrane of area $A$, thickness $l$, and the permeability $Q$ in $cm^2$.

Drug release mechanism
When controlled porosity osmotic pump is in aqueous environment the water soluble channeling agent get dissolve and forms a pore in coat. The water enter through semipermeable membrane and forms a solution of drug which get release through pores. Rate of water inlets depending ontype and concentration of osmotic agent and the drug release is dependent on hydrostatic pressure created by inlet water and size and number of pores.

Basic component of controlled porosity osmotic pump

Drug
Basic criteria for selection of drug
i. It should have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems.
ii. It should be water soluble.
iii. It should be potent.
In general, this equation, with or without some modifications, applies to all other types of osmotic systems.

\[ \frac{dM}{dt} = \frac{dV}{dt} c \]
SeveralsimplificationsinRose-Nelsonpumpwere made by Alza Corporation inearly 1970s. The Higuchi-Leeper pumpismodifiedversionofRose-Nelsonpump. It hasnowater chamber and the deviceisactivated by water imbibed from the surrounding environment. The pump is activated whenitisswallowed or implanted in the body. This pump consists of a rigid housing, and the semipermeable membrane is supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. 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.

Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. This pump comprises a rigid, rate-controlling outer semipermeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. In use, water isosmotically drawn by the salt chamber, forcing drug from the drug chamber.

In 1975, the major leap in osmotic delivery occurred as the elementary osmotic pump for oral delivery of drugs was introduced. The pump consists of a osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and the osmotic pressure of the core formulation. As the membrane is non-
expandable, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure causes the drug to be released from the tablet. The process continues at a constant rate until the entire solid agent is dissolved and only a solution fills the coating membrane. This solution is then delivered via an orifice. This process continues at a constant rate until the entire solid agent is dissolved and only a solution fills the coating membrane. This solution is then delivered at a constant rate, and there is a short lag time of 30-60 minutes before the system is obtained.

TYPES OF OSMOTIC PUMPS

Based on their design and the state of active ingredient, osmotic delivery systems can be classified as follows:

1. Osmotic delivery systems for solids
   a. Type I
      Single compartment. In this design, the drug and the osmotic agent are located in the same compartment and are surrounded by a semipermeable membrane (SPM). Both the core components are dissolved by water, which enters the compartment by osmosis. All the components in the system are dissolved by water, which affects the release rate of the drug from the system. Additionally, water-incompatible or water-insoluble drugs cannot be delivered effectively from a single-compartment configuration.

   b. Type II
      Multiple compartments. In this design, the drug is separated from the osmotic compartment by an optional flexible film, which is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension. The type II system inherently has greater utility than type I systems and can deliver drugs at a desired rate independent of their solubilities in water. One main advantage of these systems is their ability to deliver drug that are incompatible with commonly used electrolytes or osmotic agents.

2. Osmotic delivery systems for liquids
   Active ingredients in liquid form are difficult to deliver from controlled-release platforms because they tend to leak from their respective form. Therefore, liquid active agents are typically enclosed in a soft gelatin capsule, which is surrounded by a semipermeable membrane. When the system takes up water from its surroundings, the osmotic layer squeezes the innermost drug reservoir. The increasing internal pressure displaces the liquid from the system via rupturing soft gelatin capsule.

![Fig. 5: Classification of osmotic delivery systems: types I and II](image-url)
Elementary osmotic pump (EOP)
The was introduced in 1970 to deliver drug at zero or order rates for prolonged periods, and is minimally affected by environmental factors such as pH or motility. The tablet consists of an osmotic core containing the drug surrounded by a semi-permeable membrane laser drilled with a delivery orifice. Following ingestion, water is absorbed into the system dissolving the drug, and the resulting drug solution is delivered at the same rate as the water entering the tablet. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs.

Push–Pull Osmotic Pump (PPOP)
The two-layer push–pull osmotic tablet system appeared in 1980s. Push-pull osmotic pump is modified elementary osmotic pump through which it is possible to deliver both poorly water-soluble and highly water-soluble drugs at a constant rate. The push–pull osmotic tablet consists of two layers, one containing the drug and the other an osmotic agent and expandable agent. A semipermeable membrane that regulates water influx into both layers surrounds the system. While the push–pull osmotic tablet operates successfully in delivering water-insoluble drugs, it has a disadvantage that the complicated laser drilling technology should be employed to drill the orifice next to the drug compartment.

Fig. 6: Osmotic delivery system for delivery of a liquid active agent

Fig. 7: Elementary osmotic pump

Fig. 8: Push pull osmotic pump
Controlled Porosity Osmotic Pump
A controlled porosity osmotic pump-based drug delivery system Unlike the elementary osmotic pump (EOP) which consists of an osmotic core with the drug surrounded by a semipermeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of different channeling agents in the coating. The C-POP contains water-soluble additives into coating membrane, which after coming in contact with water; dissolution in situ formation of a microporous membrane. Then the resulting membrane is substantially permeable to both water and the dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simplified diffusion playing a minor role. Drug delivery from asymmetric membrane capsules is principally controlled by the osmotic pressure of the core formation. In situ formed delivery orifice in the asymmetric membrane in mainly responsible for the solubilization in the core for a drug with poor water solubility.

![Coating containing pore forming agent](image)

**Fig. 9: Controlled porosity osmotic pump**

Osmotic bursting osmotic pump
This system is similar to an EOP except delivery orifice is absent and size may be smaller. When placed in an aqueous environment, water is imbibed by a hydraulic pressure built up inside the wall and the content is released to the environment. Varying the thickness as well as the area of the semi-permeable membrane can control release of drug. This system uses a fullop to provide pulsated release.

Telescopic capsule for delayed release
This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax-like material separates the two sections. To assemble the delivery device, the desired active agent is placed into one of these sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is introduced into a completed cap of the capsule through the convex osmotic layer point into the closed end of the cap and the barrier into the closed end of the cap and the barrier layer is exposed towards the opening. The opening of the filled vesicle is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vesicle fit together tightly. As fluids are imbied by the housing of the dispensing device, the osmotic engine expands and exerts pressure on the slidable connected fist and second walls sections. During the delay period, the volume of the reservoir containing the active agent is kept constant, therefore an negligible pressure gradient exists between the environment of use and the interior of the reservoir. As a result, the net flow of environmental fluid driven by the pressure enters the reservoir, is minimal, and consequently no agent is delivered for the period.

**OROS-CT**
OROS-CT (Alzacorporation) is used dasaonceor twice a day formulation for targeted delivery of drug to the colon. The OROS-CT can be seen as a single osmotic agent or can be comprised of as many as five to six drug suspension/micronized filled in a hard gelatin capsule. After coming in contact with the gastric fluids, gelatin capsule dissolved and the enteric coating prevents entry of fluids from the stomach to the system as described by the small intestine in the entericoating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time, the flowable gelatin formed in the drug compartment, which is pushed out of the orifice at; rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane. Incorporation of the cyclodextrin-drug complex has also been used as an approach for delivery of poorly water soluble drugs from the osmotic systems. Ex. Sulbutylether-B-cyclodextrinsodium salt serves as a solubilizer and osmotic agent.
Sandwiched Osmotic Tablets (SOTS)
In this tablet core composed of polymeric push layers sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment, the middle push layer containing the swelling agent swells and the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

Longitudinally compressed tablet (LCT) multilayer formulation
The LCT multilayer formulation is the advanced design. As with the push-pull system, it consists of an osmotic push layer and can be configured to contain several drug layers. The opinion of multiple drug layers provides increased flexibility and control over the pattern of release of medication from the system as opposed to the single layer used in the push-pull system, which can deliver a drug only in a zero-order fashion. For example, two drug layers could be formulated with different drug concentration to provide modulation in the release rate profile. As with the push-pull formulation, water is absorbed through the exposed semipermeable tablet shell, expanding the push compartment and releasing the drug primarily through the first compartment through the laser drilled orifice at a predetermined controlled rate. Aftermost of the drug release begins from the second compartment at a different rate. Varying the relative viscosity and hydrophilicity of the drug layer components can control the amount of mixing between the multiple drug layers. This allows seven greater flexibility to achieve the target release profile.

Fig. 10: OROS-CT

Fig. 11: Sandwiched osmotic tab

Fig. 12: Multilayer osmotic pump
The LCT multilayer formulation can also be formulated with different drugs in different layers to provide combination therapy. Similar to the push-pull system, drug delivery by the LCT multilayer formulation can be unaffected by gastric pH, gut motility and the presence of food, depending on where in the GI tract the drug is released.

**Pulsatile delivery system**
Pulsatile systems are gaining a lot of interest as they deliver the drug at the right place of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release systems is for drugs where constant drug release, i.e., zero-order release is not desired. Therefore, the pulsatile drug is as a pulse after a lag time. This type of system consists of a core coated with a layer of swelling and rupture coatings wherein the used sprays dried lactose and microcrystalline cellulose until a drug core and then core was coated with a swelling polymer cross-linked sodium and an outer rupturable layer of ethyl cellulose. Pulsatile systems can be classified into single- and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosis-based systems. Single-unit systems are designed by coating the system either with a rifampicin soluble rupture coating. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

**KEY PARAMETERS THAT INFLUENCE THE DESIGN OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEMS**

1. **Orifice size**
   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 buildup in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values.

   Methods to create a delivery orifice in the osmotic tablet coating are:
   - Mechanical drill
   - Laser drill: This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO2 laser beam (without putting wavelength of 10.6 µm) is used for drilling, which offers excellent reliability characteristics at low costs.
   - Indentation that is not covered during the coating process. Indentation made in core tablets by using modified punches having needle or upper punch. This indentation is not covered during the coating process which acts as a path for drug release in osmotic systems.
   - Use of leachable substances in the semi-permeable coating: e.g., controlled porosity osmotic pump.

2. **Solubility**
The release rate depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low-solubility compounds, several alternative strategies may be employed. Broadly, the approaches can be divided into two categories. First, swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension. Second, the drug solubility can be modified using different methods, such as co compression of the drug with other excipients, which improve the solubility. For example, cycloextrins can be included in the formulation to enhance drug solubility. Additionally, other alternatives such as film-forming drugs can be employed to modulate solubility to a reasonable level. In one case, the solubility of oxeprenol is decreased by preparing its succinate salt so that it is reduced saturation concentration is maintained.

3. **Osmotic pressure**
The osmotic pressure directly affects the release rate. To achieve a zero-order release rate, it is essential to keep constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added to enhance osmotic pressure. For example, addition of bicarbonate salt only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acid media.
CONTROLLED POROSITY OSMOTIC PUMP- IN DETAIL
The controlled-porosity osmotic pump system was developed as an oral drug delivery system by Zenteral. The controlled-porosity osmotic pump tablet is a spray-coated oral tablet with a semipermeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drug; drug release is achieved through the pores, which are formed in the semipermeable wall during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic-pump tablet by hydrostatic pressure and diffusion through pores screened by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a tablet component, after the addition of the semipermeable membrane. 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.

Factors affecting the release of drug through controlled porosity osmotic pump
1. **Drug: Osmotic agent ratio**
   As the concentration of osmotic agent in the tablet core increases, the rate of drug release also increases. It is due to the increase in osmotic pressure on increasing the concentration of osmotic agent. As different osmotic agents possess the different osmotic pressure, the release of drug through the tablet delivery system depends on the type of osmotic agent.

2. **Level of coating thickness**
   Drug release from the system is inversely proportional to the level of coating thickness. As the thickness of coating increases, the drug release decreases.

3. **Porosity of coating membrane**
   As the porosity of the coating membrane increases, the rate of drug release increases. The porosity of coating membrane depends on the type and concentration of channelling agent.

<table>
<thead>
<tr>
<th>Table 1: Osmotic pressures of saturated solution of commonly used osmogents</th>
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<tbody>
<tr>
<td><strong>Compounds of mixture</strong></td>
</tr>
<tr>
<td>Lactose-Fructose</td>
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<tr>
<td>Dextrose-Fructose</td>
</tr>
<tr>
<td>Sucrose-Fructose</td>
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<tr>
<td>Mannitol-Fructose</td>
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<tr>
<td>Sodium chloride</td>
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<tr>
<td>Fructose</td>
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<tr>
<td>Lactose-Sucrose</td>
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<tr>
<td>Potassium chloride</td>
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<th>Table 2: Specification of Controlled Porosity Osmotic Pump</th>
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</thead>
<tbody>
<tr>
<td><strong>Subject</strong></td>
</tr>
<tr>
<td>Plasticizers and flux regulating agents</td>
</tr>
<tr>
<td>Surfactants</td>
</tr>
<tr>
<td>Wall thickness</td>
</tr>
<tr>
<td>Microporous nature of pore forming additives</td>
</tr>
<tr>
<td>Core loading (size)</td>
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<tr>
<td>Osmotic pressure developed by osmotic core</td>
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<td>Coresolubility</td>
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Table 3: Research on Controlled Porosity Osmotic Pump

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Osmoticagent</th>
<th>Semipermeable membrane</th>
<th>Channelling agent</th>
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<tbody>
<tr>
<td>Pritam et al.</td>
<td>Venlafaxine-Hydrochloride</td>
<td>Sodium chloride</td>
<td>Celluloseacetate</td>
<td>PEG-400 and HPMCK4M</td>
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<tr>
<td>Chong-kai Gao et al.</td>
<td>Salvanolic acid</td>
<td>Sodium chloride</td>
<td>Celluloseacetate</td>
<td>PEG-400 and Diethylphthalate</td>
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<td>Patel Parth et al.</td>
<td>Propranolol Hydrochloride</td>
<td>Sodium chloride</td>
<td>Celluloseacetate</td>
<td>PEG-400</td>
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<td>Harnish Patel et al.</td>
<td>Glimepiride</td>
<td>Sodium chloride</td>
<td>Celluloseacetate</td>
<td>PEG-400</td>
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Table 4: Recent patents on Controlled Porosity Osmotic Pump

<table>
<thead>
<tr>
<th>Title, Inventors, Year</th>
<th>PatentNo.</th>
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<tbody>
<tr>
<td>Salvanolicacidcontrolledporosityosmoticpump tabletsandmethodofpreparingthesame, Gao et al. 2008.</td>
<td>CN2008100276611</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Surgery controlled release therapeutic device system implanted dynamic device or system, Eric et al. 2011.</td>
<td>US20110184389</td>
</tr>
</tbody>
</table>

Table 5: Marketed formulation of controlled porosity osmotic pump

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>API</th>
<th>Strength (mg)</th>
<th>Market Status(US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiamate</td>
<td>Diltiazem Malate</td>
<td>120, 180, 240</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Teczem</td>
<td>Enalapril Diltiazem</td>
<td>280</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Acu System C</td>
<td>Vitamin C</td>
<td>NA</td>
<td>Prescription</td>
</tr>
</tbody>
</table>

EVALUATION OF OSMOTIC TABLET

Evaluation of powder
1. Weight of powder
2. Bulk density
3. Tapped density
4. Carrs index
5. Angle of repose

Evaluation of osmotic tablet
1. Hardness
2. Thickness
3. Friability
4. Weight uniformity
5. Drug content
6. In vitro dissolution study
   • Effect of osmotic pressure
   • Effect of pH on drug release
   • Stability study
   • Curve fitting analysis
   • Zero order release kinetics
   • First order release kinetics

• Burst strength
Burst strength of the exhausted shells after dissolution was determined to assure that the tablets would maintain their integrity in the gastrointestinal tract (GIT). Burst strength was determined as the
force required to break or rupture the shells after dissolution studies. The texture analyzer was used for this purpose.

- **Effect of pH**
  In order to study the effect of pH to assure a reliable performance of the developed formulations independent of pH release studies were conducted in media of different pH, simulated gastric fluid(SGF)pH 1.2, simulated intestinal fluids (SIF) pH 6. And pH change method (release media was SGF for first 2 hours followed by SIF for remaining period). The sample is withdrawn (10 ml) at predetermined interval and analysed after filtration through filter. The cumulative drug release of various pH was plotted and compared.

- **Effect of agitational intensity**
  In order to study the effect of agitational intensity of the release media release studies were carried out in dissolution apparatus at various rotational speeds. Samples were withdrawn at pre-determined intervals and analysed after filtration and percentage cumulative drug release was compared and plotted.

- **Osmotic pressure measurement**
  In order to confirm the mechanism of drug release studies were conducted in media of different osmotic pressure. To increase the osmotic pressure of release media sodium chloride was added in SIF and osmotic pressure was measured in osmometer.

- **Curve fitting analysis**
  To describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed. Release data obtained was applied to different release models in order to establish the drug release mechanism and kinetics. Best goodness of fit test ($R^2$) was taken as criteria for selecting most appropriate model.

**CONCLUSION**

It can be concluded that β1 cardio selective blockers can be formulated by CPOP with good release profiles for prolonged period of time up to 13 hours which can decrease the frequency of dose administration, prevent nocturnal attack and improves patient compliance. Further in vivo studies are required to correlate with in vitro release data.

**REFERENCES**