



A REVIEW ON CONTROLLED POROSITY OSMOTIC PUMP AS AN OSMOTIC DRUG DELIVERY APPROACH

Sakina A. Khan^{1*}, Ajay N. Talele¹, Dr. Sachin B. Narkhede¹ and Mrinanka Singha²

¹Smt. B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat.

²Glenmark Pharmaceutical Ltd. Gangtok, Sikkim.

***Corresponding Author: Sakina A. Khan**

Smt. B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat.

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ABSTRACT

Oral route is found to be more convenient route. But the inability of conventional system to utilize this route efficiently lends the pharmaceutical market for more appropriate option i.e. controlled drug delivery system which can maintains plasma drug concentration. Osmotic drug delivery is found to be superior out of them that utilize the principle of osmotic pressure to maintain the drug release at zero order rate. The drug releases is independent of the pH and thermodynamics of dissolution medium and zero order kinetics. The release of drug from Osmotic system depends upon various formulation factors like solubility, osmotic pressure (core components), size of the delivery orifice and nature of the rate controlling membrane. CPOP constitutes drug, osmogens, excipients in core and a coating of semipermeable membrane containing water soluble additives (Pore former). In CPOP pore former dissolve after coming in contact with the body fluids, resulting in an in situ formation of a microporous membrane due to the pore formers. The present study gives a glimpse about osmotic drug, CPOP, components of CPOP, factors influencing drug release from the system and its evaluation.

KEYWORDS: CPOP, Osmotic tablets, Controlled release drug delivery, Pore former, Microporous system.

INTRODUCTION

Oral route is a most explored and convenient route for the administration of various drugs for systemic delivery because of low cost and ease of administration to the patients.^[1-2] But conventional drug delivery system does not control the release of drug and provides immediate release of drug and its rate and extent of drug absorption change significantly depending on factors such as physicochemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of gastrointestinal (GI) tract, GI motility and so on.^[2] This results in to focus on more reliable approach to prevent these shortcomings, Novel drug delivery system evolved with this idea. Controlling the drug release will maintains the plasma drug concentration for prolong period of time. NDDS available in the market per oral controlled release system provides improved patient compliance, convenience and reduction in fluctuation in a steady state plasma level. In Controlled drug delivery system (CDDS) there is a maximum utilization of drug optimizing reduction in total amount of dose and delivers short biological half life of drugs.^[4]

CDDS offers temporal and spatial control over the release of drugs.^[5] But osmotic drug delivery system

(ODDS) can be consider as one of the most advanced drug delivery systems utilizing osmotic pressure as a driving force for controlling the delivery of drugs. The release of drug from osmotic system is independent of presence and absence of food, pH of gastrointestinal (GI) tract, GI motility and hydrodynamic conditions of body due to rate controlling semi permeable membrane. In ODDS the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window.^[6]

ODDS tends to delivers the drug at predetermined zero order rate for a prolonged time period. So, it is found as superior over other dosage form for constant drug delivery. ODDS provides an uniform concentration of drug at the site of absorption and thus after absorption allows maintenance of plasma concentration within therapeutic range which minimizes side effects and reduces the frequency of administration.^[5]

There are various approaches available that one can prefer for osmotic drug delivery, the classification has been provided in Table No.1^[7]

Table No. 1: Classification of Osmotic Drug Delivery System.

TYPE		EXAMPLE OF OSMOTIC PUMP
Implantable Osmotic Pump		Rose And Nelson Osmotic Device. Higuchi Theeuwes Osmotic Device. Higuchi Leeper Osmotic Device. Alzet Osmotic Device
Oral Osmotic Pump	Single Chambered	Elementary Osmotic Pump (EOP)
	Modified Osmotic Pump	Control Porosity Osmotic Pump (CPOP) Osmotic Bursting Liquid OROS
	Multi Chamber Osmotic Pump	Non Expandable Multi Chamber OP Expandable Multi Chamber OP
Multi-Particulate Delay Release System		OROS-CT Osmotic Device. Telescopic Capsule For Delay Release. Sandwich Osmotic Device. Monolithic Osmotic Device.
Some Advance Type Of Osmotic Devices		OSMAT. Osmotic bursting osmotic device. Lipid osmotic device.

This review focus on the glimpse of Controlled Porosity Osmotic Pump (CPOP). Each above approach has their advantages and disadvantages. CPOP is an approach that more reliable in terms of its ease of manufacturing, avoids expensive drilling, etc. Comparing EOP with CPOP, CPOP was found to be superior over EOP.^[8]

➤ Controlled Porosity Osmotic Pump (CPOP)^[9-11]

The Controlled-Porosity Osmotic Pump tablet concept was developed as an oral drug delivery system by Zentner, Rork, Appel and Mc Celland.^[9] The Controlled-Porosity Osmotic Pump tablet (CPOP) is a spray-coated or coated tablet with a semipermeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture or orifice to release the drugs; drug release solely depends on the pores, which are formed in the semipermeable wall *in situ* 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 created by the dissolution of pore formers incorporated in the membrane (Figure No. 1). The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a tablet component, after water is imbibed across the semipermeable membrane.^[10]

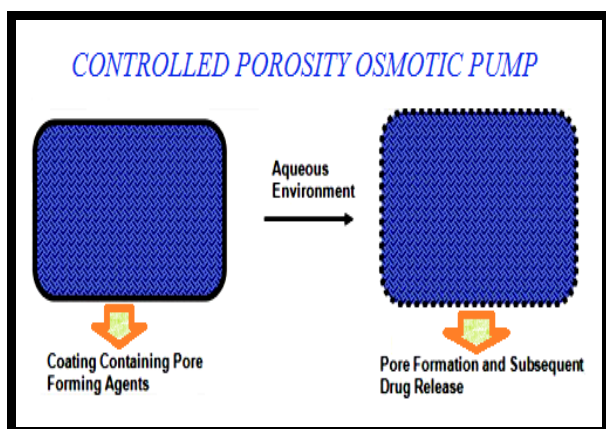


Figure No. 1: Controlled Porosity Osmotic Pump.

The membrane after formation of pores becomes permeable to both water and solutes. A controlled-porosity osmotic wall can be described as having a sponge like appearance. The pores can be continuous that have micro porous lamina, interconnected through tortuous paths of regular and irregular shapes.^[9]

This system is generally applicable for only water-soluble drugs as poorly water soluble drugs cannot dissolve adequately in the volume of water drawn into the OPT. But this problem could be resolve by enhancing the solubility of drug by the use of sulfobutyl ether-cyclodextrin (SBE)7m-β-CD or hydroxypropyl-cyclodextrin (HP-β-CD) as solubilizing and osmotic agents.^[11] Several approaches have been developed to prepare the porous membrane by spray coating using polymer solutions containing dissolved or suspended water-soluble materials. The rate of drug release can also be varied by having different amounts of osmogents in the system to form different concentrations of channeling agents for delivery of the drug from the device.^[10]

➤ Mechanism of Drug Release^[4]

When the controlled porosity osmotic pump tablets are in aqueous environment the water soluble additives get dissolved and form a micro porous structure in the coating membrane. The pores formed in SPM may be continuous with micro porous lamina, interconnected through tortuous paths of regular and irregular shapes as shown in figure no. 1. The water enters through pores of semi permeable membranes and forms a solution of drug which is released through pores. The rate of water inlet is depends on the type and concentration of osmogent and the drug release depends upon hydrostatic pressure created by inlet water, and the size and number of pores.

The pumping drug rate from the core can be expressed as,

$$\frac{dm}{dt} = \frac{A}{h} K\pi C$$

This fundamental equation is applicable to all osmotically driven pumps as well as controlled porosity osmotic pump tablets.

➤ **Advantages**

1. The drug release are independent of the gastric pH and hydrodynamic conditions, which is mainly due to the unique properties of the SPM that is used in the coating of osmotic core.
2. The delivery rate of drug is highly predictable and also can be programmed by modulating the factors.
3. Better release profile than conventional formulation.
4. It is devoid of the expensive laser drilling because the holes are formed in situ.
5. The scale up is very easy.
6. The stomach irritation problems can be avoided because the drug is released from the entire surface rather than single delivery orifice.
7. It is useful for water soluble, partially water soluble and water insoluble drugs.
8. Better *in vitro-in vivo* correlation [IVIVC] within specific limits.

➤ **Disadvantages**

1. Sometime presence of food may influence its release profile.
2. Retrieval of therapy is impossible in the case of unexpected adverse events.
3. Residence time of the system in the body depends on the gastric motility and food intake.
4. Integrity & consistency are difficult at laboratory level.
5. Dose dumping may result if the coating is faulty.
6. Development of tolerance.

➤ **General Components required for Controlled-Porosity Osmotic Pump^[13-14]**

- a. Drug
- b. Osmotic agent
- c. Semipermeable membrane
- d. Channeling agents or pore forming agents
- e. Flux regulator
- f. Plasticizer
- g. Coating solvents
- h. Wicking agent
- i. Hydrophilic and hydrophobic polymers

a) **Drug^[6]**

Criteria for selection of a drug

- Have good aqueous solubility
- Rapid absorption
- High Potency
- Short Biological Half-life (2- 6 hrs)
- Have Stability in GIT
- High Therapeutic window
- Should have dose size less than 1 gm.
- Required for prolonged treatment (e.g: Nifedipine, Glipizide, Verapamil and Chlorpromazine hydrochloride).

Table No. 2: Specification for Core of CPOP tablet^[9]

Property	Specifications
Core loading (size)	0.05 mg to 5 g or more (include dosage forms for Humans and animals).
Osmotic pressure developed by a solution of core	8 to 500atm typically, with commonly encountered water soluble drugs and excipients.
Core solubility	To get continuous, uniform release of 90% or greater of the initially loaded core mass solubility (S), to the core mass density, that is S/ρ , must be 0.1 or lower. Typically it occurs when 10% of the initially loaded core mass saturates a volume of external fluid equal to the total volume of the initial core mass.

b) **Osmotic Agent^[13]**

Osmogens are an essential ingredient of the osmotic formulations. They maintain an osmotic gradient across the membrane. 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. When the solubility of drug is low then the drug will show zero order release but at a slow rate. To enhance the release rate osmotic agent is added in the formulation.

Table No. 3: Classification of Osmogen^[13]

Category	Examples
Water soluble salts of inorganic acids	Sodium chloride Magnesium chloride, Potassium sulphate, Magnesium sulphate, Potassium chloride, Sodium bicarbonate
Water soluble salts of organic acids	Potassium acetate, Sodium Ascorbate, Sodium acetate, Sodium citrate, Sodium benzoate
Carbohydrates	Mannitol, Dextrose, Arabinose, Sucrose, Fructose, Glucose, Galactose, Lactose, Maltose, Xylose, Sorbitol
Weak acids	Tartaric acid, Citric acid, Melanic acid, Fumaric acid
Water soluble amino acids	Leucine, Glycine, Alanine, Methionine
Organic polymeric Osmogens	Hydroxyl propyl methyl cellulose, Sodium Carboxy methyl cellulose, Hydroxyl ethyl methyl cellulose, Cross linked PVP

c) **Semipermeable Membrane**

Semipermeable membrane is a selectively permeable membrane that allows water to pass across while impermeable to solute.

- **Cellulose acetate** is a most 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 anhydro glucose unit of the polymer replaced by substituting group.

• **Examples of semipermeable membrane**

- **Cellulose Esters** such as Cellulose Acetate, Cellulose Diacetate, Cellulose Triacetate, Cellulose Propionate, Cellulose Acetate Butyrate.
- **Cellulose Ethers** like Ethyl Cellulose.
- **Other** Agar Acetate, Amylose Triacetate, Betaglucan Acetate, Poly (Vinyl Methyl) Ether Copolymers, Poly (Orthoesters), Poly Acetals And Selectively Permeable Poly (Glycolic Acid), Poly (lactic acid) derivatives, and Eudragits.^[12]

• **Ideal Properties of Semipermeable Membrane**^[14]

1. The material must possess sufficient wet strength (10-5 Psi) and wet modules (10-5 Psi) so as to retain its dimensional integrity during the operational lifetime of the device.
2. The membrane must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapour transmission rates can be used to estimate water flux rates.

3. The reflection coefficient (σ) or "leakiness" of the osmotic agents should approach the limiting value of unity. But polymer membranes must be more permeable to water.

4. The membrane should be biocompatible.
5. The membrane should also be rigid and non-swelling.
6. The membrane should be sufficient thick to withstand the pressure within the device.
7. The semipermeable membrane should be a stable both to the outer inner environment of the device.

d) **Pore-Forming Agents (Channelling Agent)**^[13]

These are the water-soluble components which play an important role in the controlled drug delivery systems. When the dissolution medium comes into contact with the semipermeable membrane it dissolves the channelling agent and forms pores on the semipermeable barrier. Then the dissolution fluid enters the osmotic system and releases the drug in a controlled manner over a long period of time by the process of osmosis.

Table No. 4: Classification of Pore former^[13]

CATEGORY	EXAMPLES
Alkaline metal salts	Sodium Bromide, Sodium Chloride, Potassium Sulphate, Potassium Chloride, Potassium Phosphate
Alkaline earth metals	Calcium Chloride, Calcium Nitrate
Carbohydrates	Mannitol, Fructose, Sucrose, Sorbitol, Glucose, Mannose, Lactose, Pentaerythritol
Diols and polyols	Polyethylene Glycols (PEG), Polyhydric Alcohols (PVA), Polyvinyl Pyrrolidone (PVP)
Phthalate derivatives	Dibutyl Phthalate (DBP), Diethylphthalate,
Protiens	Bovine Serum Albumin (BSA)

- The pore-formers should be **non-toxic**, and on their removal, channels should be formed.

e) Flux Regulator

Flux regulating agents (either flux enhancing agent or flux decreasing agent) are incorporated in the wall forming material to regulate the permeability of the fluid across the membrane. They also increase the flexibility and porosity of the lamina.

- **Flux enhancing agent:** Hydrophilic substances such as poly ethylene glycols (300 to 6000 Da), polyhydric alcohols such as poly alkylene glycols and low molecular weight glycols such as poly propylene, poly butylenes and poly amylene, etc tend to enhance the flux.
- **Flux decreasing agent:** Hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethyl phthalate) tend to decrease the flux.

f) Plasticizer

Plasticizers can change viscoelastic behavior 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.

- PEG-600, PEG-200, triacetin (TA), ethylene glycol mono acetate, ethylene glycol diacetate, and diethyl tartrate used as plasticizer in formulation of SPM.

g) Coating Solvents

The primary function of solvent system is to dissolve or disperse the polymer and other additive and convey them to substrate surface.

- The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate 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) can be used.

- **The ideal solvent system should have following properties.**

- 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 create process problem.
- It should be inert, odorless, colorless, tasteless, inexpensive, nontoxic and non-irritant.
- It should have rapid drying rate.

h) Wicking Agent

The wicking agents help to increase the contact surface area of the drug with the incoming aqueous fluid ability due to their ability to draw water into the porous network to enhance the rate of drug released from the orifice of the drug. A wicking agent is of either swellaable or nonswellaable in nature.

- Materials like colloidal silicon dioxide, kaolin, titanium dioxide, fumed silicon dioxide, sodium lauryl sulfate, low molecular weight polyvinyl pyrrolidone, bentonite, polyethylene etc. may be used as wicking agents.

i) Hydrophilic and Hydrophobic Polymers

Polymers are used in the formulation 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, (e.g. HPMC as hydrophilic).

Table No. 5: Specification for CPOP^[9]

Formulation component	Specification
Plasticizers and flux Regulating agents	0 to 50, preferably 0.001 to 50 parts per 100 parts of wall material.
Surfactants	0 to 40, preferably 0.001 to 40 parts per 100 parts of wall material.
Wall thickness	1 to 1000, preferably 20 to 500 μ m.
Microporous nature Pore forming additives	5 to 95% pores between 10 μ m to 100 μ m diameter 0.1 to 60%, preferably 0.1 to 50%, by weight, based on the total weight of additive and polymer.

➤ Factors Affecting Drug Release from CPOP^[13-15]

- Drug solubility
- Osmotic pressure:
- Use of wicking agent:
- Characteristics of semipermeable membrane:
- Membrane thickness
- Type and amount of plasticizer
- **Solubility:** The solubility of the active agent within the device not only dictates the feasibility of making an osmotic system, but also determines the release rate and the percentage of the drug delivered in the desired zero-order fashion. Since the kinetics of osmotic drug release is directly related to solubility of drug within the core, drugs having intermediate water solubility are suitable candidates for controlled porosity osmotic pump to get the

optimized drug release. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by equation,

$$F(z) = 1 - S/\rho$$

Where,

$F(z)$ = fraction released by zero-order kinetics

S = drug's solubility (g/cm^3)

ρ = density (g/cm^3) of the core tablet

Drugs with a density of unity and the solubility of $\leq 0.05 \text{ g}/\text{cm}^3$ would be released with $\geq 95\%$ zero-order kinetics, according to above equation.

- **Osmotic pressure:** Osmotic pressure gradient between inside the compartment and the external environment determines the release rate of drug, since rate of drug release from an osmotic system is directly proportional to osmotic pressure of the tablet core.

In order to achieve a zero-order release rate, it is essential to keep constant osmotic pressure by maintaining a saturated drug solution inside the core.

Table No. 6: List of Commonly used Osmogen with Osmotic Pressure.

Name of osmogen	Osmotic pressure
Sodium Chloride	356
Sucrose	150
Potassium Chloride	245
Dextrose	82
Lactose	23
Fructose	355
Mannitol	38
Sorbitol	84
Citric Acid	69
Tartaric Acid	67

- **Use of wicking agent:** 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 help to enhance the rate of drug released from the orifice of the drug.
- **Characteristics of Semipermeable membrane:** Some of the membrane variables that are important in the design of oral osmotic system are:
 - **Type and nature of polymer:** Any polymer permeable to water but impermeable to solute can be selected.
 - e.g. Cellulose Acetate (398 10NF, 320 10NF)
 - **Membrane thickness:** Thickness of the membrane has a significant effect on the drug release from osmotic system, which is **inversely proportional** to each other.
- **Type and amount of plasticizer:** In pharmaceutical coatings, plasticizers or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change visco-elastic

behaviour of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films.

➤ Design of CPOP

The purpose of designing dosage form is to control the release of drug at zero order rate kinetics by osmotic drug delivery approach, whose release depends on the pH independent and insoluble coating under all physiological conditions with water soluble channelling agent and on the conc. of the osmogen. The method of application and processing conditions may influence the porosity of the coating and consequently the release mechanism.

➤ Controlled Porosity Osmotic Tablets

- **CORE:** The core contains pharmaceutical active ingredients with osmogen, polymer, diluents, lubricants and glidant, were mixed and compressed.
- **COATING:** Core is coated with semipermeable membrane (Cellulose acetate) with pore former and plasticizer.

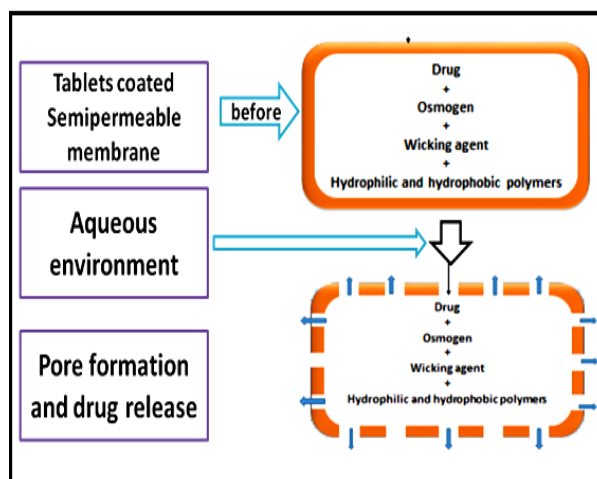


Figure No. 2 Design of Controlled Porosity Osmotic Pump.

➤ Evaluation Parameters^[16-18]

The evaluations conducted are same as that of other tablets.

Table No 7: Evaluation Parameters for CPOP.

Pre-Compressional Parameters	Post-Compressional Parameters	
	Core Tablets	Coated Tablets
<ul style="list-style-type: none"> ▪ Angle of Repose ▪ Bulk Density ▪ Tapped Density ▪ Carr's index ▪ Hausner's ratio 	Weight variation <ul style="list-style-type: none"> ▪ Friability ▪ Hardness ▪ Thickness 	<ul style="list-style-type: none"> ▪ Visual inspection of coat ▪ Thickness of film ▪ Weight gain ▪ In-vitro dissolution study ▪ Burst strength ▪ Surface morphology study ▪ Stability study

- **Burst Strength**^[18]

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/rupture the shells after dissolution studies. The study can be carried out by texture analyzer. Burst strength should be about 1.9N to withstand the force exerted by GIT.

- **Surface morphology study**^[17-18]

Coating membrane of formulation obtained before and after complete *in-vitro* dissolution of core contents were examined for their porous morphology by scanning electron microscope (SEM). It confirms the release is due to pores formed on the surface of the coating.

➤ **CONCLUSION**

From the present review it was concluded that the release of drug follows zero order kinetics and is safer than conventional dosage forms and the oral controlled-porosity osmotic pump system comprising a monolithic tablet coated with a semipermeable membrane containing different levels of pore forming agents can deliver water soluble drugs at zero order. Now approaches are also there for poorly water soluble drugs. This system is simple to prepare with no drilling required and hence it can be used in the field of controlled delivery of drugs.

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