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Review on controlled porosity osmotic pump tablets and its basic components

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Abstract

A system that can deliver drug at a controlled rate is very important for the treatment of various chronic diseases such as Diabetes, Asthma and Heart disease. Conventional drug delivery systems are known to provide an immediate release of drug in which one cannot control the release of the drug and cannot maintain effective concentration at target site for longer time. Drugs having short biological half-life and poor water solubility offers challenges in the controlled release formulation because of low dissolution rate and poor bioavailability. Hence to avoid these, various controlled drug delivery systems are developed. Among these Osmotic drug delivery system, utilizes the principle of osmotic pressure releases drug in optimised manner. Controlled porosity osmotic pump (CPOP) based drug delivery system contains active ingredient, osmogens, semi permeable membrane, channelling agent and water soluble additives. In this system, when water comes in contact with water soluble additives it results in an in situ formation of a Microporous membrane. The main driving force for the release of drug is osmotic pressure. Osmogens maintain concentration gradient across the membrane. The present study deals with Controlled porosity osmotic pump tablets and its basic components.

Key words: Osmotic drug delivery system, CPOP, Microporous, Osmogens.

INTRODUCTION

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. Yet, there are problem encountered in solid dosage forms like multiple dosing of the product due to short biological half-life of drug and low bioavailability. To overcome such problems, certain innovative drug delivery systems, like CPOP (Controlled porosity osmotic pump) tablets have been developed [1]. The most important advantages of CPOP tablets when compared to conventional oral dosage forms is its extended and controlled release of drug which avoids administration of product several times a day and increases patient compliance. Further CPOP tablet increases solubility of poorly soluble drugs with suitable solubility modifires [2].

A CPOP (controlled porosity osmotic pump) tablet is an osmotic tablet wherein the delivery orifices are formed in situ through leaching of water soluble pore-forming agent incorporated in semipermeable membrane. Drug release of CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of pore-forming agents and osmotic pressure difference across the membrane [3].It can be prepared by different techniques like, direct compression method, wet granulation of the core and coating with suitable coating solvents [4].

The release of drug from CPOP tablets is independent of presence and absence of food, pH of gastro intestinal (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 [5].

When an osmotic system comes in contact with water, water diffuses into core through the microporous membrane setting up an osmotic gradient and thereby controlling the release of the drug. Osmotic pressure is the pressure applied to the higher concentrated solution side to prevent transport of water across the semi permeable membrane. The rate of drug delivery from osmotic system is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogens. The following review concentrates on controlled porosity osmotic pump tablets and its basic components [6].

OSMOTIC DRUG DELIVERY SYSTEM

Osmotic devices are most promising strategy based systems for controlled drug delivery. 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. Osmotic pressure created by osmogens is used as driving force for these systems to release the drug in controlled manner. These systems can be used for both oral and implantation. Osmotic pump offers many advantage over other controlled drug delivery systems, that is, they are easy to formulate and simple in operation, improved patient compliance with reduced dosing frequency and prolonged therapeutic effect with uniform blood concentration [7].

TYPES OF OSMOTIC IMPLANTABLE PUMPS

An osmotic pump includes bi compartment system, separated by a piston. One of the Compartments contains osmotic engines specifically prepared with an excess of solid Sodium Chloride, such that it remains throughout the delivery time and results in a constant osmotic gradient. It also consists of Semi permeable membrane on one end through which water is drawn into the osmotic engine and establishes a constant osmotic gradient between tissue, water and osmotic engine. Other compartment consists of drug solution with an orifice from which the drug is released due to osmotic gradient. Various types of Osmotic Implantable Pumps are Rose and Nelson Pump, Higuchi leeper, Higuchi Theewus, Implantable mini osmotic pumps like Alzet and Duros Pump [7].

Oral osmotic pump

Oral osmotic pumps consist of an osmotic device for delivering active ingredient into the oral cavity. The osmotic device comprises a semi permeable membrane surrounding the compartment which contains active ingredient that is insoluble in an aqueous fluid. The passage through the semi permeable membrane connects the exterior of the device with compartment containing active ingredient for delivering from the device to oral cavity. Based on chamber in oral osmotic pump, it is classified into single chamber osmotic pump such as elementary osmotic pump and Multi chamber osmotic pump such as Push-Pull osmotic pump with expanding second chamber [8].

Specific types

Recent advances include various specific systems in osmotic pumps such as Controlled porosity osmotic Pump (CPOP),Osmotic Bursting osmotic pump, Liquid OROS, Delayed delivery osmotic device, telescopic capsule, OROS CT (Colon targeting), sandwiched oral therapeutic system, osmotic pump for insoluble drugs and monolithic osmotic system and OSMAT [9].

CONTROLLED POROSITY OSMOTIC PUMP (CPOP)

Controlled Porosity osmotic pump(CPOP) tablets is an osmotic tablet wherein the delivery orifices are formed in situ through leaching of water soluble pore forming agents incorporated in semi permeable membrane. Main advantages of CPOP are reduced stomach irritation, no complicated laser- drilling. CPOP consists of osmotic core with drug surrounded by a semi permeable membrane drilled with a delivery orifice. Controlled porosity is accomplished by the use of different channelling agent in the coating. The CPOP contain water soluble additives in coating membrane, which when comes in contact with water dissolve resulting in formation of ain situ micro porous membrane. Then the resulting membrane is substantially permeable to both water and dissolved solutes. The pump can be designed as single or multi compartment dosage. In this system the drug after dissolution inside the core is delivered from the osmotic pump tablet by hydrostatic pressure and diffusion through the pores incorporated in the micro porous semi permeable membrane. Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, water permeability, level of leachable pore-forming agents and the osmotic pressure

difference across the membrane [10]. The rate of flow of water into the device can be expressed as given below

Equation 1,

$dv/dt=Ak/h(d\pi-dp)$

where
dv/dt is rate of flow of water to device
k and *A* are membrane permeability and surface area of membrane, respectively
dπ and *dp* are osmotic pressure difference and hydrostatic difference between inside and outside of the membrane, respectively.

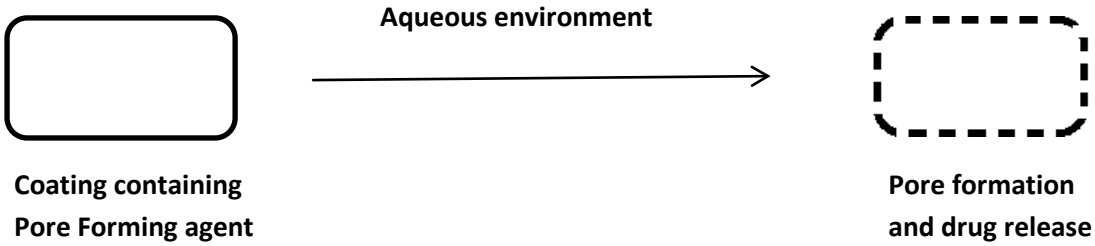

Fig. 1 Schematic representation of controlled drug delivery system.

ADVANTAGES OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS

1. The delivery of drug may be delayed or pulsatile.
2. The drug release is independent of physiological conditions of the body, gastric pH and drug of hydrodynamic condition.
3. The release of drugs from CPOP follows zero order kinetics after an initial lag.
4. The drug delivery provides high degree of *in vitro in vivo* correlation.
5. The release of drug is less affected by the presence of food in GIT.
6. The drug release is higher than conventional drug delivery system.
7. There is no need of laser drilling because the holes are formed in situ.
8. The delivery rate of drug from CPOP is predictable and programmable.
9. The stomach irritation problems are reduced because the drug is delivered from the entire surface rather than single delivery orifice.
10. The production in scale up is very easy.

DISADVANTAGES OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS

1. Retrieval therapy is not controllable in case of unexpected adverse effects
2. There is a chance for the development of drug tolerance
3. The method of preparation is very costly

4. There is a chance of dose dumping if the coating process is not well controlled.

BASIC COMPONENTS OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS

Drugs

All drugs are not suitable for CPOP as prolonged action medication.Drugs having following characteristics are suitable for formulation

1. It should have short half – life
2. Prolonged release of drug should be desired
3. It should be potent in nature
4. Solubility of drug should not be very high or very low

Osmotic agents

These are also known as osmogens or osmogents and are used to create osmotic pressure inside the system. 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. Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components are usually ionic compound consisting of either inorganic salts or hydrophilic polymer. Osmotic agents can be any salt such as sodium chloride, potassium chloride or sulphates of sodium or potassium and lithium. Additionally sugars such as glucose, sorbitol or sucrose or inorganic salts of carbohydrates can be osmotic agents [11].

Classification of osmotic agents

Table 1

S. No	Osmogens	Example
1	Water- soluble salts of inorganic acids	Sodium carboxy methyl cellulose, Magnesium chloride
2	Organic polymeric osmogent	Polyacrylamides, Sodium sulphate
3	Carbohydrates	Xylose, Arabinose
4	Water soluble salts or organic acids	Glycine, Alanine
5	Water- soluble salts of organic acids	Sodium citrate, Potassium acetate

Semi permeable membrane (SPM)

An important part of the CPOP is Semipermeable membrane housing. Therefore, the polymeric membrane selection is major key to the osmotic delivery formulation. The membrane should posses certain characteristics such as impermeability to the passages of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during dug delivery. Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. The semipermeable membrane must meet some performances.

Ideal properties of semi permeable membrane

1. The membrane should be biocompatible.
2. The material should have sufficient wet strength and wet modulus.
3. The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity.
4. The membrane should have sufficient water permeability to retain water flux rate in the desired range [12].

Wicking agents

A wicking agent also called as pore forming agent is defined as a material with the ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non- swellable nature. They are characterised 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 by Vander Waal's 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 .Materials, which suitably for act as wicking agents include colloidal silicone dioxide, kaolin [13].

Pore forming agents

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or Multiparticulate osmotic pumps. The pore forming agents cause formation of microporous membrane. The microporous wall may be formed in situ by a pore former by its leaching during the operation of the system. The pore forming 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. The examples are colloidal silicon dioxide. PVP, carbohydrates like sucrose, sorbitol and sodium lauryl sulphate [13].

Plasticizers

In Pharmaceutical coating, 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 and these changes may affect the permeability of the polymeric films. Plasticizers can turn a hard

and brittle polymer into a softener, more paliable material, and possibly make it more resistant to the mechanical stress. Plasticizers increases the workability, flexibility and permeability of coating solvents. PEG 600, PEG 200, ethylene glycol diacetate are used as plasticizers. Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulations of osmotic systems [14].

Coating solvents

The primary function of solvents system is to dissolve or disperse 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 tablet core, wall and other materials. The most common coating solvents used are methylene chloride, acetone, methanol and ethanol [15].

MECHANISM OF DRUG RELEASE

Tablet has rigid water permeable jacket with many small holes. As the tablet passes through the body, the osmotic pressure of the tablet pushes the active drug through the opening in the tablet [16]. The basic equation for osmotic system is

Equation 2,

$dM/dt=dV/dt.c$

Where

dM/dt is mass release

dV/dt is volumetric pumping rate

c is concentration of drug But,Equation 3

$dV/dt=(A/h)Lp\ (\dot{\sigma}\Delta\pi-\Delta p)$ where

A is membrane area

h is thickness of membrane

Lp is mechanical permeability

Σ is reflection coefficient

Δπ is osmotic pressure difference

Δp is hydrostatic pressure difference

As the size of orifice increases, *Δp*also increases so $\Delta\pi >> \Delta p$ and equation becomes $dV/dt=A/h\ Lp\ (\dot{\sigma}\Delta\pi)$. When osmotic pressure of the formulation is large compared to the osmotic pressure of environment, p can be substituted as *Dp* Equation 4,

$dV/d= A/h\ Lp,\ \dot{\sigma}\pi= A/hk\pi$

COMPATIBILITY STUDIES

Fourier transforms infrared spectroscopy (FTIR)

The use of FTIR technique allows pointing out the implication of the different functional groups of excipients by analysing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of the drug and excipients are grounded and mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a motar and compressed into disc by applying pressure of 5 tons for 2 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer. Then the characteristics peaks of all samples as well as mixtures are obtained [17].

Differential scanning Calorimetry

The compatibility of drug with the excipients used for the formulation development was tested using differential scanning calorimetry. Physical mixtures of drug and individual excipients in the ratio 1:1 are taken and examined n DSC. Individual samples as well as physical mixture of drug and excipient are weighed to about 5 mg in DCS pan. The sample pan was crimped for effective heat conduction and scanned in temperature range 50-300^0 C. Heating rat of 20^0 C min^{-1} was used and the thermos grams are compared with pure samples versus optimized formulation.

EVALUATION PARAMETERS

Angle of Repose (θ)

The angle of repose test is very sensitive to the method used to create the heap. Angle of repose may be determined by heap shape measurement. By using the classical method angle of repose can be measured. The diameter of powder heap is measured and angle of repose is calculated using he following equation

Equation 5,

$Tan\vartheta = tan^{-1}(2h/d)$

Where ϑ is the angle of repose, h is the height of heap in cm and d is the diameter of the circular support in cm. Angle of repose can be observed accurately by placing a dry and clean funnel on burette stand at a particular height (2-5cm). place a graph paper on flat surface that is allow accurately weighed granules to flow slowly throughout the funnel, untill the open heap of granules bounces the tip of funnel. Draw the circumference of the heap. Allocate the midpoint and measure the radius. The height of the heap is also measure. Repeat the experiment and calculate the average radius and height.

Bulk density (e_b)

Bulk density is determined by pouring the granules into graduated cylinder. The bulk volume and mass of the granules are determined. The bulk density by using the following formula

Equation 6,

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

Tapped density (e_t)

The measuring cylinder containing a known mass of granules blend is tapped 1000 times for a fixed time. The minimum volume occupied in the cylinder (V_t) and mass of the granules (m) are measured. The tapped density is measured by using the following formula.

Equation 7,

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume}}$$

Compressibility index (Carr's index)

The compressibility index determines the flow property characteristics of granules developed by Carr. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The carr's index can be calculated by the following formula

Equation 8, $$\text{Compressibility index} = \frac{\text{tapped density-bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is used for the determination of flow properties of granules. The ratio can be calculated by taking ratio of tapped density to the ratio of bulk density

Equation 9,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

POST COMPRESSION PARAMETERS OF OSMOTIC PUMP TABLETS

Thickness

The thickness of individual tablets is measures by using Vernier calliper which gives the accurate measurement of thickness. It provides information of variation of thickness between osmotic pump tablets. Generally the unit for thickness measurement is mm. the limit of the deviation of each tablet is $\pm$ 5%.

Hardness

The hardness of tablets can be determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability

Friability of tablets is performed in a Roche friabilator. Ten tablets are initially weighed *(W_0)* together and then placed in the chamber. The friabilator is operated for 100

revolutions and the tablets are subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed *(W).* The percentage of friability was calculated using following formula,

Equation 10,

Friability= (initial weight-final weight/initial weight) 100

Weight variation

The weight variation test is done by weighing 20 tablets individually calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation is calculated and the compared with USP specifications. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Disintegration test

In disintegration test apparatus disintegration time of tablets is measured by placing tablets in each tube and the basket rack assembly is positioned in a 1- litre beaker of water or simulated gastric fluid or simulated intestinal fluid at 37^0 C $\pm$ 2^0 C such that the tablet remain 2.5 cm from the bottom of the beaker. A standard motor moves the basket up and down through a distance of 5 to 6 cm at a frequency of 28 to 38 cpm (cycles per min). USP disintegration test will be passed if all the tablets disintegrate and the particles are passed through the #10 mesh screen within specified time.

Uniformity of drug content test

In this USP method 10 dosage units are individually assayed for their content according to the method described in the individual monograph. Unless otherwise stated in the monograph the requirements for content uniformity are met if the amount of active ingredient in each dosage unit lies within the range of 85- 115% of the label claim and standard deviation is less than 6%. If one or more dosage units do not meet these criteria additional tests as prescribed in USP are required.

***In vitro* dissolution studies**

In vitro dissolution study is performed by using USP type 1 Apparatus (Basket type). The tablet is kept 900 ml of dissolution fluid phosphate buffer of pH 7.4 or 0.1 N Hcl or simulated gastric fluid with stirrer rotating at a specified RPM and maintaining the temperature at 37 $\pm 0.5^0$ c of dissolution media. 5 ml of samples withdrawn at different time intervals are replaced with fresh medium and analysed in UV – Visible spectrophotometer for estimation of absorbance taking a suitable blank solution. Finally the drug release rate is calculated using a suitable equation [17].

Scanning electron microscopy

In order to observe the mechanism of drug release from the developed formulations surface coated tablets before and after dissolution studies are examined using a scanning electron microscope. Membrane are dried at 45^0 C for 12 h and stored

between sheets of wax paper in a dessicator until examination. The samples are fixed on a brass stub using a double sided tape and then gold coated in vaccum by a sputter coater. Scans are taken at an excitation voltage of 20 KV in SEM fitted with ion sputtering device. The surface morphology of coated membrane of optimized formulation film coating before and after coating before and after dissolution is examined and by comparing the porous morphology the capability of porogen and drug release can be evaluated [18].

FACTORS AFFECTING RELEASE OF MEDICAMENT

Factors affecting the release rate of medicament from osmotic drug delivery system are,

1. Solubility

2. Osmotic pressure

3. Delivery orifice

4. Membrane type

SOLUBILITY

Solubility of drug is one of the most important factors since kinetics of osmotic release is directly related to the drug solubility. In osmotic drug delivery system, solubility of drug plays a major role in the drug release. When the solubility of drug is moderate to high the mechanism of drug release can be modified.

OSMOTIC PRESSURE

Rate of drug release from an Osmotic system is directly proportional to Osmotic Pressure of the core formulation. In order to achieve optimized and constant Osmotic Pressure in compartment Osmotic agent must be added to table. So varying the osmogens vary osmotic pressure and hence drug release. Osmogens are classified as inorganic and organic osmogens [19].

Table 2: OSMOGENS

S. No.	Osmogen	Osmotic Pressure (atm)
1	NaCl	356
2	Fructose	355
3	KCl	345
4	Sucrose	150
5	Xylitol	104
6	Sorbitol	84
7	Dextrose	82
8	Citric acid	69
9	Tartaric acid	67

Table 3: COMBINED OSMOGEN

S. No	Combined osmogen	Osmotic Pressure (atm)
1	Lactose – Fructose	500
2	Dextrose – Fructose	450
3	Sucrose – Fructose	430
4	Mannose – Fructose	415
5	Lactose – Sucrose	250
6	Lactose – Dextrose	225
7	Mannose - Lactose	225

DELIVERY ORIFICE

Formation of orifice can take place by,

- Laser,
- Micro drill,
- Modified punches,
- Controlled porosity osmotic pumps can be generated by in-situ formation of delivery orifice which has been described in US Patent.

MEMBRANE TYPE

Drug release from osmotic system is largely independent of pH and agitational intensity of GIT. Examples are Cellulose Ester, Cellulose Triacetate, Cellulose Propionate, Cellulose Acetate Butyrate, Ester, Ethyl Cellulose and Eudragits.

Among above Cellulose Acetate Butyrate is most commonly used because of its,

1. High water permeability,

2. Permeability can be adjusted by varying the degree of acetylation of polymer and also by increasing plasticizer concentration,

3. Flux enhancer and,

4. Superior drying property so advantageous to thermolabile drugs.

However asymmetric membrane capsule are new type of coating which can be fully utilized for osmotic drug delivery system and offers significant advantage over membrane coating used in conventional Osmotic DDS which devoid of coating defects and they are having higher rate of water influx which allow the release of drug with lower or no osmotic pressure or lower solubility [20].

CONCLUSION

Controlled porosity osmotic pump tablets utilize the principle of osmotic pressure for drug delivery system. The drug delivery from CPOP system is independent of the physiological factors of gastrointestinal tract. By optimising formulation variables such

as osmogens, osmotic pressure of core components and nature of rate controlling membrane the drug delivery can be controlled. The release of drug follows zero order kinetics and is safer than conventional dosage forms.

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