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Review Article

OSMOTIC DRUG DELIVERY SYSTEM: A NEW APPROACH

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ABSTRACT

Osmotic drug delivery works on the principle of osmotic pressure. Osmotic drug delivery system follows zero order kinetics. This type of drug delivery system provides the controlled release and pulsatile delivery of the drug. osmotic drug delivery system also provide site specific action.(specially colon specific) the water soluble and water insoluble both types of drugs can be injected by these type of drug delivery system(push pull osmotic pump) osmotic drug delivery system are also suitable for animals. Osmotic pressures generated in these types of devices are responsible for providing the delivery of drug in a sustained form and in controlled manner. Osmotic drug delivery systems are very much popular in these days due to wide spreadability in the market.

Key Words- Zero order kinetics, Pulsatile release, Delivery orifice, Imbibe.

INTRODUCTION

Osmotic drug delivery system utilizes the principles of osmotic pressure for the controlled delivery of active pharmaceutical ingredient at a predetermined zero order rate. An appropriately designed osmotic drug delivery is not influenced by different physiologic factors but affected by pharmaceutical factors, which play a pivotal role in modulating the release of drug [1]. This delivery system can also exhibit pulsatile release, burst release and colon targeting of drug. Because of its versatility, this above system seems to have promising approach which can result in improved safety profile, stable drug concentrations, uniform drug effects and dosing frequency.[2]

These systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug(s) from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane.[3]

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Osmotic pressure

Osmotic pressure is the hydrostatic pressure produced by a solution in a space divided by a semipermeable membrane due to a differential in the concentrations of solute.[4]

Osmotic pressure is generally defined as the amount of pressure required to bring solvent movement across a semipermeable membrane to equilibrium. This model attempts to model an agent-based description of the movement of solution particles across a semipermeable membrane and illustrate the colligative nature of osmotic pressure.[5]

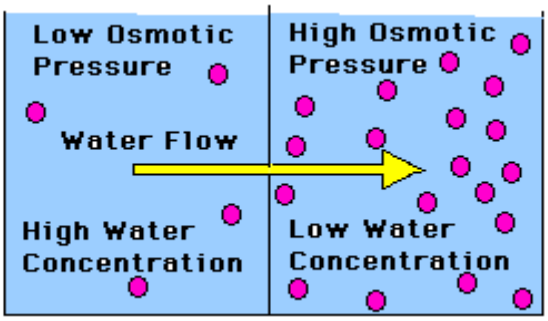

Figure:1 The movement of the drug molecules from high concentration to low concentration threw a semi permeable membrane [6].

Principle

Osmotic pump drug delivery systems (OPS) utilize osmotic pressure as the driving force for the delivery of drugs. The formulation of this system mainly consists of an osmotic core, which is coated with a semi-permeable membrane, and a delivery orifice on the membrane, which is created by a laser drill. After orally taking, as soon as the tablet comes into contact with water in stomach, water will be imbibed through the membrane because of the resultant osmotic pressure, and then the drug will be released through the orifice at a controlled rate.**[7]**

Osmotic Drug Delivery Devices

They fall in two categories

1. Implantable

- The Rose and Nelson Pump
- Higuchi Leeper Pump
- Higuchi Theuwes pump
- Implantable Miniosmotic pump

2. Oral osmotic Pump

- Single chamber osmotic pump
- Elementary osmotic pump
- Multi chamber osmotic pump
- Push pull osmotic pump
- Osmotic pump with non expanding second chamber

Specific types

- Controlled porosity osmotic pump
- 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
- Monolithic osmotic systems
- OSMAT [8]

IMPLANTABLE

The Rose and Nelson Pump

Rose and nelson the two Australian scientists described this type of pump. These pumps were not patented. The pump consist of three chambers

(1) A drug chamber

(2) A salt chamber containing excess solids

(3) A water chamber

The drug and water chamber are separated through a semipermeable membrane. The water travels from the water chamber to the salt chamber due to the difference in the osmotic pressure. As the results of this increase in water content of the salt chamber and increase the volume of the salt chamber, which distends the latex diaphragm separating the salt and water chamber there by pumping the drug out of the device. The pumping rate of the rose and nelson pump can be described by the following equation.

$$dMt/dt = (dv/dt)C$$

where dMt/dt = is the drug release rate

(dv/dt) = is the volume flow of water into the salt chamber

C = is the concentration of the drug in the drug chamber

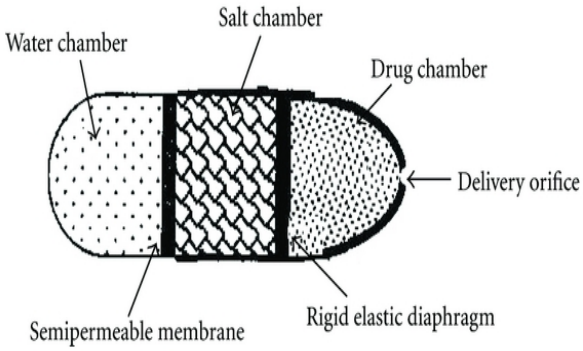

Figure2: The rose and nelson pump

Higuchi Leeper Pump

The main difference between the rose and nelson pump and higuchi leeper pump is that there is no water chamber in the higuchi leeper pump.the higuchi leeper pump is activated by the taking water from the surrounding media. These pumps are most widely used for veterinary purpose. These pumps are used for the delivery of the growth hormone and antibiotics. A layer of low melting solid is used in place of elastic diaphragm to separate the drug and osmotic chamber in comparision to the rose and nelson pump. The recent development in the higuchi leeper pump provides pulsatile release of the drug. The pulsatile release of the drug is achieved by the production of a critical pressure as a result the delivery orifice opens and deliver the drug.[9]

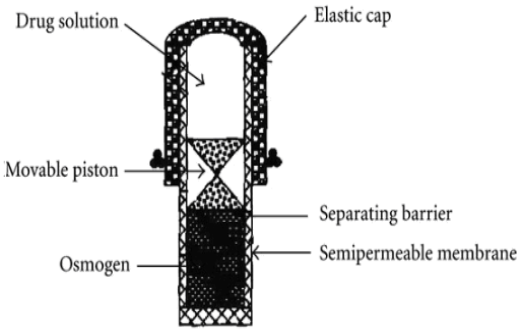

Figure3: Higuchi leeper pump [10]

Higuchi Theuwes pump

In the Higuchi-Theeuwes device the rigid housing is dispenced with the membrane acts as the outer casing of the pump. This membrane is quite strong to withstand the pumping pressure developed inside the device. This device is loaded to the desired drug prior to use. When the device is placed in an aqueous environment, release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of the device.[11]

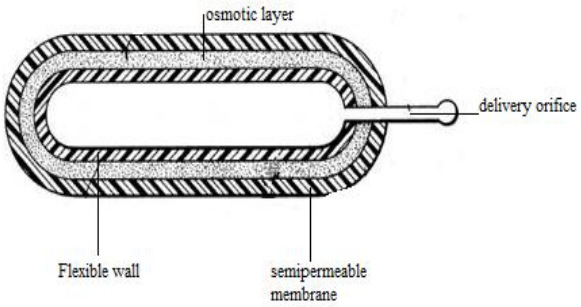

Figure4: Higuchi Theeuwes Pump [12]

Implantable Miniosmotic pump

Mini-osmotic pump will be subcutaneously implanted for chronic delivery of drugs. For this, mice will be anaesthesized with ketamine/xylazine, and osmotic pumps containing drug or placebo will be subcutaneously inserted to the mice prior to the metabolic experiments. Alternatively, drug or placebo may be administered using subcutaneous injection or oral gavage.[13]

Elementary osmotic pump

It delivers the drug at a controlled release manner. Control resides in the: Water permeation characteristics of a semi permeable membrane surrounding the formulating agent Osmotic properties of the formulation This is design by coating the osmotic agent in a rate controlling semipermeable membrane. This membrane contains a orifice of critical size that release the drug in a controlled manner. The dosage form after coming in the contact with an aqueous fluid imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation. This imbibes of the water results in the formation of the saturated solution of the drug. about 60-80 percent of the drug is released at a controlled manner there is about 30-60 minutes of a lag time is present before the drug release in a controlled manner to hydrates the system or to provide a zero order

release. These systems are most suitable for the drugs having moderate solubility.

Push Pull Osmotic Pump

Push pull osmotic pumps are modified form of elemantry osmotic pump. These are suitable for the drugs having low water solubility and also for the drugs having high water solubility. This system is similar to a standard bilayer coated tablet. Upper layer consist of a drug in a polymeric, osmotic agent and the another layer contains tablet excipients. These polymeric systems have the ability to form a suspension in situ. The two layers present are formed and bonded together by tablet compression to form a single bilayer core. Than the tablet core is coated with a semi permeable membrane. After the coating has been applied a small hole is drilled on the semi permeable membrane by the help of a laser or mechanical drill on the drug layer through a side of the tablet. When the system is placed in the aqueous environment water is attracted by osmotic agent in both layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent present in the non drug layer attracts the water into the compartment and increase the volume as a result expansion of the non drug layer which leads to push the drug suspension through the orifice.[14]

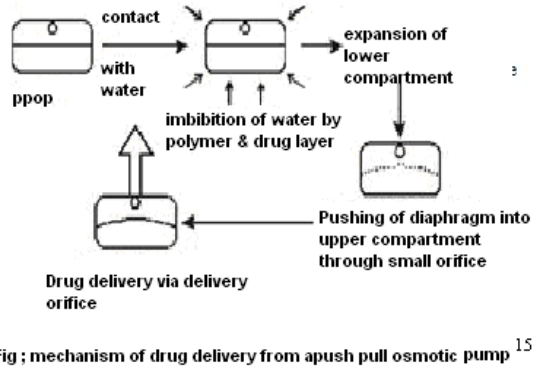

Fig ; mechanism of drug delivery from apush pull osmotic pump [15]

Figure5: Mechanism of drug delivery from apush pull osmotic pump [15]

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. [16]

Controlled porosity osmotic pump

The pump can be made as a single or multi compartment dosage form. The delivery system consists of a core with the drug surrounded by a semi permeable membrane. The membranes have an asymmetric structure and it is permeable to water and impermeable to solute. The in sensitive

pore forming additives dispersed throughout the wall. When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents. 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 [17]

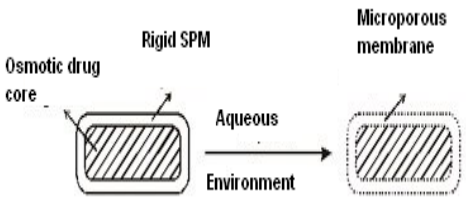

Figure6: Mechanism of drug delivery from a controlled porosity osmotic pump

Osmotic bursting osmotic pump

This system is similar to the elementary osmotic pump but it is smaller in size and the delivery orifice is absent in this type of pump. When it comes in the contact with aqueous environment water is imbibe and increase in hydraulic pressure. Thus the wall is ruptured and the content is released in the environment. The release of the drug is depending upon the thickness and area of the semi permeable membrane. This type of pumps provides pulsatile release of the drug delivery.

Liquid OROS

Liquid OROS are designed to deliver the drug in liquid form. They offer more bioavailability than extended release dosage form due to the availability in liquid nature. They are of three types: -

- L OROS hard cap,
- L OROS soft cap,
- Delayed liquid bolus delivery system.

Each of these system have a liquid drug layer (known as osmotic engine) and a semi permeable membrane which is coated over it.when the system comes in the contact with the aqueous environment the water permeates the rate controlling membrane and activates the osmotic layer as the result there is increase in the hydrostatic pressure inside the wall, and the system expand and as a result delivery of the drug through a small orifice.the L OROS hard cap & soft cap provide the continuous delivery of the drug.

Delayed Delivery Osmotic device

Due to the presence of the semipermeable membrane the osmotic device show a lag time before the drug release. The presence of the lag time is usually a dis advantage but when a delayed release of the drug is required it is beneficial. This type of drug delivery system mostly used in case of asthma and arthritis.[18]

Telescopic capsule

This device contains two chambers the first contains the drug and exit port and the second contains an osmotic engine. A layer of wax like material separates the two layers. The desired agent is placed in the one chamber manually or by automated filling. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening.the open end of the vessels is fitted on the open end of the cap and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. as fluid is imbibed the housing of the dispensing device the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections.[19]

Oros ct (colon targeting)

It is only used for the targeted delivery of the drug to the colon. It is used once or twice daily to provide a sustained release action. it can be a single osmotic unit or it can be made up of five to six push pull osmotic units filled in a hard gelatin capsule. When the capsule comes in the contact of GIT fluids the gelatin dissolves and the enteric coating prevents the drug release in the GIT and the drug release in the colon or small intestine. Enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable Membrane.[20]

Sandwiched oral therapeutic system

It is composed of polymeric push layer which is surrounded by two sides. So the push layer is sandwich between two drug layers with two delivery orifices. The middle push layer contains a swelling agent which swells and the drug is released from the delivery orifice. 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.[21]

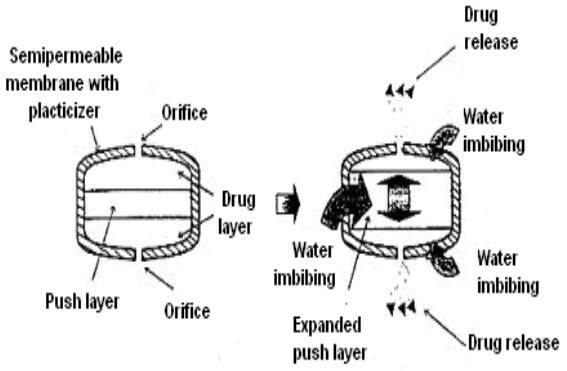

Figure7: Sandwiched osmotic tablets

Osmotic pump for insoluble drugs

For delivering of the insoluble drugs particles of osmotic agents are coated with elastic semipermeable membrane.these particles are than mixed with the insoluble drugs and then coated with the semipermeable membrane in usual way when this system is placed in the aqueous environment water is drawn the system swells and as a result increase in hydrostatic pressure and cause the drug release through a small orifice.[22]

Monolithic osmotic system

It constitutes a simple dispersion of a water-soluble agent in a polymeric matrix. When the system comes in contact with the aqueous environment, water imbibitions by the active agent takes place rupturing the polymeric matrix capsule surrounding the drug, thus liberating it to the outside environment. Initially, this process occurs at the outer environment of the polymer matrix, but gradually proceeds towards the interior of the matrix in a serial fashion. However, this system fails if more than 20 to 30% volume of the active agent is incorporated into the device, as above this level, significant contribution from the simple leaching of the substance takes place.[23]

Monolithic osmotic pump tablet (MOPT) is benefited by the simplified preparation process.In our study, the MOPT composing drug solid-dispersion, which was widely used to increase the solubility, dissolution rate and bioavailability of water-insoluble drugs, was developed to facilitate the constant drug release from the MOPT.[24]

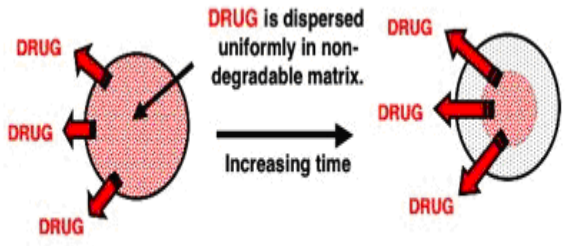

Figure8: Monolithic osmotic system [25]

OSMAT

It is a novel osmotically driven matrix system. This utilizes the hydrophilic polymers to swell. And gel in aqueous medium forming a semipermeable membrane in situ. Drug release from such a matrix system containing an osmogen could therefore modulated by an osmotic phenomenon. osmat thus judicialy

combined both matrix and osmotic characteristics resulting in quantum improvement in drug delivery from swellable matrix system.

OSMAT represents simple, versatile and easy to fabricate osmotically driven controlled drug delivery system based on low cost development.[26]

COMPONENTS OF OSMOTIC DRUG DELIVERY SYSTEM

Drugs

The drug which is potent have short half life, and which is used for prolonged treatment are prepared as a osmotic drug delivery agents.for eg. Dilitiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide are used for this type of system.

Osmotic agent

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 agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents.

Semipermeable membrane

The membrane is usually made up of cellulose acetate and it has sufficient wet strength and permeability to water. The unique feature of the semipermeable membrane is that it is only selective for water so isolation of the dissolution process in the gut environment is easy.

Hydrophilic and Hydrophobic polymers

These polymers are used for the systems containing matrix core.the selection of the polymer is based on the solubility of the polymer and rate of the drug release from the pump. The highly water soluble compounds are entrapped in the hydrophobic matrices and the moderately water soluble compounds are entrapped in the hydrophilic matrices to provide controlled release medication.

Hydrophilic polymers - Hydroxy ethyl cellulose, carboxy methyl cellulose, hydroxyl propyl methyl cellulose, etc.

Hydrophobic polymers - ethyl cellulose, wax materials

Wicking Agents

It is defined as a material with the ability to draw water into the porous network of a delivery device. The function of the wicking agent is to draw water to the surface inside the core of the

tablet, thereby creating channels or a network of increased surface area. Examples: colloidon silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight polyvinyl pyrrolidone (PVP), bentonite, magnesium aluminium silicate, polyester and polyethylene,etc. [27]

Solubilizing Agents

Non swellable solubilizing agents are most commonly used they are classified into three categories

- Agents that inhibits crystal formation of the drugs or otherwise act by complexation of drug (e.g., PVP, PEG, and cyclodextrins)
- A high HLB micelle forming surfactant, particularly anionic surfactants (e.g., Tween 20, 60, 80, poly oxy ethylene or polyethylene containing surfactants and other long chain anionic surfactants such as SLS).
- Citrate esters and their combinations with anionic surfactants (e.g., alkyl esters particularly triethyl citrate)

Surfactants

The surfactants act by regulating the surface energy of materials to improve their blending in to the composite and maintain their integrity in the environment of use during the drug release period.commonly used surfactants are polyoxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laurates, etc.

Coating Solvent

The inert polymeric inorganic and organic solvents are used . The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. 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) etc. can be used.

Plasticizer

The permeability can be increased by the incorporation of the plasticizers. The plasticizer also increases the water diffusion coefficient.commonly used plasticizers are dialkyl pthalates, trioctyl phosphates, alkyl adipates, triethyl citrate and other citrates, propionates, glycolates, glycerolates, myristates, benzoates, sulphonamides and halogenated phenyls.

Flux Regulator

These are added in the wall forming agents it assists in regulating the fluid permeability through membrane. Poly hydric alcohols such as

poly alkylene glycols and low molecular weight glycols such as poly propylene, poly butylene and poly amylene,etc. can be added as flux regulators.

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 formers can be inorganic or organic and solid or liquid in nature.For example

- Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, etc.
- Alkaline earth metals such as calcium chloride and calcium nitrate

Carbohydrates such as glucose, fructose, mannose,etc.[28]

FACTORS AFFECTING DRUG RELEASE RATE

Orifice size

The size of the orifice must larger than minimum size (0.075mm), to minimize hydrostatic pressure. This is necessary step in achieving zero order drug release. The size of the orifice must be smaller than a maximum size (0.274 mm), to minimize diffusion contribution to delivery rate.

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 costs.[29]

Drug solubility

To achieve optimized drug release, the API for osmotic delivery should have sufficient water solubility, given that the release rate is directly proportional to the solubility of the API within the core. Drugs with extremes of solubility are generally poor candidates for osmotic delivery.

For compounds have low water solubility the solubility can be enhanced by using salt form or cyclodextrin.swellable polymers are also used the uniform swelling provide the constant delivery of the drug. Wicking agent provide increase the surface area of the drug with incoming fluid**.** The use of wicking agents can help enhance the rate of drug release from the orifice of the osmotic system.

Osmotic pressure

The release rate of osmotic drug delivery system is directly proportional to the osmotic pressure of the core formulation. osmagent are used if the drug should not posses sufficient osmotic pressure. Osmotic pressure of a solution is dependent on the combination of number of

discrete entities of solute present in the solution. For controlling the drug release it is necessary to maintain a osmotic gradient between inside of the delivery system and external environment. it is possible to maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment. [30]

Semipermeable membrane

The drug release rate is affected by the type and nature of membrane forming polymer used. The drug release rate is also affected by the membrane thickness, and the presence of other additives (placticizers). The membrane permeability can be increased or decreased by the proper choice of the membrane forming polymer and other additives.[31]

EVALUATION OF OSMOTIC DRUG DELIVERY SYSTEM

Visual inspection

Visual inspections of the film for smoothness, uniformity of coating, cover edge, and luster.

Coating uniformity

The uniformity of coating among the tablets can be estimated by determining the weight, thickness and diameter of the tablet before and after the coating.[32]

Scanning Electron Microscopy

Coating membranes of formulation obtained before and after complete dissolution of core contents can be examined for their porous morphology by scanning electron microscope.

In vitro dissolution

The in vitro release of the drug from osmotic pump can be evaluated by usp paddle and basket type apparatus. US patents describe the use of commercial Vankel standard dissolution apparatus.

The dissolution media is distilled water as well as stimulated gastric fluid (for first 2-4hours)and stimulated intestinal fluid (for subsequent hours)have been used.the standard specification which are followed in controlled release formulation are equivalently applied for oral osmotic pump.[33]

Effect of pH

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were carried out at pH 1.2 in simulated gastric fluid (SGF) and pH 6.8 in simulated intestinal fluid (SIF) and distilled water.

Effect of agitational intensity

To study the effect of agitation intensity (rpm) of the dissolution medium, the release study was carried out using USP-type II dissolution apparatus (paddle type) at rotational speeds of 50,100, and 150 using the dissolution medium (900 ml) of SGF of pH 1.2 for the first 2 hours and SIF of pH 6.8 thereafter.[34]

Effect of Osmotic Pressure

To confirm the major mechanism of drug release, release studies of the optimized formulation can be conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media (pre-equilibrated to 37°C ± 1°C), mannitol (osmotically effective solute) can be added

Kinetics of Drug Release

The data obtained can be fitted in different models at different time intervals and by using satistics we can know kinetics of drug release.[35]

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