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Review Article

A REVIEW ON OSMOTIC DRUG DELIVERY SYSTEM

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ABSTRACT
Conventional oral drug delivery systems supply an instantaneous release of drug, which cannot control the release of the drug and effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Osmotic devices are the most promising strategy based systems for controlled drug delivery. They are the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems. Various patents available for osmotic drug delivery system like Rose-Nelson pump, Higuchi leeper pump, Higuchi Theeuwes pump, Elementary Osmotic pump etc. ODDS are useful for poorly soluble drug, for pulsatile drug release, zero order release. Various techniques available for preparation of ODDS include push pull osmotic Pump, osmotic Brusting osmotic pump, liquid oral osmotic system, sandwiched osmotic tablets , delayed delivery osmotic device, monolithic osmotic System and controlled porosity osmotic Pump. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents. These systems can be utilized for systemic as well as targeted delivery of drugs. The release of drugs from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core components, size of the delivery orifice, and nature of the rate-controlling membrane. In this Paper mainly focused on the Osmotic System with example, the basic component of osmotic system and evaluation parameter of the osmotic drug delivery system.
KEY WORDS: Osmotic drug delivery, Osmosis, Semipermiable Membrane, Zero-order release

INTRODUCTION

Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems. Because of the pharmaceutical agents can be delivered in a controlled pattern over a long period. Conventional oral drug delivery systems supply an instantaneous release of drug, which cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility etc. To overcome this limitation a number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral dosage form fall in the category of matrix, reservoir or osmotic system. Reservoir systems have a drug core surrounded coated by the rate controlling membrane; there has been increasing interest in the development of osmotic devices over the past 2 decades. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system. the oral osmotic pumps have certainly came a long way and the available products on this technology and number of patent granted in the last few years makes it presence felt in the market.[1, 2]

Osmotically Controlled Drug Delivery System (OCDDS) Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat.[3]

ADVANTAGES[3, 4]

- Easy to formulate and simple in operation.
- Improve patient compliance with reduced frequency.
- Prolonged therapeutic effect with uniform blood concentration.
- They typically give a zero order release profile after an initial lag.
- Deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition.
- They are well characterized and understood.
- The release mechanisms are not dependent on drug.
- A high degree of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.
- The rationale for this approach is that the presence of water in git is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

DISADVANTAGES[3, 4]

- Dose dumping.
- Rapid development of tolerance.
- Retrieval therapy is not possible in the case of unexpected adverse events.
- Expensive.
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.
- Size hole is critical.

OSMOSIS AND ITS PRINCIPLE[1]

Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Conventionally, osmosis can be defined

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

$$\Pi = Ø\ c\ RT$$

Where, Π = Osmotic pressure, Ø = osmotic coefficient, c = molar concentration, R = gas constant, T = Absolute temperature.

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

CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEM

Implantable[4]

1. The Rose and Nelson Pump
2. Higuchi Leeper Pump
3. Higuchi Theuwes pump
4. Implantable Mini osmotic pump

Oral osmotic Pump[4]

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 system and OSMAT.

Rose and Nelson were two Australian physiologists interested in the delivery of drugs to the gut of sheep and cattle. Their pump was never patented. The pump consisted of three chambers: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The drug and water chambers are separated by a rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The pumping rate of the Rose-Nelson pump is given by the Equation

$$dMt/dt = (dv/dt)\ C \quad \ldots\ldots\ldots\ldots (1)$$

Where, dMt/dt is the drug release rate, dv/dt is the volume flow of water in to salt chamber, C is the concentration of drug in the drug chamber.[5]

Alza Corporation represented the first series of Rose and Nelson pump. Which is illustrated in figure 1 there is no water chamber in Higuchi Leeper pump and the device activate after penetration of water inside the device from surrounding environment. Higuchi Leeper pump is widely used for veterinary use. This type of pump is either swallowed or implanted in the body of animal for delivery of antibiotic or growth hormones. Higuchi Leeper pump consist of rigid housing and semi permeable membrane. A layer of low melting waxy solid, such as microcrystalline paraffin wax is used in place of elastic diaphragm to separate the drug and osmotic chamber. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug.[1]

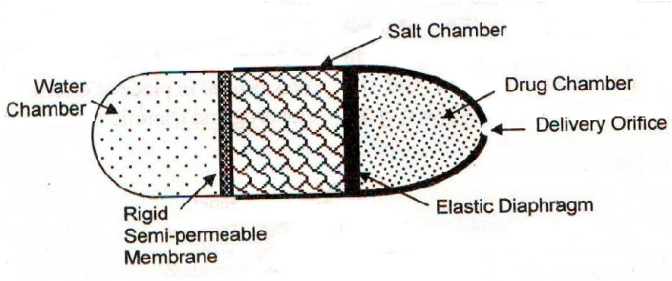

Figure 1 Higuchi Leeper Pump

Higuchi Theuwes pump is illustrated in figure 2 in this device the rigid housing is made up of semi permeable membrane which is enough strong to with stand with the pumping pressure developed inside the device due to permeation of water. The drug is loaded only to the prior of application of device. The release of drug from device can be controlled by salt used in chamber, the permeability characteristic of outer membrane and orifice. Osmotic pump of this form are available under trade name Alzet. A mixture of citric acid and sodium bi carbonate in salt chamber in presence of water generate carbon di -oxide gas. Which exert a pressure on the elastic diaphragm, eventually delivers the drug from device.[1]

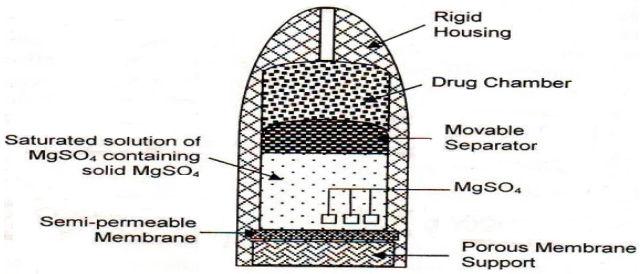

Figure 2 Higuchi Theuwes Pump

Implantable Mini osmotic pump shown in figure 3 it is composed of three concentric layers-the drug reservoir, the osmotic sleeves and the rate controlling semi permeable membrane. The additional component called flow moderator is inserted into the body of the osmotic. The inner most compartment of drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane when the system is placed in aqueous environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. These pumps are available with variety of delivery rates between 0.25 to 10ml per hour and delivery duration between one day and four weeks.[1]

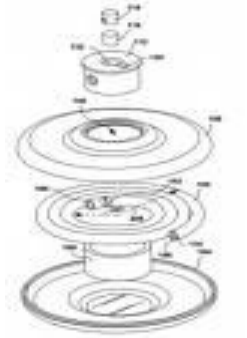

Figure 3 Implantable osmotic pump

Elementary osmotic pump

Elementary osmotic pump works on the same mechanism as the impala table pumps it is simplest possible form of osmotic pump as it does not require special equipment and technology .This device was further simplification of Higuchi – Theeuwes pump. It was developed in the year 1975 by Theeuwes (Santus et al,1995) The EOP consist of single layered tablet core containing a water soluble drug with or without other osmotic agent .A semi permeable membrane surrounds the tablet core. When such a system is swallowed water from the GIT enter through the membrane in the core, the drug dissolved and the drug solution is pumped out through the exit orifice. This process continues at a constant rate until the entire solid drug inside the tablet has been dissolved drug continues to be delivered but at a declining rate until the osmotic pressure between outside environment and saturated drug solution. Normally the EOP delivers 60 - 80% of its content at a constant rate and there is a short lag time of 30- 60 min as the system hydrates before zero order drug release from the EOP is obtained.[4, 6]

Pramod Kumar et al[7] carried out the study of Elementary osmotic pump (EOP) for highly water soluble drug tramadol hydrochloride (TRH) was developed and evaluated. Target release profile was selected and different variables were optimized to achieve the same. Formulation variables like levels of swellable polymer (10-21.87 %) and plasticizer (0-20% w/w of polymer), and coat thickness of semi permeable membrane (SPM) were found to affect the drug release from the developed formulations. TRH release was directly proportional to the level of plasticizer and osmotic pressure generated by osmotic agent but inversely proportional to the level of swellable polymer within the core and coat thickness of SPM. Drug release from developed formulations was independent of pH and agitation intensities of release media. Burst strength of the exhausted shells increased with increase in coat thickness but decreased with increase in level of plasticizer. The in-vitro results of the developed formulations were compared with performance of standard marketed formulation of TRH. The developed formulation provided more prolonged and controlled TRH release as compared to marketed formulation. The manufacturing procedure was found to be stable during six months of accelerated stability study.

Push pull osmotic pump

Push pull osmotic pump is a modified EOP (Vyas et al, 2001; Barclay et al, 1987) through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (depict as the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semi permeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet.[4]

Suresh P. Vyas et al[8] carried out the study of An oral osmotic system which can deliver theophylline and salbutamol sulphate simultaneously for extended period of time was developed and characterized in a view to reduce the problems associated with the multidrug therapy of asthma. Simple controlled porosity osmotic pump contained both drugs (in freely soluble form) did not provide satisfactory extended release of theophylline. A modified two-layered, push–pull osmotic system was developed by using the basic designs of various oral osmotic pumps, such as controlled porosity osmotic pump (CPOP), elementary osmotic pump (EOP) and push–pull osmotic pump (PPOP). Scanning electron microscopy of cellulose acetate coating membrane after dissolution revealed that 25% (w/w) of sorbitol can be used as an optimized concentration of pore forming agent with 25% (w/w) of plasticizer, which was kept constant. Formulations were initially developed for theophylline and the release was optimized by using two different soluble forms of theophylline with varying amount of hydrophilic polymer mixture in upper layer and polyethylene oxide (expandable hydrogel) in lower layer. Further, the release of salbutamol sulphate was optimized by keeping the drug in upper or lower layer or both layers. In vitro release studies showed satisfactory controlled release profiles of both drugs. The release profiles of both drug statistically compared with respective marketed controlled release formulations. An optimized system was selected to study the effect of concentration of pore forming agent and orifice diameter on the release of both drugs.

Osmotic pump with non expanding second chamber

The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber. In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs.[4]

Miscellaneous

Controlled porosity osmotic pump

The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentner et al (1985, 1991), Zentner and Rork (1990), Appel and Zentner (1991), and Mc Celland et al. (1991). The controlled-porosity osmotic pump tablet (CPOP) is a spray-coated or coated tablet with a semi permeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the

pores, which are formed in the semi permeable 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 4). 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 semi permeable membrane.[3, 9]

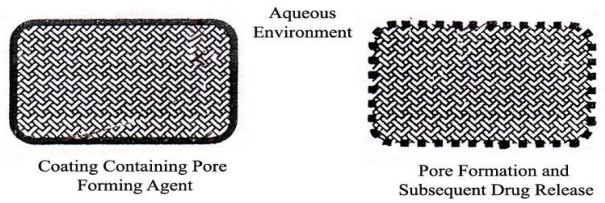

Figure 4 CPOP tablet before and after dissolution studies

Rabiu Yakubu et al.[10] carried out the study of the purpose of this study was to design a 24-hour controlled porosity osmotic pump system that utilizes polyvinyl pyrrolidone (PVP) as an osmotic-suspending/release retarding agent of drugs. Methods: Osmotic tablet cores containing various ratios of ketoprofen and PVP were prepared by wet granulation and initially spray coated with similar solution of cellulose acetate. A formulation containing ketoprofen and PVP at a ratio of 1:7 was selected for further studies. Results: The final formulation containing PVP K-30 in the tablet core augmented the release of ketoprofen (poorly water-soluble) up to 90% over 24 hours much higher than either PVP K-25 or PVP K-90 and retarded the release of pseudoephedrine HCl (highly water-soluble) up to 18 hours. Conclusion: This study proposed the dual use of PVP in osmotic pump systems containing solids to modulate the release of either poorly or highly water-soluble drug.

Liquid OROS[4]

Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types

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

Delayed Delivery Osmotic device

Because of their semi permeable walls, an osmotic device inherently show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drug (drugs for early morning asthma or arthritis) may be beneficial. The following text describe other means to further delay drug release.[4]

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 the sections by manual or automated fill mechanism. 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 filled vessel is fitted inside 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.[4]

OROS-CT

OROS-CT (Alza corporation) is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprised of as many as five to six push pull osmotic unit 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 stomach to the system as the system enters into the small intestine the 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.[11]

Sandwiched oral therapeutic system

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment. The middle push layer containing the swelling agents, swells and the drug is released from the delivery orifices. The advantage of this type of system is that 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.[4, 12]

Lipid osmotic pump

Merk describes an osmotic pump for the lipid delivery as shown in the figure. The device concerns an osmotic agent for dispensing beneficial active agent that has poor solubility in water. The core of the system comprises a beneficial amount of a substantially water- insoluble active agent, which is lipid soluble or lipid- wettable; a sufficient amount of water insoluble lipid carrier, which is liquid at the temperature of use to dissolve or suspend the drug and agent to ensure the release of the lipid carrier of the drug from the pump (God billion et al, 1985) The water insoluble wall is micro porous and is wetted by lipid carrier. The device is prepared by first dissolving the drug of interest in the lipid vehicle. The osmogent (Sodium chloride) is dispersed in the melted lipid and then quenched-cool to form a lump that are broken and made into tablet. The micro porous is coated at a moderate flow of unheated ambient air.[9]

Multiparticulate osmotic pump

MPOP consist of pellets comprises of drug with or without osmotic agent, which are coated with a semipermiable membrane. When this system comes in contact with the aqueous environment, water penetrates in the core and forms a saturated solution of soluble component (Schultzew et al, 1997). The osmotic pressure difference results in rapid expansion of the membrane, leading to the formation of pores. The osmotic agent and the drug released through the pores according to zero order kinetics. The lag time and dissolution rate were found to be dependent on the coating level and the osmotic properties of the dissolution medium.[11]

Monolithic osmotic system

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact in with the aqueous environment water imbibitions by the active agents takes place rupturing the polymer matrix capsule surrounding the drug, thus liberating it to the outside environment (Mishra et al, 2006). Initially this process occurs

at the outer environment of the polymeric matrix, but gradually proceeds towards the interior of the matrix in a serial fashion. However this system fails if more than 20 –30 volume per liter of the active agents is incorporated in to the device as above this level, significant contribution from the simple leaching of the substance take place.[4,13]

OSMAT

It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermiable membrane in-situ releases from such a matrix system containing an osmogen could, therefore be modulated by the osmotic phenomenon. Osmat thus judiciously combines both matrix osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix system. Osmat produces controlled drug release with adequate delivery rates in an agitation in dependent manner. Thus osmat represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cot technology.[4]

Basic components of osmotic systems[1]

Drug

All drugs are not suitable candidate for osmotic system as prolong action medication .Drug with biological half life > 12 hr e.g.: Diazepam and drug which have very short half life i.e. <1 hr e.g. Penicillin G, furosemide are not suitable candidate for osmotic controlled release. Drug which have biological half-life in between 1 – 6 hrs and which is used for prolonged cure of diseases are ideal applicant for osmotic systems. A variety of drug candidates such as Diltiazem HCl32, Carbamazepine, Metoprolol33, Oxprenolol, Nifedipine34, Glipizide35 etc. are formulated as osmotic delivery.

Semi permeable membrane[14, 15]

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

- It should be adequately thick to withstand the pressure generated within the device.
- It should have enough wet strength and water permeability
- It should be biocompatible.
- It should be rigid and non-swelling

The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.

Plasticizers

Plasticizers have a crucial role to play in the formation of a film coating and its ultimate structure. Plasticizers increases the workability ,flexibility and permeability of fluids .generally from 0.001 to 50 parts of plasticizer or a mixture of plasticizers are incorporated in to 100 part of wall forming material. They can change viscous-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Plasticizers can have a marked effect both quantitatively and qualitatively on the release of active materials from modified release dosage forms where they are incorporated into the rate-controlling membrane36. Some of the plasticizers used are as below: Polyethylene glycols, Glycolate, Glycerolate, myristates, Ethylene glycol monoacetate; and diacetate- for low permeability, Tri ethyl citrate, Diethyl tartarate or Diacetin- for more permeable films.

Osmotic agent[3, 16, 17]

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

- Inorganic water-soluble osmogents: Magnesium sulphate, Sodium chloride, Sodium sulphate [16], Potassium chloride [17], Sodium bicarbonate
- Organic polymer osmogents: Sodium carboxy methyl cellulose, Hydroxy propyl methyl cellulose, Hydroxyethylmethylcellulose, Methylcellulose, Polyethylene oxide, polyvinyl pyrollidine.

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. The examples are colloidal silicon dioxide, PVP & Sodium laryl sulphate.

Pore former[18]

These agents are particularly used in the development of pump for poorly water soluble drugs and in controlled porosity tablets. These agents cause the formation of micro porous membrane .The micro porous wall may be formed by the leaching of water soluble substrate from membrane leaving a micro porous structure. The pore former can be organic or inorganic and solid or liquid in nature. Some examples of pore former are given below. Alkaline earth metal salts Sodium chloride, potassium chloride, sodium bromide, potassium phosphate. Carbohydrate such as sucrose, lactose, glucose, mannitol, fructose etc is used as pore forming agent.

Coating solvents[19]

The primary function of solvent system is to dissolved or dispersed the polymer and other additive and convey them to substrate surface. solvent used to prepare polymeric solution include inert inorganic and organic solvents that do not adversely harm the core ,wall and other material .the various types of solvents and their combinations are as follows: Methylene chloride, methanol, isopropyl alcohol, di-chloromethane , ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc and the mixture of solvents such as acetone-methanol(80:20), methylene chloride- methanol (79:21),acetone-ethanol(80:20), methylene chloride-methanol-water (75:22:3).

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 odorless, colorless, tasteless, inexpensive, nontoxic and non-irritant.
- It should have rapid drying rate.

FACTORS AFFECTING DRUG RELEASE RATE[20, 21]

Solubility: APIs for osmotic delivery should have water solubility in the desired range to get optimize drug release. However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidate for osmotic delivery.

Solubility-modifying approaches

- Use of swellable polymers: Vinyl Acetate Copolymer, Polyethylene Oxide have uniform swelling rate which causes drug release at constant rate.
- Use of wicking agents: These agents may enhance the surface area of drug with the incoming aqueous fluids. e.g. Colloidal Silicon Dioxide, Sodium Lauryl Sulfate, etc. Ensotrol® technology uses the same principle to deliver drugs via osmotic mechanism.
- Use of effervescent mixtures: Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate.
- Use of Cyclodextrin derivatives: They are known to increase solubility of poorly soluble drugs. The same phenomenon can also be used for the osmotic systems.
- Use of alternative salt form: Change in salt form of may change solubility.
- Use of encapsulated excipients: Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane.
- Resin Modulation approach: Ion-exchange resin methods are commonly used to modify the solubility of APIs. Some of the resins used in osmotic systems are Poly (4-Vinyl Pyridine), Pentaerythritol, Citric and Adipic Acids.
- Use of crystal habit modifiers: Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate solubility. Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are Organic acids, Buffering agent, etc.

Osmotic pressure

The next release-controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment.

The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment.

The following table shows osmotic pressure of commonly used solutes in CR formulations.

Compound or mixture	Osmotic pump atmospheric pressure
Sodium chloride	356
Potassium chloride	245
Fructose	355
Sucrose	150
Dextrose	82
Potassium sulphate	39
Mannitol	38
Lactose-fructose	500
Dextrose-fructose	450
Sucrose-fructose	430
Mannitol-fructose	415
Lactose-sucrose	250
Lactose-dextrose	225
Mannitol-dextrose	225

Size of delivery orifice

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

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

- Mechanical drill
- 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.
- Indentation that is not covered during the coating process: Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.
- Use of leachable substances in the semi-permeable coating: e.g. controlled porosity osmotic pump

EVALUATION OF OSMOTIC TABLET[16, 22]

Evaluation of Powder

- Weight of Powder
- Bulk density
- Tapped density
- Carr's index
- Angle of repose

Evaluation of Osmotic tablet

- Hardness
- Thickness
- Friability
- Weight uniformity
- Drug content
- *In vitro* Dissolution study

Effect of Osmotic Pressure

Effect of pH on drug release

Stability study

Curve fitting analysis

Zero order release kinetic

First order release kinetic

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