REVIEW ARTICLE

Systematic Study on Osmotic Drug Delivery Device Covering Design, Types, and Elements Imparting Zero Order Release

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Abstract

Oral route is one of the most popular and successful delivery routes for the medicines. It achieved a prominent place in drug delivery due to ease of administration by all age groups. The major disadvantage of oral conventional drug therapy is that, it has to be taken 2–3 times a day, and if patient misses any dose it leads to incomplete prescribed dose and delays the time of cure. The considerable efforts have been taken to improve the success rate of oral drug delivery by modifying various parameters related to drug release. Osmosis is the movement of a substance against concentration gradient; in this instance, osmotic delivery use an osmotic gradient to successfully distribute the drug in controlled way and with zero order kinetics and emerging as the most dependable method of regulated drug delivery. The medication release from device is mostly unaffected by stomach secretions. Drug, release control polymer, osmotic agent, semipermeable membrane, and delivery orifice are the major parts of osmotic delivery system. This review mainly focuses on an osmotic drug delivery system providing detailed information regarding its design, different types, and responsible ingredients for controlled release by the virtue of osmosis.

Key words: Floating osmotic drug delivery system, floating osmotic drug delivery system, osmotic agent, osmotic drug delivery system, osmotic pressure, semipermeable membrane, zero order release

INTRODUCTION

One of the most effortless routes for medication delivery is the oral route and now considerable efforts have been seen in optimizing drug oral delivery. A handy way to produce both local and systemic effects by mouth serves as traditional and generally preferred delivery method.[1]

Transport of medicines is the regulated administration of drug into body. Advanced medication methods increases medicinal and profitable value, distinguish it, and attend as a significant source for outwitting race. By simplifying dosage regimens and improving the administration, mechanism of delivering drug improves the use and acceptance of treatment by patients.[2]

For decades, In the event of multiple intake, oral route is recognized as the most often employable among all explored systemic drug delivery.

The gastric retention time (GRT) typically takes 6–8 h, depending on the subject's fed state. In fed state, large dosage forms were found to have prolonged stomach retention compared to fasting state.

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A once-daily regimen offers the characteristic GIT retention lasting up to 24 h which is beneficial for medication absorption.[3] The gastric retention duration is an important aspect that significantly affects the drug's bioavailability.[4] It frequently consists of rate retardant polymers, and the release is managed by swelling, bio erosion, degradation diffusion, or osmotic pressure creation. After the instance of administration, drug polymer mixture is exposed in stomach fluid and drug gets released from dosage form. In controlled drug delivery rate retardant polymer plays a major role in drug release. The limitation associated with controlled drug delivery is burst release if matrix become weaker leading to dose dumping.[5] The inadequacy of conventional dosage forms in delivering specific drugs and the benefits of Osmotic systems (OS) in controlled drug release, the osmotically oral controlled-release drug delivery (OCRDD) was developed, which depends on the principle of osmosis.[6]

OCRDD offers unremitting distribution of medications at expected and reproducible kinetics in a programmed manner during GI transit.[7] Osmotic delivery devices, usually called as osmotic pump (OP), composed of compressed core tablets made of osmogen, gelling agent, and other excipients. This core tablet is lined with semipermeable membrane with the use of polymers and finally drilled in such a way that the entrapped medicament come out through it.[8] A laser beam is used to do orifice. Sometimes, drilling with mechanical way is also used to create the orifice. The factors governing the drug release form the OP includes solubility of incorporated drug, osmogen type and its quantity, permeability and thickness of semipermeable membrane, diameter of orifice, rate of release of drug from the orifice, and plasticizer type and its quantity.[9]

PRINCIPLES OF OSMOSIS

Osmosis is the phenomenon by which a semipermeable membrane allows liquid to flow from a low concentration to a high concentration. Osmotic pressure is produced as a result of liquids flowing in one direction. The generated osmotic pressure helps to push the drug out from the core tablet through delivery orifice. Drug solubility, amount and molecular weight of osmogens, and semipermeable membrane permeability all have a role in the drug's capacity to be released from OCRDD.[10]

Abbe Nollet was the first who described the initial osmotic effect using bladder of pig as semipermeable membrane. In 1877, Wihelm Pfeffer made the first quantitative measurement in which he separated sugar solution from pure water. In this experiment, the membrane was used which is permeable to water only. Pfeffer proved the relationship between the sugar solution's concentration, osmotic pressure, and absolute temperature.[11] Osmotic pressure is influenced by solute and solvent concentration and varies according to change in their concentration in the same system, and vice versa. By maintaining constant osmotic pressure and consequently a continuous intake of water, the osmotic drug delivery method maintains drug release in zero order.

Advantages of OCRDD

The advantages making distinct to OCRDD are[12,13]

1. Drug release with zero-order mechanism
2. Pulsatile or delayed release of drug
3. Osmotic system release is not have a significant effect of food present in GIT
4. Significant IVIVC correlation.

Disadvantages of OCRDD

Following are the disadvantages of OCRDD[14,15]

1. Drug may get stuck inside due to choking of hole
2. In the event of unexpected adverse outcomes, retrieval therapy is not an option.

Limitations of OCRDD

1. Drugs that irritate the stomach mucosa cannot be incorporated into OS
2. Drug substances that have problems with stability and solubility in the gastrointestinal environment cannot use the osmotic mechanism[15]
3. Fabrication of orifices in an osmotic system requires the use of specialized instruments.

CRUCIAL PARTS OF OCRDD

FODDS comprised of compress core tablet, semipermeable membrane, floating layer, and a delivery orifice. The core portion consists of one or more active ingredient/s (API), osmotic agent, swellable polymer, etc. The core tablet is coated by polymer which forms semipermeable membrane. This semipermeable membrane allows water to enter into core and wet the contents present in it. This phenomenon increases the inside volume and force the inside contents to come out from the orifice. The osmotic pressure generated by the core components and the permeability of the coated membrane determine the rate of water absorption by the core.[16]

Drug

Drugs having shorter biological half-life (2–6 h), low dose, compatible with osmotic agent, and other excipients are preferred for the delivery The drug having absorption in the proximal region of the GIT and have shorter stomach retention period, can be given by this way to prolong residence time which will significantly enhance the effectiveness of the dose In these cases, the osmotic drug delivery which work

on osmotic principle, floating principles is used to improve the GRT.[7] Many prospective medications are developed for osmotic distribution, such asazilsartan,[17] diethylcarbamazine citrate[18] diltiazem HCl,[19] carbamazepine,[20] metoprolol, and nifedipine,[21] Theophylline, salbutamol,[22] topiramate,[23] gliclazide,[24] domperidone maleate,[25] etc.

Hydrophilic polymers

Hydrophilic polymers have attracted an abundance attention and play an important role in development of controlled drug delivery. Their presence assured predictable drug release, they are economical and easily available. Various grades of HPMC are commonly used as rate retardant polymers.[26]

Osmotic agents

The basic principal of osmosis is achieved by incorporating osmotic agent into the core. Osmotic agents are the polymers which have ability to absorb water and generate osmotic pressure inside the core. This generated osmotic pressure helps the content present inside the core to come out from the orifice.[27] Mannitol, dextrose, sucrose, sorbitol, citric acid, fructose, lactose, xylitol, sodium chloride, and potassium chloride are some examples of osmogens which are used alone or in combination.[24] Polyethylene glycol, glycerol, sorbitol, lactulose, or mannitol can be used as osmotic agents for the drugs having high solubility in water. If the drug lacks osmogenic activity, salts (NaCl and KCl) and carbohydrates might be added to the formulation (Table 1). When evaluating osmotic agents, the two most essential determining parameters are water solubility and osmotic activity.

Semipermeable membrane

Semipermeable membrane acts as a barrier which allows only water to enter into core restricting drug to come out from its pore. It helps to maintain the flow of water inside the core and thus plays a role in maintaining osmotic pressure.[26]

Coating solvent

Solvents help to dissolve/suspend the polymer required for semipermeable membrane. Some examples are butyl alcohol, acetone, methylene chloride, methanol, ethanol, isopropyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water, and other compounds. Solvents either used alone or in combinations.

Plasticizers

To impart the plasticity and change the physical structure, plastisizers are added in to coating solutions. The viscoelastic characteristics of polymers can be considerably changed by plasticizers. Plasticizers make covering solvents more effective, adaptable, and safe. As a plasticizer, semipermeable membranes can be made from triethyl phosphate, triacetin, and polyethylene glycol.[29]

Wicking agent

The role of wicking agent is to absorb the water from delivery system's porous network and move solvent molecules upward.[30] Wicking agent when comes in contact with water, they swell and bind loosely with solvent molecules due to Van der Waals forces. Some examples are silicon dioxide colloidal, sodium lauryl sulfate, and polyvinylpyrrolidone.[31]

Flux regulators

Flux regulator which is present in semipermeable membrane controls fluid permeability, that is, rate of flow of water through the semipermeable membrane pores. Hydrophilic substances, such as phthalates altered with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethyl phthalate), decrease flow, while polyethylene glycols (300–6000 Da), polyhydric alcohols, polyalkylene glycols, and other hydrophilic compounds promote flow. In addition, insoluble salts or insoluble oxides that are mostly water-impermeable can be employed for this.[32]

Pore formers

Pore formers are used in pump when water insoluble drugs are to be delivered or multiparticulate pump is to be developed. The pore former screates microporous membrane *in situ* by its leaching during the process of solvation.[33] The pore-formers may be solid, liquid, or inorganic in composition. Some examples are alkaline metal salts (sodium bromide, sodium chloride, potassium sulfate, potassium chloride, potassium phosphate, etc.), alkaline earth metals (calcium nitrate and calcium chloride), carbohydrates (mannitol, mannose, glucose, sucrose, fructose, lactose, sorbitol, etc.) and diols and polyols (polyvinyl pyrrolidone [PVP], poly hydric alcohols, polyethylene glycols, etc.) triacetin, triethyl citrate can be used as pore-forming agents. With the addition of HPMC or sucrose, membrane permeability to the medication is significantly enhanced.[28]

Solubilizing agents

The solubility of poorly soluble drug is improved by mixing it with solubilizing agent. Some commonly used solubilizing agents are PVP, poly ethylene glycol (PEG 8000), and β-cyclodextrin, non-ionic surfactants, polyethylene containing surfactants and SLS (anionic surfactant),citrate esters (e.g., alkyl esters, notably triethyl citrate) and their blends with anionic surfactants are also used.[28] Complexing agents such as PVP and polyethylene glycol are commonly used in conjunction with anionic surfactants such as SLS.

FACTORS RESPONSIBLE FOR SUCCESS OF OCRDD

Solubility of drug

The level of drug solubility in the core has a direct impact on the pace of drug release. The highly water soluble or poorly water soluble drugs are not suitable for osmotic administration.[34]

Semipermeable membrane

The rate of medication release is affected by polymer properties, membrane thickness and shape, and other additives. As a result, the concentration of membrane-forming polymers and other additives determines membrane permeability and, eventually, medication release.[35]

Osmotic pressure

The pressure generated by liquid inside the core determines drug release in a proportionate manner. An outside osmogen is needed if the drug's osmotic pressure is insufficient. The osmotic agents react with water and generate the osmotic pressure (Table 2).

Size of the delivery orifice

To regulate drug release, the delivery orifice must be within the proper range. As discussed here, there are several methods for creating orifices within the membrane.[36]

Mechanical drilling

Using a mechanical may drilling is carried out to create the delivery hole in the osmotic device.

Laser drilling

In this technique, a laser beam is focused towards tablet's surface which leads to heating of tablet surface due to absorption of the energy and creates hole. The laser strength, shooting duration, wall thickness, and beam diameters can be adjusted to determine the passageway's size.[37]

Indentation

Upper punch has the needle like arrangement which is used to create the delivery hole called as indentation during the compression of core tablet. During coating process, the precaution is taken so that the indentation is protected.[17]

Leaching Agents

Polymers having leachable properties are sometimes incorporated during formulation. When such a leaching agent comes into contact with water, it generates pores through which the medicine is released.[38]

Table 1: Osmotic agents and their concentrations[28]

Osmotic agents	Concentration used (%)
Water soluble salts of inorganic acids	
Potassium chloride	10–90
Sodium chloride	10–80
Sodium sulfate	1–5
Water soluble salts of organic acids	
Sodium citrate	0.3–2
Sodium benzoate	2–5
Carbohydrates	
Glucose	Up to 50
Mannitol	10–90
Lactose	10–90
Sucrose	Up to 70
Organic polymeric osmogents	
Sodium carboxyl methylcellulose	1–5
Hydroxyethylmethyl cellulose	2–5
Polyethylene oxide	5
Carbopol	0.5–5

Table 2: Osmotic pressure of saturated solutions of pharmaceutical solutes[28]

Compounds of mixture	Osmotic pressure (atm)
Mannitol	38
Mannitol–lactose-dextrose	130
Potassium sulfate	39
Dextrose	82
Sodium phosphate tribasic	31
Sodium phosphate dibasic	31
Sodium phosphate dibasic anhydrous	21
Sodium phosphate monobasic	28
Lactose-fructose	500
Lactose-sucrose	250
Dextrose-fructose	450
Lactose-dextrose	225
Dextrose-sucrose	190
Fructose	335
Sucrose	150
Sucrose - Fructose	430
Potassium chloride	245
Mannitol-fructose	415
Sodium chloride	356
Mannitol-dextrose	225
Mannitol-sucrose	170

TYPES OF OCRDD

Rose-Nelson pump

In 1955, Australian scientists Rose and Nelson invented an osmotic pump for medicine delivery to sheep and cow guts (Figure 1). The implantable pump is made up of three chambers; one for the medication, one for the salt, and one for the water. The salt chamber is separated from the water chamber by a semipermeable membrane. Generated osmotic pressure differences across the membrane move water from the water chamber to the salt chamber. The capacity of the salt chamber is presumably increased by water flow, which distends the latex diaphragm between the salt and drug chambers leading to pushed out of drug from the device.[39]

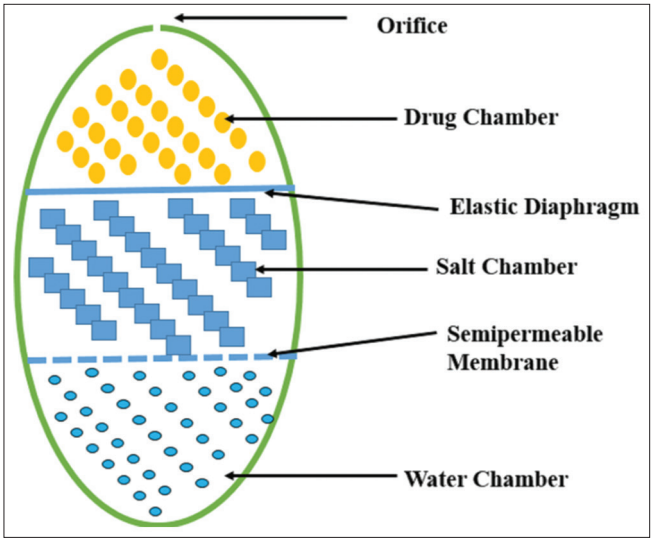

Figure 1: Rose nelson pump

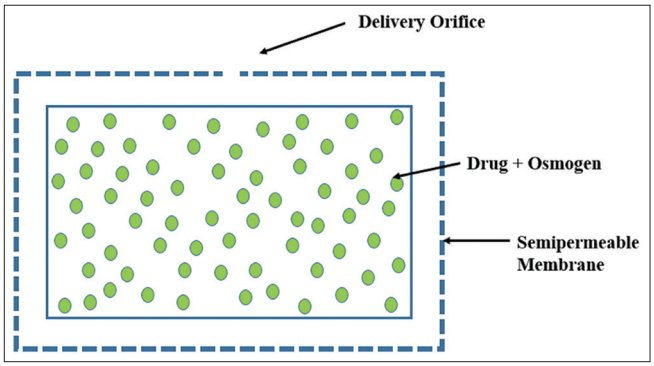

Figure 2: Elementary Osmotic Pump

Higuchi-Leeper osmotic pump

Higuchi and Leeper presented some changes in the Rose-Nelson pump, which constitute the Alza Corporation's initial series of simplifications of the Rose Nelson pump. The Higuchi-Leeper pump does not have a water chamber, and it activates after absorbing water from the surrounding environment which increased its self-slife.

Pumps of the Higuchi-Leeper type typically have a salt chamber containing saturated solution of $MgSO_4$ and solid $MgSO_4$, a semi-permeable membrane, moveable separator, drug chamber, and rigid housing. When administered/implanted, the surrounding biological fluid penetrates the device through the semipermeable membrane and dissolves salt, causing osmotic pressure inside the device that pushes the moveable separator towards the drug chamber, removing the drug from the device. It is commonly used in veterinary medicine. This sort of pump is placed in an animal's body to provide antibiotics or growth hormones.[28]

Elementary osmotic pump (EOP)

Rose-Nelson pump further simplified by Theeuwes F and created the EOP in 1974, a revolutionary invention that established osmotic delivery as a key technique for obtaining regulated drugs release (Figure 2). This technique eliminated the requirement for a separate salt chamber using the drug as an osmotic agent. Using a tableting machine, this device is created by compressing the drug to get tablets having ability to generate the osmotic pressure. The core tablet is then covered with a semi-permeable layer of cellulose acetate, and drilled up to core tablet.[40]

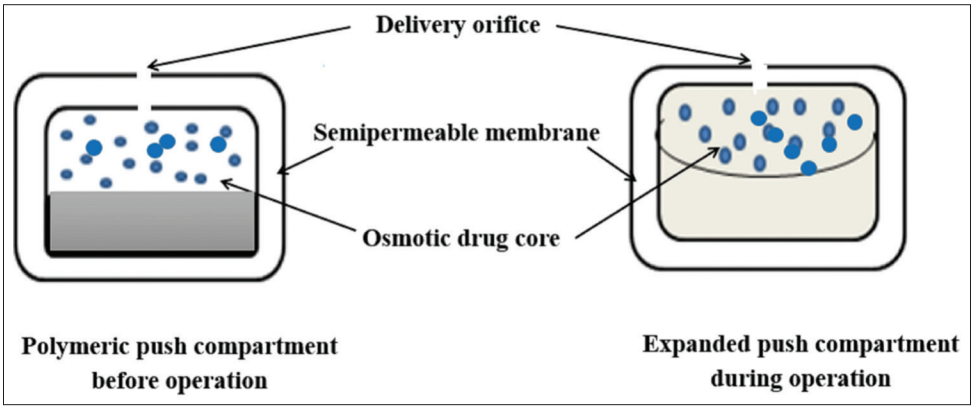

Figure 3: Push-Pull Osmotic Pump

Osmotic pump with non-expanding second chamber

These systems have a second chamber that is not expanding, making them multi-chamber devices.[41] The second chamber of this system is used to dilute the drug solution exiting the device or to deliver a second drug at the same time. Insoluble drugs can also be given by this type of osmotic pump.[42]

Push-pull osmotic pump (PPOP)

This system is made of two compartments which are parted using elastic diaphragm. The one compartment has tiny hole and drug is placed in it. The osmotic agent is placed in another compartment which makes up 20–40% of the tablet and is located in the lower compartment (Figure 3). About 60–80% of the weight of a tablet is made up of the top layer, which houses the medicine and the delivery hole.[43] PPOP can be utilized to administer medications that are extremely water soluble. Different variations of push-pull systems exist, such as push-stick systems, delayed push-pull systems, multiplayer push-pull systems.[27,44-46]

Sandwiched osmotic pump (SOPs)

SOTs comprises of two drug layer each having delivery orifice and a polymeric push coat is present in between the swelling agent present in middle push layer, swells after mixing with water which results in outward flow of drug through the delivery orifices.[47] This type of mechanism is beneficial for medications that locally irritate the gastric mucosa (Figure 4). SOPs releases drugs separately Nifedipine controlled delivery by sandwiched osmotic tablet system.[48]

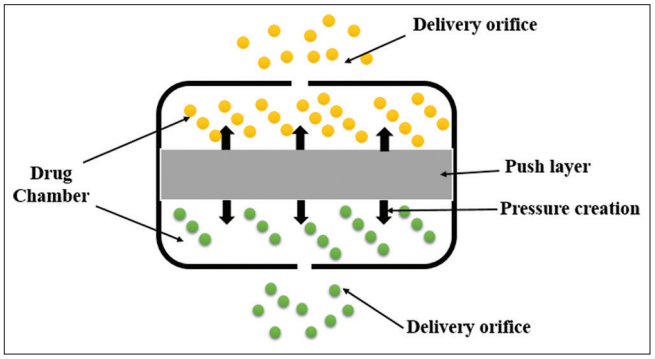

Figure 4: Sandwiched osmotic pump

Controlled porosity osmotic pump (CPOP)

During formulating CPOP, the water-soluble additives are placed in coating layer which gets dissolve when the CPOPs-coated membrane come into contact with water, creating an *in situ* microporous barrier.[34,49] A controlled porosity wall appears like a sponge. In general, materials with pores ranging from 5 to 95% and pore sizes ranging from 10A to 100 m can be used (Figure 5). Dimethyl sulfone, saccharides, amino acids, sorbitol, and other water-soluble additions are utilized for this purpose.[50] The resultant membrane has a high permeability to both water and dissolved solutes. YingKu Lin investigated the drug release mechanism from an asymmetrically membrane-coated capsule with a delivery hole generated *in situ*.[9]

Osmotic pump for insoluble drugs

It involves the osmotic agent (osmogens) particle which covered with an elastic semipermeable layer. Insoluble medications are mixed with these particles before being compacted into a tablet. After that, a semipermeable membrane is placed over the tablet, and a hole is made in the membrane. Water comes in contact with osmotic agent particles through the two membranes which leads to swelling of osmotic agent particles and the insoluble drug is hydrostatically forced through the delivery hole as a result of the osmotic agent particles swelling.[51]

Multiparticulate delayed-release system

A semipermeable layer is formed over the pellets of pure drug using cellulose acetate. When water comes in contact with core materials, it starts dissolving the soluble materials and a saturated solution is formed. A water influx due to rise in osmotic pressure gradient leads the membrane to rapidly expand and create holes. Schultz and Kleinebudde reported that the kinetics of osmotic agents and drug release through these holes often exhibit zero-order behavior. The coating thickness and osmogens ability to create osmotic pressure impacts on lag time and dissolving rates.[52]

Monolithic osmotic system

Monolithic osmotic system combines the drug and the osmotic core into a single unit. Monolithic means water soluble drug is embedded in osmotic core. A solid matrix is formulated

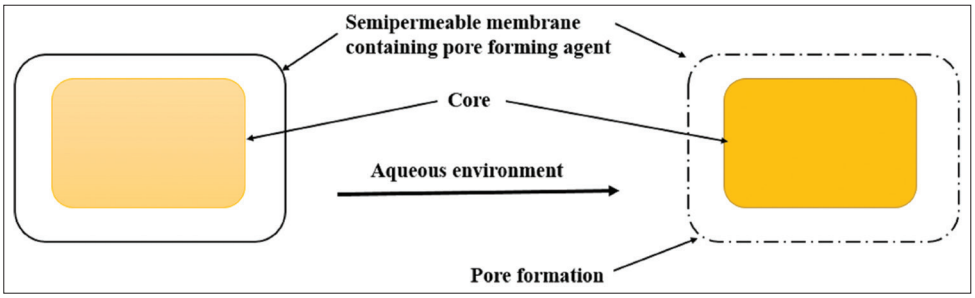

Figure 5: Controlled porosity osmotic pump

by combining osmotic core materials with drug and then coated with semipermeable membrane. When system comes in contact with water the osmotic pressure differential causes water to be pulled through the semipermeable membrane into the solid matrix which leads to therupture of osmotic device and burst release of drug.[53] Advantage of this system is, the drug release rate can be alter by changing the solid matrix's composition, giving it flexibility in the delivery of various medications.[54]

Oral osmotic colon targeted pump (OOCTP)

Colon is a preferred place for the target of delivery of drug specially required for effect in large intestine.[55] A specialized drug delivery device called a "colon-targeted oral osmotic system" is developed to deliver medication into the colon in a regulated manner. This technique might be useful for administering medications to the colon for a variety of therapeutic goals or for the treatment of colon site disease. It is a device consisting of capsule in which many enteric-coated osmotic push-pull units are place. Gelatin capsule when comes in contact with GI environment dissolves and the enteric coat prevents stomach fluids from entering the system.[56] The enteric coating disintegrates as the OOCTP system enters the small intestine, and water passes from the semipermeable and absorbed by the core, expanding the push compartment. Flowable gel simultaneously forms and driven from tiny hole.[57]

Liquid oral osmotic system (LOOS)

LOOS systems for controlled delivery of liquid drug formulations include a two-type delayed liquid bolus delivery system, an LOOS hard cap, and an LOOS soft cap. Each of these systems has a liquid medication.[58] In hard capsule type, a liquid drug and osmotic agent is paced in hard gelatin capsule and coated with semipermeable layer. The osmotic layer is activated when the system comes into contact with an aqueous environment because water flows across the rate-controlling membrane. The expansion of the osmotic layer generates hydrostatic pressure to inside the system, causing the liquid formulation to be come out via the delivery orifice. In soft capsule system, the liquid drug and osmotic agent is placed inside the soft gelatine capsule and then coated with semipermeable membrane. The LOOS hard cap and soft cap systems are intended for continuous delivery of liquid drugs.[59]

Osmotic matrix tablet (OMT)

It is an exceptional osmotically driven matrix system that makes use of the ability of hydrophilic polymers to expand and gel in aqueous conditions, producing an in situ structure that is semi-permeable. As a result, osmotic processes may be used to regulate the release from a matrix system that contains an osmogent.[8] Thus, OMT successfully blends matrix and osmotic properties, resulting in a significant improvement in drug delivery from swellable matrix systems. Osmotic matrix tablets are simple to make because they don't involve coating a semi-permeable membrane or drilling a delivery hole. It is a low-cost method that works with a variety of drugs.[60]

Floating osmotic controlled drug delivery system

The absorption of drug having limited solubility in gastric environment is always a challenge. Many literature documents the successful development of floating drug delivery system which is able to release the drug in acidic environment. When osmotic principle (leading to selling and expansion) is combined with the floating principle, the controlled release of acidic drug in stomach with zero order kinetics can be assured. Floating osmotic drug delivery system consists of core tablets coated with semipermeable layer and then compressed with floating layer. The floating layer consists of gas-generating agents such as sodium bicarbonate and citric acid. with gelling agents like HPMC. When the osmotic pump comes in contact with the gastric fluid, the materials present in floating layer absorbs water which leads to swelling of HPMC and generation of gases by gas generating agent. The gas get entrapped into the gelling layer which increases the buoyancy of the pump and pump come into the surface of the GI fluid. Floating layer keeps the osmotic pump to float over the gastric fluid.[26]

CONCLUSION

Osmotic drug delivery systems are well known for providing delayed and controlled drug release by maintaining an effective concentration at the target site for a longer period of time. Osmotic pressure acts as the catalyst for the release of drugs in osmotic delivery systems. The drug is released from the systems as the pressure inside the pump increases due to water intrusion. This method of administering drugs is quite popular and uses numerous components and pumps. The osmotic delivery of the drugs based on above review concluded that this type of drug delivery definitely offers a better delivery mechanism for pharmaceuticals and improves therapeutic efficacy.

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