Review Article

Osmotic Controlled Drug Delivery System: A Review

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ABSTRACT

Conventional drug delivery systems have slight control over their drug release and almost no control over the 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 controlled or modified release drug delivery systems. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). Among the available techniques to improve the bioavailability of these drugs fabrication of osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT. This review brings out new technologies, fabrication and recent clinical research in osmotic drug delivery.

Keywords: extended release dosage form, oral route, gastro-intestinal tract.

INTRODUCTION

There are many Novel drug delivery systems are in the market, per oral controlled release (CR) systems hold the major part in market share due to its obvious advantages like ease of administration and better patient compliance.[1-3] there are many designing options available to control or modify the drug release from a dosage form. Numerous technologies have been used to control the systemic delivery of drugs. One of the most interesting one is that employs osmotic pressure as an energy source for release of drugs.

ORAL OSMOTIC PUMPS

Elementary osmotic pump

In 1975, the major leap in osmotic delivery occurred as the elementary osmotic pump for oral delivery of drugs was introduced. The pump consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation.

As the membrane is non-expandable, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. This residual dissolved agent continues to be delivered at a declining rate until the osmotic pressure inside and outside the tablet are equal. Normally, the Elementary osmotic pump delivers 60-80% of its contents at a constant rate, and there is a short lag time of 30-60 min as the system hydrates before zero order delivery from the Elementary osmotic pump is obtained.[8]

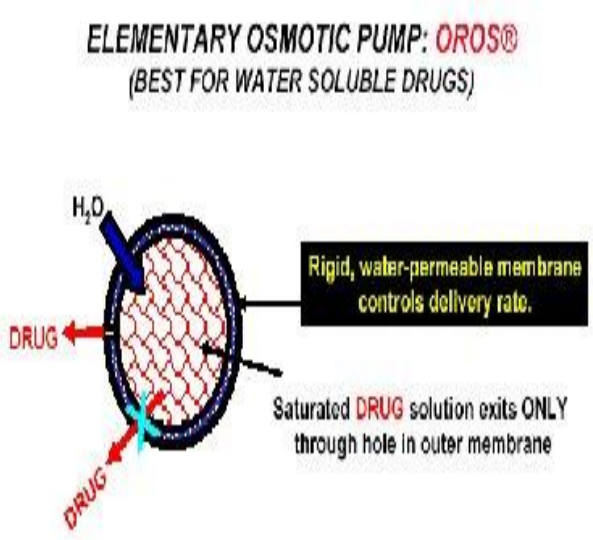

Fig. 1: Schematic diagram of Elementary osmotic pump

Push pull Osmotic Pump

Push-pull osmotic pimp (PPOP) can be used for delivery of drugs having extremes of water solubility. As shown below fig 5. It is bilayer tablet coated with a SPM.Drug along with osmagents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents.The drug compartment is connected to the outside environment via a delivery orifice. After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug as fine dispersion via the orifice. A number of modifications are available for this type of system such as delayed push-pull system (as used in covera HS, extended release for verapamil), multi-layer push-pull system (for pulsatile or delayed drug delivery), and push-stick system (for delivery of insoluble drugs requiring high loading, with an optional delayed, patterned or pulsatile release profile).[9]

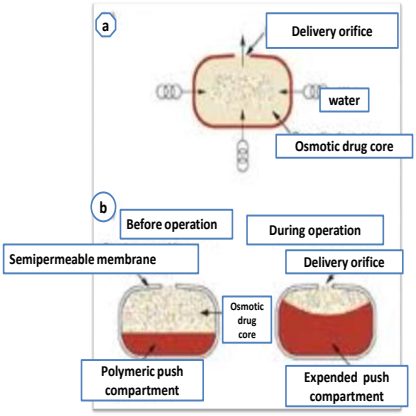

Fig. 2: Schematic diagram of Push pull Osmotic Pump

Controlled porosity Osmotic Pumps (CPOP)

Controlled porosity osmotic pumps (CPOP) are similar to elementary osmotic pump, the only difference being that the delivery orifice from which the drug release takes place is formed by incorporation of a water-soluble additive in the coating. Once the tablet comes in contact with the aqueous media in the gastrointestinal tract (GIT), the water-soluble component dissolves and an osmotic pumping system results as shown below in Fig 6.[10]

Nevertheless, the solubility of the agents to be delivered can be modulated, and these systems can be designed to deliver drugs having extremes of water solubility.[11]The modification required depends mainly upon the dose intrinsic water solubility and osmotic pressure, and desired release rate of the drug.

OROS CT System

The OROS-CT [TM] system was designed for colon-targeted drug delivery. The system either comprises a single osmotic unit or it might contain as many as push-pull units enclosed within a hard gelatin capsule, immediately after ingestion the hard gelatin capsule shell dissolves. However, the push pull unit is prevented from absorbing water in the acidic environment of the stomach by the enteric coating. The osmotic pumping action results when the coating dissolves in the higher pH environment (pH>7) of the small intestine and the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane.

Swellable core technology (SCT) is a new emerging field in osmotic drug delivery that can deliver drugs with moderate or poor aqueous solubility per and extended period of time. The SCT formulation consists of a core tablet that contains a drug composition and a water swellable composition. The drug composition contains the drug, an entraining polymer like polyethylene oxide, and osmotic agents. Whereas the swellable portion contains a non-ionic polymer (PEO) or and ionic polymer (croscamellose sodium or sodium starch glycolate) which swells and expands in volume after absorption of water.

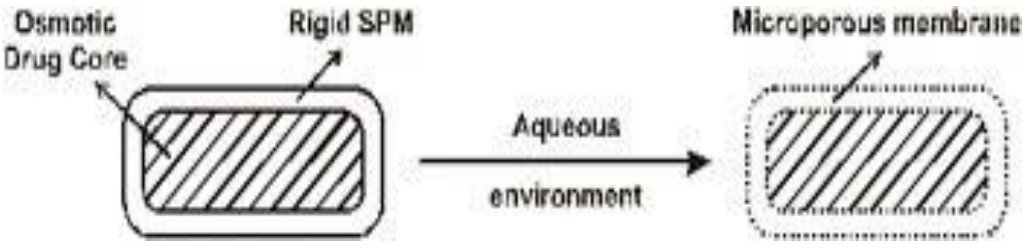

Fig. 3: Schematic diagram of Controlled porosity Osmotic Pumps (CPOP)

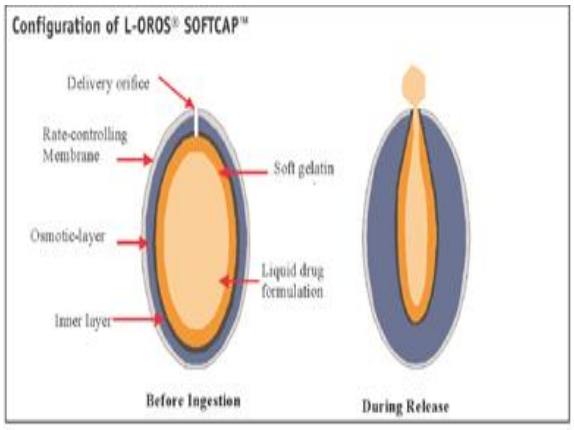

Fig. 4: Schematic diagram of OROS CT System

FACTORS AFFECTING DRUG RELEASE RATE

Before discussing the formulation variables that affect the release of oral osmotic systems, it will be prudent to deal with some of the theoretical aspects.

- Use of wicking agents
- Use of effervescent mixtures
- Use of cyclodextrin derivatives
- Use of alternative salt form
- Use of encapsulated excipients
- Resin Modulation approach
- Use of crystal habit modifiers
- Co-compression of drug with excipients

OSMOTIC PRESSURE

Osmotic pressure is of a solution depending on number of discrete entities of solute presents in the solution. The release rate of a drug from a osmotic system is directly proportional to the osmotic pressure of the sore formulation in EOP design or in the drug reservoir of agent reservoir-osmotic engine-SPM design (e.g., AlzetR osmotic pump). For controlling drug release from these systems, it is important to optimize the osmotic pressure gradient between the inside compartment and the external environment. It is possible to achieve maintain a constant osmotic pressure by maintaining solution of osmotic agent in the core compartment. If a drug does not possess sufficient osmotic pressure, an osmotically active agent can be added to the formulation.

Polymeric osmogens are mainly used in the fabrication of PPOPs and other modification devices for controlled release of drug with poor water solubility. There are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expend to an equilibrium state. These polymers have a capacity to remain a significant portion of the imbibed water within the polymer stricter.[16]

Table 1: List of Compound that can be used as osmogens

Category	Compound or Mixture	Osmotic pressure (atm)
Water-soluble salt of inorganic acids	Potassium chloride	245
	Potassium sulfate	39
	Potassium hydrogen phosphate	105
	Sodium hydrogen phosphate	28
	Sodium chloride	356
Carbohydrates	Mannitol	38
	Sucrose	150
	Lactose-fructose	500
	Dextrose-fructose	450
	Sucrose-fructose	430
	Fructose	23
	Lactose	82
	Dextrose	415
	Mannitol-fructose	130
	Mannitol-lactose	170
	Mannitol-sucrose	225
	Mannitol-dextrose	225
	Lactose-dextrose	225
Inorganic sodium salts	Sodium phosphate tribasic, 12 H_2o	36
	Sodium phosphate dibasic $7H_2o$	31
	Sodium phosphate monobasic, H_2o	28
	Sodium phosphate dibasic, $12H_2o$	31
	Sodium phosphate dibasic anhydrous	29
Other miscellaneous substances	Citric acid	69
	Trataric acid	67
	Fumaric acid	10
	Adipic acid	8
	Sorbitol	84
	Xylitol	104
	Maleic acid	117

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 process42: 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.[17]
- Use of leachable substances in the semipermeable coating: e.g. controlled porosity osmotic pump.

Some of the reported processes created delivery orifaces on the osmotic systems are:

LASER DRILLING

Laser drilling is one of the most commonly used techniques to create deliver orifice in the osmotic tablets. In simple words, the tablets in which holes are to be formed are changed in the hopper. The tablets drop by gravity into the slots of the rotation feed wheel are carried at a predetermined velocity to the passageway forming station. At the passageway forming station, each tablet is tracked by an optical tracking system. If the speed of the moving tablets during increases, the hole may become elliptical because of movement of tablets during the laser firing time. [18]

Use of modified punches

Use of modified punches for producing a delivery orifice in osmotic dosage forms has also been described in the literature.

The dosage form is pierced using a piercing and unsheathed upon application of compression force. The coating powder top be compressed in charged to the die mold and unpierced tablet core is placed upon it. Additional quotation of coating powder is added to the die mod, subsequent to which both compression and piercing are done simultaneously.[19]

Use of pore formers

CPOP are extension of EOPs and are essentially similar, expect that there is no need to create a delivery orifice, drug release from these types of system takes place through controlled porosity pores formed in situ. In corporation of water-soluble additive in the membrane wall is the most widely reported method for the formation of pores in CPOP.[20 ,21]

These water soluble additives dissolve on coming in contact with water, leaving behind pores in the membrane through which drug release takes place. Drug release from these types of system is independent of pH and has been shown to follow zero-order kinetics**.**[22, 23]

Membrane type and characteristics

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. Recalling Eq.4, which describes the volume flow, one can easily recognize the importance of the SPM in controlling release of the drug. The membrane must possess certain performance criteria.

Such as sufficient wet strength and water permeability. Moreover, it should be selectively permeable to water and should be biocompatible. Drug release from osmotic systems in independent of the pH and agitational intensity of the GI tract to a large extent. This is because of selectively water permeable membrane and effectively isolating the dissolution process from the gut environment.[24, 25]

This problem can be overcome by using coating materials with high water permeability. Another approach that can be explored is to use a multilayer composite coating around the tablet. The first layer is a thick microporous film that provides the strength required to withstand the internal pressure, while the second layer is a relatively thin SPM that produces the osmotic flux[26]**.**

Type and nature of polymer

Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate,

cellulose diaceate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, etc. Cellulose ethers like ethyl cellulose and eudragits.

Table 2: List of semipermeable polymers with their water vapour transmission rates[27]

Polymer membrane	Water vapour transmission rates
Polyvinyl alcohol	100
Polyurethene	30-150
Ethylcellulose	75
Methylcellulose	70
Cellulose acetate	40-75
Cellulose acetate butyrate	50
Polyvinylchloride(cast)	10-20
Polyvinylchloride(extruded)	6-15
Polycarbonate	8
Ethylene vinyl acetate	1-3
Poly vinyl chloride	1
Polypropylene	0.7

Effect of type of plasticizer on release profile

Plasticizers can change viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films. The effect of different types of plasticizers (TA and polyethylene glycols) on the water permeation and mechanical properties were studied. The water permeability of CA films was found to decrease with increasing plasticizer concentration to a minimum and then increases with higher concentration of plasticizer**.**[28]

MEMBRANE THICKNESS

Thickness of the membrane has a profound effect on the drug release from osmotic systems. It can be seen Eq. 4, that release rate from osmotic systems is inversely proportional to membrane thickness. Pellets of phenylpropanolamine coated with aqueous ethyl cellulose based films were found to release drugs mainly through the mechanism of osmotic pumping and diffusion.[29, 30]

On studying the release as function of coating thickness, it was found that as the coating thickness increased from 9 to 50 µm, the drug release decreased in an inversely proportional manner. In case of monolithic osmotic tablets of nifedipine, release rates were found to decrease with increase in membrane thickness from 85 to 340µm[31]**.**

An increased resistance of the membrane to water diffusion resulted in this effect. On the other hand, thickness of the membrane in case of asymmetric coating was found to have insignificant effect on drug release. Release rates were found to be virtually unaffected by the overall membrane thickness in the range of 95-150 µm.[32]

Evaluation of Osmotically controlled drug delivery systems

Over the past few years there is increase in the development and commercialization of controlled-release dosage forms has necessitated changes in evaluation aspects of them. This is to provide in-house quality control tests and to furnish regulatory agencies with the experimental evidence that the dosage forms delivers the drug in a controlled and reproducible manner. There is a need for establishing in-vitro-in-vivo correlations to simulate the drug evaluation in the in-vivo system[33].

ADVANTAGES

A part from the general advantages shared by conventional CR systems. OCODDSs have several other unique advantages. Osmotic delivery is a versatile technology that can be used as a powerful research tool to determine various pharmacokinetic parameters and pharmacodynamic response of drugs in animals and humans.

1. Delivery of drug from osmotic pumps can be designed to follow true Zero-order Kinetics. Constant delivery rate is an important specification for chronic treatment. In addition, based upon the requirements, drug delivery can be modulated to achieve pulsatile or delayed zero-order delivery.

2. Drug release from osmotic pumps is minimally affected by the gastric pH and hydrodynamic condition of the body. This is mainly because of the special properties of this semi-permeable membrane employed in the coating of osmotic formulations. The delivery rate is independent of the variation in pH throughout the GIT and GI motility.
3. Higher release rates can be obtained from osmotic systems than with conventional diffusion based drug delivery systems.
4. The delivery of drug takes place in solution form, which is ready for absorption. Thus it is an in situ prepared liquid dosage form.
5. It is possible design an osmotic pump for drug with wide range of water solubility.
6. The delivery rate of drug(s) from these systems is highly predicable and programmable. The in vitro rate can be accurately predicated since the system well described by the equation.
7. A high degree of in vitro/in-vivo correlation can be obtained from osmotic pumps. The Significant in vitro and in vivo correlation for a verapamil oral osmotic system was studied[33].
8. Drug release from the osmotic systems is minimally affected by the presence of food.

DISADVANTAGES

1. Dose dumping
2. Rapid devlopement of Tolerence
3. Retrieval therapy is not possible in the case of un expected adverse events.
4. expensive
5. If the coating process is not well controlled there is a risk of film defects,
6. Which results in dose dumping
7. Size hole is critical.

CONCLUSION

In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system. The major advantages include precise control of zero-order or other patterned release over an extended time period—consistent release rates can be achieved irrespective of the environmental factors at the delivery site. Controlled delivery via osmotic systems also may reduce the side-effect profile by moderating the blood plasma peaks typical of conventional (e.g., instant release) dosage forms. Moreover, since efficacious plasma levels are maintained longer in osmotic systems, avoidance of trough plasma levels over the dosing interval is possible. However, a complex manufacturing process and higher cost compared with conventional dosage forms limit their use. Although not all drugs available for treating different diseases require such precise release rates, once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance.

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