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Osmotic Controlled Released Oral Drug Delivery System: A Review

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ABSTRACT

Controlled drug delivery system have spatial control over the drug release. Osmotic pumps are the most advantageous system for controlled drug delivery. Theses system are useful for oral administration and implantation. Osmotic drug delivery system works by imbibition of water through body fluids, as core of system absorb water it expands which pushes the drug solution out through delivery ports. The development of osmotic system includes development of the Rose- Nelson pump, Higuchi-Leeper pump, Higuchi- Theeuwes pump, Elementry osmotic pump, controlled porosity osmotic pump, multiparticulate delayed release system, Monolithic osmotic system. This paper covers the principle of osmosis, advantages & disadvantages of osmotic system, osmotic pumps.

INTRODUCTION

For decades an acute illness or chronic disease is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms such as tablets, capsules, pills, creams, liquids, ointments, aerosols, injectable and suppositories. Presently, these conventional dosage forms are primarily prescribed pharmaceutical products. To achieve and to maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dosage several times a day. This also results in fluctuating drug levels in plasma.[1]

Oral ingestion is the preferred route of drug administration providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is a very little control over release of the drug.[2] Controlled drug delivery systems have been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms.

Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reaches the sites of action, and hence drug delivery technologies have assumed importance. Scientists are pursuing the discovery and development of new molecules that have better absorptive and pharmacokinetic properties. Drug delivery systems such as oral controlled release dosage forms, transdermal patches and implants are used to overcome these challenges. Although the cost of these drug delivery technologies is considerable, it is substantially less than the cost of developing a new molecule. Hence, a continued interest exists in developing novel drug delivery systems for temporal and spatial delivery of active agents.[3]

CONTROLLED DRUG DELIVERY

The controlled release systems are intended to exercise control on drug release on the body, whether this be of temporal or spatial nature or both. In other words, the system attempts to regulate drug concentration within the tissue or cells.[4]

The controlled drug delivery attempts to:

1. Sustain drug action at predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

2. Localize drug action by spatial placement of a controlled release systems (usually rate controlled) adjacent to or in the diseased tissue or organ.

Idealistically to maintain a constant drug level in either plasma or target tissue, release rate from a controlled release system should be equal to the elimination rate from plasma or target tissue. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of therapeutically active moieties by using either polymer or by modifying parameters inherent in a selected route of administration.[4]

Oral controlled drug delivery

For controlled release systems, the oral route of administration has, by far, received the most attention. This is, in part, because there is more flexibility in dosage form design for the oral route than that is the parenteral route. Patient acceptance of the oral route is quite high.[5]

Design and fabrication of OCRDDS

The majority of the oral controlled release systems are either tablets or capsules although a few liquid products are also available. Sustained release tablet and capsule dosage forms usually consists of two parts an immediately available dose to establish the blood level quickly and sustaining part that contains several times the therapeutic dose for protracted drug levels.

The majority of the controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal tract. Starting with limited data on a drug candidate for sustained release, such as dose, rate constants for absorption and elimination, some elements of metabolism and some physical and chemical properties of the drug, one can estimate a desired release for the dosage form, the quantity of drug needed and a preliminary strategy for the dosage form to be utilized.

More common methods that are used to achieve sustained release of orally administered drugs are as follows.[6]

1. Dissolution controlled release systems

a) Encapsulation dissolution control

b) Matrix dissolution control

2. Diffusion controlled release systems

a) Reservoir devices

b) Matrix devices

3. Diffusion and dissolution controlled release systems

4. Ion exchange resins

5. pH dependent formulations

6. Altered density formulations

7. Osmotically controlled release systems

Advantages of Oral Controlled Drug Delivery System[6]

- Decrease incidence and/or intensity of adverse effects and side effects.
- Predictable and reproducible release rates for extended duration.
- Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations.
- Delivery of drug in the vicinity of site of action.
- More efficient utilization of active agent.
- Improved patient compliance.
- Elimination of frequent dosing and wastage of drug, inconvenience of night time administration of drug.
- A greater selectivity of pharmacological activity.
- Reduction in GI irritation and dose-related side effects.
- Enhanced bioavailability.

Disadvantages of Oral Controlled Drug Delivery System[6]

- Toxicity due to dose dumping.

- Increased cost.
- Unpredictable and often poor *in-vitro-in vivo* correlations.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counselling.
- Increased potential for first-pass clearance.

Osmotic Controlled Drug Delivery Systems

Principle of Osmosis:

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.[10]

Components for controlled drug delivery system

Table No. 1: Materials used in different layer formulations

Component	Examples
Hydrophilic layer (water permeable)	Polysaccharides, hydroxyl propyl methyl cellulose, hydroxyl ethyl cellulose, poly(vinyl alcohol-co-ethylene glycol)
Water-impermeable layer	Kollicoat, SR latex, Eudragit SR
Barrier layer	Styrene butadiene, calcium phosphate, polysilicone, nylon, Teflon, polytetrafluoroethylene, halogenated polymers

Development of osmotic pump[8]

1. Rose-Nelson pump

The present day osmotic devices are the modified versions of Rose and Nelson pump. Rose and Nelson uses the principles of osmotic pressure in drug delivery for the first time. Rose and Nelson were two Australian physiologists interested in the delivery of drugs to the gut of sheep and cattle.[9]

This 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 semipermeable membrane. Due to 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, which swells the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device.

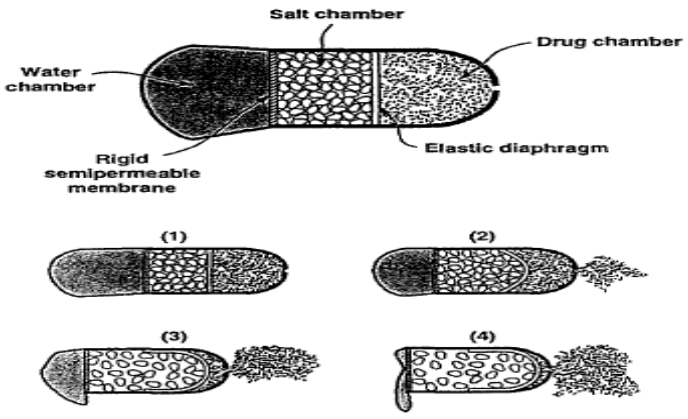

Figure No. 1: Principle of Rose - Nelson osmotic pump

2. Higuchi-Leeper pump

The Higuchi-Leeper pump represents the first of a series of simplifications of the Rose-Nelson pump made by the Alza Corporation beginning in the early 1970s. This type of pump has no water chamber, and the device is activated by water imbibed from the surrounding environment. Activation of pump occur when it is swallowed or implanted. These pumps contain a rigid housing, and the semipermeable membrane is supported on a perforated frame. In this type of pump a salt chamber contain a fluid solution with excess solid salt. Higuchi Leeper pump is widely employed for veterinary use.

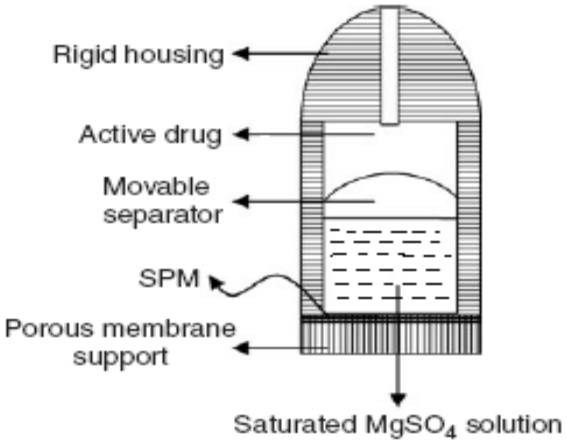

Figure No. 2: Higuchi-Leeper pump

3. Higuchi-Theeuwes Pump

In the early 1970s, Higuchi and Theeuwes developed another, even simpler variant of the Rose-Nelson pump, which is simpler than the Higuchi Leeper pump. Like the Higuchi-Leeper pump, water uses to activate the osmotic action of the pump is obtained from the surrounding environment.

In the Higuchi-Theeuwes device, however, the rigid housing is dispensed with and the membrane acts as the outer casing of the pump. This membrane is strong enough to pumping pressure developed inside the device. The device is loaded with the drug before use. When the device is placed in an aqueous environment, release of the drug follows a time course because of 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.[9] The pump comprises a rigid, rate-controlling outer semipermeable membrane surround by a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. The water is osmotically drawn by the salt through the semipermeable membrane. This water increases the volume of the salt chamber, forcing drug from the drug chamber. Small osmotic pumps of this form are available under trade name Alzet. They are used as implantable controlled release delivery systems in experimental studies.

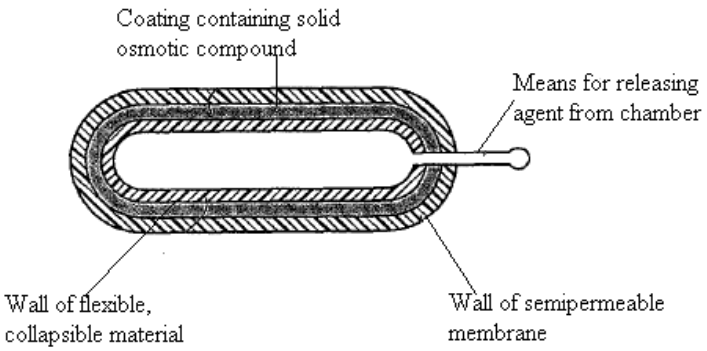

Figure No. 3: Higuchi-Theeuwes pump

4. Elementary osmotic pump

Rose and Nelson pump was further simplified within the sort of elementary osmotic pump (Theeuwes 1975, 1985), which made osmotic delivery as a serious method of achieving controlled drug release. The device may be a further simplification of the Higuchi-Theeuwes pump and eliminates the separate salt chamber by using the drug itself because the osmotic agent.[10] The device is made by compressing a drug with suitable osmotic pressure into a tablet using a tableting machine. The tablet is then coated with a semipermeable membrane, usually cellulose acetate, and a small hole is drilled through the membrane coating.[11] When this tablet is placed in an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semipermeable coat, forming a saturated aqueous solution inside the device. The increase in volume because of the imbibition of water raises the hydrostatic pressure inside the tablet slightly. This hydrostatic pressure is relieved by a flow of saturated agent solution out of the device through the tiny orifice. Thus, the tablet acts as a small pump, in which water is drawn osmotically into the tablet through the membrane wall and then leaves as a saturated agent solution via the orifice. This process occurs at a constant rate until all the solid drug inside the tablet has been dissolved and only a solution-filled shell remains. This residual dissolved drug deliver at a declining rate until the osmotic pressure inside and outside the tablet is equal. The drive to draw water into the device is that the difference in pressure between the surface environment and a saturated drug solution. The osmotic pressure of the dissolved drug solution has, therefore, utilized for a number of drugs.[12] Though 60-80% of drugs is released at a constant rate from elementary osmotic pump, a lag time of 30 – 60 min is observed in most of the cases, as the system has to be hydrated before zero-order delivery from the system begins.[13] This pump was developed by Alza under the name OROS. The conventional high-speed tableting machinery is utilized for

producing the devices. The tablet is coated which is semipermeable and laser drilling use for drilling small hole in the coated tablet.[2]

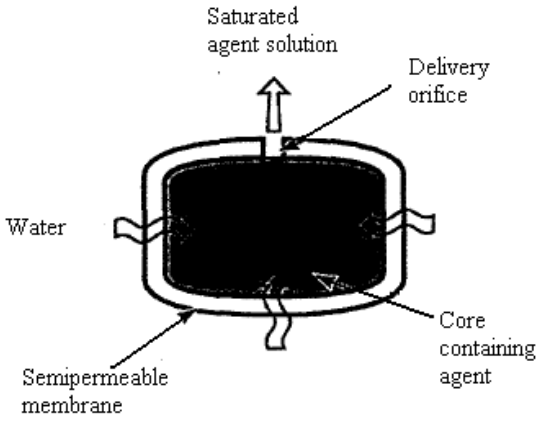

Figure No. 4: Theeuwes elementary osmotic pump

Other osmotic systems

1. Controlled porosity osmotic pump

Controlled porosity osmotic pump is simplest sort of osmotic pumps. These are not having any aperture to release the drugs. The drug release is achieved by the pores, which are formed within the semipermeable wall up situ after administration. The semipermeable coating membrane contains water-soluble pore forming agents. This membrane after formation of pores becomes permeable for both water and solutes. A controlled porosity wall can be described as having a sponge like appearance. The pores are often continuous that have a gap on both faces of a microporous lamina, interconnected through tortuous paths of normal and irregular shapes including curved, curve-linear, randomly oriented continuous and hindered connected. Generally, microporous lamina is defined by the pore size, number of pores, the tortuosity of the microporous path and the porosity, which relates to the size and number of pores. Generally, materials producing from 5 to 95 % pores with a pore size from 10 Å – 100 μm can be used.[1]

The amount of active agent mixed with other osmotically effective solutes present in the device is initially in excess of the amount that can be dissolved in the fluid that enters the reservoir. Under this physical state when the agent is in excess, the device osmotically operates to offer substantially constant rate of release. The rate of drug release can also be

varied by having different amounts of osmogents in the system to form different concentration of agents for delivery from the device.

The release rate from these type of systems has been reported to be dependent on the coating thickness, level of soluble components in the coating, solubility of the drug in the core, and osmotic pressure difference across the membrane, but is independent of the pH and agitation of the release media.[4]

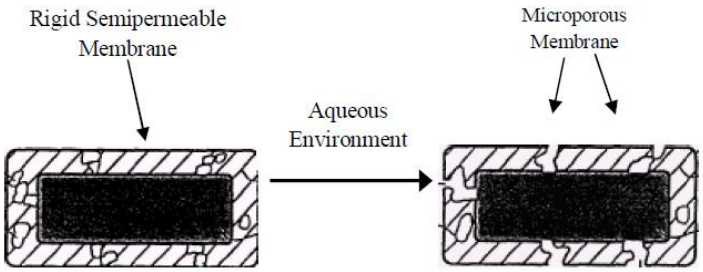

Figure No. 5: Working principle of controlled porosity osmotic pump

2. Sandwich osmotic tablet

In sandwich osmotic tablet (SOTS), a tablet core consisting of a middle push layer and two attached drug layers is coated with a semipermeable membrane. Both the drug layers are connected tom the outside environment via two delivery orifices (one on each side). After coming in contact with the aqueous environment, the middle push layer containing swelling agents and swells and the drug is released from the delivery orifices. The advantage with this type of system is that the drug is released from the two orifices situated on two opposite sides of the tablet and thus can be advantageous in case of drugs which are prone to cause local irritation of gastric mucosa.[14]

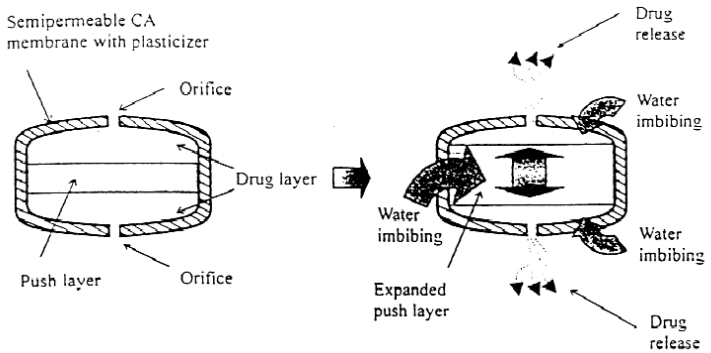

Figure No. 6: Schematic diagram of sandwiched osmotic pump before and during operation

3. Multiparticulate Delayed-Release System

In the multiparticulate delayed-release system, pellets containing drug with or without osmotic agent are coated with an SPM-like cellulose ester. On contact with an aqueous environment, water penetrates into the core and forms a saturated solution of soluble components. The pressure gradient induces a water influx, leading to a rapid expansion of the membrane, resulting in the formation of pores.[25] The osmotic ingredient and therefore the drug are released through these pores according to zero order kinetics. In a study by Schultz and Kleinebudde, lag time and dissolution rates were found to be hooked in to the coating level and osmotic properties of the dissolution medium. Furthermore, dissolution characteristics were found to be influenced by such membrane components as incorporation of plasticizer and its concentration and lipophilicity.[14, 15]

4. Monolithic Osmotic Systems

In the monolithic osmotic system, a simple dispersion of a water-soluble agent is made in a polymer matrix. When the system comes in contact with the aqueous environment, water imbibition by the active agent takes place that ruptures the polymer matrix capsule surrounding the agent, thus liberating it to the outside environment. Initially, this process occurs at the outer environment of the polymer matrix, but it gradually proceeds toward the inside of the matrix during a serial fashion. However, this system fails if more than 20 to 30 vol % of the active agent is incorporated into the device because, above this level, significant contribution from the simple leaching of the substance takes place.[16]

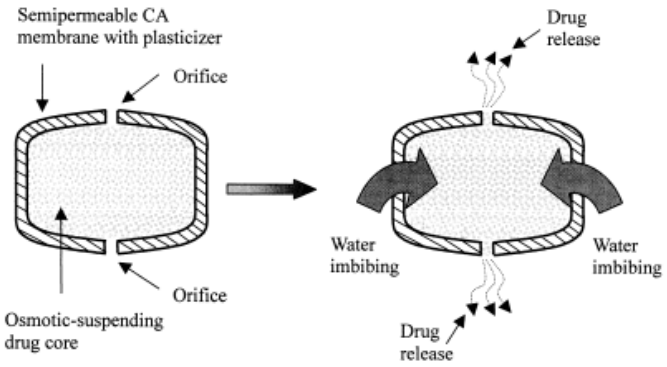

Figure No. 7: Schematic diagram of monolithic osmotic tablet before and during operation

RELEASE KINETIC MODELLING [14,17]

There are number of kinetic models, which describe the overall release of drug from the dosage form. Because qualitative and quantitative changes in the formulation may alert drug release and *in vivo* performance.

In this regards, the use of *in vivo* drug dissolution data to predict *in vivo* bio performance can be considered as the rational development of controlled release formulation.

Zero order release	**First order release**	**Higuchi model**	**Hixoncrowell model**	**Kosmeyerpeppas model**
Drug dissolution from dosage form that does not disaggregates and releases the drug slowly.	This model has also been used to describe absorption and/or elimination of some drug.	This model is often applicable to the different geometrics and porous system.	This describes the release of dose from the system, where there is change in surface area and diameter of particle or tablet.	This method describes the release of drug from polymeric system.
Qo - Qt = Kot	logC = log Co-Kt/2.303	$C=[D(2qt-Cs)Cst]^{1/2}$	$C_0^{1/3}-C_t^{1/3}=K_{HC}t$	$C_t/C\infty=kt^n$
Plotted as cumulative amount of drug released versus time.	Plotted as log cumulative percent of drug remaining versus time.	Plotted as cumulative percent of drug release versus square root of time.	Plot made in between cube root of drug percent remaining in matrix versus time.	Plot made by log cumulative percent drug release versus log time.
Used to describe the drug dissolution of several types	Used to describe the drug dissolution of water	By using this model dissolution of the drug from several modified release dosage	This expression is applied to pharmaceutical dosage form i.e. tablet, where the	This model describes the drug release from several modified release of dosage

of modified drug release. E.g. transdermal patches, matrix tablet, osmotic tablet etc.	soluble drugs in porous matrices.	form like some transdermal system and matrix tablet with water soluble drug are studied.	dissolution occurs in planes which is parallel to drug surface if dimensions of the tablet diminish proportionally, in such a manner the initial geometry from keep constant all the time.	form.

CONCLUSION

Osmotic oral controlled release dosage form provides prolong drug release & also provide increasing therapeutic efficacy. Various osmotic system include Rose-Nelson pump, Higuchi-Leeper pumps, elementary osmotic pump, sandwich osmotic pump, monolithic osmotic pump. In future various attempts are made to produce successful osmotic release oral controlled drug delivery.

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