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Osmotic drug delivery system of valsartan

Syed mujtaba pasha*[1], Syed abid ali[2], Omair sohail ahmed[5], Omer wasiq[3], Mohammed mukaram[1], Mohammed abdul aala[3], Mohammed abdul ali[4]

[1]Department of Pharmacology, Nalanda college of pharmacy, Nalgonda, Telangana, India.
[2]Department of Pharmaceutics, Holy mary institute of technology and science, Ghatkesar, Kondapur, Telangana, India.
[3]Department of Pharmacology, Sultan ul uloom college of pharmacy, Banjara Hills, Hyderabad, Telangana, India
[4]Department of Hospital and clinical pharmacy, Anwar ul uloom college of pharmacy, Hyderabad, Telangana, India
[5]Department of Pharmaceutics, Nizam institute of pharmacy, Hyderabad, India

ABSTRACT

The objective of this study is to design and evaluate a new EOP called swellable elementary osmotic pump (SEOP) of the freely water soluble drug, amitriptyline hydrochloride (1 g /mL) by adding water swellable polymers in the core. The hydrophilic polymers included in the core retard the highly water soluble drug by producing hydrogel within the core, which may restrict and delay the solvent contact with drug molecules and may increase the diffusional length of the solvent to achieve a constant release rate. Thus, this technology can be exploited to achieve constant drug release at predetermined rate especially for highly water soluble drugs.

Keywords: Olmesartan medoxomil; urea; Solid dispersion; dissolution rate.

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Corresponding Author

Name: Mr. Syed mujtaba pasha
Email: Syedmujtabapasha@gmail.com
Contact: + 91-

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INTRODUCTION

Osmotically Controlled release delivery systems of drugs have recently become an important field of research because of their extended and safe use. Among various controlled release devices, osmotically driven system hold a prominent place because of their reliability and ability to devices, Elementary osmotic pumps (EOPs) are the most commercially important osmotic devices because they are easy to formulate, simple in operation, production scale up is easy and most importantly releases the drug at an approximate zero order rate. Drugs of extreme solubility can be formulated as osmotically controlled systems. Amitriptyline hydrochloride, the model drug is a widely used tricyclic anti-depressant. It is rapidly absorbed from GI after oral administration because of its high solubility[1].

In a typical therapeutic regimen the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Survey indicated that dosing more than one or twice daily, greatly reduces patient compliance. So in recent year considerable attention has been focused on the development of novel drug delivery system and the main reason for this paradigm shift is relatively low development cost and time required for introducing a novel drug delivery system as compared to a new chemical entity[2]. In the form of novel drug delivery system, an existing drug molecule can get a new life there by increasing its market value competitiveness and patent life among the various novel drug delivery system available in the market, per oral controlled release system hold the major market share because of their obvious advantages of ease of administration and better patient compliance. These products provide significant benefits over immediate release formulation, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule.

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. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded\coated by the rate controlling membrane. However factor like pH, presence of food and other physiological factor may affect drug release from conventional controlled release systems. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. 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[2]. 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[3]. They are also known as gastro intestinal therapeutic system. Alza corporation of the USA was first to develop an oral osmotic pump and today also they are the leaders in this field with a technology named OROS. Osmotic drug delivery has come long way since Australian pharmacologist Rose and Nelson developed an implantable osmotic pump in 1955. Next quantum leap in osmotic dosage form came in1972 when Theuwes[12] invented elementary osmotic pump. After that many of have been invented which enable controlled delivery of almost all drugs.

Controlled release dosage forms are designed to release drug in-vivo according to predictable rate that can be verified by in-vitro measurement. Potential development and new approaches to oral controlled release dosage form includes,

1. Hydrodynamic pressure controlled system

2. Intragastric floating tablet

3. Transmucosal tablet

4. Microporous membrane coated tablet

Advantages of osmotic drug delivery system

- Easy to formulate and simple in operations
- Improve patients compliance with reduce frequency.
- Prolong therapeutic effect with uniform blood concentration
- They typically give 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 co relation (IVIVC) is obtained in Osmotic systems
- The rationale for the approach is that the presence of water in GIT is relatively constant, at least in terms amount required for activation and controlling osmotically base technologies.
- Higher release rates are possible for Osmotic systems compared with conventional diffusion-controlled drug delivery systems
- The release from Osmotic systems is minimally effects 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 of osmotic drug delivery system

- Toxicity due to Dose dumping.
- Rapid development of tolerance.
- Re-trieval therapy is not possible in the case unexpected adverse events.
- Expensive.
- If the coating process is not well controlled there is a risk of slip defects, which results in dose dumping.
- Size whole is critical.
- Additional patient education and counseling is required.
- Hypersensitivity reaction may occur after implantation.

Applications of odds

Theeuwes et al (1985) developed elementary osmotic pump for metoprolol and oxprenolol for once daily administration. For the desired solubility succinate salt of oxprenolol and fumarate salt of metoprolol were used along with sodium bicarbonate as osmotic agent. Highly efficient method of laser drilling was used with rate of failure less than one in million. The systems were found to be stable after storage period of 2, 1, and 1 years at 23°, 37° and 51°C, respectively. In vitro release study was conducted using differential method apparatus, which indicated substantial drug delivery (60%) at zero-order rates.

Systemic & Site-specific Administration These technologies allow drug delivery for site-specific as well as systemic use for delivery periods of days to 1 year. To deliver drug systemically, the DUROS® system is placed just under the skin e.g., in the upper arm, in an out-patient procedure that is completed in just a few minutes using local anesthetic. Removal or replacement of the product is also a simple and quick procedure completed in doctor's office. To deliver a drug to a specific site, DURECT is a developing proprietary miniaturized catheter technology. Catheter can be attached to a DUROS® system to direct the flow of drug

to the target organ, tissue or synthetic medical structure such as a graft

ALZET osmotic pumps are miniature, implantable pumps used for research in mice, rats, and other laboratory animals. ALZET pumps can be used for systemic administration when implanted subcutaneously or intraperitoneally. ALZET pumps have been used successfully to deliver hundreds of different compounds including antibodies, chemotherapeutic drugs, cytokines, growth factors, hormones, and peptides.

liquid oral osmotic system (l-oros): To deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. Suitable for controlled delivery of lipophilic drugs.

Types of osmotic pumps

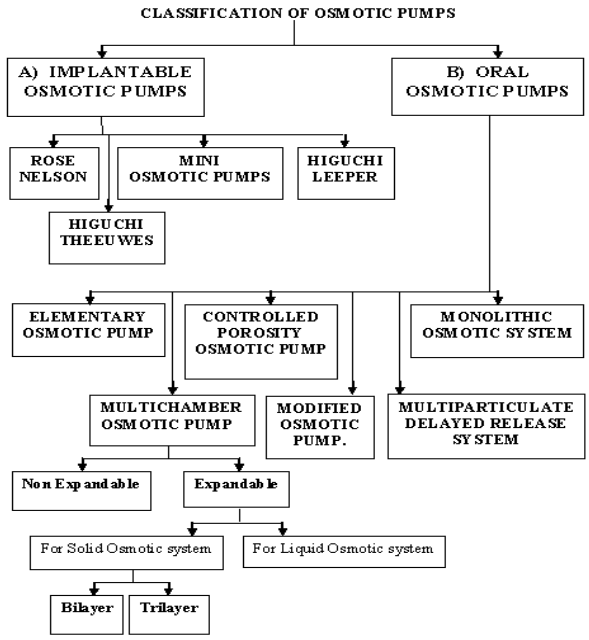

Figure 1: Classification of Osmotic Pumps

Rose-Nelson Pump

Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump for the delivery of drugs to the sheep and cattle gut.

The Rose-Nelson implantable pump is composed of three chambers: a drug chamber, a salt chamber holding solid salt, and a water chamber. A semi permeable membrane separates the salt from water chamber. The movement of water from the water chamber towards salt chamber is influenced by difference in osmotic pressure across the membrane. Conceivably, volume of salt chamber increases due to water flow, which distends the latex diaphragm dividing the salt and drug chambers: eventually, the drug is pumped out of the device.

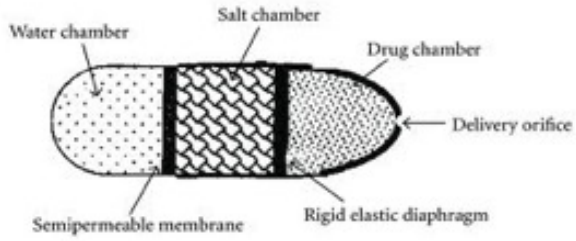

Figure 2: Rose-Nelson Pump

The kinetics of pumping from Rose Nelson pump is given by the following equation:

$$\frac{dMt}{dt}=\left(\frac{dV}{dt}\right)\cdot C,$$

Where dMt/dt is the drug release rate, dV/dt is the volume flow of water into the salt chamber, and C represents the concentration of drug in the drug chamber.

$$\frac{dMt}{dt}=A\theta\Delta\pi\frac{C}{l},$$

where, A is the area of semi permeable membrane, $\Delta\pi$ is the osmotic pressure gradient, θ is the permeability of semi permeable membrane, and l is the thickness of semi permeable membrane. These basic equations are applicable to the osmotically driven controlled drug delivery devices. The saturated salt solution created a high osmotic pressure compared to that pressure required for pumping the suspension of active agent. Therefore, the rate of water entering into the salt chamber remains constant as long as sufficient solid salt is present in die salt chamber to maintain a saturated solution and thereby a constant osmotic pressure driving force is generated.

The major problem associated with Rose-Nelson pumps was that the osmotic action began whenever water came in contact with the semi permeable membrane. This needed pumps to be stored empty and water to be loaded prior to use.

Higuchi-Leeper Osmotic Pump

Higuchi and Leeper have proposed a number of variations of the Rose-Nelson pump and these designs have been described in US patents, which represent the first series of simplifications of the Rose-Nelson pump made by the Alza Corporation.

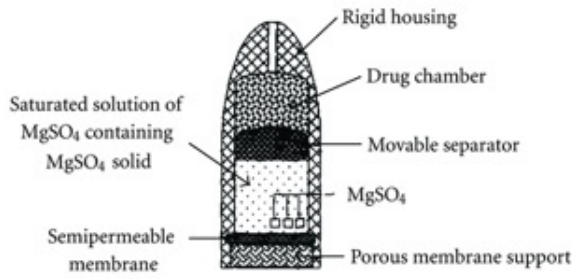

Figure 3: Higuchi-Leeper Osmotic Pump

The Higuchi-Leeper pump has no water chamber, and the activation of the device occurs after imbibition of the water from the surrounding environment. This variation allows the device to be prepared loaded with drug and can be stored for long prior to use. Higuchi-Leeper pumps contain a rigid housing and a semi permeable membrane supported on a perforated frame; a salt chamber containing a fluid solution with an excess of solid salt is usually present in this type of pump. Upon administration/implantation, surrounding biological fluid penetrates into the device through porous and semi permeable membrane and dissolves the $MgSO_4$, creating osmotic pressure inside the device that pushes movable separator toward the drug chamber to remove drug outside the device. It is widely employed for veterinary use. This type of pump is implanted in body of an animal for delivery of antibiotics or growth hormones to animals.

Pulsatile delivery could be achieved by using Higuchi Leeper pump. The Pulsatile release of drug is achieved by drilling the orifice in elastic material that stretches under the osmotic pressure. Pulse release of drug is obtained after attaining a certain critical pressure, which causes the orifice to open. The pressure then reduces to cause orifice closing and the cycle repeats to provide drug delivery in a pulsatile fashion. The orifice should be small enough to be substantially closed when the threshold level of osmotic pressure is not present.

Higuchi-Theeuwes Osmotic Pump

Higuchi and Theeuwes in early 1970s developed another variant of the Rose-Nelson pump, even simpler than the Higuchi-Leeper pump.

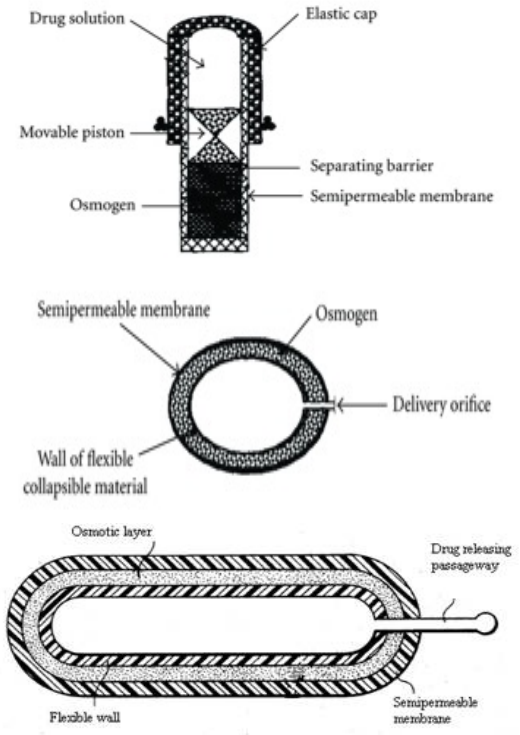

Figure 4: Higuchi-Theeuwes Osmotic Pump

In this device, the rigid housing consisted of a semi permeable membrane. This membrane is strong enough to withstand the pumping pressure developed inside the device due to imbibition of water. The drug is loaded in the device only prior to its application, which extends advantage for storage of the device for longer duration. The release of the drug from the device is governed by the salt used in the salt chamber and the permeability characteristics of the outer membrane.

Small osmotic pumps of this form are available under trade name Alzet made by Alza Corporation in 1976. They are used frequently as implantable controlled release delivery systems in experimental studies requiring continuous administration of drugs.

Elementary osmotic pump (EOP)

Rose-Nelson pump was further simplified in the form of elementary osmotic pump, which made osmotic delivery as a major method of achieving controlled drug release. Elementary osmotic pump shown in was invented by Theeuwes in 1974 and it essentially contains an active agent having a suitable osmotic pressure; it is fabricated as a tablet coated with semi permeable membrane, usually cellulose acetate. A small orifice is drilled through the membrane coating. When this coated tablet is exposed to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semi permeable coating and a saturated aqueous solution of drug is formed inside the device. The membrane is nonextensible and the increase in volume due to imbibition of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through a small orifice.

The pump initially releases the drug at a rate given by the following equation;

$$\frac{dMt}{dt} = \left(\frac{dV}{dt}\right) \cdot Cs,$$

where *dV/dt* depicts the water flow into the tablet and Cs is the solubility of the agent inside the tablet.

Push-Pull Osmotic Pump (PPOP)

Push-pull osmotic pump is a modification of EOP. Push-pull osmotic pump is delivered both poorly water soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (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. When the system is placed in aqueous environment, water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the nondrug layer simultaneously attracts water into that compartment, causing it to expand volumetrically, and the expansion of nondrug layer pushes the drug suspension out of the delivery orifice.

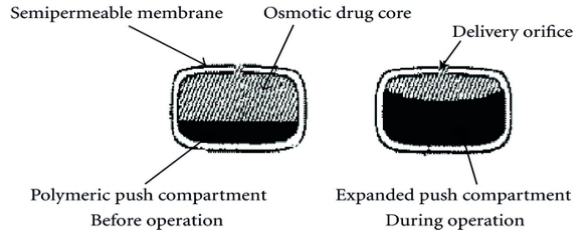

Figure 5: The push-pull osmotic pump (PPOP)

Controlled Porosity Osmotic Pump (CPOP)

It is an osmotic tablet wherein the delivery orifices (holes) are formed in situ through leaching of water soluble pore-forming agents incorporated in semipermeable membrane (SPM) (e.g., urea, nicotinamide, sorbitol, etc.). Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane.

Mechanism of action of controlled porosity osmotic pump.

There are several obvious advantages inherent to the CPOP system. The stomach irritation problems are considerably reduced, as drug is released from the whole of the device surface rather from a single hole. Further, no complicated laser-drilling unit is required because the holes are formed *in situ*. Scheme describes the drug release phenomenon from a typical CPOP .

Liquid-Oral Osmotic (L-OROS) System

Various L-OROS systems available to provide controlled delivery of liquid drug formulations include L-OROS hardcap, L-OROS softcap, and a delayed liquid bolus delivery system. Each of these systems includes a liquid drug layer, an osmotic engine or push layer, and a semi permeable membrane coating. When the system is in contact with the aqueous environment, water permeates across the rate-controlling membrane and activates the osmotic layer.

The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered at the delivery orifice. Whereas L-OROS hardcap and L-OROS softcap systems are designed to provide continuous drug delivery, the L-OROS delayed liquid bolus delivery system is designed to deliver a pulse of liquid drug.

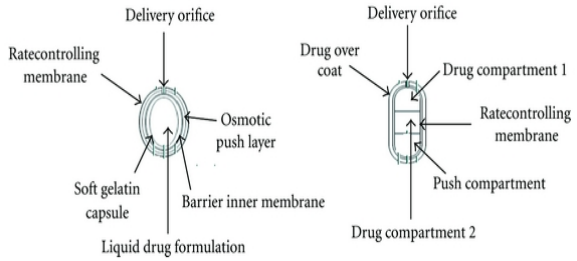

Figure 6: Liquid oral osmotic pump

Liquid oral osmotic pump.

The delayed liquid bolus delivery system comprises three layers: a placebo delay layer, a liquid drug layer, and an osmotic engine, all surrounded by a rate-controlling semi permeable membrane (SPM). The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine expands, the placebo is released first, delaying release of the drug layer Drug release can be delayed from 1 to 10 hours, depending on permeability of the rate-controlling membrane and the size of placebo

Sandwiched Osmotic Tablet (SOT)

This shows that sandwiched osmotic tablet 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 two orifices situated on opposite sides of the tablet; thus sandwiched osmotic tablets (SOTS) can be suitable for drugs prone to cause local irritation of the gastric mucosa.

Mechanism of osmosis

Core contain water soluble osmotically active agent and blended with water soluble or insoluble drug, additives and coating has been carried out which functions as semi permeable membrane.

Since barrier is only permeable to water, initial penetration of water dissolves the critical part of the core, resulting in development of an osmotic pressure difference across the membrane.

The device delivers a saturated volume equal to the volume of water uptake through the membrane. Initial lag time (per hour) during which delivery rate increases to its maximum value, drug release is zero order, until all solid material is dissolved.

Osmotic system theory

Osmotic system release a therapeutic agent at a predetermined, typically zero order delivery rater based on the principle of osmosis. Osmotic system imbibe

water from the body through a semipermiable membrane in to an osmotic materials, which swell resulting in slow and even delivery of drug formulations.

MATERIALS AND METHODS

Components of dosage form

- Drug
- Semipermeable membrane
- Osmogen / osmogent / osmotic driving agent
- Hydrophilic and hydrobhobic polymers
- Wicking agents
- Solubilizing agents
- Surfactants
- Coating solvents
- Plasticizers
- Flux regulators
- Pore forming agents

Method of preparation (by wet granulation):

Mix drug, lactose sodium carboxy methyl cellulose and PVP K30 in mortar and pestle. Mix it and prepare a dough. Keep the dough in an autoclave and then make granules by passing through seive no. 20. Allow the granules to dry by keeping them in oven at 40^0C for 20 minutes. Add magnesium stearate, talc, mannitol to the granules. Now compress the granules by using tablet compression machine, The size of the dye was 3x5mm.

Coating:

Ingredients:

Guar gum - 1 gm

Cellulose acetate - 5gm

Poly vinyl pyrrolidine - 250mg

Propane-2-one(solvent)

Preparation of coating solution:

Mix the above ingredients (guar gum, cellulose acetate, PVP) in a mortor and pestle. Now slowly add the solvent along with continuous stirring until a homogenous slurry is obtained.

Coating procedure

Coating in done by using pan coating machine. First the coating solution is filled in the sprayer. Now the tablets are placed in the coating pan, and are allowed to rotate at 70-100 rpm and temperature is maintained at 50^0C, by passing hot air. After the coating is completed the tablets are collected and packed

Factors affecting release of medicament

Factors affecting the release rate of medicament from osmotic drug delivery system are,

1. Solubility
2. Osmotic pressure
3. Delivery orifice
4. Membrane type

Solubility

Solubility of drug is one of the most important factors since kinetic of osmotic release is directly related to the drug solubility.

The fraction of a drug release with zero order kinetic is given by, F (z) = 1 – S / P

Where F (z) = fraction release by zero order

S = drug solubility in g / cm 3

P = density of core tablet.

Drug with density of unity and solubility less than 0.05 g / cm 3 would release greater than or equals to 95 % by zero order kinetics

Drug with density > 0.3 g / cm 3 solubility would demonstrate with higher release rate > 70 % by zero order.

Solubility-modifying approaches;

Use of swellable polymer vinyl acetate copolymer, polyethylene oxide have uniform swelling rate which causes drug releases at constant rate.

Use of wicking agents: These agents may enhance the surface area of drug with the incoming aqueous fluids.

eg: colloidal silicon dioxide, sodium lauryl sulphate, 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 pressure in the osmotic system and ultimately controls the release rate.

Osmotic pressure

Rate of drug release from an Osmotic system is directly proportional to Osmotic Pressure of the core formulation, EQN

In order to achieve optimized and constant Osmotic Pressure in compartment Osmotic agent must be added to tablet.

So varying the osmogen vary osmotic pressure and hence drug release. Osmogen are classified as inorganic and organic osmogens

Delivery orifice

- Laser,
- Microdrill,
- Modified punches,
- Controlled porosity osmotic pumps can be generated by in-situ formation of delivery

orifice which has been described in US Patent.

In case of Propranalol HCL Oral Osmotic Tablet,

1. Tablet with orifice diameter of 200 – 800 μm showed zero order release and

2. The same with 1 mm orifice diameter showed abnormal release.

So infact orifice diameter should be below Amax and should be greater than Amin since in vivo drug tablet will swell and still minimize the bore. So uneven and unpredictible release will occur.

For delivery containing KCl, orifice should be between 75 to 275 microns in diameter

Membrane type

Drug release from osmotic system is largely independent of pH and agitational intensity of GIT

Examples are Cellulose Ester, Cellulose Triacetate, Cellulose Propionate, Cellulose Acetate Butyrate, Ester, Ethyl Cellulose and Eudragits.

Among above Cellulose Acetate Butyrate is most commonly used since of its,

1. High water permeability,

2. Permeability can be adjusted by varying the degree of acetylation of polymer and also by increasing plastisizer concentration,

3. Flux enhancer and,

4. Superior drying property so advantageneous to thermolabile drugs.

However asymmetric membrane capsule are new type of coating which can be fully utilized for osmotic drug delivery system and offers significant advantage over membrane coating used in conventional Osmotic DDS which devoid of coating defects and they are having higher rate of water influx which allow the release of drug with lower or no osmotic pressure or lower solubility.

Evaluation of osmotic drug delivery system

hardness: It is tested mainly by using Monsanto-hardness tester.

friability: It is mainly tested by using Roche friabrilator.

Disintegration time: It was determined by using thermionic tablet disintegration test machine using water as test fluid.

Dissolution: Dissolution rate studies was studied in phosphate buffer of Ph-6.8 by using 8 station dissolution apparatus with paddle as a stirrer at 50RPM at a temperature of 37$\pm$ 1^{0}C was maintained throughout the study.

1 tablet of 4omg of valsartan was used in each test samples of dissolution media (5ml) were withdrawn through a filter (0.45 micron) pore size at different intervals of time suitably diluted and assayed at 225nm for valsartan.

The samples of dissolution fluid were replaced with fresh fluid. The dissolution experiment were replicated 3 times each (N= 3).

Formulation and methodology

Table 1: Ingredients (for 40 tablets)

Sl.NO	Ingredients	Quantity
1	Drug	40mg
2	Lactose	60mg
3	Sodium carboxy methyl cellulose	10mg
4	PVP K30 in hot water	10mg
5	Starch insoluble	25mg
6	Magnesium stearate	10mg
7	Talc	10mg
8	Mannitol (10%)	15mg

Invitro evaluation

The in vitro release of drugs from oral osmotic systems has been evaluated by the conventional USP paddle and basket type apparatus.

The dissolution medium is generally distilled water as well as simulated gastric fluid (for first 2-4 h) and intestinal fluids (for subsequent hours) have been used.

The standard specifications, which are followed for the oral controlled drug delivery systems are equivalently applicable for oral osmotic pumps.

In vivo evaluation of oral osmotic systems has been carried out mostly in dogs. Monkeys can also be used but in most of the studies the dogs are preferred.

In vivo evaluation

This evaluation has been usually camed out in dogs,

moneys can also be used. But in most cases dogs are preferred.

Osmotic were evaluated for following parameters namely

- Physical appearance
- Dimensions
- Hardness
- Friability
- Invitro dmg release
- Type of polymer used
- Concentration of polymer
- Concentration of osmo agent
- PH modulating agent on release rate.

Grarimetric erosion studies were also performed in some selected formulations. Influence of dissolution medium, osmotic P, and agitation on dmg release was also investigated

Future brands

Drug delivery in general will continue to see significant growth in the pharmaceutical industry corporation of dmg delivery concepts such as bioavailability enhasment and controlled release in to the development of new chemical entilies (NCE) is the logical steps.

Products Incorporating ALZA's OROS® Technology

Alpress™ LP (prazosin) once-daily extended-release tablet sold in France for the treatment of hypertension. Cardura® XL (doxazosin mesylate) sold in Germany for the treatment of hypertension. Concerta® (methylphenidate HCl) CII once-daily extended- release tablet for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients age six and older. Covera-HS® (verapamil) a Controlled Onset Extended Release (COER-24™) system for the management of hypertension and angina pectoris. Ditropan XL® (oxybutynin chloride) extended-release tablet for the once-a-day treatment of overactive bladder characterized by symptoms of urge urinary incontinence, urgency and frequency. DynaCirc CR® (isradipine) once-daily, Extended-release tablet for the treatment of hypertension. Efidac 24® (chlorpheniramine) over-the-counter, extended-release tablet providing 24-hour relief from allergy symptoms and nasal congestion. Glucotrol XL® (glipizide) extended-release tablet used as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes. Sudafed® 24 Hour (pseudoephedrine) over-the-counter nasal decongestant for 24-hour relief of colds, sinusitis, hay fever and other respiratory allergies. Procardia XL® (nifedipine) extended-release tablet for the treatment of angina and hypertension. Volmax® (albuterol) extended-release tablet for relief of bronchospasm in patients with reversible obstructive airway disease

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