

Innovative Approaches in Medication: Exploring Osmotic Pump Systems

B. Akhila*¹ and Keerthi Patil ²

Dr.K.V. Subba institute of pharmacy, JNTUA, Kurnool-518218, Andhra Pradesh, India.

ABSTRACT: In the past few years, novel drug delivery systems (NDDS) play main role in the food and pharmaceutical industries. NDDS is a broad term that encompasses many dosage forms, one of which is osmotic pumps. Osmotic pumps are considered to be the most reliable source of controlled drug delivery, both in humans and in animals. These pumps are osmotically controlled and release active agents through osmotic pressure. The release of drug from ODDS follows zero order kinetics. This form of dosage pattern can lead to plasma concentration fluctuation. Osmotic systems are the most effective strategy-based drug delivery control system. To a large extent, drug release from such a system is independent of gastric fluids. The reason is the low cost of development and shorter time required to launch the NDDS compared to the new chemical molecule development. they work on the principle of osmotic pressure for controlling the delivery of the drug. Based on such unique properties and advantages, osmotic pumps have their mark on the pharmaceutical industry. This review summarizes the available osmotic devices for implementation and osmotic tablets for oral administration. It summarizes how to administer drugs like nifedipine, glipizide, indomethacin etc through the osmotic pumps.

Keywords: osmosis, osmotic pressure, osmotic pressure, osmotic pump, controlled release systems, alzet osmotic pump, rose and nelson osmotic pump.

INTRODUCTION

Oral administration is one of the oldest and most widely used drug administration route, providing an easy way to effectively achieve local and systemic effects. The complete action of a drug molecule depends on its therapeutic function and the efficiency brought to the aid site. Conventional oral drug dosage forms are known to provide a prompt release of active ingredients, but one cannot control the release of the medication and cannot maintain a therapeutic concentration at the desired site for a long time. Various factors affect the rate and extent to which the drug reaches systemic circulation after administration, including the excipients used, physicochemical properties of the active ingredient, physiology and pH

of the gastrointestinal tract, gastric emptying rate, and GI motility. As the drug concentration in plasma varies with a conventional dosage form, it is challenging to obtain a steady-state drug concentration in plasma. These fluctuating drug levels may hamper the achieving and maintaining of an effective concentration, which may result in an undesirable drug response or may not produce a therapeutic response. To overcome these limitations with conventional dosage forms, controlled-release drug delivery systems, through which the drug is released in a predicted and sustained manner, have been developed. They maintain the drug concentration between the minimum effective concentration (MEC) and maximum therapeutic concentration (MTC) for a prolonged time, ensuring sustained therapeutic action. Osmotic delivery systems or osmotic pumps are mainly composed of a core containing a drug and an osmogen. These are coated with a semi-permeable membrane containing one or more ports for drug delivery, such that the drug is released over time in the form of a solution or suspension. Oral osmotic systems are composed of a compressed tablet core coated with a semi-permeable membrane through which delivery orifices are created using a laser beam or mechanical drill. These controlled systems are based on osmosis and osmotic pressure and are independent of various gastrointestinal factors.

In the field of medicine and agriculture it is often describe to maintain an effective concentration of an active agent e.g. a pesticides, herbicides, fertilizer or drug at some site of action for prolonged period. One method of achieving this goal is to deliver a large excess of agent so that even though it is metabolized, excreted or degraded sufficiently remains to maintain the effective dose. A better pattern of delivery is to dispense the agent from a sustained release delivery system, which releases the active agent at a slow rate, throughout the delivery period. Recently, several technical Advancement has been made. They have resulted in the development of new techniques for drug delivery.

These techniques are:

1. Capable of controlling rate of drug delivery.
2. Sustain the duration of therapeutic activity.
3. Targeting the delivery of drug to tissues.

The new drug delivery programs (NDDS) are an important area for drug research and development. The reason is the low cost of development and the time required to launch the NDDS (\$ 20-50 million and 3 - 4 years, respectively) compared to the new chemical molecule (about \$ 500 million and 10 - 12 years, respectively). Treatment for serious illness or chronic illness is achieved through the delivery of medicines to patients for many years. These drug delivery systems include pills, not to mention, suspensions, creams, ointments, liquids and aerosols. Today these standard drug delivery systems are widely used.

HISTORICAL BACKGROUND

The osmosis principle was first used in the design of drug delivery systems by Rose and Nelson. In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. First osmotic drug delivery concept was developed by Theeuwes in 1974 [Vincent et al.2009]. In 1975, Theeuwes further simplified the Rose-Nelson pump made by Alza Corporation of the USA and developed a system known as the elementary osmotic pump (EOP) and hold major number of patents and also marketed several products [Ajay et al.2010]. Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. They design tablet composed of tablet-core surrounded by a semipermeable membrane with a single passageway (orifice), the so-called elementary osmotic pump (EOP) [Higuchi & Leeper 1973].

Drugs administered intravenously benefit from avoiding the acidic and enzymatic gastric environment. However, the drawback of the intravenous route is its invasiveness. The place where needle is to be applied it requires proper cleanliness, as there is a risk of infection when the therapy is continued for several weeks. The implanted pump was the next advancement— a device designed for implantation under the skin to bypass the application of the catheter. These devices provide constant drug release.

Nifedipine PPOP (Procardia XL) was one of the most successful drug delivery systems of the last century, marking the revival of the OODS.

Rationale for Design of Osmotic Controlled Drug

Delivery Systems:

The ideal situation in most drug therapies is the maintenance of a uniform concentration of drug at the site of action, since the pharmacological action elicited by a drug generally is proportional to its concentration at the site of action. Drugs having narrow therapeutic windows especially require a close monitoring of blood levels to avoid untoward effects. Constant intravenous infusion is a popular method of drug administration in clinical settings to maintain a constant blood concentration. However, with this method, patient compliance is compromised, and infusion is not economically feasible for long-term therapies. Non-invasive routes such as oral administration of multiple doses at a particular frequency can be used to achieve this goal. However, patient compliance is again compromised with the increased frequency of administration. Therefore, the demand has increased for controlled delivery systems that can achieve relatively constant blood concentrations of drug over a prolonged period of time. The objective of controlled drug release is to deliver a pharmacologically active agent in a predetermined, predictable, and reproducible manner. Since the formulation is metered as a portion of the entire dose at any given time and provides a reduced or once-a-day dosage regimen, controlled drug delivery offers improved patient compliance with reduced side effects. However, providing a constant drug concentration is not necessarily the best treatment regimen. For example, widely fluctuating levels of a drug such as insulin sometimes are required to mimic natural biofeedback mechanisms. Therefore, the term-controlled release includes modulated release systems as well as zero-order release systems. These systems provide actual therapeutic control despite not providing constant drug concentrations. Many forms of controlled drug delivery systems are reported in the literature, including delayed release dosage forms, targeted release dosage forms, stimulating circadian rhythm systems, external stimuli controlled dosage forms (including pH changes, magnetic or electrical fields, ultrasound, and chemical responsive systems), and matrix and reservoir systems, including solvent controlled and diffusion controlled systems. All these controlled drug delivery systems suffer from one or more disadvantages, as outlined in their respective chapters. Among all Osmotic Controlled Drug Delivery Systems the controlled drug delivery systems, oral controlled drug delivery has received

major attention because of its greater popularity and utility. Ideal oral drug-controlled delivery systems are those that steadily meter out a measurable, reproducible amount of the drug over a prolonged period. Despite this advantage, drug release from oral controlled release dosage forms may be affected by pH, gastric motility, and the presence of food. One improvement that addresses these disadvantages is the osmotic drug delivery system. In 1974, Theeuwes and Higuchi invoked the principles of osmotic pressure to develop a new generation of controlled drug delivery devices with many advantages over existing drug delivery systems. These delivery systems provide a sustained delivery rate, preventing the sudden increases in plasma concentration that may produce side effects, as well as sharp decreases in plasma concentrations that may lower the effectiveness of the drug. The following sections discuss the different principles necessary for the design of osmotically controlled delivery systems.

OSMOSIS:

Osmosis is a passive process and happens without any expenditure of energy. It involves the movement of molecules from a region of higher concentration to lower concentration until the concentrations become equal on either side of the membrane.

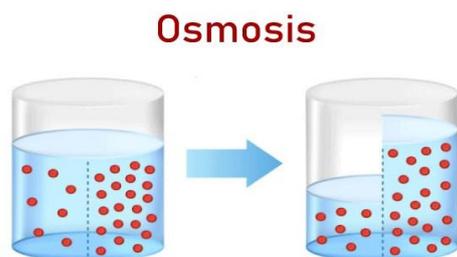


Figure 1: osmosis

OSMOTIC PRESSURE:

The pressure applied to the higher-concentration side to inhibit solvent flow is called osmotic pressure. Osmotic pressure is colligative property, which depends on concentration of solute that contributes to osmotic pressure. membrane having water permeability but impermeable to sugar solute is used to separate a sugar solution from pure water. The flow of water then occurs in a sugar solution that cannot be stopped until pressure is applied to the sugar solution. Pfeffer has shown that this pressure, the osmotic pressure of the sugar solution, is directly proportional to the concentration of the solution and the absolute temperature.

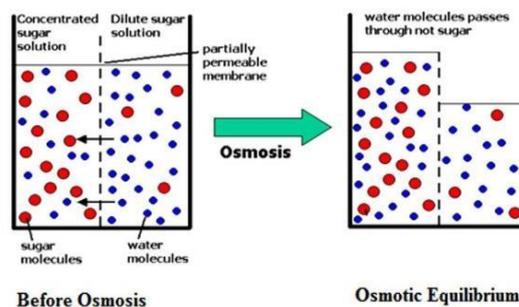


Figure 2: osmotic pressure

OSMOTIC PRINCIPLE:

Solutions of different concentrations having the same solvent and solute system show an osmotic pressure proportionate to their concentrations. Thus, a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic drug delivery system. This results a constant zero order release rate of drug. The rate of drug release from osmotic pump depends on the osmotic pressure of the core and the drug solubility; hence, these systems are suitable for delivery of drugs with moderate water solubility. Osmotic pressure is proportionate to temperature and concentration and the relationship can be described by following equation:

$$\pi = n^2 RT$$

Where

π = osmotic coefficient

n^2 = molar concentration of solute in the solution

R = gas constant

T = Absolute temperature

ADVANTAGES:

1. they typically give a Zero order release profile after an initial lag
2. the release mechanisms are independent on drug concentration.
3. Sustained and consistent blood levels within the therapeutic window.
4. Reduced side effects.
5. Deliveries may be delayed or pulsed if desired.
6. The release of drug is less affected by the presence of food in gastrointestinal tract.
7. They are well characterized and understood.
8. Delivery rate is independent of agitation outside, including GI motility.
9. Enhanced bioavailability of drug.
10. Reduced inter patient variability
11. Decrease dosing frequency.
12. Improved patient compliance

13. Increased safety margin of high potency drugs
14. Drug release from the OCODDSs exhibits significant in vitro-in vivo correlation [IVIVC] within specific limits.
15. It is possible to attain better release rates than those obtained with conventional. Diffusion based drug delivery systems.
16. Release rate of drug is highly predictable and programmable.
17. It is useful for water soluble, partially water soluble and water insoluble drugs.

DISADVANTAGES:

1. Expensive.
2. If the coating process is not well controlled there is a risk of film defects, which results change of toxicity due to dose dumping.
3. Hole Size is critical in case of Elementary osmotic
4. integrity and consistency are difficult.
5. Drug release from the osmotic systems is affected to some extent by the presence of food.
6. Retrieval of therapy is not possible in the case of unexpected adverse event.
7. Rapid development of tolerance.

MECHANISM OF OSMOTIC CONTROLLED RELEASE:

Its mechanism depends upon Vant's Hoff rule: which describes about the relationship between the osmotic pressure of a dilute solution and concentration.

$$\text{Equation: } V\pi = n RT$$

Where

π = osmotic pressure in atmospheres

V = volume of the solution in litres

R = gas constant, equal to 0.082 L.atm/mol. K

n = number of moles of solute

T = absolute temperature in K

The Vant's Hoff equation also can Written as follows:

$$\pi = (n/v) RT$$

BASIC COMPONENTS OF OSMOTIC PUMP SYSTEMS:

- Drug
- Osmotic agent
- Semipermeable membrane
- Wicking agent
- Pore - forming agent
- Coating solvents
- Emulsifying agents
- Solubilizing agents.

- Flux-regulating agent
- Plasticizers
- Barrier layer forms
- Polymers
- Surfactants
- Hydrophilic and hydrophobic

DRUG:

Characteristics of drug candidate for osmotically controlled drug delivery.

- It is supposed to have short half-life (2-4 hours).
- It is necessary to desire prolonged release of the drug.
- In nature, it should be potent
- Drug solubility should not be either very high or very low.

Example: Glipizide, Albuterol, Pseudoephedrine, Diltiazem, Verapamil etc.,

Generally, drugs are to provide a prolonged release. So, the osmotic pump system is not suitable for all drugs. The drug's half-life should be short so that it can be sustained or maintained in plasma, and its prolonged release should be the requirement. To be incorporated into this system, drugs should also be neither highly soluble nor very poorly soluble, and the nature of the drug should be potent for this purpose.

1. Drug itself act as an osmogen and shows good aqueous solubility

Eg: Potassium chloride pumps

2. But if the drug does not possess an osmogenic property, osmogenic salt and other sugars can be incorporated in the formulation.

OSMOTIC AGENT:

Osmogens and osmotics are essential ingredient of the osmotic pump, and they create the osmotic pressure in the osmotic delivery system. When the solubility of drug is low then the drug will show zero order release but at a slow rate. osmotic agents maintain a concentration gradient across the membrane. When biological fluid enters the osmotic pump through a semi permeable membrane. The osmotic agents available on the market include lactose, fructose, sorbitol, dextrose, sodium chloride, citric acid, potassium chloride, sucrose, xylitol, and mannitol. Osmogens may also consist of mixtures, such as mannitol + sucrose, dextrose + fructose, sucrose + fructose, dextrose + sucrose, mannitol + fructose, lactose + fructose, mannitol + dextrose, or

lactose + dextrose. Drugs with good water solubility can be used as osmotic agents, such as mannitol, glycerol, lactulose, sorbitol, or polyethylene glycol. For the selection of osmogen, the two most critical properties to be considered are osmotic activity and aqueous solubility.

SEMI PERMEABLE MEMBRANE:

It is a outer layer of the osmotic pump. The mechanism of drug follows is Facilitated diffusion. The semi permeable membrane is generally 200–300 μm thick to withstand the pressure within the device.

Semipermeable role is a selectively permeable to allow water only, not permeable for solutes and ions. the release rate is essentially independent of the pH of the environment. In osmotic pump preparation, the polymer that is most commonly and extensively use is cellulose acetate, which is provided in various grades of acetyl content. The grades containing 32% and 38% acetyl content are most commonly employed. The degree of substitution (average no. of hydroxyl groups replaced by substituting groups) determines the acetyl content. The other semipermeable forming polymers are group consisting of acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose dimethyl amino acetate, polyamides, polyurethanes etc. Other digestive polymers used for this purpose include cellulose esters, like diacetate, propionate, cellulose acetate, triacetate, and cellulose acetate butyrate. Ethers of cellulose can also be included in this, such as ethyl cellulose.

Criteria for the semipermeable membrane:

1. The membrane should be stable to both outside and inside environments of the device.
2. The material must possess sufficient wet strength.
3. It must exhibit sufficient water permeability.
4. It must be sufficiently rigid so as to with stand the pressure within the device, to retain its dimensional integrity during the operational lifetime of the device.
5. The reflection coefficient or “leakiness” of the osmotic agents should approach the limiting value of unity. But polymer membranes must be more permeable to water.
6. It should also be relatively impermeable to the contents of dispenser so that osmogen is not lost by diffusion across the membrane.
7. It should be non- swelling.
8. It should be biocompatible.

Common biocompatible polymers include PEG, HPMA, PGA, chitosan, and dextran. These materials,

when used in oral systems, can be ingested and then excreted in feces once the osmotic pump is exhausted. Oral and implant fractions that may have been absorbed are very likely to be eliminated by glomerular filtration in the kidney, provided that they are below the glomerular threshold.

WICKING AGENT:

Wicking agents are substances with the ability to absorb water into the porous network of a delivery system. These may be swellable or non swellable. their main function is to carry solvent molecules to surfaces inside the core of the osmotic device, thereby creating channels of enhanced surface area. It is the ability to undergo physisorption with water. Physisorption is a form of vanderwaals interaction where the solvent molecules can loosely adhere to the surface of the wicking agent. Some examples are Sodium lauryl sulfate, kaolin, titanium dioxide, colloidal silicon dioxide, alumina, niacinamide, polyvinyl pyrrolidone, bentonite. The use of the wicking agent helps to enhance the rate of drug released from the orifice of the drug.

PORE FORMING AGENT:

The pore forming agents causes formation of micro porous structures in the membrane due to their leaching out usually in such condition used for poorly water-soluble drugs. When dissolution medium contact with semipermeable membrane the pores may be formed. It releases the drug over a long period of time by the process of osmosis. The pore formers may be inorganic and organic in nature. Alkaline metal salts such as potassium chloride, sodium chloride, sodium bromide, potassium sulphate, potassium phosphate, and others may be used as pore-forming agents. Alkaline earth metals such as calcium nitrate, calcium chloride etc, carbohydrates such as fructose, sucrose, glucose, mannose, lactose, sorbital, mannitol, diols, polyols.

COATING SOLVENTS:

The primary function of solvent system is to dispersed or dissolved the polymer and other additives to the substrate surface. Solvents that are inert and either organic or inorganic in nature are employed to prepare a polymeric solution. These solvents should not cause adverse actions in the core or other materials. Examples of such solvents include methanol, ethanol, cyclohexane, methylene chloride, isopropyl alcohol, and water, Methylene chloride, isopropyl alcohol,

dichloromethane, ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water. The mixtures of solvents such as acetone-methanol (80: 20), acetone-ethanol (80: 20), acetone-water (90: 10), methylene chloride-methanol (79: 21), methylene chloridemethanol-water (75: 22: 3) can be used.

SOLUBILIZING AGENTS:

For osmotic drug delivery system, highly water-soluble drugs would demonstrate a high release rate of zero order. Most drugs with low intrinsic water solubility are poor candidates for osmotic delivery. However, the solubility of drugs within the core. Addition of solubilizing agents into the core tablet dramatically increases the drug solubility. Nonswellable solubilizing agents are classified into three groups,

- (i) Agents that inhibit crystal formation of the drugs or otherwise act by complexation with the drugs (e.g., PVP, poly (ethylene glycol) (PEG 8000) and β cyclodextrin),
- (ii) (i) a micelle-forming surfactant with high HLB value, particularly non-ionic surfactants (e.g., Tween 20, 60, and 80, polyoxymethylene or poly ethylene containing surfactants and other long-chain anionic surfactants such as SLS),
- (iii) citrate esters (e.g., alkyl esters particularly triethyl citrate) and their combinations with anionic surfactants. The combinations of complexing agents such as polyvinyl pyrrolidone (PVP) and poly (ethylene glycol) with anionic surfactants such as SLS are mostly preferred.

EMULSIFYING AGENTS:

Emulsifying agents are added to wall forming material to produce an integral composition which is useful to make the wall of the device. They regulate the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. The examples of emulsifying agents are polyoxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laureates, glycerol (sorbitan oleate, stearate or laurate) etc.

FLUX-REGULATING AGENTS:

It mainly designed to regulate the permeability of the fluid by incorporating flux-regulating agents in the layer. Hydrophilic substances such as polyethethylene

glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethyl phthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose.

PLASTICIZERS:

Plasticizers lower the temperature in phase transition of the wall. Permeability of membranes can be increased by adding plasticizer. The ranges of plasticizers or mixture of plasticizers are between 0.01 parts to 50 parts which are incorporated into 100 parts of wall forming materials. Examples: Di alkyl phthalates, Tri octyl phosphates, alkyl adipates, triethyl citrate and other citrates, propionates, glycolates, myristates, benzoates, sulphonamides and halogenated phenyls.

BARRIER LAYER FORM:

The function of barrier former is to restrict water entry into certain parts of the delivery system and to separate the drug layer from the osmotic layer. The examples of barrier layer formers are high density polyethylene, wax, rubber etc.

POLYMERS:

These polymers are used in the formulation of osmotic systems to constitute a drug layer. Highly water-soluble drug can be trapped in hydrophobic matrix and medium-soluble drug can be added to hydrophilic matrices to obtain more controlled release. Typically, a mixture of hydrophilic and hydrophobic polymers has been used in the formation of osmotic pumps of water-soluble drugs. The selection is based on the drug solubility, it's the amount of drug and rate of drug release from the dosage form. Polyethylene Oxide and Hydroxy ethyl cellulose are most widely used polymer for osmotic dosage form. Other hydrophilic polymers such as carboxy methylcellulose, hydroxy propyl methylcellulose, poly (vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose can be used for this purpose.

SURFACTANTS:

Surfactants are added to wall forming agents. They produce an integral composite that is useful for making the wall of the device operative. The

surfactants act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. Typical surfactants such as polyoxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laurates, and glycerol etc.

HYDROPHILLIC AND HYDROPHOBIC:

- These polymers are used in the formulation development of osmotic systems containing matrix core.
- The selection of polymer is based on the solubility of drug as well as the amount and rate of drug released from the pump.
- Examples of hydrophilic polymers are Hydroxy ethyl cellulose, carboxy methyl cellulose, hydroxy propyl methyl cellulose, etc.
- Examples of hydrophobic polymers are ethyl cellulose, wax materials, etc.

FACTOR AFFECTING THE RELEASE RATE OF DRUG FROM OSMOTIC SYSTEM:

- Drug solubility
- Osmotic pressure
- Membrane characteristics
- Orifice size
- Plasticizer amount

DRUG SOLUBILITY:

- Drug have high water solubility
- Addition of solubility modulating agent
- Use of polymer coated buffer components to modulate the drug solubility within the core
- Use of buffers

OSMOTIC PRESSURE:

- The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment.
- The release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation.

MEMBRANE CHARACTERISTICS:

The semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment.

ORIFIZE SIZE:

The orifice is one of the most important components in the lining of the drug. The size of the orifice should be adjusted to control the release of the drug into the osmotic system. The drug is delivered through an orifice via the process of diffusion to achieve an optimal, zero-order drug delivery rate. The optimum size range for a delivery orifice is 600 μm to 1 mm.. Leaching materials can also be employed for creating in situ orifices or pores in the membrane.

Plasticizer Amount:

Plasticizers were added to transform the visible structures and improve the film-forming feature of the polymers. Plasticizers can convert polymer solid and thin to a softer, more flexible material and make it more resistant to mechanical pressure. The polymer can affect the penetration of the polymer films can lead to a level of drug release from osmotic tablets.

Some osmotic drug deliveries are used a variety of medications, especially those are sustained and controlled release;

Some examples:

- Antihypertensives: drugs like NIFIDIPINE are used to manage high blood pressure.
- Anti diabetics: medications like GLIPIZIDE help control blood sugar level.
- Antipsychotics: drugs such as RISPERIDONE for psychiatric conditions.
- Pain relievers: medications like MORPHINE and HYDROMORPHONE for chronic pain management.
- Cardiovascular Diseases: like angina and heart failure, drugs like ISOSORBIDE MONONITRATE are used.
- Asthma and COPD: Bronchodilators and corticosteroids for respiratory conditions.
- Neurological Disorders: medications like MEMANTINE for treating Alzheimer's disease.
- Cancer: chemotherapeutic agents for sustained release to target tumors.
- Hormone Replacement Therapy: these systems can deliver hormones like estrogen or testosterone in a controlled manner.

TYPES OF OSMOTIC PUMP DRUG DELIVERY SYSTEMS:

Depending on the active ingredient, design, and purpose of use, osmotic systems are principally classified as;

1. Implantable osmotic pump
2. Oral osmotic pump

IMPLANTABLE OSMOTIC PUMP:

THE ROSE AND NELSON PUMP;

The first implantable osmotic technique pump was reported in 1955 by Rose and Nelson, Australian physiologists. The pump was designed to deliver drugs into the guts of animals (sheep and cattle). The pump consists of three chambers:

- A drug chamber with an orifice
- A salt chamber with elastic diaphragm containing excess solid salt
- A water chamber

The drug and water chamber are separated by a semi-permeable barrier. The difference in osmotic pressure across the membrane moves water from the water

chamber into salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating salt and drug chamber there by pumping drug out of this device. Example: Indomethacin, Acutrim TM (containing phenylpropanolamine)

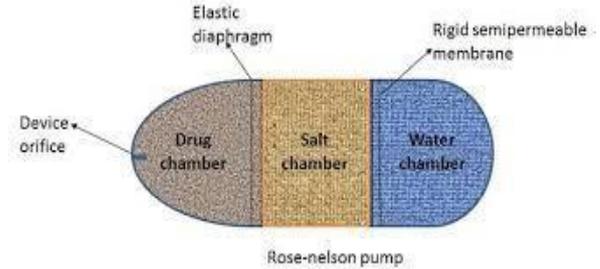
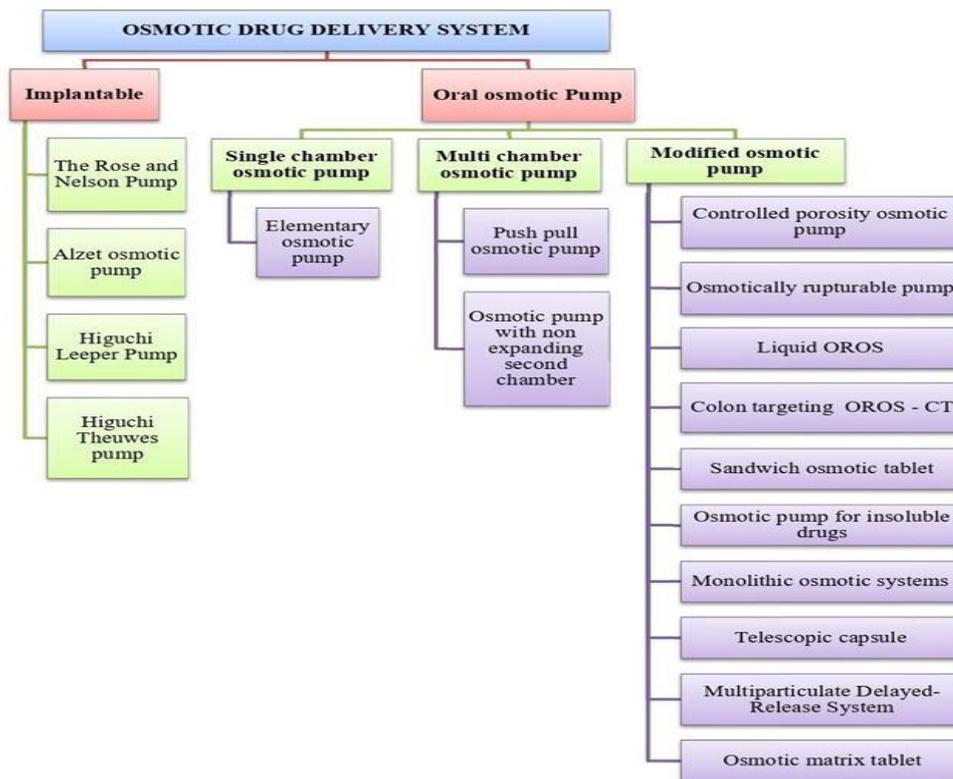


Figure 3: Rose and nelson pump



ALZET OSMOTIC PUMP:

For research purpose in laboratory animals, implantable Alzet mini pumps are utilized. It consists of drug reservoir, osmotic sleeve A thermoplastic elastomer made of hydrocarbon forms a collapsible reservoir, and around it is a coating of the osmotic agent. Over this layer, another coating is present; a semi permeable membrane made of a cellulose ester blend. The drug is loaded into the reservoir. Water enters through a semi permeable membrane and

reaches the osmotic agent layer, which creates pressure on the inside and thus releases the drug out of the device. The drug release rate depends on the water volume permeating through the selectively permeable wall and the drug concentration in the solution. This rate can be controlled by controlling the permeation of the semi permeable walls. Volumes of 100µL, 200µL, and 2mL are the capacities in which the device is available, and it provides rates of drug delivery in the range 0.11-10µL.

Examples: hormones- estrogen and testosterone
 These pumps are used to deliver homogenous solutions or suspensions continuously at a controlled rate for extended period.

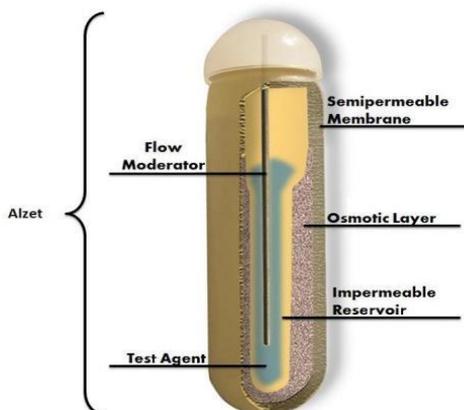


Figure 4: Alzet device

HIGUCHI LEEPER PUMP:

In the 1970s, Alza Corporation introduced the Higuchi–Leeper pump, a simplified form of the Rose–Nelson pump. The water chamber is absent in the Higuchi–Leeper pump. A major modification of their plans is the removal of the water chamber from the device. the device is activated by water imbibed from the surrounding environment with semipermeable membrane. this means the pump is first prepared and then loaded with the drug and then store for weeks or months prior to use.

Examples: Antibiotics- penicillin and tetracycline
 Growth hormone- somatotropin
 Chemotherapy agents- doxorubicin

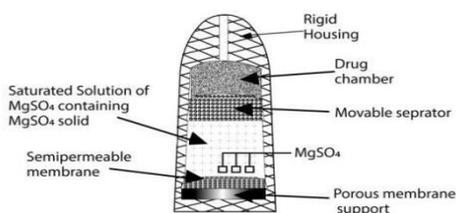


Figure 5: Higuchi Leeper pump

HIGUCHI THEUWEES PUMP:

In the 1970 Higuchi Theuwees developed a similar form of Rose Nelson pump. The semipermeable wall acts as a rigid outer casing of the pump. The pump contains a SPM that surrounds a layer of salt. the drug is loaded into the device before use. When the device is put in an aqueous environment, the release of the drug follows a time course set by the salt used in the

salt chamber and the permeability of the outer membrane casing.

Example: Albuterol inhalers

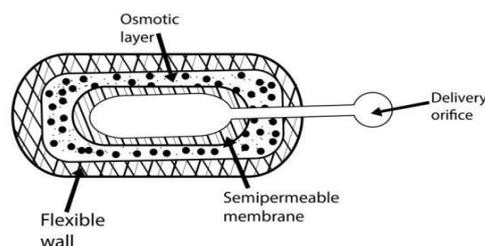


Figure 6: Higuchi Theuwees pump

ORAL OSMOTIC PUMP:

SINGLE CHAMBER OSMOTIC PUMP

ELEMENTARY OSMOTIC PUMP {EOP}:

It is the simplest form of osmotic pump. This device was further simplification of Higuchi –Theeuwes pump. It was developed in the year 1975 by Theeuwes. The release rate of drug controlled by the semi permeable membrane. Drug is compressed into a tablet by the osmotic pressure. The drug is coated with a cellulose acetate. A semi permeable membrane surrounds the tablet core. When such a system is swallowed water from the GIT enter through the membrane in the core, the drug dissolved and the drug solution is pumped out through the exit orifice. An orifice of about the size ranges from 0.5 to 1.5 mm is drilling may be done by Mechanical drilling, laser drilling (CO2 laser beam with a wavelength of 10.6μ). When the dosage form is exposed to the aqueous atmosphere, the core absorbs water osmotically at a controlled rate, which creating the osmotic pressure of the core and the water permeability of semi-permeable membrane. The drug solution volume is proportional to the solvent volume. The rate of drug release is zero order. While 60-80% of the drug is released from the Elementary Osmotic Pump Devices (EOP) at a constant rate, a lag time of 30-60 minutes is observed.

Examples: lovastatin, ranitidine HCL

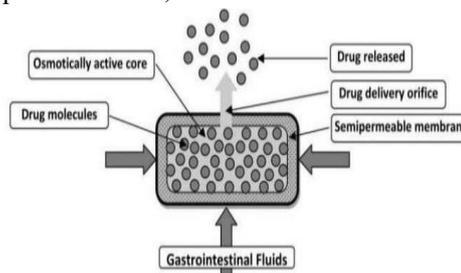


Figure 7: Elementary osmotic pump

MULTI CHAMBER OSMOTIC PUMP:

A) PUSH PULL OSMOTIC PUMP [POPP]:

The PPOP was developed by Alza Corporation, consists of two compartments separated by an elastic diaphragm. This system possible to deliver both poorly water-soluble and highly water-soluble drugs at a constant rate. It similar to bilayer coated tablets-upper and lower layer. The upper compartment contains the drug and is connected through a small orifice to the outside environment. A polymeric osmotic agent in the lower compartment and there is no orifice for delivery. The drug layer accounts for 60–80% of the tablet weight and 20–40% of the osmotic polymer layer. When the dosage comes into contact with the water, water is absorbed by both the drug layer and the polymer layer. Since the lower compartment has no orifice, it extends and moves the diaphragm into the upper chamber, pushing the drug through the delivery orifice. At the same time, the osmotic agent in the non-drug layer draws water into that compartment, causing it to expand volumetrically, and the expansion of the non-drug layer forces the drug suspension out of the delivery orifice. The most widely used polymer in the push layer is Carbopol (around 20-40 percent wt. of the tablet). The main disadvantage is cost of the device is high.

Examples: verapamil, glipizide.

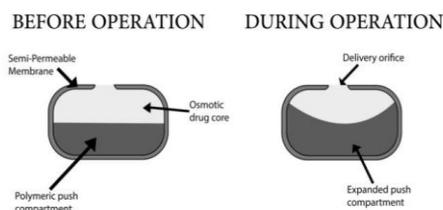


Figure 8: push pull osmotic pump

B) OSMOTIC PUMP WITH NON-EXPANDING SECOND CHAMBER:

These multi chamber devices contain systems that contain a non-expandable second chamber. The purpose of the second chamber is to dilute the drug solution leaving the device (which is very useful in treating drugs with a severe GI irritation) or simultaneous delivery of two drugs. Poorly or insoluble drugs can also be delivered by formulating them into this type of device

Examples: diltiazem hydrochloride, metoprolol

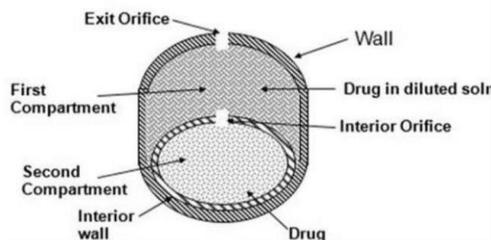


Figure 9: osmotic pump with non-expanding second chamber

MODIFIED OSMOTIC PUMP:

A) CONTROLLED POROSITY OSMOTIC PUMP[CPOP]:

In 1985, Zenter describes the simplest osmotic system for the oral delivery of a drug. The pump can be made with single or multicompartiment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a semipermeable membrane which has an asymmetric structure. This osmotic pump tablet consists of a core compartment loaded with drugs with some water-soluble drugs. The membrane has selective permeability for water only. The controlled osmotic porosity pump contains water-soluble additives in the coating membrane, which after contact with liquid environment, it dissolves and results in the formation of a microporous membrane, giving it a sponge like appearance. the microspores wall permeable to water and drug is dissolved. Generally, materials that produce from 5 to 95% pores with a pore size from 10A - 100µm can be used. The resulting membrane is permeable to both, dissolved solute and water. Water-soluble additives used for this purpose are dimethyl sulfone, saccharides, amino acids, sorbitol, etc. Ying-Ku Lin (2003) studied the mechanism of release of moderate-to high-soluble drugs using various solubility modifying agents. Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent and the osmotic pressure difference across the membrane. This system does not depend on Ph or physiological conditions.

Examples: metformin HCL, pioglitazone HCL

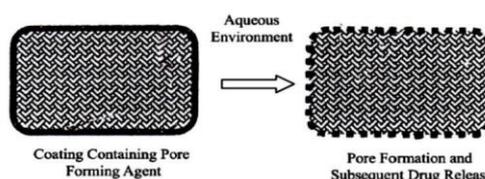


Figure 10: controlled porosity osmotic pump

B) OSMOTICALLY RUPTURABLE PUMP:

Baker introduced this system of controlling drug release. This system is similar to an Elementary osmotic pump. The orifice of drug delivery is absent and size may be smaller.

When it is placed in an aqueous environment, water is imbibed and hydraulic pressure forms. This rupture and the content are released to the environment. Pulsatile release can be achieved by this system. Thickness and area of the semi-permeable membrane, the drug release rate can be controlled in this system.

Examples: methylphenidate, doxazosin

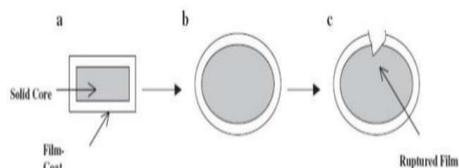


Figure 11: osmotically rupturable pump

C) LIQUID ORAL OSMOTIC SYSTEM:

The various LOROS systems available to provide controlled delivery of liquid formulations include a L-OROS soft cap, L-OROS hard cap and a delayed liquid bolus delivery system. Each of these systems includes a layer of liquid drugs, an osmotic engine or a Push layer and a SPM. Alza designs these systems. This system increases the permeation of drugs.

When this system comes in contact with a water, the water penetrates inside the layer through SPM and will activate an osmotic layer. The expansion of the osmotic layer leads to the formation of hydrostatic pressure within the system, thereby forcing the liquid formulation to extrude it from orifice at the delivery site. While, L-OROS hard caps and LOROS soft cap systems are designed to provide continuous drug delivery, the L-OROS delayed delivery of liquid bolus system is designed to deliver pulse of liquid drug.

Examples: MiraLAX, Dulcolax

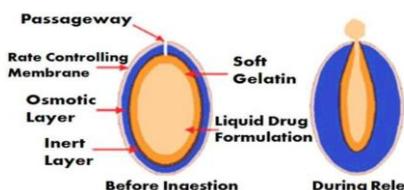


Figure 12: liquid oral osmotic system

D) COLON TARGETING ORAL OSMOTIC SYSTEM[OROS-CT]:

The system can be used once or twice a day to administer medications for targeted delivery of drugs to the colon. The device is coated with 5-6 enteric coating and osmotic push-pull units loaded with hard gelatine capsule for controlled delivery of colonic drugs. When gelatine capsule shell dissolves upon contact with GI fluids, the outer shell of the product prevents the entry of fluid from the stomach and dissolves after it reaches the intestine. The water imbibes to the core and the swelling of push compartment takes place. At the same time, the flowable gel is formed that is forced out at a predetermined rate via the delivery orifice. About 80% of the drug is delivered to the large intestine by OROS-CT. drugs that are poorly soluble in water can be delivered through osmotic system by forming a complex with cyclodextrin.

Examples: sulfasalazine, hydrocortisone, prednisolone

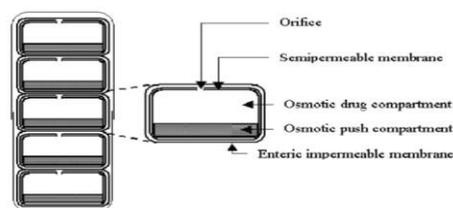


Figure 13: colon targeting oral osmotic system

E) SANDWICH OSMOTIC TABLET:

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 central push layer containing the swelling agents swells and the drug started released from the two orifices situated on opposite sides of the tablet and thus sandwiched osmotic tablets (SOTS) can be suitable for drugs prone to cause local irritation of the gastric mucosa.

Example: Nifedine

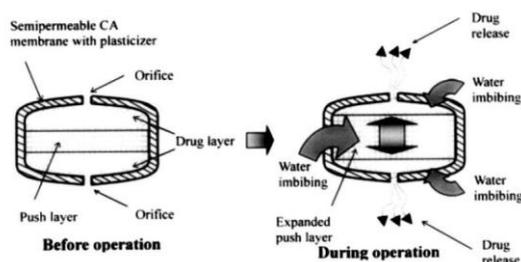


Figure 14: sandwich osmotic tablet

F) OSMOTIC PUMP FOR INSOLUBLE DRUGS:

It consists of coating the particles of the osmotic agent (osmogens) with a SPM. These particles are mixed with an insoluble drug substance and pressed in the form of a tablet, after which they are encased in a SPM, and an orifice is formed on the membrane. After its contact with the liquid, the water is drawn through both layers to the particles of the osmotic agent, then swells and push the drug hydrostatically through a delivery orifice. Examples: carbamazepine

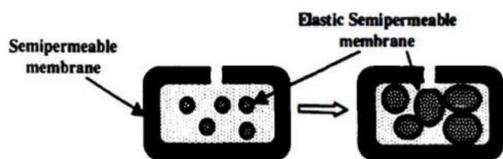


Figure 15: Osmotic pump for insoluble drugs

G) MONOLITHIC OSMOTIC SYSTEM:

It consists of a simple dispersion of a water-soluble substance in a polymeric matrix. When the system comes in contact with a liquid environment. The drug particles are encapsulated by polymers. The water uptake by the drug substance occur that rupture the polymer matrix capsule surroundings, thereby releasing drug to the external environment. Initially, this process takes place in the outer surface of the polymer matrix, but gradually progresses to the inner surface of the matrix in a consistent manner. However, this system fails if more than 20 to 30% of the active agent incorporated into the osmotic system. The osmotic pressure is the main principle. The release kinetics of drug delivery is zero order.

Examples: oxprenolol

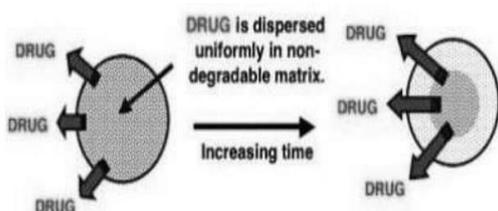


Figure 16: Monolithic osmotic system

H) TELESCOPIC CAPSULE:

This device consists of two chambers, the first chamber contains the delivery orifice and drug, and the second chamber contains osmotic engine. A wax like layer separates the two Chamber. To assemble the delivery device, the drug substance is placed in one of the Chamber with a manual or automatic filling mechanism. The capsule cap contains a bilayer tablet, while the cap's closed end includes a barrier. The capsule's open end is fitted with a filled vessel. Compression is applied to this assembly. When water

enters the system, the expansion of the osmotic layer occurs, resulting in pressure generation on the wall of sections. The drug volume is constant in the delay period to minimize the fluid's net flow into the core of the system.

Examples: isosorbide mononitrate, felodipine, acetaminophen

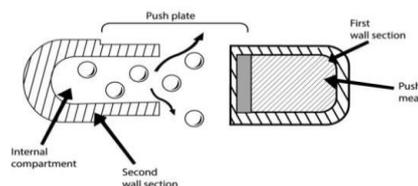


Figure 17: Telescopic capsule

I) MULTIPARTICULATE-DELAYED RELEASE SYSTEM:

In this type of design, pure drugs in pellets that may or may not contain osmotic agents are coated with semi-permeable membrane like cellulose acetate. When exposed to water, water enters the core and forms a saturated drug solution. The osmotic pressure causes a water flow, leads to the membrane expands rapidly, resulting in pore formation. The drug is released at a zero-order rate. Bioavailability can also be increased by using this technique.

Examples: omeprazole, lansoprazole

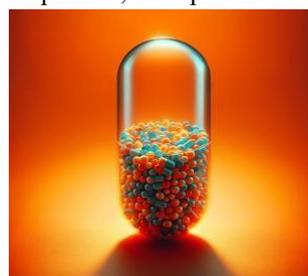


Figure 18: Multiparticulate delayed release system

J) OSMOTIC MATRIX SYSTEM[OSMAT]:

It is an osmotically operated matrix system, which uses hydrophilic polymer material to swell and gel into a liquid that makes it semi-permeable in situ. OSMAT thus follow both matrix and osmotic aspects leading to quantum improvement in drug delivery from swellable matrix systems. Osmotic matrix tablets are very easy to produce and does not require SPM coating and orifice for drug delivery. Therefore, it is a less expensive technology and can be utilized for a variety of drugs.

Examples: felodipine, alfuzosin, verapamil, theophylline, prazosin.

PRECAUTIONS:

1. Avoid physical damage: don't crush or chew the tablets, as this can cause uncontrolled drug release
2. Monitor hydration: ensure the patient remains hydrated to facilitate the osmotic mechanism
3. Check for allergies: always verify that the patient is not allergic to any component of the system.
4. Observe for adverse reactions: unexpected side effects or reactions
5. Store properly: keep the osmotic pump in the recommended storage conditions to maintain its integrity
6. Avoid interference: be mindful of other medications or dietary factors that could interact with the pump's operation
7. Follow dosage instructions: stick to the prescribed dosage and schedule to prevent complications

These precautions ensure safe and effective drug delivery.

EVALUATION OF OSMOTIC PUMP TABLETS:

PRECOMPRESSION PARAMETERS OF OSMOTIC PUMP TABLETS:

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index [Carr's index]
- Hausner's ratio

POSTCOMPRESSION PARAMETER OF OSMOTIC PUMP TABLETS:

- Thickness
- Hardness
- Friability
- Weight variation
- Disintegration test
- Uniformity of drug content test
- In vitro dissolution studies □ Scanning electron microscopy

CONCLUSION

Osmotic pumps are one of the systems for controlled release. These systems invented in recent years. The drug release pattern, which is independent of pH and physiological factors, is one of the significant benefits of this system. This system follows zero order and having a predetermined rate. The osmotic drug development is slightly costly type of drug delivery system but it tends to provide a good rate of drug release which tends to increase its acceptance in the pharmaceutical world. It allows targeted delivery of

agents to virtually any tissue. It ensures around the clock exposure to test agent at predictable levels. Osmotic pumps have excellence control on the drug delivery so these are mostly used now a days.

Future scope of the work:

The future scope of osmotic pumps is promising, with the market expected to grow from \$8.5 billion in 2024 to \$18.4 billion by 2034. These systems evaluate to grow in precision medicine, combination therapies, chronotherapy, improved bioavailability.

These advancements suggest a bright future for osmotic drug delivery systems, with the potential to revolutionize how medications are administered and improve patient care globally.

ACKNOWLEDGEMENT

We acknowledge faculty and staff of Dr.K.V. Subba Reddy Institute of Pharmacy, JNTUA, for their tremendous support.

REFERENCES

- [1] Verma, R.K., Mishra, B. and Garg, S., Osmotically controlled oral drug delivery, *Drug Dev. Ind. Pharm.*, 2000; 26: 695-708.
- [2] Jayendrakumar Patel, Shwetaben Patel, Major Obstacles in Technology Transfer of Nanomedicine from Conception to Commercialization, *International Journal of Pharmaceutical Research and Applications*, Volume 5, Issue 2, pp: 333-342.
- [3] Rao AA, Rao VN, Devi AS, Anil K, Naik VV, Rajesh A. Oral controlled release drug delivery system: an overview. *International Journal of Pharma and Chemical Research*. 2015;1(1):6-15.
- [4] Kaparissides C, Alexandridou S, Kotti K, Chaitidou S. Recent advances in novel drug delivery systems. *Journal of Nanotechnology online*. 2006 Mar; 2:1-1
- [5] Patel, J.; Parikh, S.; Patel, S. Comprehensive review on osmotic drug delivery system. *World J. Pharm. Res.* 2021, 10, 29.
- [6] Bruschi, M.L. *Strategies to Modify the Drug Release from Pharmaceutical Systems*; Woodhead Publishing: Sawston, UK, 2015.
- [7] Cheng L, Gao S, Ouyang D, Wang H, Wang Y, Pan W, Yang X. Release mechanism between ion osmotic pressure and drug release in ionic-

- driven osmotic pump tablets (I). AAPS Pharm SciTech. 2018 Feb; 19:803-11.
- [8] Siddique W, Zaman M, Sarfraz RM, Butt MH, Rehman AU, Fassih N, Albadrani GM, Bayram R, Alfaifi MY, Abdel-Daim MM. The Development of Eletriptan Hydrobromide Immediate Release Buccal Films Using Central Composite Rotatable Design: An In Vivo and In Vitro Approach. *Polymers*. 2022 Sep 23;14(19):3981.
- [9] Arafat, M. Approaches to achieve an oral controlled release drug delivery system using polymers: A recent review. *Int. J. Pharm. Pharm. Sci.* 2015, 7, 16–21.
- [10] Ratnaparkhi, M.; Gupta Jyoti, P.J.T. Sustained release oral drug delivery system—An overview. *Int. J. Pharm. Res.* 2013, 3, 10–22270.
- [11] Farooqi S, Yousuf RI, Shoaib MH, Ahmed K, Ansar S, Husain T. Quality by design based numerical and graphical optimization technique for the development of osmotic pump controlled-release metoclopramide HCl tablets. *Drug Design, Development and Therapy*. 2020 Nov 26:5217-34.
- [12] Swathi B, Mani Chandrika KP, Niharika R, Pravalika G, Sahithya D, Meghana M. Formulation and evaluation of quinidine osmotic drug delivery system. *Int. J. Adv. Res. Med. Pharm. Sci.* 2019; 4:17-22.
- [13] Hanif M, Zaman M, Chaurasiya V. Polymers used in buccal film: a review. *Designed Monomers and Polymers*. 2015 Feb 17;18(2):105-11.
- [14] Ghosh T, Ghosh A. Drug delivery through osmotic systems—an overview. *Journal of Applied Pharmaceutical Science*. 2011 Apr 30(Issue):38-49.
- [15] Sahoo CK, Rao SR, Sudhakar M. Evaluation of controlled porosity osmotic pump tablets: A Review. *Research Journal of Pharmacy and Technology*. 2015;8(12):1340-6.
- [16] Sharma A, Kumar D, Painuly N. A review on osmotically controlled drug delivery systems. *Asian Journal of Pharmaceutical Research and Development*. 2018 Aug 23;6(4):101-9.
- [17] Gundu R, Pekamwar S, Shelke S, Kulkarni D, Gadade D, Shep S. Development and pharmacokinetic evaluation of osmotically controlled drug delivery system of Valganciclovir HCl for potential application in the treatment of CMV retinitis. *Drug Delivery and Translational Research*. 2022 Nov;12(11):2708-29.
- [18] Syed SM. Osmotic Drug Delivery System: An Overview. *International journal of pharmaceutical research & Allied sciences*. 2015 Jul 1;4(3).
- [19] Santus G, Baker RW. Osmotic drug delivery: a review of the patent literature. *Journal of controlled release*. 1995 Jul 1;35(1):1-21.
- [20] Sareen R, Jain N, Kumar D. An insight to osmotic drug delivery. *Current drug delivery*. 2012 May 1;9(3):285-96.
- [21] Patil PB, Uphade KB, Saudagar RB. A REVIEW: OSMOTIC DRUG DELIVERY SYSTEM. *Pharma Science Monitor*. 2018 Apr 1;9(2).
- [22] Patel KN, Mehta TA. A review on oral osmotically driven systems. *Int. J. Pharm. Pharm. Sci.* 2013; 5:1005-13.
- [23] Sanap SL, Savkare AD. Controlled porosity osmotic pump: A review. *Int. J. Pharm. Res. Dev.* 2014 Feb; 5:70-80.
- [24] Babu CA, Rao MP, Ratna JV. Controlled-porosity osmotic pump tablets-an overview. *Asian Journal of Pharmaceutical Research and Health Care*. 2010;2(1):114-26.
- [25] Verma RK, Mishra BA, Garg S. Osmotically controlled oral drug delivery. *Drug development and industrial pharmacy*. 2000 Jan 1;26(7):695-708.
- [26] Udawant SV, Gondkar SB, Saudagar RB. A review: osmotic drug delivery system. *World Journal of Pharmaceutical Research*. 2015;4(3):1787-801.
- [27] Gupta SK, Kumar V, Singh S, Sharma D, Das BK. Next generation sequencing based forward genetic approaches for identification and mapping of causal mutations in crop plants: A comprehensive review. *Plants*. 2020 Oct 14;9(10):1355.
- [28] Sowjanya M, Rao CV, Srinivasa Babu P, Pallavi K. Osmotic drug delivery systems: a review. *Research Gate*. 2017.
- [29] Singla D, Hari Kumar S, Nirmala G. Osmotic pump drug delivery: A novel approach. *Int. J. Res. Pharm. Chem.* 2012; 2:661-70.
- [30] Okimoto K, Rajewski RA, Stella VJ. Release of testosterone from an osmotic pump tablet utilizing (SBE) 7m-β-cyclodextrin as both a solubilizing and an osmotic pump agent. *Journal of controlled release*. 1999 Mar 8;58(1):29-38.

- [32] Herrlich S, Spieth S, Messner S, Zengerle R. Osmotic micropumps for drug delivery. *Advanced drug delivery reviews*. 2012 Nov 1;64(14):1617-27.
- [33] Jerzewski RL, Chien YW. Osmotic drug delivery. IN *Treatise on controlled drug delivery* 2017 Oct 2 (pp. 225-253). CRC Press.
- [34] Banerjee A, Verma PR, Gore S. Controlled porosity solubility modulated osmotic pump tablets of Gliclazide. *AAPS Pharm SciTech*. 2015 Jun; 16:554-68.
- [35] Siew A. Controlling drug release through osmotic systems. *Pharmaceutical Technology*. 2013 Jul 2;37(7).
- [36] Kydonieus AF, editor. *Treatise on controlled drug delivery: fundamentals-optimization applications*. CRC Press; 2017 Oct 2.
- [37] Suman S, Chauhan M. Asymmetric Membrane Capsule: New Prospects in Osmotic Delivery. *International Journal of Drug Delivery*. 2011 Apr 1;3(2):185.
- [38] Gupta BP, Thakur N, Jain NP, Banweer J, Jain S. Osmotically controlled drug delivery system with associated drugs. *Journal of Pharmacy & Pharmaceutical Sciences*. 2010 Nov 20;13(4):571-88.
- [39] Jain NK, editor. *Controlled and novel drug delivery*. New Delhi: CBS publishers & distributors; 1997.
- [40] Sharma S. Osmotic controlled drug delivery system, *Pharma info. net*, 2008; 6: 3 [Internet].
- [41] Malaterre V, Ogorka J, Loggia N, Gurny R. Oral osmotically driven systems: 30 years of development and clinical use. *European Journal of Pharmaceutics and Biopharmaceutics*. 2009 Nov 1;73(3):311-23.
- [42] Sahoo CK, Sahoo NK, Rao SR, Sudhakar M, Satyanarayana K. A review on controlled porosity osmotic pump tablets and its evaluation. *Bulletin of Faculty of Pharmacy, Cairo University*. 2015 Dec 1;53(2):195-205.
- [43] Thakkar HP, Pancholi N, Patel CV. Development and evaluation of a once-daily controlled porosity osmotic pump of tapentadol hydrochloride. *AAPS PharmSciTech*. 2016 Oct; 17:1248-60.
- [44] Almoshari Y. Osmotic pump drug delivery systems—a comprehensive review. *Pharmaceutics*. 2022 Nov 18;15(11):1430.
- [45] Lindstedt B, Ragnarsson G, Hjærtstam J. Osmotic pumping as a release mechanism for membrane-coated drug formulations. *International Journal of Pharmaceutics*. 1989 Dec 1;56(3):261-8.
- [46] Keraliya RA, Patel C, Patel P, Keraliya V, Soni TG, Patel RC, Patel MM. Osmotic drug delivery system as a part of modified release dosage form. *International Scholarly Research Notices*. 2012;2012(1):528079.
- [47] Singh K, Walia MK, Agarwal G, Harikumar SL. Osmotic pump drug delivery system: a novel approach. *Journal of Drug Delivery and Therapeutics*. 2013 Sep 14;3(5):156-62.
- [48] McClelland GA, Sutton SC, Engle K, Zentner GM. The solubility-modulated osmotic pump: in vitro/in vivo release of diltiazem hydrochloride. *Pharmaceutical research*. 1991 Jan; 8:88-92.
- [49] Patel J, Parikh S, Patel S. Comprehensive review on osmotic drug delivery system. *World J. Pharm. Res*. 2021 Mar 1; 10:29.
- [50] Mathur M, Mishra R. A review on osmotic pump drug delivery system. *International journal of pharmaceutical sciences and research*. 2016 Feb 1;7(2):453.
- [51] Khatri N, Nikam S, Bilandi A. Oral osmotic drug delivery system: a review. *International Journal of Pharmaceutical sciences and research*. 2016 Jun 1;7(6):2302.
- [52] Gohel MC, Parikh RK, Shah NY. Osmotic drug delivery: an update. *World J. Pharm. Res*. 2009; 7:1-7.
- [53] Chourasia PK, Sheeba FR, Pardhe HA, Lodh H. A comprehensive review on osmotic controlled drug delivery system. *Am J PharmTech Res*. 2020; 10:92-113.
- [54] Palanichamy S, Rajesh M, Sherly D, Solairaj P. Osmotic Drug Delivery Systems-A Review. *International journal of universal pharmacy and bio sciences*. 2015;4(1):250-67.