Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

A Review on Key Parameters and Components in Designing of Osmotic Controlled Oral Drug Delivery Systems

NB KHAVARE[1], FATIMA S DASANKOPPA*[1], NG NAJUNDASWAMY[2]

[1] Department of Pharmaceutics, K.L.E.S College of Pharmacy, Vidyanagar, Hubli, 580 031, INDIA

[2] Department of Pharmaceutics, Government College of Pharmacy, Subbaih circle, Bangalore, INDIA

ARTICLE DETAILS

Article history:
Received on 12 November 2010
Modified on 28 November 2010
Accepted on 12 December 2010

Keywords:
Osmotically controlled oral drug delivery systems,
Osmosis,
Release kinetics,
Formulation factors

ABSTRACT

During the past three decades significant advances have been made in the area of controlled drug delivery. In a typical therapeutic regimen, the drug dose and the dosing interval are optimized to maintain drug concentration within therapeutic window, thus ensuring efficacy while minimizing toxic side effects. Surveys indicated that dosing more than once or twice daily greatly reduces patient compliance. Hence, the primary objective for controlled drug release is to deliver a pharmacologically active agent in a predetermined, predictable and reproducible manner. Numerous technologies have been used to control the systemic delivery of drugs. One of the most interesting systems employs osmotic pressure as a source of energy. Drug delivery from osmotically controlled oral drug delivery systems (OCODDS), to a large extent, is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug(s) from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane. By optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of diverse nature at a pre-programmed rate. In the present review, various types of osmotically controlled oral drug delivery systems, osmosis and mechanism of osmotic controlled release, release kinetics, key parameters that influence the design of osmotic controlled drug delivery systems and critical formulation factors are discussed.

INTRODUCTION

Oral route of administration is one of the oldest and most extensively used routes for the administration of drug providing convenient method of effectively achieving both local and systemic effect. In conventional oral drug delivery systems, there is little or no control over release of the drug and effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. This kind of dosing pattern result is constantly changing, unpredictable and sub or supra therapeutic plasma concentrations, leading to marked side effects in some cases.

Author for Correspondence:
Email: sanjeri@yahoo.co.uk

Moreover, the rate and extent of absorption of drug from conventional formulations may very greatly depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility and so on. Uncontrolled rapid release of drug may also cause local gastro intestinal or systemic toxicity. Hence better dosage form design and delivery can minimize many of these problems. Various approaches are made in designing the formulations, which will overcome the disadvantages of conventional dosage forms, which include sustained/controlled drug delivery system. There are three main categories of controlled-release drug delivery system; intravenous, transdermal, and oral systems. Oral osmotically controlled release (CR) delivery system provide a uniform concentration/amount of drug at the site of absorption and thus after

absorption, allow maintenance of plasma concentration within therapeutic range, which minimizes side effects and also reduces the frequency of administration. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system[1-5]. In present review is an update on the osmosis and mechanism of osmotic controlled release, release kinetics, key parameters that influence the design of osmotic controlled drug delivery systems and critical formulation factors that are important in the development of osmotically controlled oral drug delivery systems

KINETICS AND MECHANISM OF OSMOTIC CONTROLLED RELEASE

Osmosis can be defined as 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 and impermeable to solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called osmotic pressure[6].

Osmotic pressure is a colligative property that depends on the concentration of solute (neutral molecule or ionic species). Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water, can be achieved by an osmotic drug delivery system that results in a constant release rate of drug. Therefore, zero-order release, which is important for a controlled release delivery system when indicated, is possible to achieve using these platforms[7]. In 1974, Theeuwes and Higuchi[8]applied the principle of osmotic pressure to a new generation of controlled drug delivery devices with many advantages over other existing controlled drug delivery systems. The first of these devices (Table 1), the elementary osmotic pump, is considered a typical delivery system that operates on osmotic principles.

Release Kinetics:

The osmotic drug delivery system consists of an osmotic core containing drug and as necessary, an osmogen surrounded by a semipermeable membrane with or without an aperture. The rate of delivery generally follows the zero order kinetics and declines after the solution concentration falls below saturation. The solute delivery rate from the system is controlled by solvent influx through the semipermeable membrane[9].

KEY PARAMETERS THAT INFLUENCE THE DESIGN OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

1. Orifice size:

To achieve an optimal zero-order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size S_{max} to minimum drug delivery by diffusion through orifice. Furthermore, the area must be sufficiently large, above a minimum size S_{min}, to minimize the hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross sectional area of the orifice S_o should be maintained between minimum and maximum values. Typically, a diameter of about 0.2 mm through a membrane thickness of 0.2 mm thickness is needed to maintain a delivery rate on the order of 10 mg/h for water soluble compounds[10]. The minimum cross sectional area can be estimated from the following equation:

$$S_{\min} = 5\left[\left(\frac{L}{P_{\max}}\right)\mu\left(\frac{dV}{dt}\right)\right]^{1/2}$$

Where,

dV/dt = volume of flux through an orifice

L = length of the orifice (usually the same as thickness of the membrane)

μ = viscosity of the drug solution flowing through the orifice

P_{max} = maximum tolerated hydrostatic pressure difference across the membrane before occurrence of deformation of the housing

The maximum cross sectional area of the orifice is obtained by specifying that the release rate must be smaller than a fraction *f* of the zero order pumping rates and is defined by following equation:

$$S_{\max} = \frac{M_{tz} fL}{D_s C_s}$$

Where M_{tz} is the amount of the drug delivered in zero order fashion, and Ds is the drug diffusion coefficient in the permeating solvent.

Table 1: Types of Osmotically Controlled Oral Drug Delivery Systems [5]

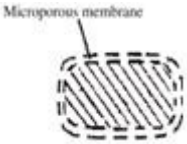
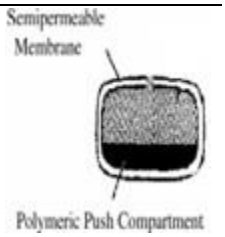
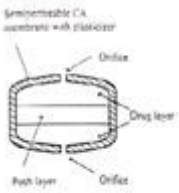
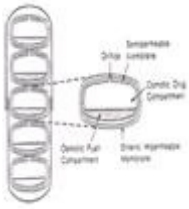
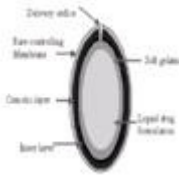
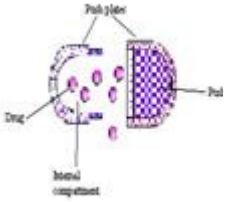
Osmotic System	Design of Dosage Form	Mechanism	Applications	Figures
Oral osmotic tablets				
Single chamber osmotic pumps				
Elementary Osmotic Pump (EOP)	**Core:** API ± osmogents **Coat:** Semi permeable membrane with delivery orifice	The water penetrates inside the dosage form at the rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation. This will result in formation of saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane.	Moderately soluble API 60-80% constant release	
Controlled-porosity osmotic pump (CPOP)	**Core:** API ± osmogents **Coat:** Semi permeable membrane with water soluble additives	Water-soluble additives dissolve after coming in contact with water, resulting in an in situ formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release was found to be osmotic.	Overcome the need for complicated and expensive laser drilling.	
Osmotic bursting osmotic pump	**Core:** API ± osmogents **Coat:** Semi permeable membrane without delivery orifice	When placed in aqueous environment, water is imbibed and hydraulic pressure is built up inside the system, then wall ruptures and the contents are released.	For pulsated release	
Multi-chamber osmotic pumps				
Push-pull osmotic pump (PPOP)	**Core Tablet:** Layer 1: API ± osmogent Layer 2: Polymeric osmotic agents **Coat:** Semi permeable membrane with delivery orifice	After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, and thus releasing drug in the form of fine dispersion via the orifice.	For delivery of APIs having extremes of water solubility Modifications can be done: delayed push-pull, multi-layer push-pull, push-stick system	
Sandwiched Osmotic tablets (SOTS)	**Core tablet:** 3 layers Middle layer: push layer 2 attached layers: API **Coat:** Semi permeable membrane with **two side** delivery orifice	The middle push layer swells and drug is released from delivery orifices.	API release from two sides of tablets.	
Oral osmotic capsules				
OROS-CT	Single osmotic unit or a unit containing as many as five to six PPOP filled in hard gelatin capsule. The osmotic system is enteric coated.	Gelatin capsule shell dissolves after coming in contact with GI fluids. Enteric coating on the system prevents entry of fluid from stomach to the system and it dissolves after entering into intestine. The water imbibes into the core and push compartment will swell. At the same time, the flowable gel is formed which is pushed out via delivery orifice at predetermined rate.	For colon-targeting and can be used as local or systemic therapy.	

Table 1: ***continued***

L-OROS (Soft-Cap & Hard-Cap)	Liquid API formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate-controlling membrane. A delivery orifice is formed through these three layers.	When the system comes in contact with 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 break through the hydrated gelatin capsule shell at the delivery orifice.	To deliver APIs as liquid formulations and combine the benefits of extended release with high bioavailability. Suitable for controlled delivery of lipophilic APIs	
Pelleted delayed release	Multi-particulate delayed release systems consist of pellets of API (with or without osmogents) coated with SPM.	Rapid expansion of membrane after coming in contact with aqueous environment resulting in pore-formation and API release	High flux rates and thus having higher release rates for poorly water-soluble APIs	
Asymmetric membrane capsule	Capsule wall made up of water insoluble semipermeable polymer	Imbibition of water through the capsule wall and dissolving soluble components within it and releasing from same wall	High water permeability and controlled porosity	
Telescopic capsule for delayed release	This device consists of two chambers, the first contains the drug and an exit port, and the second contains osmotic engine. Layer of wax-like material separates the two sections.	As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections.		

In practice, a fraction smaller than 0.025 generally is necessary to minimize diffusional contributions[11]. Some methods to create a delivery orifice in osmotic tablet coating are use of mechanical drill[12], laser drilling[13], use of an apparatus with slidable punches[14], indentation that is not covered in coating process[15] and use of leachable substances in the coating[16].

2. Solubility:

The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation [17,18]:

$$F(z)=1- S/\rho$$

where $F(z)$ is the fraction released by zero-order kinetics, S is the drug's solubility (g / cm^3), and ρ is the density (g / cm^3) of the core tablet. Drugs with a solubility of ≤ 0.05 g / cm would be released with ≥ 95% zero-order kinetics according to above equation. However, the zero-order release rate would be slow, due to the small osmotic pressure gradient. Conversely, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core, and thus, extend this technology for delivery of drugs that might otherwise have been poor candidates for osmotic delivery. Some of the approaches that have been used to deliver drugs having extremes of solubility are:

- *Use of wicking agents:* These agents may enhance the surface area of drug with the incoming aqueous fluids. E.g. colloidal silicon dioxide, sodium lauryl sulfate, etc. Ensotrol®

technology uses the same principle to deliver drugs via osmotic mechanism [5].

- *Resin Modulation approach:* Ion-exchange resin methods are commonly used to modify the solubility of drugs[18]. Some of the resins used in osmotic systems are Poly (4-vinyl pyridine), Pentaerythritol, citric and adipic acids.
- *Use of swellable polymers:* Polymers such as vinyl acetate copolymer, polyethylene oxide have uniform swelling rate which causes drug release at constant rate [19].
- *Use of effervescent mixtures:* Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate[20].
- *Use of cyclodextrin derivatives:* They are known to increase solubility of poorly soluble drugs[21]. The same phenomenon can also be used for the osmotic systems.
- *Use of alternative salt form:* Change in salt form of drug may change solubility, as was reported for oxprenolol[22]. It was found that hydrochloride salt of oxprenolol was too soluble to maintain a saturated solution and hence zero order delivery for the anticipated delivery life of dosage form. Subsequently succinate salt was found to have optimum solubility, and osmotic pump was formulated with this salt form that give extended release up to 24 h.
- *Use of encapsulated excipients:* Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane[23].
- *Use of crystal habit modifiers:* Different crystal form of the drug may have different solubility[24], so the excipients which may change crystal habit of the drug can be used to modulate solubility.
- *Co-compression of drug with excipients:* Different excipients can be used to modulate the solubility of drugs with different mechanisms like saturation solubility, pH dependent solubility[25]. Examples of such excipients are organic acids, buffering agent, etc.

3. Osmotic Pressure:

To achieve a zero-order release rate, it is essential to keep constant osmotic pressure by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acidic media[15].

4. Semipermeable membrane:

Since 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[22]. The materials used for the preparation of the membrane are described in next section.

COMPONENTS OF OSMOTIC SYSTEMS

Osmotic components:

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Polymeric osmogents are mainly used in the fabrication of osmotically controlled drug delivery systems and other modified devices for controlled release of relatively insoluble drugs. Osmotic pressures for concentrated solution of soluble solutes commonly used in controlled release formulations are extremely high, ranging from 28 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture. These osmotic pressures can produce high water flows across semi permeable membranes. The osmotic water flow across a membrane is given by the equation,

$$dv/dt = A P \pi / l$$

Where dv/dt, is the rate of water flow across the membrane of area A, thickness *l*, permeability P, π is constant osmotic pressure[4].

Osmogents used for fabrication of osmotic dispensing device are agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents. A water soluble drug by it self can serve the purpose of an osmogent. Table 2 displays list of osmogens commonly used in preparation of osmotic pumps.

Hydrophilic polymers encompass osmopolymers, osmogels or hydrogels. These materials maintain a concentration gradient across the membrane. They also

generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Swellable polymers such as poly(alkylene oxide), poly(ethylene oxide), and poly (alkalicar- boxymethylcellulose) are also included in the push layer of certain osmotic systems.

TABLE 2: List Of Osmogens Commonly Used In Preparation Of Osmotic Pumps[26]

Compound or mixture	Osmotic pressure
Lactose-fructose	500
Dextrose-fructose	450
Sucrose-fructose	430
Mannitol-fructose	415
Sodium chloride	356
Fructose	335
Lactose-sucrose	250
Potassium chloride	245
Lactose-dextrose	225
Mannitol-dextrose	225
Dextrose-sucrose	190
Mannitol-sucrose	170
Sucrose	150
Mannitol-lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic.12 H_20	36
Sodium phosphate dibasic. 7 H_20	31
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic. H_20	28

Further, hydrogels such as Carbopol (acidic carboxy- polymer), Cyanamer (polyacrylamides) and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used[27]. These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The highly soluble drug can be co-entrapped in hydrophobic matrices and moderately water soluble drugs can be co-entrapped with hydrophilic matrices to obtain controlled release. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the osmotic pump.

Semipermeable membrane–forming polymers for osmotic pumps:

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery[28].Numerous polymers are currently available to form semipermeable membranes. One class includes cellulosic polymers such as cellulose ethers, cellulose esters and cellulose ester-ethers. The cellulosic polymers have a degree of substitution (DS) of 0 to 3 on the anhydroglucose unit. The DS is the number of hydroxyl groups present on the anhydroglucose unit being replaced by a substituting group. Examples of this group include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and mono-, di-, and tricellulose alkanylates. Cellulose acetate is available in different grades, such as cellulose acetate having a DS of 1 to 2 and an acetyl content of 21 to 35 % or cellulose acetate having an acetyl content of 32 to 39.8 %. Other forms of cellulose polymers with a more specific substitution are cellulose propionate with a DS of 1.8, a propyl content of 39.2 to 45 % and a hydroxyl content of 2.8 to 5.4 % or cellulose acetate butyrate with a DS of 1.8, an acetyl content of 13 to 15 % and a butyrate content of 34 to 39 %. Moreover, the semipermeable membrane may consist of a mixture of cellulose acetates, alkanylates, or acrylates with different degrees of substitution. Generally, in osmotic pumps, the semipermeable must be 200-300 µm thick to withstand the pressure within the device[15].

Additional semipermeable membrane–forming polymers are selected from the group consisting of acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose dimethylamino acetate, semipermeable polyamides, semipermeable polyurethanes, or semipermeable sulfonated polystyrenes. Semipermeable cross-linked selectively permeable polymers formed by co-precipitation of a polyanion and a polycation also can be used for this purpose[29]. Other polymer materials such as lightly cross-linked polystyrene derivatives, semipermeable cross-linked

poly(sodium styrene sulfonate), and semipermeable poly(vinylbenzyltrimethyl ammonium chloride) may be considered[30].

The osmotic water flow across a membrane is given by Equation 6 in terms of membrane performance and predictability, it is important to select a material whose reflection coefficient is close to 1. Water permeabilities of membranes can vary over a wide range, but most osmotic devices generally use relatively water permeable materials. Table 3 gives a list various semipermeable membranes.

Table 3: List of Semipermeable Membrane With Their Water Vapor Transmission Rate (Wvtr)[2,3]

Polymer Membrane	WVTR (g/100 m^2/24h/mm thick)
Polyvinyl alcohol	100
Polyurethane	30-150
Methyl cellulose	70
Cellulose acetate	40-75
Ethyl cellulose	75
Cellulose acetate butyrate	50
Poly vinyl chloride (cast)	10-20
Polyvinyl chloride (extruded)	6-15

The membrane must meet several performance criteria which includes following[2]:

- The material must possess sufficient wet strength and wet modulus so as to retain its dimensional integrity during the operational life of the device.
- The polymer membrane must exhibit sufficient water permeability so as to attain water flux rate in the desired range.
- The reflection coefficient, "leakiness" of the membrane to the osmotic agent, should approach the limiting value of 1.
- The membrane should be biocompatible.

Coating solvents:

Solvents suitable for making polymeric solutions that is used for manufacturing the wall of osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water, etc. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) can be used[2,3].

Emulsifying agents:

These are particularly useful when added to wall forming material. They produce an integral composite that is useful for making the wall of the device operative. They act by regulating the surface energy of materials to improve their blending in to the composite and maintain their integrity in the environment of use during the drug release period. Some patented technologies invoke self-emulsifying agents to deliver liquids from osmotic delivery systems. Typical surfactants such as poly oxy ethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laureates, glycerol (sorbiton oleate, stearate or laurate), etc have been used to serve the purpose[6,27].

Flux-regulating agents:

Flux regulating or flux enhancing agent or flux decreasing agents are added to the wall forming materials. It assists in regulating the fluid permeability of flux through wall. This agent can be pre-selected to increase or decrease the liquid flux. They also increase the flexibility and porosity of lamina. 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 ethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose[27].

Wicking agents:

A wicking agent is a type of material with the ability to draw water in to the porous network of a delivery device. A wicking agent is of either swellable or non swellable nature. They are characterized by having the ability to undergo physisorption with water. Physisorption is the form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via vander waal's interactions between the surface of the wicking agent and the absorbed molecule. The function of the wicking agent is to carry water to the surfaces inside the core of the tablet thereby creating channels or a network of increased surface area. For bioactive agents with low solubility in water, the wicking

agent aids in the delivery of partially solubilized bioactive agent through the passageway in the semipermeable coating. Materials, which suitably act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulfate, low molecular weight poly (vinylpyrrolidone) (PVP), m-pyrol, bentonite[31,32].

Plasticizers:

Plasticizers lower the temperature of the second order phase transition of the wall or the elastic modulus of the wall and also increase the workability, flexibility and permeability of the fluids. Generally from 0.001 to 50 parts of a plasticizer or mixture of plasticizers are incorporated in to 100 parts of wall forming materials. Suitable solvents should have high degree of solvent power for materials, compatible with the materials over both the processing and the temperature range, exhibit permanence as seen by their strong tendency to remain in the plasticized wall, impart flexibility to the materials and should be non toxic. Exemplary plasticizers include phthalates (dibenzyl, dihexyl, or butyl octyl), triacetin, epoxidized tallate, or tri-isoctyl trimellitate, alkyl adipates, citrates, acetates, propionates, glycolates, myristates, benzoates and halogenated phenyls. In the design of osmotic controlled release systems, these plasticizers help to modulate and achieve the required release rate[6,31,33].

Pore forming agents:

These agents are particularly used in the pumps developed for poorly water soluble drugs and in the development of controlled porosity or multi particulate osmotic pumps. These pore forming agents cause the formation of microporous membrane. The microporous wall may be formed in-situ by a pore former by its leaching during the operation of the system. The pores may also be formed in the wall prior to operation of the system by gas formation within the coating polymer solutions which results in void pores in the final form of the wall. The pore formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, diols and polyols can be used as pore forming agents.

Pores may also be formed in the wall by the volatilization of components in a polymer solution or by chemical reactions in a polymer solution which evolves gases prior to application or during the application of the solution to the core mass resulting in the creation of polymer foams serving as the porous wall. The pore formers should be non-toxic and on removal, channels should be formed. The channels become a transport path for fluid[31,33].

Barrier layer formers:

To restrict water entry into certain parts of the delivery system and to separate the drug layer from the osmotic layer, different materials are used as barrier layers. In a multilayered reservoir, the water-permeable coat consists of hydrophilic polymers. In contrast, water-impermeable layers are formed from latex materials such polymethacrylates. Further, a barrier layer can be provided between the osmotic composition and the drug layer that consists of substantially fluid-impermeable materials such as high-density polyethylene, a wax, a rubber, and the like[34].

CONCLUSION:

Drug delivery from osmotically controlled oral drug delivery systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract. The release of drug(s) from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane. By understanding of kinetics and release pattern of osmotically controlled oral drug delivery systems and optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of controlled and targeted nature at a zero order rate.

REFERENCES:

[1] Parmar NS, Vyas SK, Vaya N. Osmotic Pump-A Novel Drug Delivery System. In: Jain NK, Editors. Advances in Controlled and Novel Drug Delivery Systems. New Delhi: CBS Publishers and Distributors; 2004. 18-37.

[2] Jerzewski RL, Chein YW. Osmotic Drug Delivery. In: Kydonieus A, Editors. Treatise on Controlled Drug Delivery: Fundamentals, Optimization and

Applications. New York: Marcel Dekker Inc.; 1992. 225-253.

[3] Chiao CSL, Robinson JR. Sustained and Controlled-Release Drug Delivery Systems, 19th Ed. Philadelphia: Mark Publishing Company; 1995.

[4] Sharma S, Osmotic controlled drug delivery system. Pharmaceutical Reviews 2008; 6(3). Available at www.pharmainfo.net

[5] Gohel MC, Parikh RK, Shah NY. Osmotic Drug Delivery – An Update. Pharmaceutical Reviews 2009; 7 (2). Available at www.pharmainfo.net

[6] Martin A, Bustamante P, Chun AHC. Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences, 4th Ed. Philadelphia: Lea and Febiger; 1993.

[7] Banakar UV. Drug delivery systems of the 90s: Innovations in controlled release. Am. Pharm 1987; NS 27(2): 39–42, 47–48.

[8] Theeuwes F, Higuchi T, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Osmotic dispensing device for releasing beneficial agent. US patent 3 845 770. 1974 Nov 5.

[9] Laxminarayanaiah N. Transport Phenomena in Membranes. New York: Academic Press; 1969. 247–248.

[10] Good WR, Lee PI. Membrane-controlled reservoir drug delivery systems. In: Langer RS, Wise DL. Medical Applications of Controlled Release. Vol 1, Boca Raton: CRC Press; 1984. 1–39.

[11] Theeuwes F, Higuchi T, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Osmotic dispensing device with maximum and minimum sizes for the passageway. US patent 3 916 899. 1975 Nov 4.

[12] Ozdemir N, Sahin J. Design of controlled release osmotic pump system of ibuprofen. Int J Pharm 1997; 158(1): 91-97.

[13] Theeuwes F, Saunders RJ, Mefford WS, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Process for forming outlet passageways in pills using a laser. US patent 4 088 864. 1978 May 9.

[14] Ayer AD, Balkie HH, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Method and apparatus for forming a hole in a drug dispensing device. US patent 5 071 607. 1991 Dec 10.

[15] Santus G, Baker RW. Osmotic drug delivery: A review of the patent literature. J Control Release 1995; 35(1):1–21.

[16] Zentner GM, Rork GS, Himmelstein KJ. The controlled porosity osmotic pump. J Control Release 1985; 1(4): 269-282.

[17] McClelland GA, Sutton SC, Engle K, Zenter GM. The solubility modulated osmotic pump: Invitro/ Invivo release of diltiazem hydrochloride. Pharm Res 1991; 8(1): 88-92.

[18] Zentner GM, McClelland GA, Sutton SC. Controlled porosity solubility and resin modulated osmotic drug delivery systems for release of diltiazem hydrochloride. J Control Release 1991; 16(1-2): 237-244.

[19] Khanna SC, Inventor; Ciba-Geigy Corporation, Ardsley, NY, Assignee. Therapeutic system for sparingly soluble active ingredients. US patent 4 992 278. 1999 Feb 12.

[20] Theeuwes F, Inventor; ALZA Corporation, Palo Alto, CA, Assignee. Osmotic dispenser with gas generating means. US patent 4 036 228. 1977 Jul 19.

[21] Okimoto K, Miyake M, Ohnishi N, et al. Design and evaluation of an osmotic pump tablet for prednisolone usng (SBE)-7m-ß-CD. Pharm Res 1998; 15: 1562-1568.

[22] Theeuwes F, Swanson DR, Guittard G, et al. Osmotic delivery systems for the beta-adrenoceptor antagonists metoprolol and oxprenolol: Design and evaluation of systems for once-daily administration. Br J Clin Pharmacol 1985; 19 (suppl 2):69S–76S.

[23] Thombre AG, DeNoto AR, Gibbes DG. Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. J Control Release 1999; 60: 333-341.

[24] Koparkar AD, ShahSB, Inventors; Ciba-Geigy Corporation, Ardsley, NY, Assignee. Oral osmotic system for slightly soluble active agents. US patent 5 284 662. 1994 Feb 8.

[25] Swanson D, Edgren D, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Osmotic device that improves delivery properties of agent in situ. US patent 4326525. 1982 Apr 27.

[26] Zenter GM, Rork GS, Himmelstein KJ, Inventors; Merck & Co, Inc, Assignee. Controlled porosity osmotic pump. US patent 4 968 507. 1990 Nov 6.

[27] Wong PSL, Edgen DE, Dong LC, Dove Cp, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Controlled release liquid active

agent formulation dosage forms. US patent 6 596 314. 2003 Jul 22.

[28] Eckenhoff B, Theeuwes F, Urquhart J. Osmotically actuated dosage forms for rate-controlled drug delivery. Pharm Technol 1987; 11:96–105.

[29] Dong LC, Dealey MH, Burkoth TL, et al, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Process for lessening irritation caused by drug. US patent 5 254 349. 1993 Oct 19.

[30] Loeb S, Sourirajan S, Inventors; The Regents of University of California, Berkeley, CA, Assignee. High flow porous membranes for separating water from saline solution. US patent 3 133 132. 1964 May 12.

[31] Verma RK, Krishna DM, Garg S, Formulation aspects in the development of osmotically controlled oral drug delivery systems. Journal of Controlled Release 2002; 79:7–27.

[32] Rudnic E M, Burnside B.A., Flanner H.H., Wassink S.E.,Couch R.A., Pinkett J.E., Osmotic drug delivery system.US patent 6 110 498, 2000 Aug. 29.

[33] Babu CA, Rao MP, Ratna V, Controlled-porosity osmotic pump tablets- an overview. JPRHC 2010 January; 2(1):114-26.

[34] Dong LC, Espinal S, Wong PSL, Inventors; ALZA Corporation, Mountain View, CA, Assignee. Dosage form comprising liquid formulation. US patent 6 174 547. 2001 Jan 16.