DEVELOPMENT OF CONTROLLED POROSITY OSMOTIC PUMP OF METOPROLOL SUCCINATE: DESIGN, OPTIMIZATION AND CHARACTERIZATION

A Thesis Submitted To

NIRMA UNIVERSITY

In Partial Fulfillment of The Requirements For The Degree Of

MASTER OF PHARMACY
IN
PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS

BY

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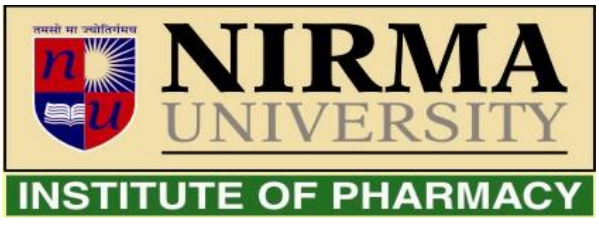

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CERTIFICATE

This is to certify that the Dissertation Work Entitled "Development of Controlled Porosity Osmotic Pump of Metoprolol Succinate: Design, Optimization and Characterization" Submitted By Ms. Mahima Mathur with Regn. No. (11MPH107) in Partial Fulfillment for the Award of Master of Pharmacy in "Pharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute Of Pharmacy, Nirma University under our guidance. This work is original and has not been submitted in part or full for any other Degree or Diploma to this or any other University or Institution.

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DECLARATION

I hereby declare that the Dissertation entitled "Development Of Controlled Porosity Osmotic Pump of Metoprolol Succinate: Design, Optimization And Characterization", is based on the original work carried out by me under the guidance of Dr. Renuka D. Mishra, Assistant Professor, Department of Pharmaceutics, Institute of Pharmacy, Nirma University and Dr. Vipan Dhall, Vice-President & Head, Piramal Pharmaceutical Develpoment Services Limited, Ahmedabad. I also affirm that this work is original and has not been submitted in part or full for any other Degree Or Diploma to this or any other University Or Institution.

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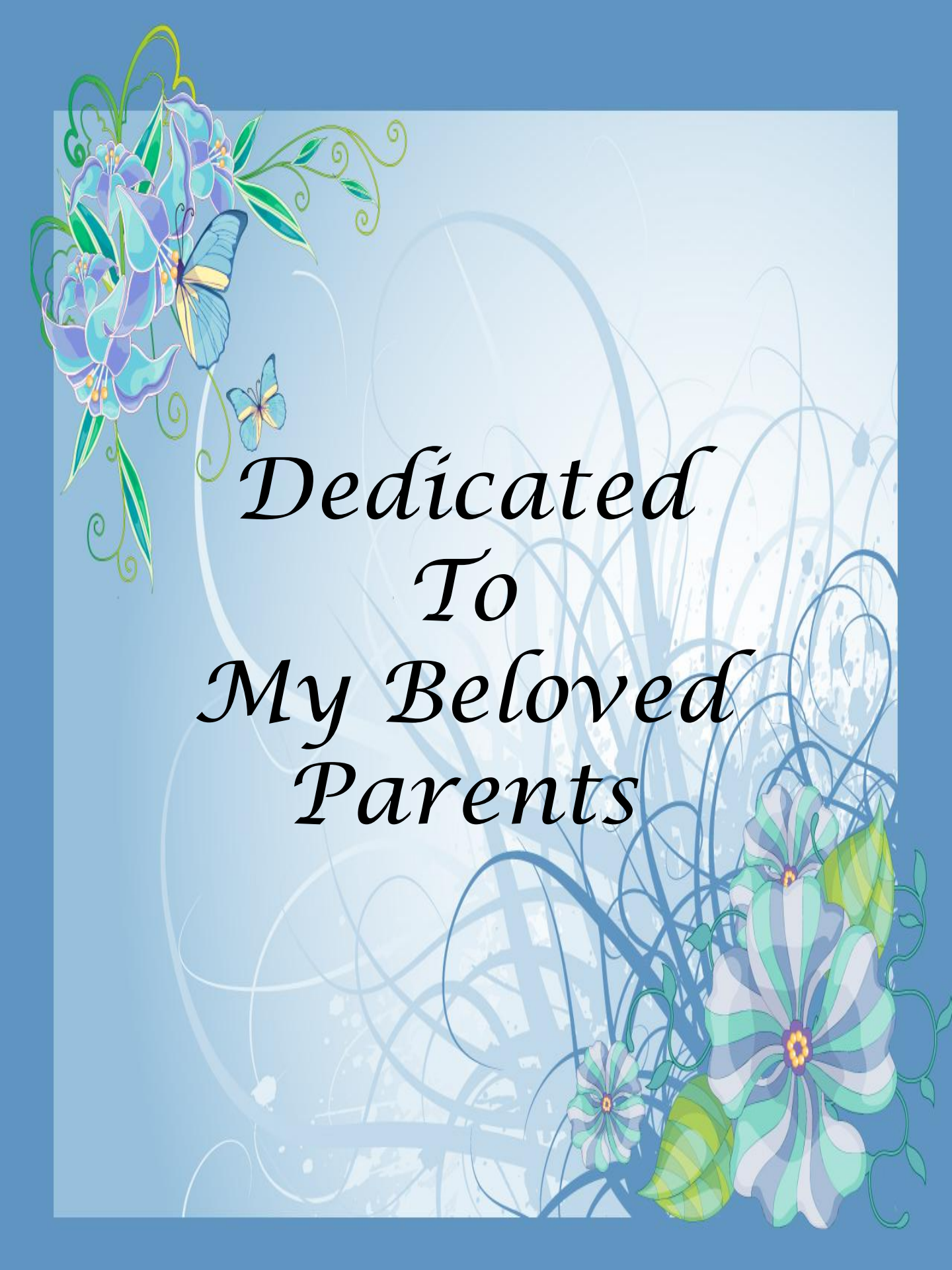
Dedicated
To
My Beloved
Parents

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Date: *Mahima Mathur*

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List of Abbreviations

Abbreviation	Full Form
IP	Indian Pharmacopoeia
BP	British Pharmacopoeia
USP	United States Pharmacopoeia
PhEur	European Pharmacopoeia
OCDDS	Osmotically Controlled Drug Delivery System
NDDS	Novel Drug Delivery System
CPOP	Controlled Porosity Osmotic Pump
Conc.	Concentration
RH	Relative Humidity
USPNF	United States Pharmacopoeia National Formulary
FTIR	Fourier Transfer Infra Red
UV	Ultra Violet
CA	Cellulose acetate
NaCl	Sodium chloride
IP-QC	In-Process Quality Control
KCl	Potassium chloride
PEG-4000	Poly Ethylene Glycol 4000
GI	Gastro Intestinal
EOP	Elementary Osmotic Pump
PPOP	Push-Pull Osmotic Pump
L-OROS	Liquid Oral Osmotic Pump
SOTS	Sandwiched Osmotic Tablets
OROS-CT	Colon Targeted Oral Osmotic System
OSMAT	Osmotic Matrix Tablet
KBr	Potassium Bromide
°C	Degree centigrade
CPR	Cumulative Percentage Release
avg.	Average
hr	Hour
min	Minute
w/w	Weight by weight
w/v	Weight by volume
atm	Atmospheric pressure

Development of Controlled Porosity Osmotic Pump of Metoprolol Succinate: Design, Optimization and Characterization

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Controlled porosity osmotic pump (CPOP) drug delivery system is a dosage form which follows a zero order release and provide a controlled release for a long duration and makes it one of the most promising drug delivery systems in the recent times.

In this study, a cardioselective β1-adrenergic blocking agent, Metoprolol Succinate is used as the drug of choice for the formulation, development and evaluation of the CPOP using two different osmogens viz. Sodium Chloride and Potassium Chloride, at three different ratios and three different concentrations of cellulose acetate coating as the semi permeable agent. Polyethylene Glycol 4000 was used as a plasticizer and Sorbitol was used as a pore forming agent. Drug release profile of the batches and burst strength of the exhausted shells were evaluated for the optimization of the formulations and these optimized formulations were studied for the effect of pH, agitational intensity and osmotic pressure. A comparative study between various osmogens was also done. The drug release profiles of all the batches were compared with marketed product-Seloken. A 3^2 Full Factorial Design using Statistica Software version 9.0 was applied on the batches to get the optimized result. Dissolution data of optimized formulation was fitted to various mathematical models to describe kinetics of drug release.

Chapter 1

AIM OF PRESENT INVESTIGATION

1. AIM OF PRESENT INVESTIGATION

Oral drug delivery has been extensively used for both local and systemic effect. Conventional drug delivery involves the formulation of the drug into a suitable form, such as compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dosage required, higher frequency of administration, uncontrolled release of drug, lower effectiveness, toxicity and adverse effects. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems. They are known as controlled drug release systems and targeted drug delivery systems. Controlled release drug delivery system attempts to control the drug concentration in the blood at relatively constant and effective levels in the body by spatial placement or temporal delivery. Thus, controlled release drug delivery system offer various advantages *viz.* reduce blood level fluctuations, minimize drug accumulation, employs less amount of total drug, improved patient compliance and minimized local and systemic side effects.

A significant milestone in oral Novel Drug Delivery System is the development of the osmotic drug delivery system. Osmotic drug delivery system utilizes the principle of osmotic pressure, as the prime mechanism, for the delivery of water soluble as well as water insoluble drugs. Oral osmotic drug delivery systems with their versatility and highly predictable drug release rates offer various advantages. The drug delivered from these systems is independent of pH and the physiological conditions. Semipermeable membrane and osmotic agents can modulate drug release from this system.

Metoprolol Succinate, a cardio selective β1-adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches. The average terminal half-life of Metoprolol Succinate is 3 to 7 hours. The standard formulation undergoes rapid absorption and extensive hepatic biotransformation. These factors necessitate the development of an alternative formulation of Metoprolol Succinate in order to reduce the frequency of daily

dosing and improve the patient compliance. As Controlled Porosity Osmotic Pump has a zero order drug release, the effect of the drug remains in the therapeutic range for the maximum period of time, as a result of which the side effects reduces and the patient compliance is increased.

The aim of the present work is to develop a controlled osmotic porosity pump formulation of Metoprolol Succinate which provides zero order drug release up to 24 hours and thereby helpful in chronic hypertensive conditions.

An attempt has been made to design, develop and characterize Osmotically Controlled Drug Delivery formulation of Metoprolol Succinate. A 3^2 full factorial design will also be utilized to optimize systematically the formulation & process parameters influencing drug release. The optimized formulation was selected based on the duration of the drug release profile and also on the pattern of drug release. Effects of the various important parameters of these optimized batches were also evaluated.

Chapter 2

INTRODUCTION

2. Introduction:

2.1. Introduction to Controlled Drug Delivery Systems [1, 2]:

Controlled drug delivery system delivers the drug at a controlled rate and follows a particular pattern of its release, which helps in minimizing the limitations of conventional drug delivery system. Unlike the conventional dosage forms, controlled drug delivery systems have 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 results is a constant and predictable drug release leading to minimal side effects of the drug. The rate and extent of controlled drug delivery systems are independent of the various 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 etc.

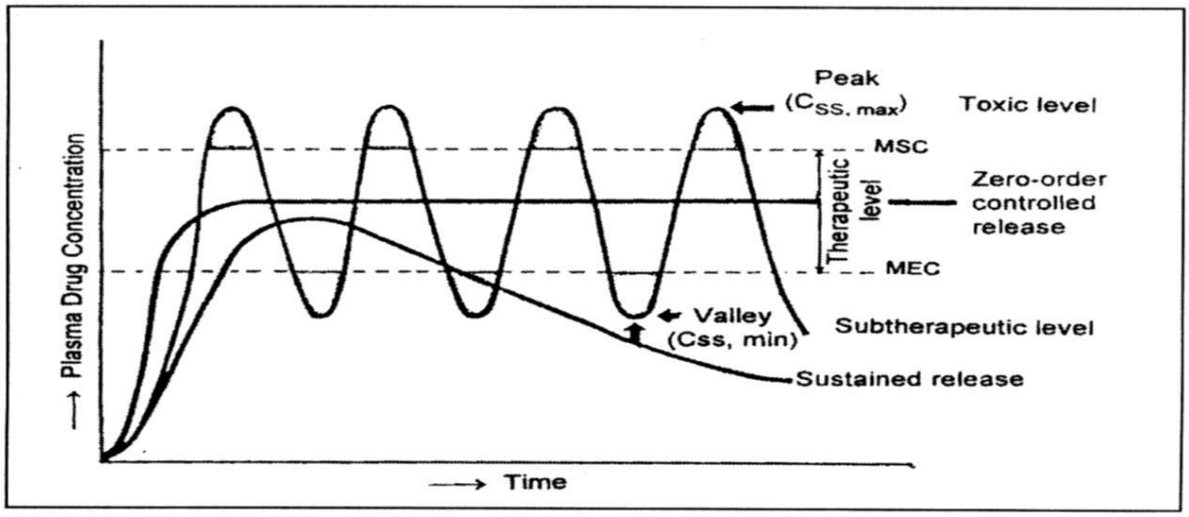

Figure2.1: Plasma Level Profiles Following Conventional and Controlled Release Dosing

A number of design options are available to control or modulate the drug release from a dosage form, which are matrix, reservoir and osmotic system. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium.

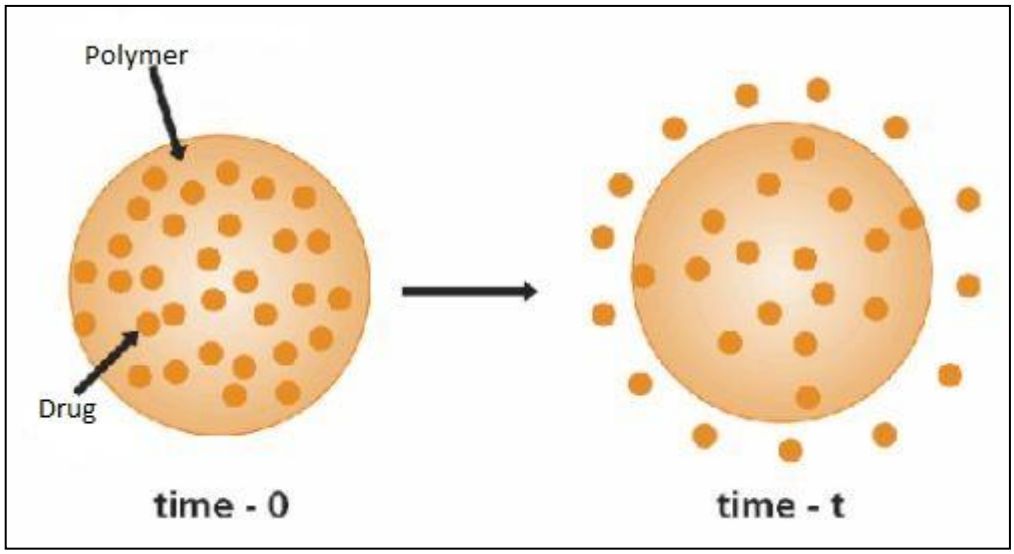

Figure2.2: Schematic Representation of Matrix Diffusion Controlled Drug Delivery Device [15]

In contrast, reservoir systems have a drug core surrounded/coated by the rate controlling membrane. However factors like pH, presence of food and other physiological condition may affect drug release from conventional controlled release systems.

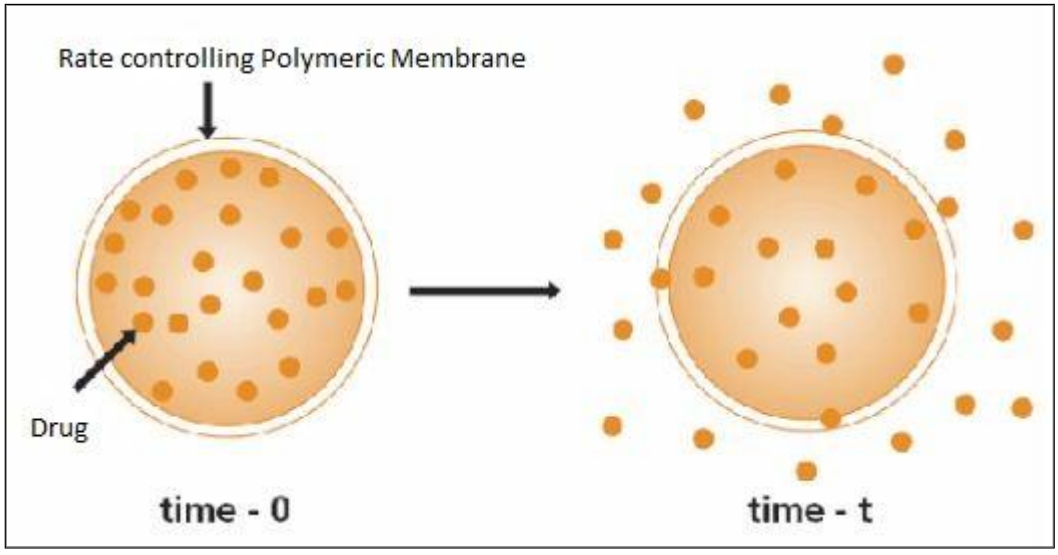

Figure 2.3: Schematic Representation of Reservoir of Reservoir Diffusion Controlled Drug Delivery Device [15]

2.2 Introduction to Osmotically Controlled Drug Delivery Systems

One of the most promising drug delivery system is osmotic drug delivery system, where osmotic pressure is used as the driving force. Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmotic pressure, created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Osmotic pressure is a colligative property of a solution and dependent on the solubility and molecular weight and activity coefficient of the solute (osmogen) [3].

The osmotic pressure π (*Pi*) of an ideal solution with low concentration containing *n* moles of solute particles in a solution of volume *V* is given by the **Van't Hoff equation as given in equation (1):**

$$\pi V = nRT \quad (1)$$

Where, π - osmotic pressure in atmosphere.
V - Volume of solution in litres
n - Number of moles of solute
R - Gas constant, (0.082 L atm/mol K)
T - Absolute temperature in K

The osmotic water flow through a membrane is given by the equation:

$$dv\backslash dt = A\ Q\ \Delta\ \pi\backslash\ L \quad (2)$$

Where, dv\dt - water flow across the membrane of area A in cm^2,
L - Thickness,
Q - Permeability
Δ π - The osmotic pressure difference between the two solutions on either Side of the membrane.

Osmotic drug delivery system provides a uniform concentration of drug at the site of absorption and thus allows the 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 hence it is possible to modulate the release characteristics by optimizing the properties of drug and system. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semipermeable membrane coat.

2.2.1. Advantages [4, 7]

- Provides Zero-order delivery rate.
- Delayed or pulsed drug delivery is obtainable with osmotic system.
- The delivery rate is significantly greater than that attainable with diffusion based system(s) of comparable size.
- Delivery rate is independent of pH variations in the environment, including those in the gastrointestinal tract (GIT).
- Delivery rate is independent of agitation outside, including GI motility.
- Release rate from osmotic system is highly predictable and programmable.
- Delivery of drug takes place in the solution form ready for absorption, with osmotic pump simulating as a liquid dosage form prepared in-situ.
- Drugs with widely varying solubility can be incorporated.
- The device is relatively simple to fabricate using conventional pharmaceutical manufacturing equipment.

2.2.2. Limitations:

- Special equipment is required for making an orifice in the system.
- Residence time of the system in the body varies with the gastric motility and food intake.
- It may cause irritation or ulcer due to release of saturated solution of drug.

2.2.3. Types of Osmotic Pump drug delivery systems [7, 8, 16]:

2.2.3.1. Elementary osmotic pump (EOP):

An EOP is the most basic osmotic pump device which is a compressed tablet consisting of an osmotic core with the drug, surrounded by a semipermeable membrane which is provided with a laser drilled orifice. Following ingestion, water is absorbed into system dissolving the drug, and the resulting drug solution is delivered at the same rate as the water entering the tablet. The rate of drug release is determined by the fluid permeability of the membrane and the osmotic pressure of the compressed tablet when the dosage form is placed in the aqueous environment. Though 60% to 80% of drug is released at a constant rate from EOP, a lag time of 30 to 60 minutes is observed in most of the cases as the system hydrates before zero-order delivery from the system begins. The delivery of the drug is for a prolonged period of time and is minimally affected by the environmental factors such as pH or motility. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs.

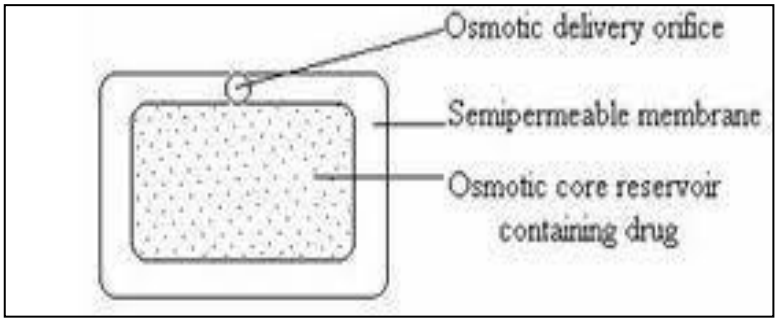

Figure2.4: Elementary Osmotic Pump Tablet

2.2.3.2. Push-Pull Osmotic Pump (PPOP) [27]:

Push pull osmotic pump is a bilayer tablet coated with semi permeable membrane. It is a modified elementary osmotic pump through which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system consists of two compartments separated usually by an elastic diaphragm. The upper compartment contains the drug and is connected to the outside environment via a small delivery orifice which accounts for 60-80 per cent of tablet weight and the lower compartment contains a swellable polymer osmotic agent accounting for around 20-40 per cent of the tablet. PPOP can be used to deliver drugs with extremes of water solubility. The semipermeable

membrane present in PPOP regulates water influx into both layers and surrounds the entire system. The complication associated with the laser drilling technology is a major disadvantage.

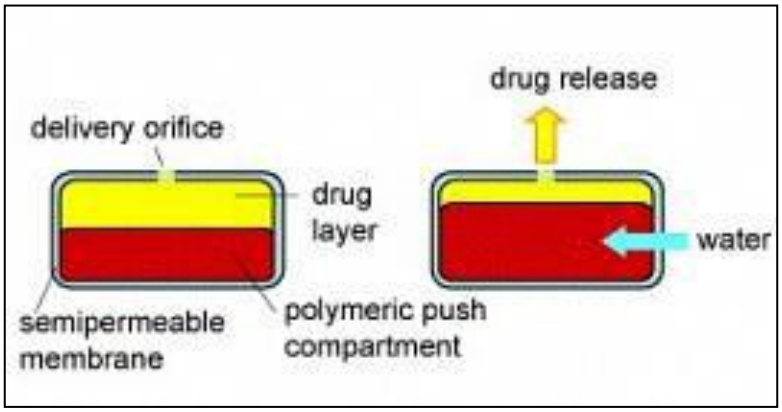

Figure2.5: Push Pull Osmotic Pump Tablet

2.2.3.3. Controlled Porosity Osmotic Pump (CPOP) [29, 30, 31]:

Unlike the elementary osmotic pump (EOP), a controlled porosity osmotic pump-based drug delivery system consists of a drug with osmogen core surrounded by a semipermeable membrane which uses different pore forming agents in the coating and is responsible for the formation of the pores in the aqueous environment leading to the formation of the microporous membrane. Generally, materials producing from 5 to 95% pores with a pore size from 10A - 100µm can be used. This microporous membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic. Simple diffusion also plays a minor role. The drug release from this membrane is basically controlled by the osmotic pressure produced by the osmogen embedded in the formulation.

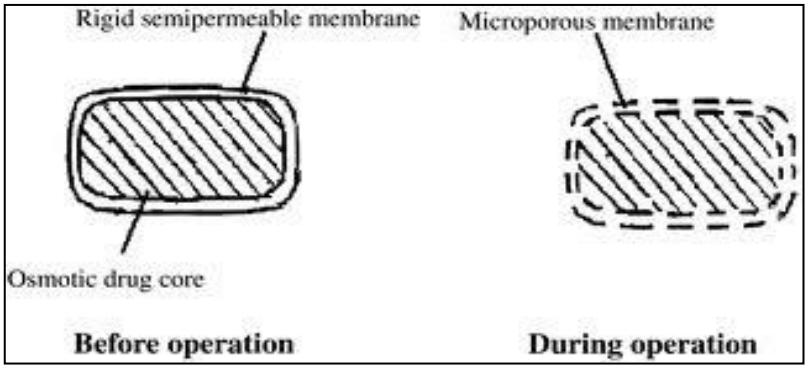

Figure2.6: Controlled Porosity Osmotic Pump Tablet

2.2.3.4. Osmotic Bursting Osmotic Pump:

This system is similar to an EOP. Unlike EOP, delivery orifice is absent and size of the formulation is smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release.

2.2.3.5. Liquid Oral Osmotic System (L-OROS):

These systems include a liquid drug layer, an osmotic engine or push layer and a semi permeable membrane coating. When the system is in contact with the aqueous environment water permeates across the rate controlling membrane and activate the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice. Whereas L-OROS hard cap or soft cap systems are designed to provide continuous drug delivery, the L- OROS delayed liquid bolus drug delivery system is designed to deliver a pulse of liquid drug.

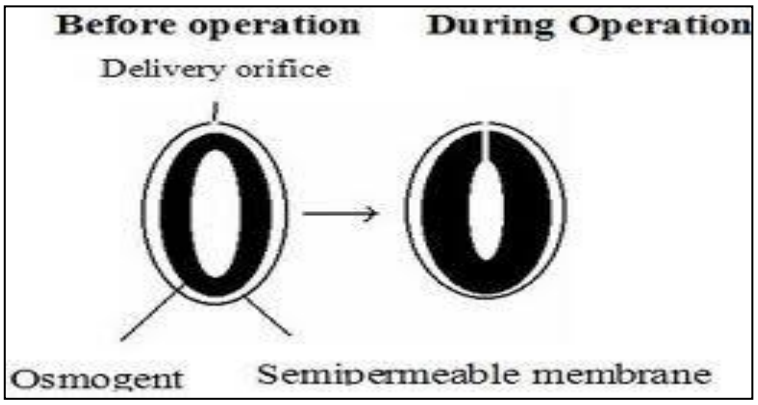

Figure2.7: Liquid Oral Osmotic System

2.2.3.6. Sandwiched Osmotic Tablets (SOTS):

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment**,** the middle push layer containing the swelling agents, swells and the drug is released from the delivery orifices. The advantage of this type of system is that the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

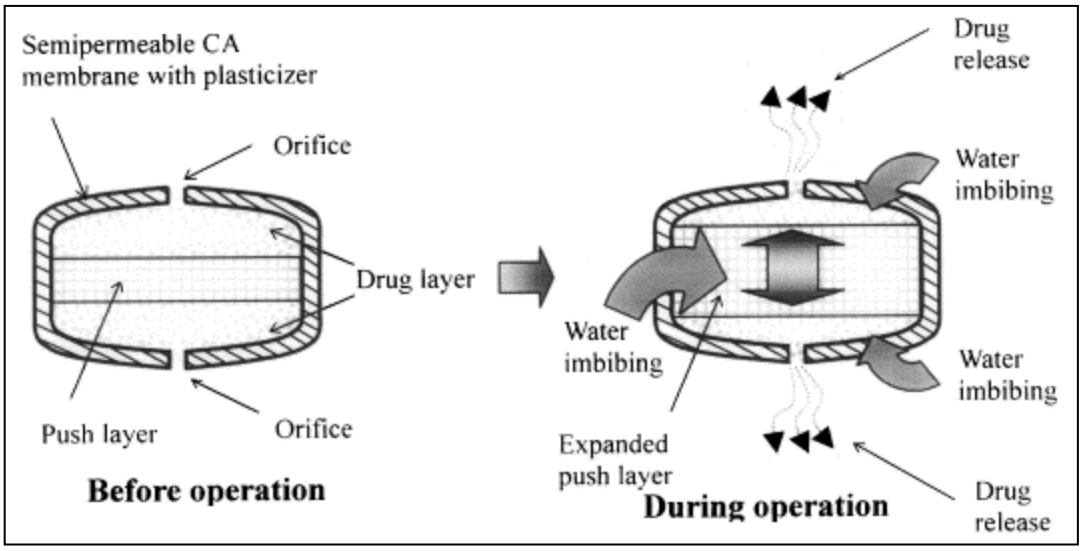

Figure2.8: Sandwiched Osmotic Tablets

2.2.3.7. Multiparticulate Delayed-Release System:

In this system, pellets containing pure drug with or without osmotic agent are coated with a semi-permeable membrane like cellulose acetate. On contact with the aqueous environment, water penetrates into the core and forms a saturated solution of soluble components. The osmotic pressure gradient induces a water influx, leading to rapid expansion of the membrane and formation of the pores. The release of osmotic ingredient(s) and the drug through these pores tend to follow zero-order kinetics.

2.2.3.8. Monolithic Osmotic System:

It constitutes a simple dispersion of a water-soluble agent in a polymeric matrix. When the system comes in contact with the aqueous environment, water imbibition by the active agent takes place which ruptures the polymeric matrix capsule surrounding the drug and thereby liberates it to the outside environment. Initially, this process occurs at the outer environment of the polymer matrix, but gradually proceeds towards the interior of the matrix in a serial fashion.

2.2.3.9. Colon Targeted Oral Osmotic System (OROS-CT):

OROS-CT is used as once or twice a day formulation for targeted delivery of drugs to the colon. It is a system with 5-6 enteric-coated push-pull osmotic units filled in hard gelatin capsule for targeted colonic drug delivery. After coming in contact with GI fluids, the

gelatin capsule dissolves and the enteric coating prevents the entry of fluids from stomach into the system. As the OROS-CT system enters into the small intestine, the enteric coating dissolves and water is imbibed into the core, thereby causing the push compartment to swell. At the same time, flowable gel is formed in the drug compartment, which is pushed out of the orifice at the rate precisely controlled by the rate of water transport across the semi-permeable membrane. About 80% of the drug is delivered to the large intestine by OROS-CT.

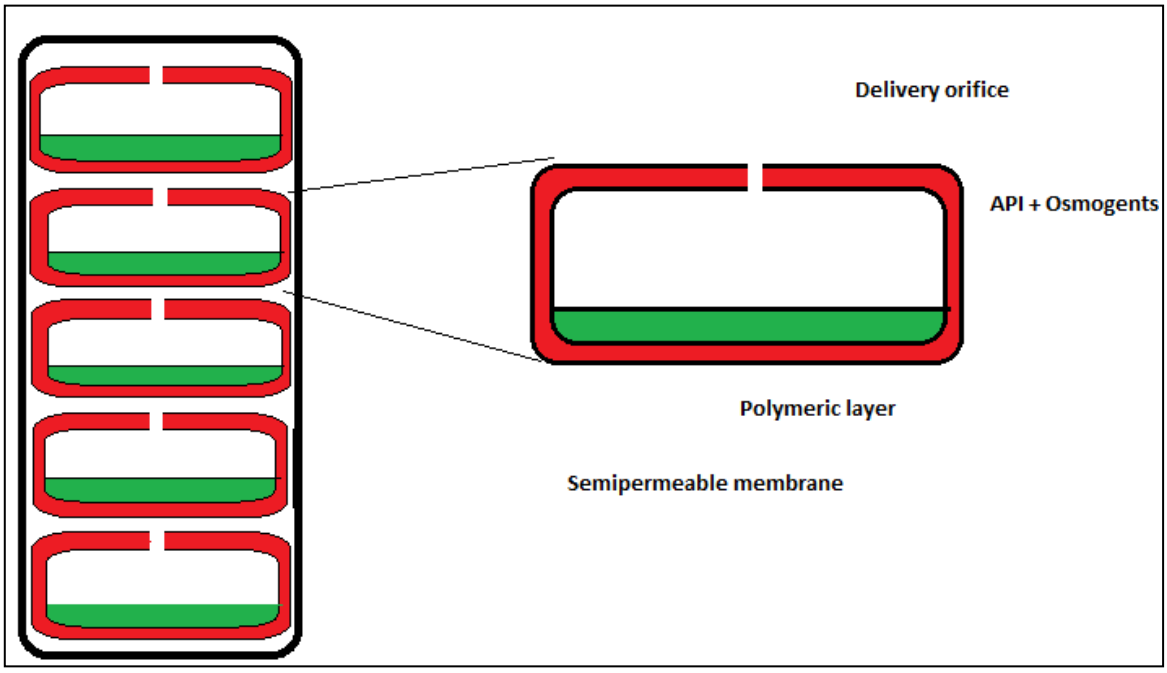

Figure2.9: Colon Targeted Oral Osmotic System.

2.2.3.10. Osmotic Matrix Tablet (OSMAT):

It is a novel osmotically driven matrix system, which utilizes the property of hydrophilic polymers to swell and gel in aqueous medium forming a semi-permeable in situ. Release from such a matrix system containing an Osmogen could, therefore, be modulated by the osmotic phenomenon. OSMAT thus judiciously combines both matrix and osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix systems. Osmotic matrix tablets are very simple to manufacture and precludes the procedures of coating a semi-permeable membrane and drilling a delivery orifice.

2.2.4. Basic components of osmotic systems [4, 6, 7, 8, 12]:

2.2.4.1. Drug

Drugs having short biological half-life and which can be used for prolonged treatment are ideal candidates for osmotic systems.

2.2.4.2. Semipermeable membrane [6]

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. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation.

The membrane should possess certain characteristics, such as

- The material must possess sufficient wet strength and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
- The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
- The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
- The membrane should also be biocompatible.
- Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. E.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragit.

2.2.4.3. Osmotic agent

Osmotic agents 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. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers.

Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulphates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents.

Table 2.1: Osmotic Pressures of Saturated Solution of Commonly Used Osmogens [20]

Osmogen	Osmotic pressure (atm)
Lactose fructose	500
Sucrose-fructose	430
Sodium chloride	**356**
Lactose-sucrose	250
Lactose-dextrose	225
Dextrose-fructose	450
Mannitol-fructose	415
Fructose	335
Potassium chloride	**245**
Mannitol-dextrose	225
Dextrose-sucrose	190
Mannitol-sucrose	170
Sucrose	150
Mannitol-lactose	130
Dextrose	82
Potassium sulphate	39
Mannitol	38
Sodium phosphate tribasic. $12H_2O$	36

2.2.4.4. Flux regulating agent

Delivery systems can be 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. Hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethyl phthalate) tend to decrease the flux.

2.2.4.5. Wicking agent

A wicking agent is defined as a material with the ability to draw water into 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 a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area.

Materials, which suitably act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly vinyl pyrrolidone (PVP), m-pyrole, bentonite, magnesium aluminium silicate, polyester and polyethylene.

2.2.4.6. Pore forming agent [28]

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate 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 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 sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol and, diols and polyols such as poly hydric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

2.2.4.7. Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the 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) etc.

2.2.4.8. Plasticizer

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change viscoelastic behaviour of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used are polyethylene glycols, ethylene glycol monoacetate and diacetate, tri ethyl citrate, diethyl tartarate.

2.2.5. Key parameters that influence the design of osmotic controlled drug delivery systems [20, 21]:

2.2.5.1. Orifice size

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Further, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure build up 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 should be maintained between the minimum and maximum values.

Methods to create a delivery orifice in the osmotic tablet coating are:

- **Mechanical drill**
- **Laser drill:** This technology is well established for producing sub-millimetre size hole in tablets. Normally, a laser beam (with output wavelength of 10.6μ) is used for drilling purpose, which offers excellent reliability characteristics at low costs.
- **Indentation that is not covered during the coating process:** Indentation is made in core tablets by using modified punches having needle on upper punch. This

indentation is not covered during coating process which acts as a path for drug release in osmotic system.

- **Use of leachable substances in the semipermeable coating:** e.g. controlled porosity osmotic pump

2.2.5.2. Solubility of drug

- The release rate depends on the solubility of the solute inside the drug delivery system.
- Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low solubility compounds, the approaches can be divided into two categories.
- Swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension.
- The drug solubility can be modified employing different methods such as co compression of the drug with other excipients, which improve the solubility. For example, cyclodextrin can be included in the formulation to enhance drug solubility. Additionally, alternative salt forms of the drug can be employed to modulate solubility.

2.2.5.3. Osmotic pressure

The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant 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.

2.2.5.4. 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.

2.2.6. Evaluation [13]:

Oral osmotic drug delivery systems can be evaluated using following evaluation parameters.

2.2.6.1. In Vitro Evaluation

The designed Oral Osmotic Drug Delivery System mainly Osmotic Pump Tablets can be evaluated by:

- **Visual inspection**: Visual inspection of the film for smoothness, uniformity of coating, edge coverage and lustre.

- **Coating uniformity:** The uniformity of coating among the tablets can be estimated by determining the weight, thickness and diameter of the tablet before and after the coating.

- **Coat weight and thickness**: The coat weight and thickness can be determined from depleted devices following careful washing and drying of the film, using standard analytical balance and screw gauge, respectively.

- **Orifice diameter**: The mean orifice diameter of osmotic pump tablet can be determined microscopically using pre calibrated ocular micrometer.

- **In vitro drug release**: The in vitro delivery rate of drugs from osmotic systems can be determined using diverse methodologies, including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc

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2.2.6.2. In Vivo Evaluation

As the environment in the intestinal tract of the dog is quite similar to that of the human beings in terms of pH and motility, dogs have widely been used for in vivo delivery rate measurement of drug(s) from oral osmotic drug delivery systems and also to establish in vitro /in vivo correlation (IVIVC). In vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters (Cmax, Tmax, AUC and MRT) and relative bioavailability are calculated.

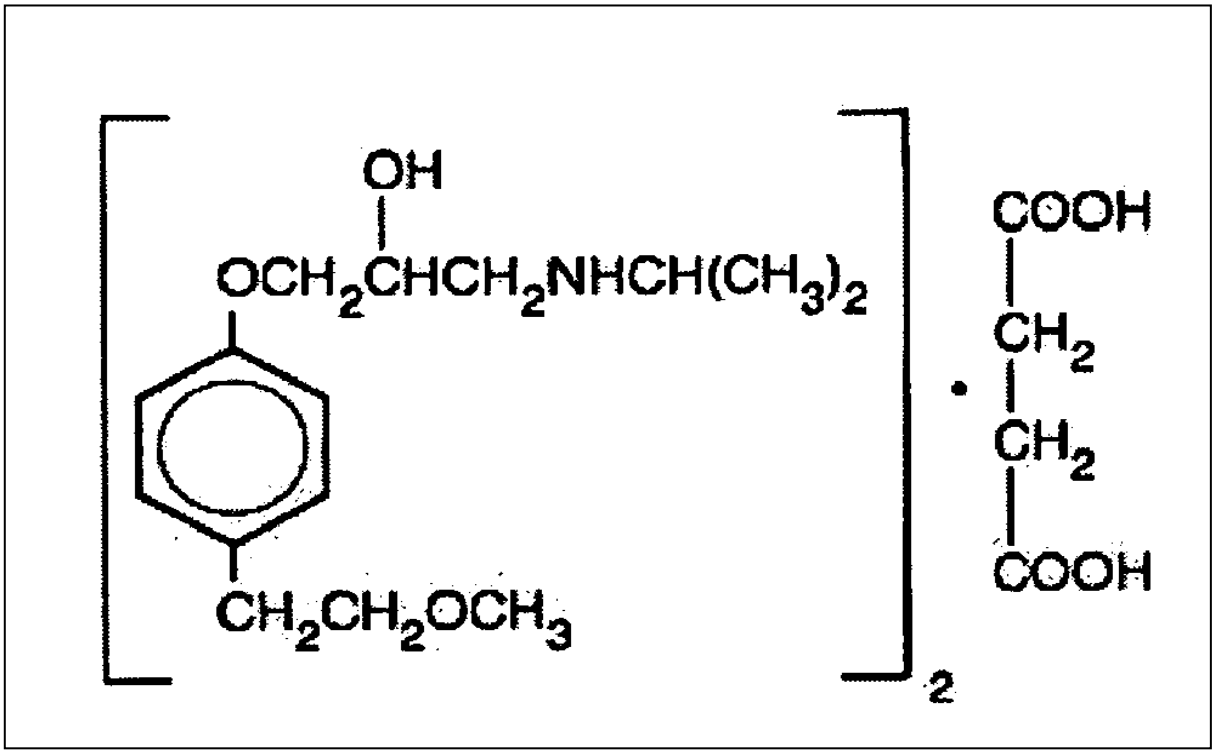
2.3. Introduction to Metoprolol Succinate

2.3.1 General Introduction [11, 14, 34]

IUPAC Name: (±) 1(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate

Empirical formula: $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$

Structural formula:



Molecular Weight: 652.81 g/mol

Melting point: 135-137^{o}C

Solubility: Freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl acetate, acetone, diethyl ether and heptanes.

Description: Metoprolol Succinate is a cardio selective β1-adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches. At low doses, it selectively blocks cardiac β-1-adrenergic receptors with little activity against β2-adrenergic receptors of the lungs and vascular smooth muscle. Receptor selectivity decreases with higher doses. It does not exhibit membrane-stabilizing or intrinsic sympathomimetic activity and are observed only at doses much higher than those needed for β-adrenergic blocking activity. It possesses a single chiral centre and is administered as a racemic mixture.

Category:

- Antihypertensive Agents
- Adrenergic Agents
- Adrenergic beta-Antagonists
- Sympatholytics
- Antiarrhythmic Agents
- Anti-Arrhythmia Agents

2.3.2. Pharmacology

2.3.2.1. Mechanism of action:

Metoprolol Succinate competes with adrenergic neurotransmitters such as catecholamines for binding at beta (1)-adrenergic receptors in the heart. Beta (1)-receptor blockade results in a decrease of heart rate, cardiac output and blood pressure.

2.3.2.2. Pharmacodynamics:

Metoprolol Succinate, a competitive beta1-selective (cardioselective) adrenergic antagonist has moderate lipid solubility, lack of intrinsic sympathomimetic activity (ISA) and weak membrane stabilizing activity (MSA).

2.3.2.3. Pharmacokinetics:

Absorption: Rapid and Complete

Bioavailability: Approximate 50% of levels following intravenous administration, indicates about 50% first-pass metabolism. Metoprolol Succinate crosses the blood-brain barrier and has been reported in the Cerebro-Spinal Fluid in a concentration 78% of the simultaneous plasma concentration.

Plasma protein Binding: About 12% of the drug is bound to human serum albumin.

Metabolism: It is a racemic mixture of R- and S- enantiomers and is primarily metabolized by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations and can be inhibited by several drugs.. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver.

Plasma half-life: Approximately 3 to 7 hours.

Elimination: Less than 5% of an oral dose is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity. Following intravenous administration, the urinary recovery of unchanged drug is approximately 10%.

2.3.3. Interactions:

2.3.3.1. Drug interactions:

Table 2.2: Drug Interactions

Drug	Interaction
Catecholamine-depleting drugs like reserpine, mono amine oxidase (MAO) inhibitors, Hydralazine**,** Verapamil	Additive effect

Inhibiting CYP2D6 like quinidine, fluoxetine, paroxetine and propafenone	Increases the concentration of Metoprolol
Anti- Diabetic Drugs	The beta-blocker, metoprolol, may decrease symptoms of hypoglycaemia
Cimetidine	Cimetidine may increase the serum concentration of metoprolol by decreasing its metabolism.
Citalopram, Escitalopram, Fluoxetine, Paroxetine, sertraline	The SSRI, citalopram, may increase the bradycardic effect of the beta-blocker, metoprolol.
Dilteazem	Increased risk of bradycardia
Phenobarbital	The barbiturate decreases the effect of the metabolized beta-blocker
Prazosin, Terazosin	Risk of hypotension at the beginning of the therapy.
Primidone	The barbiturate reduces the effect of metabolized beta-blocker.
Propafenone, Telithromycin	Increases the effect of Metoprolol
Terbinafine	Reduces Metabolism of Metoprolol
Treprostinil	Additive hypotensive effect. Monitor antihypertensive therapy during concomitant use.

2.3.3.2. Food Interactions:

- Avoid alcohol.
- Avoid natural liquorice.
- Take with food.

2.3.4. Adverse Reactions:

Hypertension and Angina: Mild to moderate hypertension and anginal pain can occur as the adverse reaction. Pruritus or rashes have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion, short-term memory, Headache, somnolence, nightmares, and insomnia, reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional ability, slightly clouded sensorium, and decreased performance on neuropsychometrics have also been reported..

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients.

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients.

Gastrointestinal: Diarrhoea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

2.3.5. Dosage:

2.3.5.1. General dosing:

50 to 400 mg once daily is given over the 24-hour dosing interval. Any extended-release tablet of metoprolol succinate is intended for once daily administration.

Hypertension

Adults: The usual initial dosage is 25 to 100 mg daily in a single dose. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Pediatric Hypertensive Patients ≥ 6 Years of age: The recommended starting dose is 1.0 mg/kg once daily, but the maximum initial dose should not exceed 50 mg once daily.

Angina Pectoris

The usual initial dosage is 100 mg daily, given in a single dose.

Heart Failure

The starting dose of metoprolol succinate is 25 mg once daily for two weeks in patients with Class II heart failure and 12.5 mg once daily in patients with more severe heart failure. Double the dose every two weeks to the highest dosage level tolerated by the patient or up to 200 mg.

2.3.5.2. Dosing in Special populations:

Pregnancy: The daily dose is of 200 mg in a 60-kg patient. The dosage in pregnant women is not very clear as only pre-clinical studies have been performed

Nursing mothers: The drug is excreted in breast milk in very small quantities.

Paediatric use: Safety and effectiveness in paediatric patients have not been established.

Geriatric use: Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

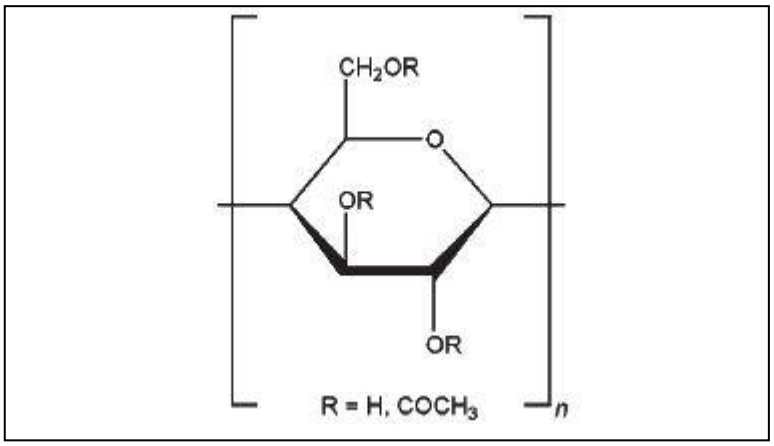
2.3.6. Contraindications:

Metoprolol succinate is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome.

2.4. INTRODUCTION TO POLYMERS [35, 36, 37, 38, 39, 40]

2.4.1 Cellulose Acetate

Structural Formula:



Functional category: Coating agent; extended release agent; tablet and capsule diluent.

Solubility: The solubility of cellulose acetate is greatly influenced by the level of acetyl groups present. In general, cellulose acetates are soluble in acetone–water blends of varying ratios, Dichloromethane–ethanol blends, dimethyl formamide, and dioxane.

Viscosity (dynamic): 10% w/v solutions in organic solvents with viscosities of 10–230 mPas. Blends of cellulose acetates may also be prepared with intermediate viscosity values.

Description: Cellulose acetate occurs as a hygroscopic white to off-white, free flowing powder, pellet, or flake. It is tasteless and odourless, or may have a slight odour of acetic acid.

Applications:

- Cellulose acetate is widely used in pharmaceutical formulations both in sustained release applications and for taste masking.
- Cellulose acetate is used as a semipermeable coating on tablets, especially on chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Table 2.3: Comparison of Different Types of Cellulose Acetate (CA)

Type	Acetyl (%)	Viscosity (mPas)	Hydroxyl (%)	Melting range (°C)	*Tg* (°C)	Density (g/cm^3)	MWn (g/mol)
CA-320S	32.0	210.0	8.7	230-250	180	1.31	38000
CA-398-3	39.8	11.4	3.5	230-250	180	1.31	30000
CA-398-6	39.8	22.8	3.5	230-250	182	1.31	35000
CA-398-10	39.8	38.0	3.5	230-250	185	1.31	40000
CA-398-30	39.7	114.0	3.5	230-250	189	1.31	50000
CA-394-60S	39.5	228.0	4.0	240-260	186	1.32	60000

2.4.2. Sodium Chloride

Functional category: Osmotic agent, Tablet and capsule diluent; tonicity agent.

Table 2.4: Uses of Sodium Chloride

Use	Concentration (%)
Capsule diluent	10-80
Controlled flocculation of suspension	41
Direct compression tablet diluent	10-80
To produce isotonic solutions in intravenous or ophthalmic preparations	40.9
Water soluble tablet lubricant	5-20

Table 2.5: Solubility of Sodium Chloride

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	Slightly soluble
Ethanol (95%)	1 in 250
Glycerine	1 in 10
Water	1 in 2.8 1 in 2.6 at 100°C

Viscosity (dynamic): A 10% w/v solution has a viscosity of 1.19 mPas (1.19 cps).

Description: Sodium chloride occurs as a white crystalline powder or colourless crystals; it has a saline taste. The crystal lattice is a face-centred cubic structure. Solid sodium chloride contains no water of crystallization although, below 08C, salt may crystallize as a dihydrate.

Applications:

- Sodium chloride is used to produce isotonic solutions.
- Sodium chloride has also been used as a channelling agent and as an osmotic agent in the cores of controlled-release tablets. It has been used as a porosity modifier in tablet coatings and to control drug release from microcapsules.
- Sodium chloride can also be used to modify drug release from gels and from emulsions.
- It can be used to control micelle size and to adjust the viscosity of polymer dispersions by altering the ionic character of a formulation.

2.4.3. Potassium Chloride

Functional category: Osmotic agent, Therapeutic agent; tonicity agent.

Table 2.6: Solubility of Potassium Chloride

Solvent	**Solubility at 20°C unless otherwise stated**
Acetone	Practically insoluble
Ethanol (95%)	1 in 250
Glycerine	1 in 14
Water	1 in 2.8 1 in 1.8 at 1008C
Ether	Practically insoluble

Description: Potassium chloride occurs as odourless, colourless crystals or a white crystalline powder, with an unpleasant, saline taste. The crystal lattice is a face-centred cubic structure.

Applications:

- Potassium chloride is used to produce isotonic solutions and therapeutically in the treatment of hypokalemia.
- Many solid-dosage forms of potassium chloride exist including: tablets prepared by direct compression and granulation; effervescent tablets; coated sustained-release tablets; sustained- release wax matrix tablets; microcapsules; pellets and osmotic pump formulations.
- Potassium chloride is also used widely in the food industry as a dietary supplement, pH control agent, stabilizer, thickener, and gelling agent.

2.4.4. Microcellac 100

Description: Microcellac 100 is a spray-dried compound containing 75 % α-lactose monohydrate [Ph.Eur./USP-NF/JP] and 25 % microcrystalline cellulose [Ph.Eur./USP-NF/JP] dry matter. Both filling properties of lactose and binding capacity of MCC have been synergistically coprocessed to one-body excipient providing better tableting performance at lower cost.

Particle size distribution:

- < 32 µm: ≤ 15 %
- < 160 µm: 45-70 %
- < 250 µm: ≥ 90 %

  [Air jet sieve]

Typical values:

Density poured [g/l]:500

Density tapped [g/l]: 588

Special features Microcellac 100:

- Excellent compressibility for high dosage formulations
- Low aggregation tendency guarantees consistent flowability
- Constant tablet hardness through fixed ratio of lactose / MCC
- High weight consistency at various compaction speeds

Flowability:

Microcellac 100 demonstrates improved flow properties in comparison to physical mixtures of spray-dried lactose and MCC type 102 resulting in better weight uniformity and extended tableting speed.

Compressibility

Microcellac 100 is setting new standards in compatibility performance, even superior to the physical mixture of spray-dried lactose and MCC type 102 resulting in:

- lowest machine stress
- reliable compression properties at various speeds
- extended dilution potential for actives

Application Microcellac 100

- Production of small tablets
- Formulations containing minerals
- Oblong tablets
- Formulations with high content of active ingredients
- Formulations with poor flowable, micronized active ingredients

2.4.5. Talc

Functional category: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Table 2.7: Uses of Talc

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents and water.

Description: Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Applications:

- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended-release pellets and as an adsorbent.
- In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.
- Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.
- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

2.4.6. Magnesium Stearate

Functional category: Tablet and capsule lubricant.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin

Applications:

- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

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2.4.7. Colloidal Silicon Dioxide (Aerosil 200)

Functional category: Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Table 2.8: Uses of Colloidal Silicon Dioxide

Use	Concentration (%)
Aerosols	0.5–2.0
Suspending and thickening agent	2.0–10.0
Emulsion stabilizer	1.0–5.0
Glidant	0.1–1.0

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. It forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 25^{o}C (pH 7).

Description: Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-coloured, odourless, tasteless, amorphous powder.

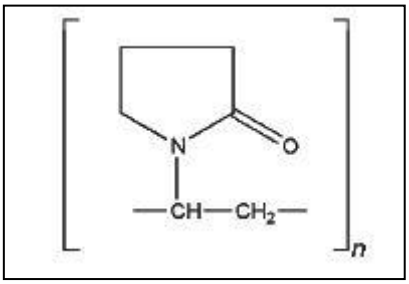
Applications:

- Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products.

- Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.
- It is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar refractive index, transparent gels may be formed.
- It is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

2.4.8. Povidone (kollidon 30)

Structural formula:



Functional category: Disintegrant; dissolution enhancer; suspending agent; tablet binder.

Uses:

Table 2.9: Uses of Povidone

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Tablet binder, tablet diluent, or coating agent	0.5–5
Suspending agent	Up to 5

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

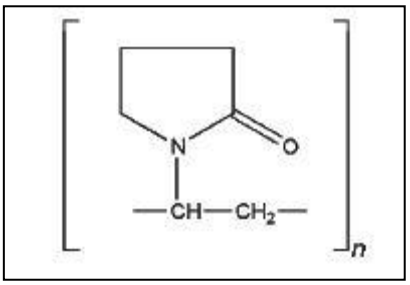
Description: Povidone occurs as a fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Applications:

- Povidone is used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions.
- Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.
- Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads.
- Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

2.4.9. Polyethylene Glycol 4000

Structural formula:



Functional category: Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Solubility: All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols. Aqueous solutions of higher molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerine and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Description: The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200–600) occur as clear, colourless or slightly yellow-coloured, viscous liquids. They have a slight but characteristic odour and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures. Solid grades (PEG>1000) are white or off-white in colour, and range in consistency from pastes to waxy flakes. They have a faint, sweet odour. Grades of PEG 6000 and above are available as free flowing milled powders.

Applications:

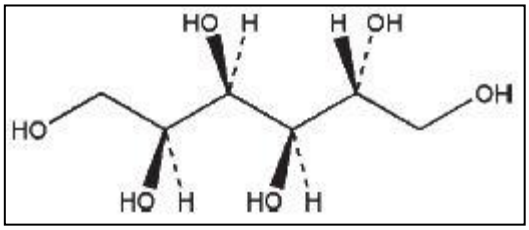
- Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations.
- Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. They are stable, hydrophilic substances that are essentially non-irritant to the skin.
- Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.
- Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats.
- In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.
- In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules

Table 2.10: Structural Formula and Molecular Weight of Typical Polyethylene Glycol Polymers

Grade	Average molecular weight
PEG 200	190-210
PEG 300	285–315
PEG 400	380–420
PEG 540 (blend)	500–600
PEG 600	570–613
PEG 900	855–900
PEG 1000	950–1050
PEG 1450	1300–1600
PEG 1540	1300–1600
PEG 2000	1800–2200
PEG 3000	2700–3300
PEG 3350	3000–3700
PEG 4000	3000–4800
PEG 4600	4400–4800
PEG 8000	7000–9000

2.4.10. Sorbitol

Structural formula:



Functional category: Humectant; plasticizer; stabilizing agent; sweetening agent; tablet and capsule diluent.

Table 2.11: Uses of Sorbitol

Use	Concentration (%)
Humectant	3-15
IM injections	10-25
Moisture control agent in tablets	3-10
Oral solutions	20-35
Plasticizer for gelatin and cellulose	5-20
Prevention of 'cap locking' in syrups and elixirs	15–30
Substitute for glycerine and propylene glycol	25–90
Tablet binder and filler	25–90
Topical emulsions	2–18
Toothpastes	20–60
Oral suspensions	70

Solubility:

Table 2.12: Solubility of Sodium Chloride

Solvent	Solubility at 20°C
Chloroform	Practically insoluble
Ethanol (95%)	1 in 25
Ethanol (82%)	1 in 8.3
Ethanol (62%)	1 in 2.1
Ethanol (41%)	1 in 1.4
Ethanol (20%)	1 in 1.2
Ethanol (11%)	1 in 1.14
Ether	Practically insoluble
Methanol	Slightly soluble
Water	1 in 0.5

Description: Sorbitol is D-glucitol. It is a hexahydric alcohol related to mannose and is isomeric with mannitol. Sorbitol occurs as an odourless, white or almost colourless, crystalline, hygroscopic powder.

Applications:

- Sorbitol is used as a diluent in tablet formulations prepared by either wet granulation or direct compression. It is particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation.
- In capsule formulations it is used as a plasticizer for gelatin. Sorbitol has been used as a plasticizer in film formulations.
- In liquid preparations, sorbitol is used as a vehicle in sugar-free formulations and as a stabilizer for drug, vitamin and antacid suspensions.
- Sorbitol is additionally used in injectable and topical preparations, and therapeutically as an osmotic laxative.

Chapter 3

LITERATURE REVIEW

3. LITERATURE REVIEW:

3.1. Review of work done on Osmotically Controlled Drug Delivery System:

Modi SA et al provided basic information regarding sustained-release formulation as change in the conventional process of manufacturing is a suitable and optimized way to make some drugs more effective by slight alteration in the drug delivery. Sustained Release also provides promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body [1].

Elbary AA, Tadros MI and Eldin AA designed and evaluated controlled porosity osmotic pump (CPOP) tablets of etodolac. Variables influencing the design of (1) core tablets viz., (a) osmogent type (sodium chloride, potassium chloride, mannitol, and fructose) and (b) drug/osmogent ratio (1:0.25, 1:0.50, and 1:0.75), and (2) CPOP tablets viz., (a) coating solution composition, (b) weight gain percentage (1–5%, w/w), and (c) pore former concentration (5%, 10%, and 20%, v/v), were investigated. Statistical analysis and kinetic modeling of drug release data were estimated. Fructose-containing core tablets showed significantly ($P<0.05$) more retarded drug release rates. An inverse correlation was observed between drug/fructose ratio and drug release rate. Coating of the optimum core tablets (F4) with a mixture of cellulose acetate solution (3%, w/v), diethyl phthalate, and polyethylene glycol 400 (85:10:5, v/v, respectively) till a 4% w/w weight gain enabled zero-order sustained drug delivery over 24 h. Scanning electron microscopy micrographs of coating membrane confirmed pore formation upon contact with dissolution medium. When compared to the commercial immediate-release Napilac® capsules, the optimum CPOP tablets (F4–34) provided enhanced bioavailability and extended duration of effective etodolac plasma concentration with minimum expected potential for side effects in healthy volunteers [41].

Zentner GM et al investigated the zero-order release of water soluble, osmotically active agents from tablets coated with controlled porosity walls. The walls were sponge-like in appearance and substantially permeable to both water and dissolved solutes. Mechanical strengths of the walls were measured and the rate of release was a function of the wall thickness, level of leachable additives incorporated and permeability of the polymer

component of the walls, the total solubility of the core tablet, the drug load, and the osmotic pressure difference across the wall. Release was insensitive to the pH and degree of agitation in the receptor media. Release was primarily due to an osmotic pump mechanism. Steady-state release rates were calculated from basic water and solute permeabilities of the walls and correlated with actual device performance. The concept of osmotically actuated drug delivery on an equivalent mass per unit surface area basis was demonstrated and extended, as well, to multiparticulate dosage forms [7].

Kumaravelrajan et al developed controlled porosity osmotic pump tablet to deliver Nifedipine (NP) and Metoprolol (MP) in a controlled manner up to 12 h. It was prepared by incorporating drugs in the core and coated with various types (PVP, PEG-400 and HPMC) and levels (30, 40 and 50% w/w of CA) of pore former at a weight gain of 8, 12 & 15%. Formulation variables like type and level of pore former and percent weight gain of membrane was found to affect the drug release from the developed formulations. Drug release was inversely proportional to the membrane weight but directly related to the level of pore former. Burst strength of the exhausted shell was inversely proportional to the level of pore former, but directly affected by the membrane weight. Results of scanning electron microscopy (SEM) studies showed the formation of pores in the membrane from where the drug release occurred. Dissolution models were applied to drug release data in order to establish the mechanism of drug release kinetics. In vitro release kinetics was subjected to superposition method to predict in vivo performance of the developed formulation. The developed osmotic system is effective in the multi-drug therapy of hypertension by delivering both drugs in a controlled manner [11].

Sinchaipanid N. et al fabricated micro/nanoporous osmotic pump tablets coated with cellulose acetate containing polyvinylpyrolidone (PVP) as pore formers and Propranolol hydrochloride as a model drug. Formulation optimization based on USP 31 requirements was conducted following a central composite design using a two-level factorial plan involving two membrane variables (pore former and coating levels). Effect of molecular weight of pore former (PVP K30 and PVP K90) was also evaluated. Responses of drug release to the variables were analyzed using statistical software (MINITAB 14). Scanning electron microscopy and atomic force microscopy showed the pores formed by PVP. The

drug release was dependent on the molecular weight and concentration of PVP and the level of coating. The results showed that acceptable 12-h profile could be achieved with only specific range of PVP K30-containing membrane at the defined membrane thickness. However, satisfactory 24-h profile could be accomplished by both PVP K30 and PVP K90-containing membrane at the range and membrane thickness tested [18].

Gupta BP et al investigated that conventional drug delivery systems have slight control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems. They include dosage forms for oral and transdermal administration as well as injectable and implantable systems. For most of drugs, oral route remains as the most acceptable route of administration. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). Among the available techniques to improve the bioavailability of these drugs fabrication of osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT [4].

Dasankoppa FS et al studied that 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 preprogrammed 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 [3].

Rathee P et al investigated an osmotic-controlled release oral delivery system (OROS), as an advanced drug delivery technology that uses osmotic pressure as the driving force to deliver pharmacotherapy, usually once-daily, in several therapeutic areas. Oral route is one of the most extensively used routes of drug administration because of its obvious advantages of ease of administration, improved patient compliance and convenience. The main clinical benefits of OROS are their ability to improve treatment tolerability and patient compliance. These advantages are mainly driven by the capacity to deliver drugs in a sustained manner, independent of the drug chemical properties, of the patient's physiological factors or concomitant food intake. However, access to these technologies has been restricted by the crowded patent landscape and manufacturing challenges. In this review, we intend to give an overview of the OROS development in the last 30 years, detailing the technologies, specific products and their clinical use. General guidance on technology selection is described in light of the recent advances in the field. The clinical performance of these technologies is also discussed, with a focus on food effects and the in vivo– in vitro correlation. Special attention is paid to safety given the controversial case study of Osmosin. Overall, oral osmotically driven systems appear to be a promising technology for product life-cycle strategies [31].

Kapoor D et al fabricated Controlled porosity osmotic pump containing water soluble additive in the coating membrane which dissolves when it comes in contact with aqueous environment creating a micro porous membrane. The resulting membrane is substantially permeable to both water and dissolved drug. This results in the benefit of pH and independent release performance leading to similar in vitro / in vivo delivery.

Osmotically driven systems have a prominent place in achieving predetermined zero-order rates for extended periods. In the present investigation, efforts have been made to study the release mechanism of drug having low water solubility by means of controlled porosity osmotic pump. The capsule membrane was prepared by phase inversion technique. The delivery orifices so formed were inveterate by release of an encapsulated dye from the capsule and scanning electron microscope (SEM).The drug selected for this study is valsartan and is claimed to have low water solubility leading to the inability of the formulation to create osmotic pressure to cause drug release. To augment the solubility and its osmotic pressure, this study was conducted with a solubility enhancer HPMC (Hydroxy propyl methyl cellulose), PEG-6000 and osmogents KCl. Valsartan has a short plasma half life of 3-5 h. Hence, valsartan was chosen as a model drug to develop a controlled porosity system for periods of 9 hours. This system was found to deliver valsartan at a zero order rate for 9 hours [9].

Rajewski RA et al investigated the general application of a controlled-porosity osmotic pump tablet (OPT) utilizing (SBE)7m-β-CD as both a solubilizer and an osmotic agent for drugs with varying physical properties. OPTs utilizing (SBE) 7m-β-CD were prepared for five poorly soluble and two highly water-soluble drugs. The Japanese Pharmacopoeia dissolution method was used to study the drug and (SBE) 7m-β-CD release from the OPTs and was assayed gravimetrically and by HPLC. An appropriate composition ratio (ACR) of (SBE) 7m-β-CD to drug at which drug release from the OPT was complete and pH independent within the physiological pH range of the GI tract was determined for each drug. The ACR values correlate to the drug concentration in the OPT core when the OPTs were placed in the release medium for two hours. The release profiles of prednisolone (a poorly water-soluble drug) and sodium chloride (a water-soluble compound) from the OPTs were almost the same as that of (SBE) 7m-β-CD. Also, the release rate of each drug per unit membrane surface area from the OPTs was similar, regardless of the differences in drug solubility. The present results confirmed that (SBE) 7m-β-CD serves as both a solubility modulator and as an osmotic pumping agent for OPTs, from which the release rate of both water-soluble and poorly water-soluble drugs can be controlled [2].

Edavalath S. et al designed the porous osmotic pump tablets using D-Optimal design and numerical optimization technique to find out the best formulation. Osmotic agent sodium chloride and pore former PEG 400 was considered as independent variables. Drug release rate at 2 h, 4 h, 8 h, 12 h, T50% and release exponent (n) were taken as responses. The increase in concentration of pore former and osmotic agent after a limit, changes the release from zero order to Higuchi based release. The optimized formulation follows non-Fickian release mechanism. The FT-IR and DSC studies revealed that no physicochemical interaction between excipients and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through osmosis. Stability studies revealed that optimized formulation was stable. The result of D- Optimal design and ANOVA studies reveals that osmotic agent and pore former have significant effect on the drug release up to 12 h. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of porous osmotic pump tablets containing diclofenac sodium by using sodium chloride and PEG 400 as key excipients [17].

Verma RK et al developed extended release formulations of isosorbide mononitrate (IMN), based on osmotic technology. Target release profile was selected and different formulation variables like type (PVP, PEG-4000, and HPMC) and level of pore former (0–55%, w/w of polymer), percent weight gain were optimized to achieve the same. Drug release was inversely proportional to the membrane weight but directly related to the initial level of pore former in the membrane. Burst strength of the exhausted shells was inversely proportional to the level of pore former, but directly affected by the membrane weight. Satisfactory burst strength (more than 320 g) was obtained when PVP was used as pore former (up to 55%, w/w of polymer) at the membrane weight of 7.5% and more. The release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The formulations were found to be stable after 3 months of accelerated stability studies. Prediction of steady-state levels showed the plasma concentrations of IMN to be within the desired range [5].

Kumar G. et al designed a controlled pororsity osmotic pump capsule of carvedilol containing pore forming water soluble additives which after coming in contact with water dissolve resulting in the formation of a micro porous structure. The effect of formulation variables like drug: osmogen ratio, solubilising agent and level of pore former, different environmental media and stirring rate on in vitro release was studied. Cellulose acetate was used as a semi permeable membrane and it was found that the drug release increased with the increase in the amount of osmogent and the solubilising agent independent of the different environmental media and the stirring rate. Carvedilol release was directly proportional to the level of the pore former and glycerine in the membrane. The system was found to deliver the drug at a zero order rate [19].

Vavia PR et al described a controlled porosity osmotic pump-based drug delivery system by the use of different channelling agents in the coating. This system is unlike the elementary osmotic pump (EOP) which consists of an osmotic core with the drug surrounded by a semipermeable membrane drilled with a delivery orifice. The usual dose of pseudoephedrine is 60 mg to be taken three or four times daily, with a short plasma half life of 5–8 h which makes it an appropriate choice to be used as a model drug. Sodium bicarbonate was used as the osmogent. The effect of different ratios of drug:osmogent on the in-vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. Different channeling agents tried was diethylphthalate (DEP), dibutylphthalate (DBP), dibutylsebacate (DBS) and polyethyleneglycol 400 (PEG 400). The effect of polymer loading on in-vitro drug release was studied and was found that drug release rate increased with the amount of osmogent due to the increased water uptake, and hence increased driving force for drug release. This could be retarded by the proper choice of channeling agent in order to achieve the desired zero order release profile. Also the lag time seen with tablets coated using diethylphthalate as channeling agent was reduced by using a hydrophilic plasticizer like polyethyleneglycol 400 in combination with diethylphthalate. This system was found to deliver pseudoephedrine at a zero order rate for 12 h. The effect of pH on drug release was also studied. The optimized formulations were subjected to stability studies as per ICH guidelines at different temperature and humidity conditions [6].

Ratna VJ et al studied that the conventional drug delivery systems have little control over their drug release and almost no control over the effective concentration at the target site, which may result in constantly changing, unpredictable plasma concentrations. It was found that drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis, which are the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems. When these systems are exposed to water, low levels of water soluble additive is leached from polymeric material i.e. semipermeable membrane and drug releases in a controlled manner over an extended period of time. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Studies on the various types of osmotically controlled drug delivery systems and their basic components were done briefly [20].

Himmelstein KJ et al studied that Controlled drug delivery devices that release the drug from an osmotic core by a pumping mechanism are promising for the oral administration of water-soluble drugs. This study considers various possible paths for the transport of water through a porous cellulose acetate membrane which constitutes the outer wall of a particular osmotic device. It is shown that the mechanism of water transport is not solely by diffusion through the semipermeable cellulose acetate or water-filled voids: solute-excluding water-filled regions in the coat as well as the polymeric portion of the coat are important in water ingress into the osmotic pump [8].

Rao BP et al developed swellable controlled porosity osmotic pump tablet of theophylline and defined the formulation and process variables responsible for drug release by applying statistical optimization technique. Formulations were prepared based on Taguchi Orthogonal Array design and Fraction Factorial design for core and coating, respectively. The tablets were prepared by direct compression and wet granulation methods; spray coated with ethyl cellulose solution containing varying amounts of PEG 400 and plasdone. Drug release from the osmotic drug delivery system was studied using USP Type I paddle type apparatus. The membrane morphology of the delivery system

was determined by scanning electron microscopy (SEM).Optimization results indicated that the release rate of theophylline is directly proportional to the levels of osmotic agent, solubilizing agent and pore former in the tablet core and the membrane, respectively. The best formulation showed 98.2 % drug release and complied with USP requirements [22].

Garg S et al developed osmotically controlled oral drug delivery systems which utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems 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, different types of oral osmotic systems, various aspects governing drug release from these systems, and critical formulation factors are discussed [23].

Uma Maheswari A. et al formulated and evaluated controlled release formulation of lornoxicam based on osmotic technology. Basic pH modifier tromethamine and wicking agent SLS were incorporated into the core tablet to create basic environmental pH inside the tablets. The effect of different formulation variables namely level of osmogen (mannitol) in the core tablet and level of pore former (sorbitol) in the coating membrane on in-vitro release was studied. Lornoxicam release from controlled porosity osmotic pump was directly proportional to the pore former (sorbitol) and level of osmogen (mannitol). Drug release from the developed formulations was independent of pH and agitational intensity and was dependent on osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred [10].

Vyas SP et al formulated and evaluated elementary osmotic pumps of Diltiazem hydrochloride, which had shown higher release rate. Drug entrapment in polymer matrix or addition of release retardant materials (various polymers) can reduce the release rate of

drug. Effect of appropriate hydrophilic polymers (HP) on the release pattern was investigated. Ingredients of the system were optimized for parameters like drug:polymer ratio and amount of osmogent, for the desired release pattern. Two optimized formulations were selected for further characterization. Theoretical release rate of the formulations were also determined and compared. Different dissolution models were applied to drug release data in order to establish release mechanism and kinetics. Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals [16].

Jiang ZQ et al studied a monolithic osmotic tablet system (MOTS) with two orifices in both side surfaces by using water-insoluble drug, naproxen. Gum arabic was used as an osmotic, suspending and expanding agent and cellulose acetate (CA) was used as semipermeable membrane. Polyethylene glycol 400 (PEG-400) was employed as plasticizer for controlling membrane porosity. The influences of gum arabic, PEG-400, membrane thickness and orifice size on the naproxen release profiles were investigated, and the optimal MOTS was evaluated in different environment media and stirring rates. The optimal MOTS was found to be able to deliver naproxen at a rate of approximately zero order up to 12 h in pH 6.8, cumulative release at 12 h is 81%, independent on environment media and stirring rate. Therefore, MOTS can be used in oral drug controlled delivery field, especially for water-insoluble drug [32].

Lin et al developed a micropore-controlled release tablet for Theophylline. The tablets were composed of a drug core surrounded by a microporous film. The major components of coating film included a biocompatible semipermeable polymer, cellulose acetate, and a water soluble pore-forming agent, poly(ethylene glycol). The effect of the coating film composition and the type of excipient incorporated in the drug core on drug release were demonstrated via an in vitro release study. The optimized formulation was further investigated in vivo of rabbits. The results showed that micropore-controlled release tablets continuously released drug for 24-36 hours depending on the type of excipient in the drug core and the coating film composition. Incorporation of lactose in the drug core enhanced drug release from micropore controlled release tablets. In vivo animal study

revealed that the micropore-controlled release tablets reduced the maximum concentration and prolonged the mean residence time of drug [40].

Hou et al developed controlled porosity osmotic pump system with biphasic release of theophylline for the nocturnal therapy of asthma. The developed system was composed of a tablet-in-tablet (TNT) core and a controlled porosity coating membrane. Release pattern of the developed system was influenced by amount of pore former (18.2-45.5%, w/w of polymer), weight gain (16-26 mg per tablet) of the coating membrane and osmotic agents used in inner layer of the TNT core. When sodium phosphate and sodium chloride were selected as the osmotic agents in inner and outer layer of the TNT core respectively, target release profile was obtained with coating solution cellulose acetate–polyethylene glycol 400–diethyl phthalate (54.5–36.4–9.1%, w/w) at a weight gain of 16-22 mg per tablet. To examine the mechanism of drug release, release profiles of osmotic agents, micro-environmental osmotic pressure and micro-environmental pH of the formulation during dissolution were studied. Microenvironmental osmotic pressure and microenvironmental pH of the developed formulation were proved to be two dominant factors for the biphasic release. The first slow theophylline release was dominated by the osmotic pressure originated from the dissolution of sodium chloride. By adjusting the components of the TNT core, this osmotic pump system may be applicable for the biphasic delivery of other drugs [25].

Parth et al developed controlled porosity osmotic tablets of Propranolol Hydrochloride which will deliver the drug at zero order for 12hour. Core tablet of Propranolol Hydrochloride was prepared using sodium chloride, PVP K30, MCC, talc & Mg. stearate; and the tablets of selected batch was coated with coating solution containing different proportions of cellulose acetate, sodium chloride, castor oil and PEG400 and evaluated for in vitro drug release studies. The observed result revels that osmotic agent and pore former have significant effect on drug release up to 12h. In successful development of micro porous osmotic pump tablets containing Propranolol Hydrochloride by using sodium chloride and PEG400 as key excipients [13].

Kanagale et al developed controlled porosity osmotic pump for controlled release of Oxybutynin. The porous osmotic pump contains pore-forming water-soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a microporous structure. The dosage regimen of oxybutynin is one 5-mg tablet 2 to 3 times a day. The plasma half-life ranges from ~2 to 3 hours. Hence, oxybutynin was chosen as a model drug with an aim to develop a controlled release system for a period of 24 hours. Linear and reproducible release similar to that of Ditropan XL was achieved for optimized formulation independent of hydrodynamic conditions. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain, and level of pore former on the in vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. It was found that drug release rate increased with the amount of osmogent because of the increased water uptake, and hence increased driving force for drug release. Oxybutynin release was inversely proportional to the membrane weight gain; however, directly related to the level of pore former, sorbitol, in the membrane. This system was found to deliver oxybutynin at a zero-order rate for 20 hours. The effect of pH on drug release was also studied.

Mahalaxmi.R et al developed extended release controlled porosity osmotic pump formulations of model drug Glipizide using a wicking agent and a solubilizing agent. Glipizide osmotic tablets were evaluated for their flow properties, weight variation, hardness, friability and content uniformity. The effect of different formulation variables like level of wicking agent, solubilizing agent, level of pore former and membrane weight gain on in vitro release were studied. Drug release was found to be affected by the level of wicking agent and solubilizing agent in the core. Glipizide release from controlled porosity osmotic pump was directly proportional to the pore former (sorbitol) and inversely proportional to membrane weight gain. Drug release from the developed formulations was independent of pH and agitational intensity and was dependent on osmotic pressure of the release media. The optimized formulation was also found to stable upon stability studies [38].

3.2. Literature Review on Metoprolol Succinate

Kumaravelrajan R et al fabricated a system that can deliver multi-drug at a prolonged rate for the treatment of various chronic diseases such as diabetes, asthma and heart disease. Controlled porosity osmotic pump tablet (CPOP) system was designed to deliver Nifedipine (NP) and Metoprolol (MP) in a controlled manner up to 12 h. It was prepared by incorporating drugs in the core and coated with various types (PVP, PEG-400 and HPMC) and levels (30, 40 and 50% w/w of polymer) of pore former at a weight gain of 8, 12 & 15%. Formulation variables like type and level of pore former and percent weight gain of membrane was found to affect the drug release from the developed formulations. Drug release was inversely proportional to the membrane weight but directly related to the level of pore former. Burst strength of the exhausted shell was inversely proportional to the level of pore former, but directly affected by the membrane weight. Results of scanning electron microscopy (SEM) studies showed the formation of pores in the membrane from where the drug release occurred. Dissolution models were applied to drug release data in order to establish the mechanism of drug release kinetics. In vitro release kinetics was subjected to superposition method to predict in vivo performance of the developed formulation. The developed osmotic system is effective in the multi-drug therapy of hypertension by delivering both drugs in a controlled manner [11].

Sathyaraj. A et al developed controlled release tablets of Metoprolol succinate using Natural polymer, guar gum and synthetic polymer, carbopol as a rate controlling polymers. It was also desired to study the effect of polymer concentration. Metoprolol succinate, β1- selective adrenergic receptor- blocking agent used in the management of hypertension, angina pectoris, cardiac arrthymias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6 hrs and in normal course of therapy drug administration is required every 4-6 hrs, thus warrants the use of controlled release formulation for prolong action and to improve patient compliance. In the present investigation Natural polymer, guar gum and synthetic polymer, carbopol have been selected as matrix forming materials for the drug. The formulations are made by employing the conventional wet granulation method, to achieve prolonged release of medicaments [43].

Akter M, Banik S and Hossain MS studied the development of a sustained release matrix tablet of Metoprolol Succinate by cost saving and production efficient process. Among various tablet manufacturing process, direct compression is the simplest and cost saving process. Different trials were formulated and evaluated using different concentrations of directly compressible grade Kollidon SR as release retardant. The formulated tablets were evaluated for physical and dissolution study using buffer medium. The most outstanding aspect of this study is to monitor the influence of different percentage of Kollidon SR on release rate from the matrix tablet. In this study, influence of different ratio of polymer concentration on drug release was evaluated. The release pattern of different batches were evaluated for Zero order, Higuchi, First order, Krosmeyer-Peppas and Hixson-Crowell kinetics and showed that all the batches followed best the Higuchi kinetics. The drug release kinetics was found to be governed by the amount of the polymer in the matrix system. The higher polymeric content in the matrix decrease the release rate of the drug. The nature of the drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomales release. The studies indicated that the drug release can be modulated by varying the concentration of the polymer. Among the four formulations, formulation 1 is the best formulation as it controls the release best and best linearity for zero order plots [43].

Boldhane SP and Kuchekar BS formulated Metoprolol succinate (MS) gastroretentive (GR) controlled release system to increase gastric residence time leading to improved drug bioavailability. Box-Behnken model was followed using novel combinations of sodium alginate (SA), sodium carboxymethylcellulose (NaCMC), magnesium alumino metasilicate (MAS) as independent variables. Floating lag time (Flag), *t*25, *t*50, *t*75, diffusion exponent as dependent variables revealed that the amount of SA, NaCMC and MAS have a significant effect ($p < 0.05$) on *t*25, *t*50, *t*75 and Flag. MSGR tablets were prepared and evaluated for mass, thickness, hardness, friability, drug content and floating property. Tablets were studied for dissolution for 24 h and exhibited controlled release of MS with floating for 16 h. The release profile of the optimized batch MS01 fitted first--order kinetics ($R2 = 0.9868$, $n = 0.543$), indicating non- Fickian diffusion or anomalous transport by diffusion and swelling.

Gohel MC et al investigated the modified release tablet of metoprolol succinate using hydroxypropyl methylcellulose (HPMC) and xanthan gum as a matrixing agent. A 3^2 full factorial design was employed for the optimization of formulation. The percentage drug released at a given time (Y_{60}, Y_{240} and Y_{720}) and the time required for a given percentage of drug to be released ($t_{50\%}$) were selected as dependent variables. The *in vitro* drug dissolution study was carried out in pH 6.8 phosphate buffer employing paddle rotated at 50 rpm. The similarity factor (f_2) was calculated for selection of best batch considering mean *in vitro* dissolution data of Seloken® XL as a reference profile. It was concluded that the desired drug release pattern can be obtained by using a proper combination of HPMC (high gelling ability) and xanthan gum (quick gelling tendency). The economy of xanthan gum and faster hydration rate favors its use in modified release tablets. The matrix integrity during dissolution testing was maintained by using hydroxypropyl methylcellulose [45].

Rani KRV et al made an attempt to reduce the frequency of dose administration, to prevent nocturnal heart attack and to improve the patient compliance by developing extended release (ER) matrix tablet of Metoprolol succinate. Eight batches of ER matrix tablets of Metoprolol succinate were developed by using wet granulation technique and coated with hydroxy propyl methyl cellulose (KM 100) and hydroxyl methyl cellulose for extended release. Compressed tablets were evaluated for weight variation, hardness, friability and *in vitro* dissolution using paddle (USP type II) method. All formulation showed compliance with pharmacopoeial standards. Among the eight formulations, F8 showed extended release of drug for 20 hours with 87.1% drug release and subjected to stability studies for 3 months at 40^{o}C/75% RH and 60^{o}C/80%RH [46].

Chapter 4

EXPERIMENTAL WORK

4. EXPERIMENTAL WORK

4.1 Materials Used

Table 4.1: List of materials used

Materials	Company name
Metoprolol Succinate	Aarti Drugs Limited, Thane, India.
Sodium chloride	Macron Fine Chemicals Limited, USA.
Potassium chloride	Finar Reagents, Ahmedabad.
Talc	Imerys Private Limited, Paris, France.
Povidone	BASF Corporation, Geismer, LA.
Magnesium stearate	Ferro Corporation, Cleveland.
Aerosil-200	Evonik Industries, Germany.
Microcellac 100	Meggle Group Wasserburg, Germany.
Tablettose 80	Meggle Group Wasserburg, Germany.
Microcyrstalline cellulose PH102	FMC Biopolymers, Wallingstown.
Cellulose acetate	Central Drug House Pvt. Ltd, New Delhi.
Polyethylene glycol 4000	Clariant, Mumbai.
Acetone	Fischer Scientific India Pvt. Ltd, Mumbai.
Sorbitol	Roquette, Tokyo, Japan.

4.2. Equipments Used:

Table 4.2: List of equipments used

Equipments	Company name
Electronic Weighing Balance	Mettler Toledo, Mumbai, India
Moisture analyzer	Mettler Toledo, Mumbai, India
Sieve Shaker	Retsch GmbH, Germany
Roche Friabilator	Labindia, Thane, India
Texture analyzer	Brookfield, Toronto, Canada
Tap density tester	Labindia, Thane, India
USP dissolution apparatus-I	Labindia, Thane, India
Tablet Compression machine	Korsch, Silverwater, Australia
Coating pan	Ganson, Thane, India
Rapid Mixer Granulator	Ganson, Thane, India
UV Spectrophotometer	Shimadzu, Shanghai, China
Disintegration apparatus USP	Labindia, Thane, India
Hardness Tester	Dr. Schleuniger Pharmatron, Switzerland
Turbula Blender	WAB (Willy A.Bachofen AG Maschinenfabrik), Mahopac, New York.
Tray Drier	Precikot Pharma Pvt Ltd, Thane, India.
16 station punching machine	Cadmach, Ahmedabad, India

4.3. Identification of Metoprolol Succinate

4.3.1 Melting Point Determination [37]:

Melting point is the temperature at which the pure liquid and solid exist in the equilibrium. In the practice, it is taken as equilibrium mixture at an external pressure of 1 atmosphere; this is sometime known as normal melting point. The Thiel's tube method of melting point determination in liquid paraffin was used in the present study. Melting point was found to be 136 °C.

Table 4.3: Melting Point Determination of Metoprolol Succinate

Reported Melting Point	Observed Melting Point
135-137°C	136°C

Conclusion: The melting point of Metoprolol Succinate was found to be 136˚C. The melting point determined is within the range of standard value, hence, it is concluded that the drug sample having intimate physical property as standard drug.

4.3.2 FTIR Spectra [14]

IR spectra of drug in KBr pellets at moderate scanning speed between 4000-400 cm-1 was carried out using FTIR (Jasco FTIR 6100 TYPE A). All the powder samples were dried under vacuum prior to obtaining any spectra in order to remove the influence of residual moisture.

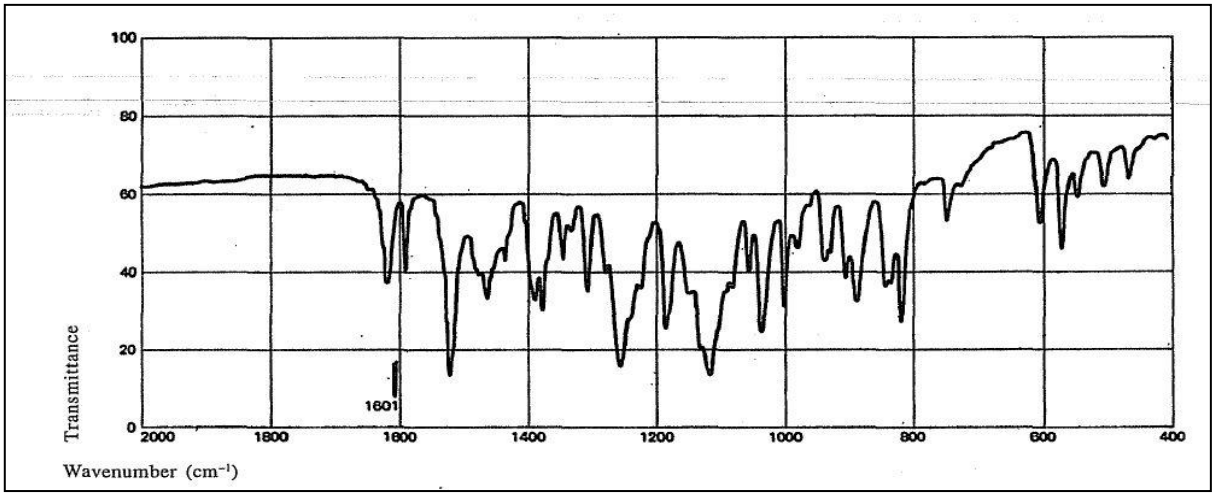


Figure 4.1: Reference FTIR Spectra of Metoprolol Succinate (Reference: Indian Pharmacopoeia- 2010, Volume-I, Page: 372, Section: 3.1)

Table 4.4: Comparison of Reference and Test IR Frequency of Metoprolol Succinate

Functional group	Standard frequency (cm^{-1})	Observed frequency (cm^{-1})
Benzene stretching	1618	1614.13
NH bending	1583	1563.02
C-O Stretching in C-O-C	1110.84	1114.65
C=O	1245	1241.95
C-O Stretching (1^{o} Alcohol)	1045.52	1051.98
C-O Stretching in C=C-O-C	1238.39	1241.93

Conclusion: According to assigned functional group in molecular structure of Metoprolol Succinate, the relevant peaks were obtained. No other non relevant peaks were obtained. So, it can be concluded that the given drug sample is pure.

4.3.3 UV Absorbance Spectra

4.3.3.1. UV Absorbance Spectra in Distilled Water

Metoprolol Succinate was accurately weighed equivalent to 100 mg and transferred into a 100 ml volumetric flask and then volume was made up using Distilled water which gives concentration of 1000 µg/ml. From the above stock solution (1000 µg/ml), 1.5 ml was taken in a 100 ml volumetric flask and making up the volume with distilled water. The resultant solution was scanned in the range of 200 nm to 400 nm using Shimadzu double beam UV/Visible spectrophotometer.

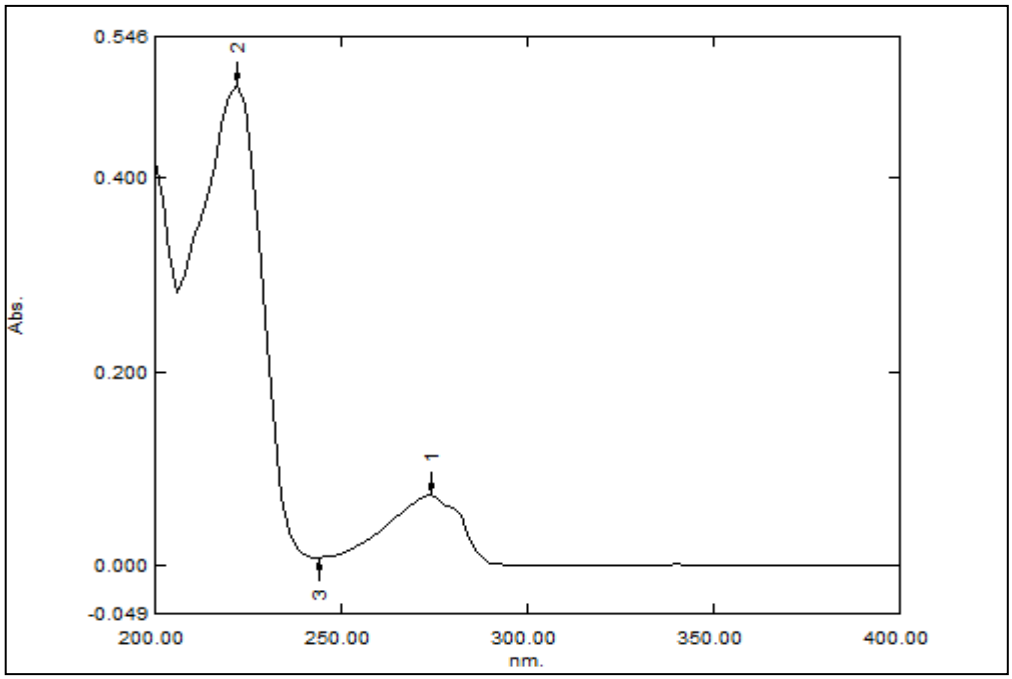


Figure 4.3: UV Absorbance Spectra in Distilled Water

Table 4.5: Peak Points of UV Spectra of Metoprolol Succinate in Distilled Water

Wavelength (nm)	Absorbance
274	0.074
222	0.496
244	0.008

Discussion: The absorption maximum was found to be 222 nm and the absorbance value was 0.496.

4.3.3.2. UV Absorbance Spectra in 0.1N Hydrochloric Acid

Metoprolol Succinate was accurately weighed equivalent to 100 mg and transferred into a 100 ml volumetric flask and then volume was made up using 0.1N Hydrochloric acid which gives concentration of 1000 µg/ml. From the above stock solution (1000 µg/ml), 1.5 ml was taken in a 100 ml volumetric flask and making up the volume with 0.1 N Hydrochloric Acid. The resultant solution was scanned in the range of 200 nm to 400 nm using Shimadzu double beam UV/Visible spectrophotometer.

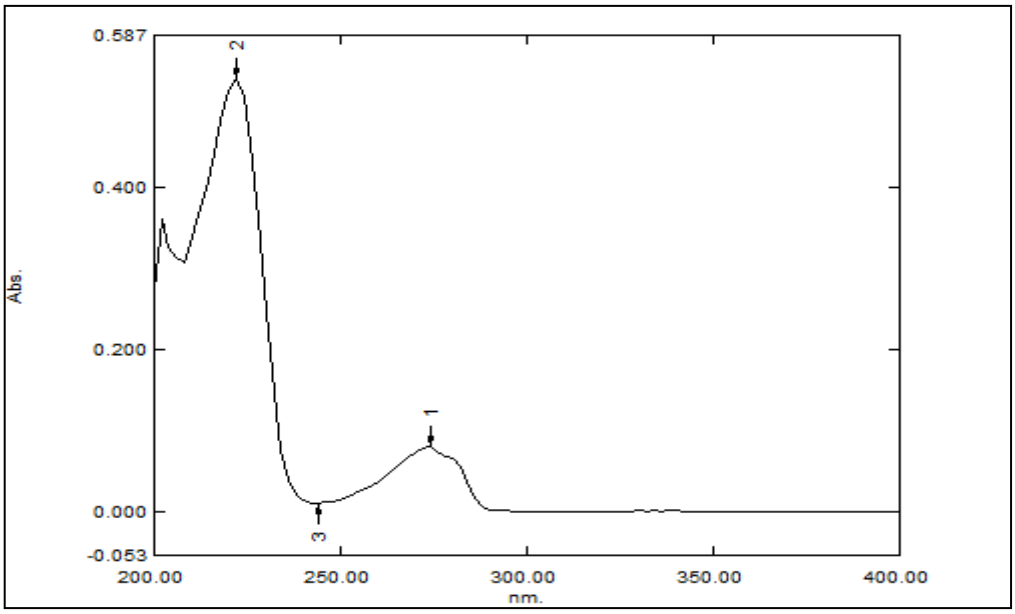


Figure 4.4: UV Absorbance Spectra in 0.1N Hydrochloric Acid

Table 4.6: Peak Points of UV Spectra of Metoprolol Succinate in 0.1N Hydrochloric Acid

Wavelength (nm)	Absorbance
274	0.080
222	0.534
244	0.011

Discussion: The absorption maximum was found to be 222 nm and the absorbance value was 0.534.

4.3.3.3. UV Absorbance Spectra in Acetate Buffer pH 4.5

Metoprolol Succinate was accurately weighed equivalent to 100 mg and transferred into a 100 ml volumetric flask and then volume was made up using Acetate buffer pH 4.5 which gives concentration of 1000 µg/ml. From the above stock solution (1000 µg/ml), 1.5 ml was taken in a 100 ml volumetric flask and making up the volume with Acetate buffer pH 4.5. The resultant solution was scanned in the range of 200 nm to 400 nm using Shimadzu double beam UV/Visible spectrophotometer.

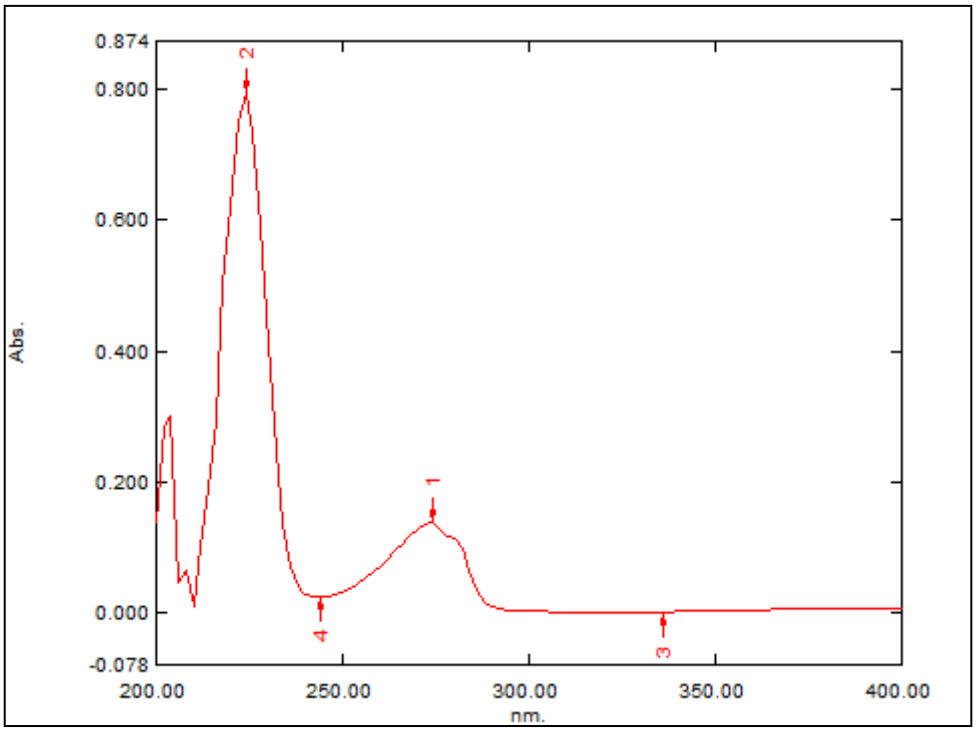


Figure 4.5: UV Absorbance Spectra in Acetate Buffer pH 4.5

Table 4.7: Peak Points of UV Spectra of Metoprolol Succinate in Acetate Buffer pH 4.5

Wavelength (nm)	Absorbance
274.00	0.140
222.00	0.794
244.00	0.025
208.00	0.466

Discussion: The absorption maximum was found to be 222 nm and the absorbance value was 0.794.

4.3.3.4. UV Absorbance Spectra in Phosphate Buffer pH 6.8

Metoprolol Succinate was accurately weighed equivalent to 100 mg and transferred into a 100 ml volumetric flask and then volume was made up using Phosphate Buffer pH 6.8 which gives concentration of 1000 µg/ml. From the above stock solution (1000 µg/ml), 1.5 ml was taken in a 100 ml volumetric flask and making up the volume with Phosphate buffer pH 6.8.

The resultant solution was scanned in the range of 200 nm to 400 nm using Shimadzu double beam UV/Visible spectrophotometer.

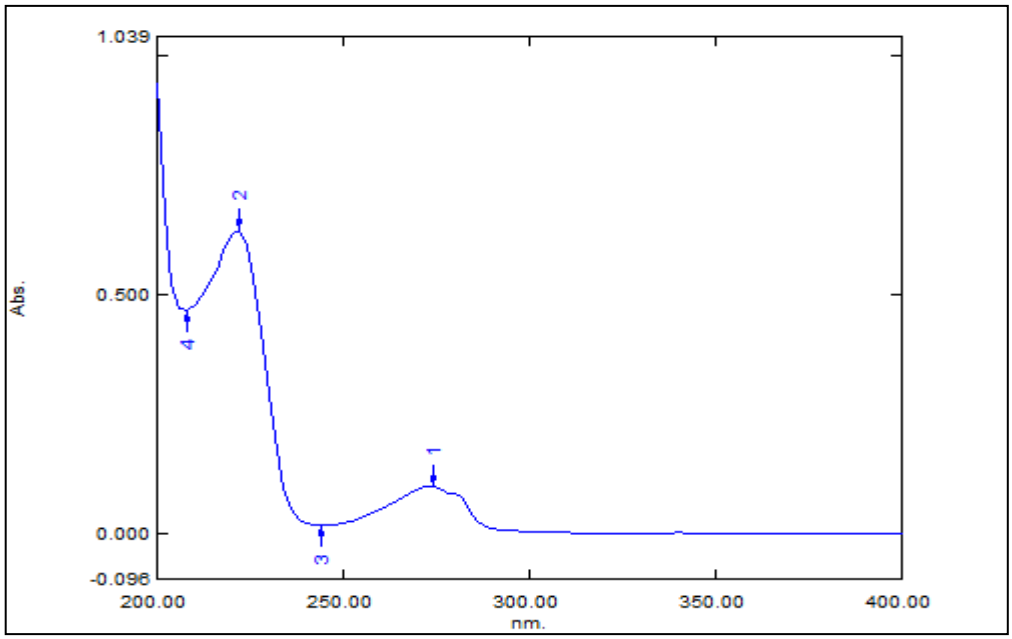


Figure 4.6: UV Absorbance Spectra in Phosphate Buffer pH 6.8

Table 4.8: Peak Points of UV Spectra of Metoprolol Succinate in Phosphate Buffer pH 6.8

Wavelength (nm)	Absorbance
274.00	0.098
222.00	0.633
244.00	0.016
208.00	0.466

Discussion: The absorption maximum was found to be 222 nm and the absorbance value was 0.633.

4.4 Preparation of Calibration Curve of Metoprolol Succinate in Different Solvents [14, 37]:

4.4.1. Preparation of reagents and solutions:

4.4.1.1. Preparation of 0.1 N Hydrochloric Acid:

8.5 ml of concentrated hydrochloric acid was transferred to 1000 ml volumetric flask to produce 0.1N Hydrochloride acid.

4.4.1.2. Preparation of Phosphate Buffer pH 6.8

36 grams of potassium dihydrogen phosphate and 9 grams of sodium hydroxide is dissolved in 10 litres of distilled water to produce phosphate buffer pH 6.8.

4.4.1.3. Preparation of 0.2 M Sodium Hydroxide solution

8.0 gm of sodium hydroxide was dissolved in distilled water and was further diluted with distilled water to produce 1000 ml, which is 0.2 M sodium hydroxide solution.

4.4.1.4. Preparation of Acetate Buffer pH 4.5

2.99grams of sodium acetate was accurately weighed and 1.67ml of glacial acetic acid was measured and added into 1 litre of distilled water, until completely dissolved. Adjust the pH to 4.5 using glacial acetic acid.

4.4.1.5. Preparation of stock solution of drug

Accurately about 100 mg Metoprolol Succinate drug was weighed and transferred to 100ml volumetric flask and dissolved in an appropriate solvent and was further diluted with the same solvent to produce a concentration of 1000 µg/ml.

4.4.2. Establishment of calibration curve of Metoprolol Succinate in Distilled Water: Preparation of dilutions

From the stock solution (1000 µg/ml), serial dilutions were made by taking 0.5 ml, 0.8 ml, 1 ml, 1.3 ml, 1.5 ml, 1.8 ml, 2 ml, 2.3 ml, 2.5 ml, 2.8 ml and 3 ml in 100 ml volumetric flask, dissolving with distilled water and making up the volume with distilled water to give 5, 8, 10, 13, 15, 18, 20, 23, 25, 28 and 30 µg/ml concentration respectively. The absorbances of dilutions were measured at λ_{max}= 222 nm using Shimadzu double beam UV/Visible spectrophotometer in triplicate and the plot of average absorbance vs. concentration were established.

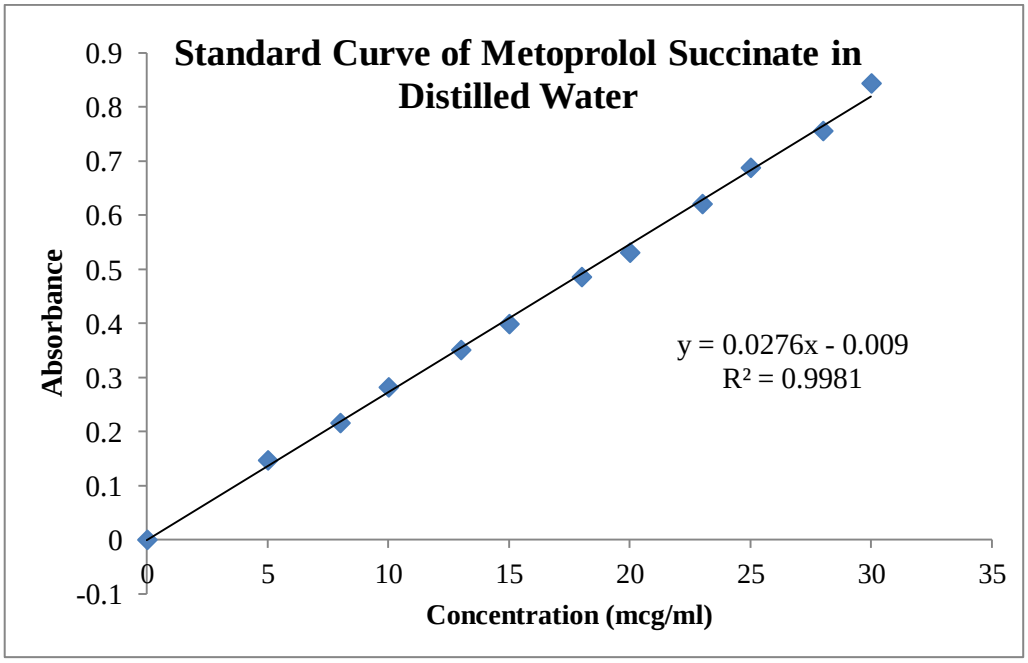


Figure 4.7: Standard Curve of Metoprolol Succinate in Distilled Water

Regression Analysis

Table 4.10: Regression Analysis for Standard Curve of Metoprolol Succinate in Distilled Water

Regression parameter	Value
Correlation coefficient	0.9981
Slope	0.0276
Intercept	-0.009

4.4.3. Establishment of calibration curve of Metoprolol Succinate in 0.1 N Hydrochloric acid.

Preparation of dilutions

From the stock solution (1000 µg/ml), serial dilutions were made by taking 0.5 ml, 0.8 ml, 1 ml, 1.3 ml, 1.5 ml, 1.8 ml, 2 ml, 2.3 ml, 2.5 ml, 2.8 ml and 3 ml in 100 ml volumetric flask, dissolving in 0.1N Hydrochloric acid and making up the volume with 0.1 N Hydrochloric Acid to give 5, 8, 10, 13, 15, 18, 20, 23, 25, 28 and 30 µg/ml

concentration respectively. The absorbance of dilutions were measured at λ_{max} 222 nm using Shimadzu double beam UV/Visible spectrophotometer in triplicate and the plot of average absorbance vs. concentration was established.

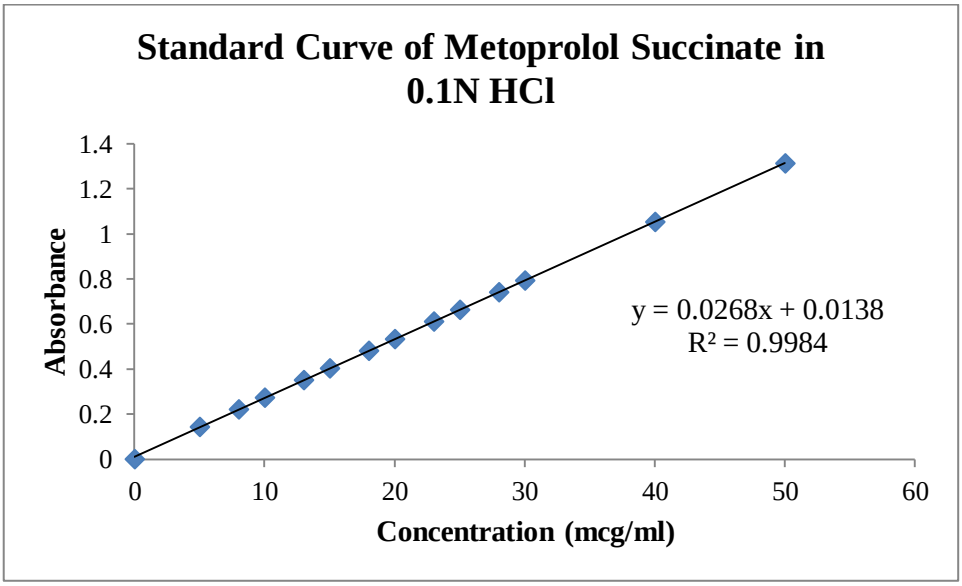


Figure 4.8 Standard Curve of Metoprolol Succinate in 0.1 N Hydrochloric Acid

Regression Analysis

Table 4.12: Regression Analysis for Standard Curve of Metoprolol Succinate in 0.1 N Hydrochloric Acid

Regression parameter	Value
Correlation coefficient	0.9984
Slope	0.0268
Intercept	0.0138

4.4.4. Establishment of calibration curve of Metoprolol Succinate in acetate buffer pH 4.5

Preparation of dilutions

From the above stock solution (1000 µg/ml), serial dilutions were made by taking 0.5 ml, 0.8 ml, 1 ml, 1.3 ml, 1.5 ml, 1.8 ml, 2 ml, 2.3 ml, 2.5 ml, 2.8 ml and 3 ml in 100 ml

volumetric flask, dissolving in acetate buffer pH 4.5 and making up the volume with acetate buffer pH 4.5 to give 5, 8, 10, 13, 15, 18, 20, 23, 25, 28 and 30 µg/ml concentration respectively. The absorbance of dilutions were measured at λ_{max} 222 nm using Shimadzu double beam UV/Visible spectrophotometer in triplicate and the plot of average absorbance vs. concentration was established.

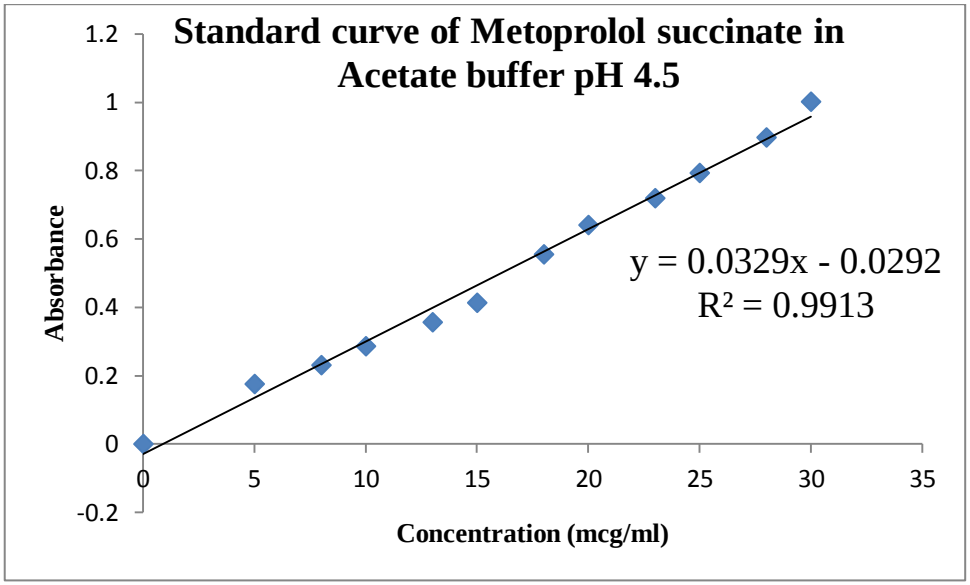


Figure 4.5 Standard Curve of Metoprolol Succinate in Acetate Buffer pH 4.5

Regression Analysis

TABLE 4.14: REGRESSION ANALYSIS FOR STANDARD CURVE OF METOPROLOL SUCCINATE IN ACETATE BUFFER pH 4.5

Regression parameter	Value
Correlation coefficient	0.9913
Slope	0.0329
Intercept	-0.0292

4.4.5. Establishment of calibration curve of Metoprolol Succinate in phosphate buffer pH 6.8

Preparation of dilutions

From the above stock solution (1000 µg/ml), serial dilutions were made by taking 0.5 ml, 0.8 ml, 1 ml, 1.3 ml, 1.5 ml, 1.8 ml, 2 ml, 2.3 ml, 2.5 ml, 2.8 ml and 3 ml in 100 ml volumetric flask, dissolving in phosphate buffer pH 6.8 and making up the volume with phosphate buffer pH 6.8 to give 5, 8, 10, 13, 15, 18, 20, 23, 25, 28 and 30 µg/ml concentration respectively. The absorbance of dilutions were measured at λ max 222 nm using Shimadzu double beam UV/Visible spectrophotometer in triplicate and the plot of average absorbance vs. concentration was established.

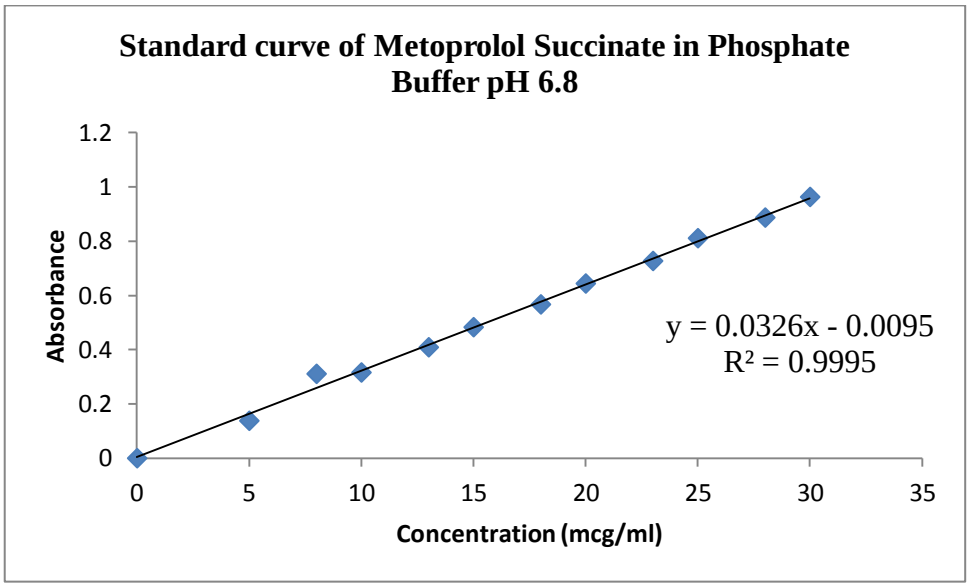


Figure 4.10: Standard Curve of Metoprolol Succinate in Phosphate Buffer pH 6.8

Regression Analysis

Table 4.16: Regression Analysis for Standard Curve of Metoprolol Succinate in Phosphate Buffer pH6.8

Regression parameter	Value
Correlation coefficient	0.9995
Slope	0.0326
Intercept	-0.0095

4.5 Preparation of Controlled Porosity Osmotic Pump Tablets

4.5.1. Preformulation Studies

4.5.1.1. Flow properties of Metoprolol succinate [32, 33]

Result: As per the specifications of USP, the flow property of Metoprolol Succinate is found to be very poor and different diluents were used to get a better flow property.

4.5.1.2. Marketed formulations of Metoprolol Succinate [34]

4.5.1.3. General Information of Marketed Product- Seloken [33, 34]

4.5.2 Preliminary trials for the Formulation of Controlled Porosity Osmotic Pump (CPOP) tablets [5, 9, 10, 13]:

4.5.2.1. Trial-1 using Microcrystalline Cellulose PH102 as diluent and Povidone at 2% concentration Trial-1 comprises of the formulation and evaluation of CPOP tablets containing microcrystalline cellulose (MCC) PH102 as diluent and 2% concentration of povidone (kollidon 30) as the dry binder. The details of trial-1 are provided in the Tables 4.21, 4.22 and 4.23:

Table 4.21: Composition Formula of Trial-1

Ingredients	Quantity (mg/tablet)	Quantity (%)
Metoprolol Succinate	50	25
Sodium Chloride	25	12.5
Microcrystalline Cellulose PH 102	116	58
Talc	2	1
Colloidal Silicon Dioxide (Aerosil 200)	1	0.5
Povidone (Kollidon 30)	4	2
Magnesium Stearate	2	1
Total	**200**	**100**

Result: Based on the USP specifications, the flow property of the powder blend was found to be very poor. Capping was observed. Hence, lactose monohydrate (Tablettose 80) was added to the above blend in a ratio of 70:30 (MCC: lactose monohydrate) in order to improve the flow property and to reduce the capping of the tablets.

4.5.2.2. Trial-2 based on the addition of lactose monohydrate in a ratio of 70:30 (lactose monohydrate: MCC PH102): Trial-2 comprised of formulation and evaluation of CPOP tablets containing microcrystalline cellulose (MCC) PH102 and lactose monohydrate (Tablettose 80) as diluents in a ratio of 30:70 respectively to improve the flow property of the powder blend. The details of the powder blend and tablet compression are provided in the Tables 4.24, 4.25 and 4.26:

Result: Flow property improved upon addition of lactose monohydrate. Since capping was observed, Microcellac 100 (having better flow properties) was used as diluent in the next trial. Moreover, Concentration of povidone as a dry binder was increased from 2% to 3% to eliminate capping.

4.5.2.3. Trial-3 using Microcellac 100 as diluent and increased concentration of Povidone to 3%: Trial-3 comprised of the formulation and the optimization of the CPOP tablets consisting of Microcellac 100 [40] as diluent which is a co-processed tablet diluent used for direct compression and contains 70:30 of Lactose monohydrate: Microcrystalline Cellulose PH102. The concentration of povidone was increased from 2% to 3% to check its effect on capping which was observed in the previous trials. The other ingredients and their concentrations were kept same. The details of the powder blend and tablet compression are provided in the Tables 4.27, 4.28, 4.29:

Result: Capping tendency is eliminated and hardness of 10kp was targeted as the friability of the batches having 9-11kp and 13-15 kp was almost the same. Hence, tablets with lesser hardness and minimal friability were considered to be optimized.

4.5.2.4. Trial-4 (Finalized Characters of tablet):

The composition of Trial-4 included Microcellac 100 as diluent which is a co-processed diluent as mentioned before. At 3% concentration of povidone which was used in Trial-3, no capping was observed. Other ingredients and their concentrations were kept same. The tablet weight was reduced to 400mg from 450mg. The details of the powder blend and tablet compression are furnished in the following tables 4.30, 4.31, 4.32:

Result: Flow property remained poor and concentration of Aerosil 200 was increased to 2% to make the flow property better.

Result: Powder analysis was performed and the flow property of the powder blend was found to be improved with an increase of Aerosil from 0.5% to 2%, hence can be further used for direct compression of the tablets.

Result: Tablet with average weight of 400mg, hardness of 9-11 kp and thickness of 5-6mm were optimized for direct compression of core tablets and their coating. IP-QC tests were performed for these tablets.

Result: On the basis of the results of the IP-QC tests of the tablets, it was concluded that tablets with 400mg weight, hardness of 9-11 kp and thickness of 5-6mm were found to be optimized for direct compression of core tablets and their coating.

4.5.3. Formulation of CPOP tablet:

4.5.3.1. Formulation and development of uncoated core tablets [18, 19, 22, 23]:

Table 4.35: Composition Formula of uncoated core tablets

Ingredients	Quantity (mg/tablet) (Batch size: 200 gram)					
	A	**B**	**C**	**D**	**E**	**F**
Metoprolol Succinate	50	50	50	50	50	50
Sodium Chloride	25	50	75	-	-	-
Potassium Chloride	-	-	-	25	50	75
Microcellac 100	297	272	247	297	272	247
Talc	4	4	4	4	4	4
Colloidal Silicon Dioxide (Aerosil 200)	8	8	8	8	8	8

Povidone (kollidon 30)	12	12	12	12	12	12
Magnesium stearate	4	4	4	4	4	4
Total	**400**	**400**	**400**	**400**	**400**	**400**

Procedure of CPOP tablet:

Core tablets were formulated using sodium chloride and potassium chloride as osmogens at three different concentrations. The batches A, B and C were containing sodium chloride as osmogen and the batches D, E and F were containing potassium chloride as osmogen at three different concentrations. Batch A and D contains drug: osmogen ratio as 1:0.5, Batch B and E contains drug: osmogen ratio as 1:1 and Batch C and F contains drug: osmogen ratio as 1:1.5. Various types and concentration of osmogens, Metoprolol Succinate, Microcellac 100 and Povidone (kollidon 30) were accurately weighed and passed through a sieve of mesh size# 40. These ingredients were then transferred into a turbula blender (WAB (Willy A.Bachofen AG Maschinenfabrik), Mahopac, New York) of 1 litre capacity and were rotated at 40rpm for 15 minutes. The other ingredients like colloidal silicon dioxide (Aerosil 200), talc and magnesium stearate were passed through sieve of mesh size# 40 and were added to lubricate the entire powder blend. Core Tablets was prepared using Korsch tablet compression machine (Silverwater, Australia), using 10 mm punch, with a target tablet weight of 400mg, thickness of 5-6 mm and hardness of 9-11 kp. The machine was made to work at 30 rpm to give the optimized results as follows:

Result: From the observation of the IP-QC tests, it can be concluded that all the six batches, A to F complied with the acceptable range.

4.5.3.2. Coating of the core tablets of CPOP (Batches A to F):

Table 4.38: Composition of the coating solution [38]

Ingredients	Quantity/100g	Quantity/ 500g	% Quantity
Cellulose acetate	9	45	9.081
PEG4000	1	5	1.009
Sorbitol	0.9	4.5	0.9081
Water	9	45	9.081
Acetone	81	405	79.9209

Total	**100.9**	**504.5**	**100**

Procedure for coating of the core tablets:

The coating was carried out in the coating machine, Ganscoater with a capacity of coating pan as 1 kilogram. A batch of 800 grams which included placebos and the actual core tablets were fed into the coating pan made up of stainless steel, having diameter of 28 cm and rotating at a speed of 15-16 rpm. The spray rate was fixed at 1.4-1.8g/min. Inlet temperature was kept between 30-40^{o}C and exhaust temperature was kept between 25-32^{o}C. The bed temperature was maintained at 20-30^{o}C, atomization speed was 0.8-1kg/cm^2 and fan speed was 0.8-1.0 kg/cm^2. The pump rpm and pan rpm was set at 14-16. Coated tablets were dried at 40-45 ˚C for 12-16 h till the weight of the tablets was found to be constant.

Each batch of uncoated tablets was coated at three different percentage weight gains *viz*. 3%, 5% and 7% using the above composition of coating solution and using different parameters as given above. On the basis of the percentage coating done of each batch of uncoated tablets, the total numbers of batches formulated were 18 and their nomenclature was done accordingly. The following batches were prepared:

4.5.4. Evaluation Parameters [20, 25, 28]:

4.5.4.1. In- vitro drug release studies

According to USP specifications, the drug release studies for Metoprolol Succinate were carried out using an USP Type II: paddle apparatus, at a speed of 50 rpm, temperature of 37 $\pm$0.5 ^{o}C for 24 hours in 500 ml of phosphate buffer pH 6.8. During each sampling period, 5ml of samples were withdrawn and filtered with whatmann filter paper and replenished with the same amount of fresh dissolution media. The samples were withdrawn at time intervals of 1, 4, 8, 20 and 24 hours and analyzed for Metorpolol Succinate content by UV spectrophotometry method at λ_{max} of 222nm. As per the USP specifications, the acceptance values of Metoprolol Succinate extended release tablets are given as follows:

4.5.4.1.1. Results and discussion:

4.5.4.1.1.1. In- vitro drug release study of the marketed product- Seloken

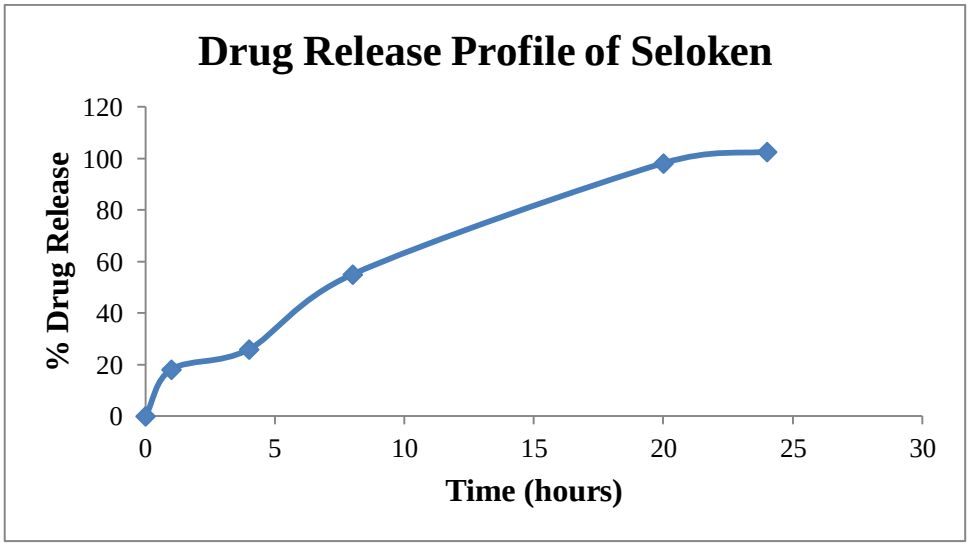


Figure 4.11: Drug Release Profile of Seloken

4.5.4.1.1.2. Dissolution study of Batch A at three different percentages of coating

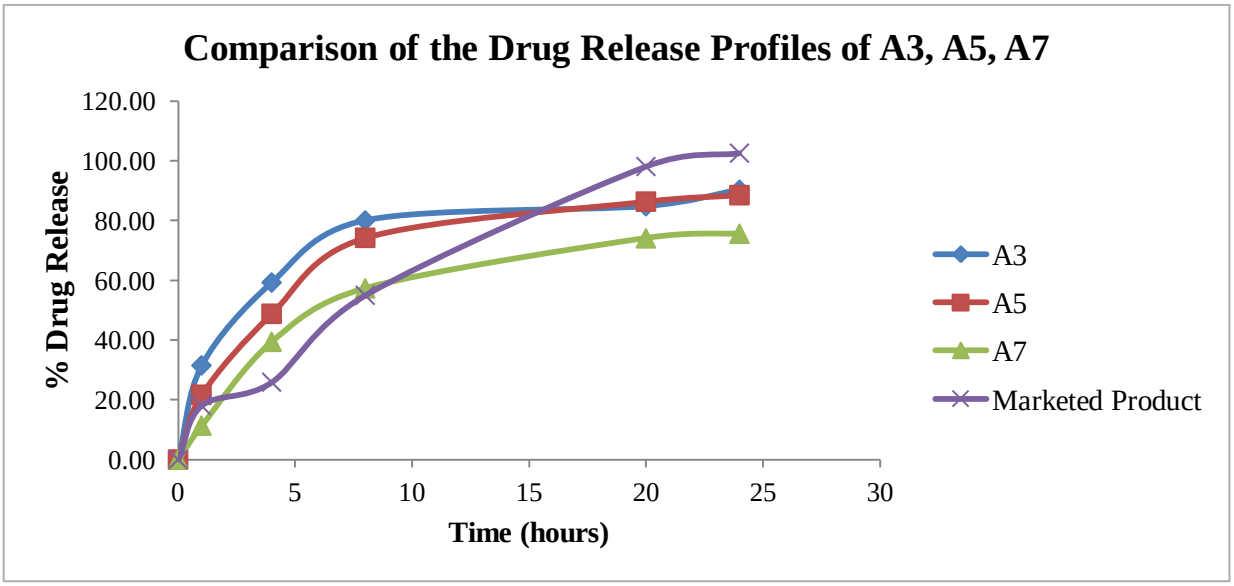


Figure 4.12: Comparative study of the drug release profiles of Batch- A3, A5, A7 and the marketed product- Seloken

Result: The amount of drug release at the end of 24 hours for batches A3, A5 and A7 containing sodium chloride in drug: osmogen ratio of 1:0.5 and % coating of 3%, 5% and 7% was found to be 90.35, 88.55 and 75.62 respectively. The amount of drug release of Seloken was found to be 102.62. Hence, the drug release profiles of the batches A3, A5 and A7 did not match with the marketed product and the batches fail when their drug release profile is compared to the innovator product, Seloken.

4.5.4.1.1.3. Dissolution study of Batch B at three different percentages of coating

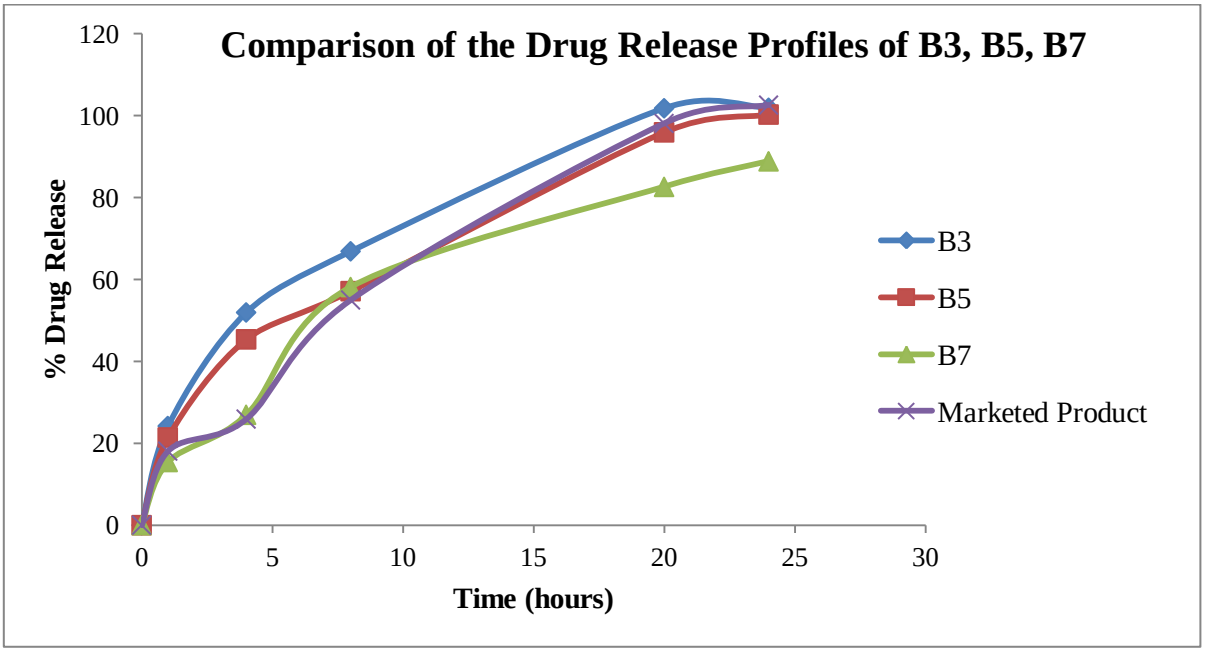


Figure 4.13: Comparative study of the drug release profiles of Batch- B3, B5, B7 and the marketed product- Seloken

Result: The amount of drug release at the end of 24 hours for batches B3, B5 and B7 containing sodium chloride in drug: osmogen ratio of 1:1 and % coating of 3%, 5% and 7% was found to be 101.96, 100.30 and 88.87 respectively. The amount of drug release of Seloken was found to be 102.62. Thus, the drug release profiles of the batches B3, B5 and B7 match with that of marketed product and the batches pass when their drug release profile is compared to the innovator product, Seloken. Here, the best batch among the three batches was found to be B5.

4.5.4.1.1.4. Dissolution study of Batch C at three different percentages of coating

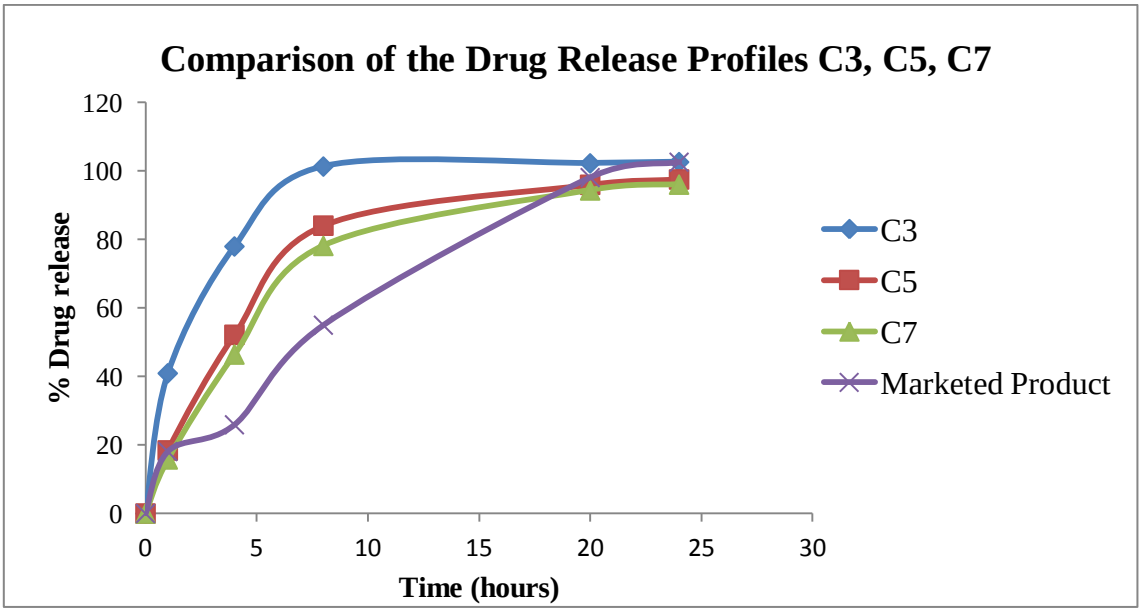


Figure 4.14: Comparative study of the drug release profiles of Batch- C3, C5, C7 and the marketed product- Seloken

Result: The amount of drug release at the end of 24 hours for batches C3, C5 and c7 containing sodium chloride in drug: osmogen ratio of 1:1.5 and % coating of 3%, 5% and 7% was found to be 102.65, 97.58 and 96.08 respectively. The amount of drug release of Seloken was found to be 102.62. Hence, the drug release profiles of the batches C3, C5 and C7 did not match with the marketed product and the batches fail when their drug release profile is compared to the innovator product, Seloken.

4.5.4.1.1.5. Dissolution study of Batch D at three different percentages of coating:

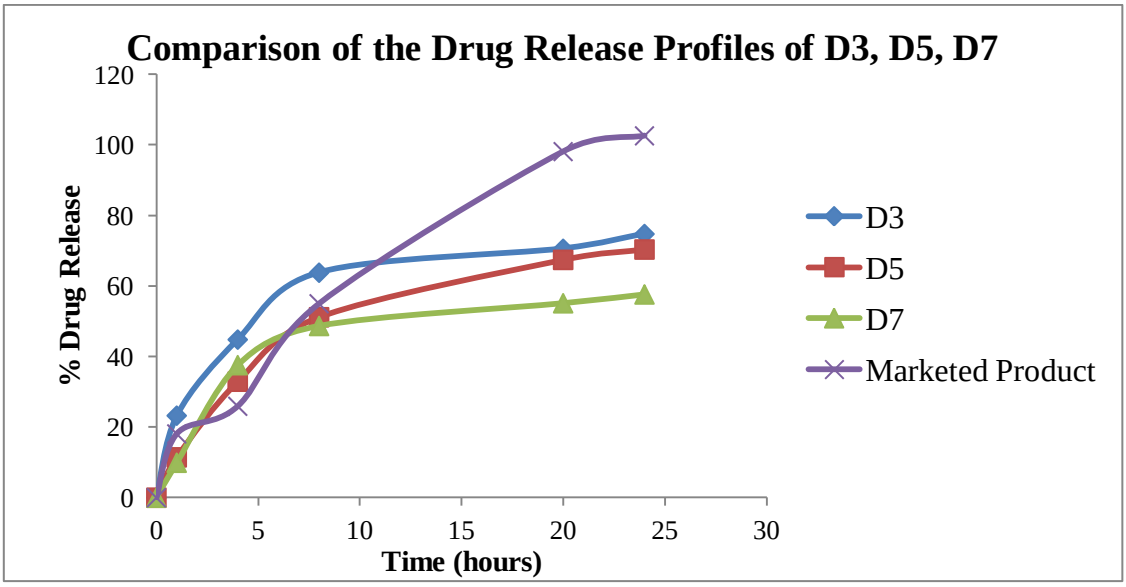


Figure 4.15: Comparative study of the drug release profiles of Batch- D3, D5, D7 and the marketed product- Seloken

Result: The amount of drug release at the end of 24 hours for batches D3, D5 and D7 containing potassium chloride in drug: osmogen ratio of 1:0.5 and % coating of 3%, 5% and 7% was found to be 74.77, 70.38 and 57.64 respectively. The amount of drug release of Seloken was found to be 102.62. Hence, the drug release profiles of the batches D3, D5 and D7 did not match with the marketed product and the batches fail when their drug release profile is compared to the innovator product, Seloken.

4.5.4.1.1.6. Dissolution study of Batch E at three different percentages of coating

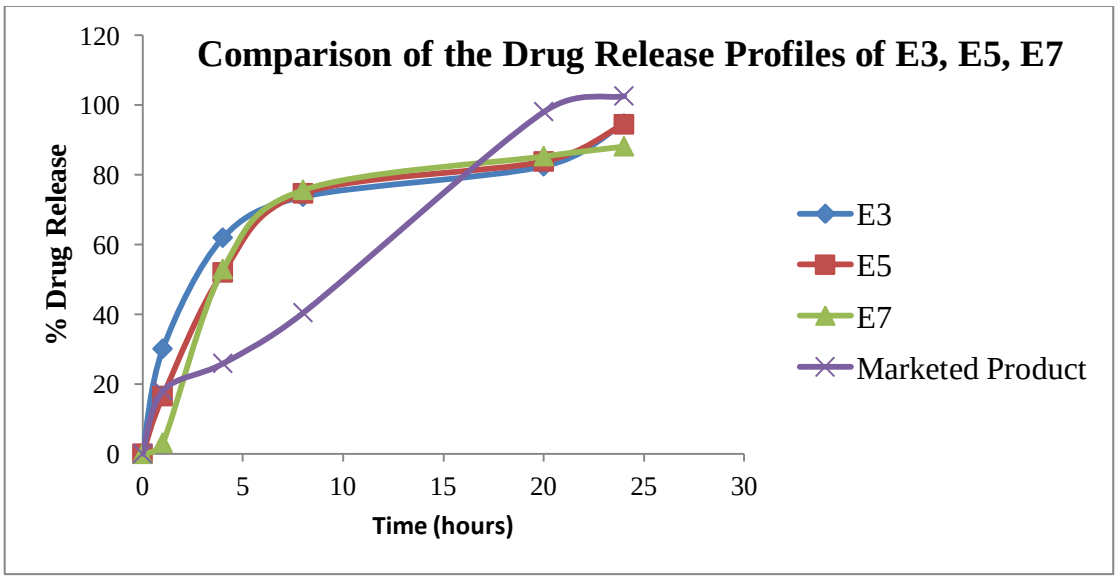


Figure 4.16: Comparative study of the drug release profiles of Batch- E3, E5, E7 and the marketed product- Seloken

Result: The amount of drug release at the end of 24 hours for batches E3, E5 and E7 containing potassium chloride in drug: osmogen ratio of 1:1 and % coating of 3%, 5% and 7% was found to be 94.66, 98.93 and 88.18 respectively. The amount of drug release of Seloken was found to be 102.62. Thus, the drug release profiles of the batches E3, E5 and E7 match with that of marketed product and the batches pass when their drug release profile is compared to the innovator product, Seloken. Here, the best batch among the three batches was found to be E5.

4.5.4.1.1.7. Dissolution study of Batch F at three different percentages of coating

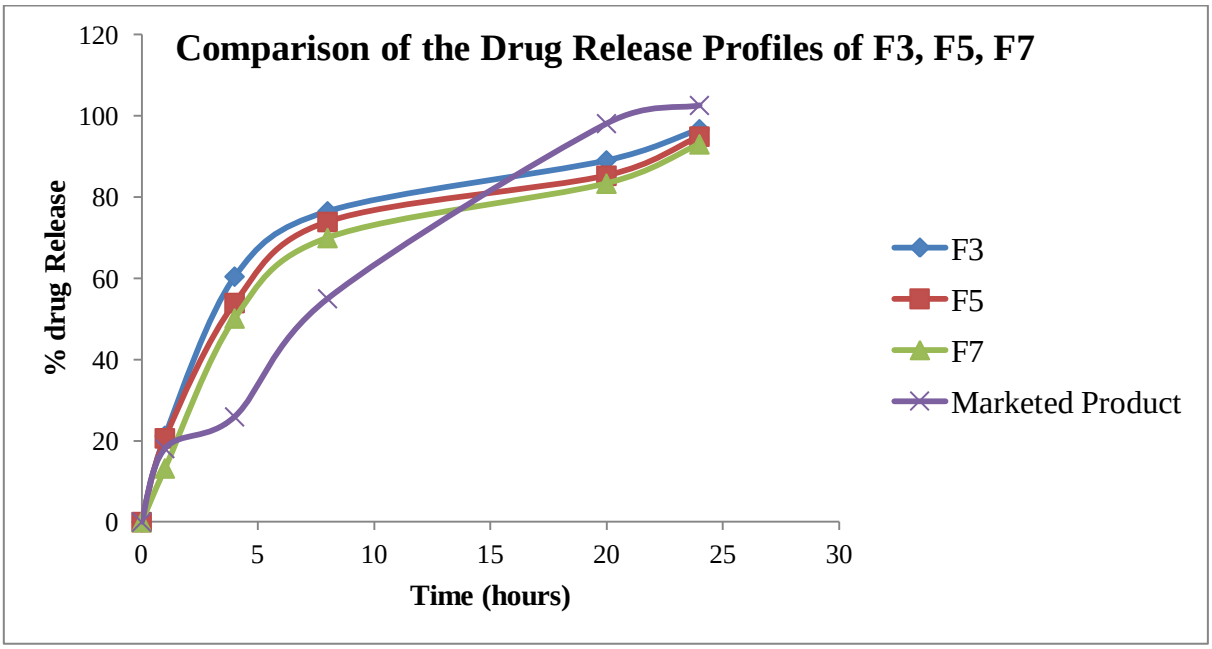


Figure 4.17: Comparative study of the drug release profiles of Batch- F3, F5, F7 and the marketed product- Seloken

Result: The amount of drug release at the end of 24 hours for batches F3, F5 and F7 containing sodium chloride in drug: osmogen ratio of 1:1.5 and % coating of 3%, 5% and 7% was found to be 96.74, 94.93 and 93.03 respectively. The amount of drug release of Seloken was found to be 102.62. Hence, the drug release profiles of the batches F3, F5

and F7 did not match with the marketed product and the batches fail when their drug release profile is compared to the innovator product, Seloken.

4.5.4.1.1.8. Figures of Tablet of Batch B5 before and after dissolution

As seen from the results of the drug release profile of all the batches containing the different types and concentration of the osmogens and different percentages of % coating, the best batch which follows a similar drug release profile as that of the innovator was found to be the batch B5 which contains sodium chloride at a drug: osmogen ratio of 1:1 and % coating of 5%. Figures 4.18, 4.19 and 4.20 respectively depicts the condition of the tablet before, during and after the dissolution of the tablets of the batch B5

Figure 4.18: Tablet before dissolution (Intact tablet)

Figure 4.19: Tablet during dissolution

Figure 4.20: Collapsed tablet after dissolution

Figure 4.18 shows that a CPOP tablet looks similar to conventional tablet. Figure 4.19 shows swelling of CPOP tablet upon dissolution for 24 hours due to absorption of water from the surrounding. Figure 4.20 shows that the tablet becomes hollow after dissolution as the drug gets released into the body. Applying force on such a tablet, the tablet releases the excipients as the tablet becomes hollow, but the coating remains intact.

4.5.4.2. Studies of Drug Release Rate Kinetics [17, 26]:

Release of drug from the controlled porosity osmotic pump tablets is extremely important. To obtain the dissolution rate constants of drug from the dosage form, various models are reported. Various models were tried to fit the optimized batch to determine the mechanism of drug release.

4.5.4.2.1. Zero order model:

In many of the controlled release dosage forms, the drug release kinetics which is followed is zero-order kinetics.

$$M = k*t \quad (4.1)$$

Where,

k is zero order rate constant,

M is % drug unreleased (or released) and t is time.

The plot of % drug unreleased (or released) vs. time is linear.

4.5.4.2.2. First order model:

Most conventional dosage forms and some modified release preparations, particularly prolonged release formulations, adhere to this type of dissolution pattern.

$$M = e^{a} * e^{-bt} \quad (4.2)$$

Where,

a is intercept and b is slope.

It assumes that the drug molecules diffuse out through a gel like layer formed around the drug during the dissolution process. A plot of log % drug released vs time is linear.

4.5.4.2.3. Higuchi model:

A large number of modified released forms contain some sort of matrix system, where the drug gets dissolved from this matrix. The dissolution pattern is based on water penetration rate which is diffusion controlled and the following relationship applies.

$$M = (100-q) * \text{sqrt of time} \quad (4.3)$$

Where,

q is the Higuchi constant (% per square root of time)

In Higuchi model, a plot of % drug unreleased (or released) vs. sqrt of time is linear.

4.5.4.2.4. Korsmeyer-Peppas model:

$$M_t/M = k*t^{n} \quad (4.4)$$

Where,

Mt/M is the fraction of drug released at time‘t’.

n is diffusion exponential; If n = 1, the release is of zero order; 0.5<n<1, release is through anamolous diffusion or case-II diffusion

N = 0.5, release best explained by Fickian diffusion,

A plot of log fraction of drug release vs. log t is linear.

4.5.4.2.5. Hixon-Crowell model:

Cube root law can express the dissolution process for the dosage forms which contain many particles of the same size and shape or their agglomerates that dissolve evenly.

$$M = (100^{1/3} - (k*t))^{3} \quad (4.5)$$

Where,

k is the Hixon-crowell constant (mass/time) 1/3.

In this model, the % drug unreleased vs. cube root of time is linear.

4.5.4.2.6. Results and discussion:

Result: Out of all the models applied, the best fitting model is the Higuchi model for all the batches as the value of R^2 in this model is nearest to 1. The same release can be observed in the study performed by Elbary A., Tadros MI., Eldin AA., on controlled porosity osmotic pump tablets of Etodolac. [41] Higuchi Model describes the drug release following the mechanism of diffusion based on the water penetration principle.

4.5.4.3. Burst strength:

Burst strength is defined as the force required to rupture the shells after dissolution studies. Burst strength of the exhausted shells (n = 3), after 24 h of dissolution, was determined to assure that the tablets would maintain their integrity in the GIT, thereby determine the strength of the semipermeable membrane used in the coating of the controlled porosity osmotic pump tablets. Texture analyzer (Brookefield, Toronto, Canada) with 5 gram load cell and 20 mm acryl cylindrical probe was utilized for this purpose. Test speed of 10.00 mm/min and the distance to be moved was selected to be 25 mm.

4.5.4.3.1. Results and discussion:

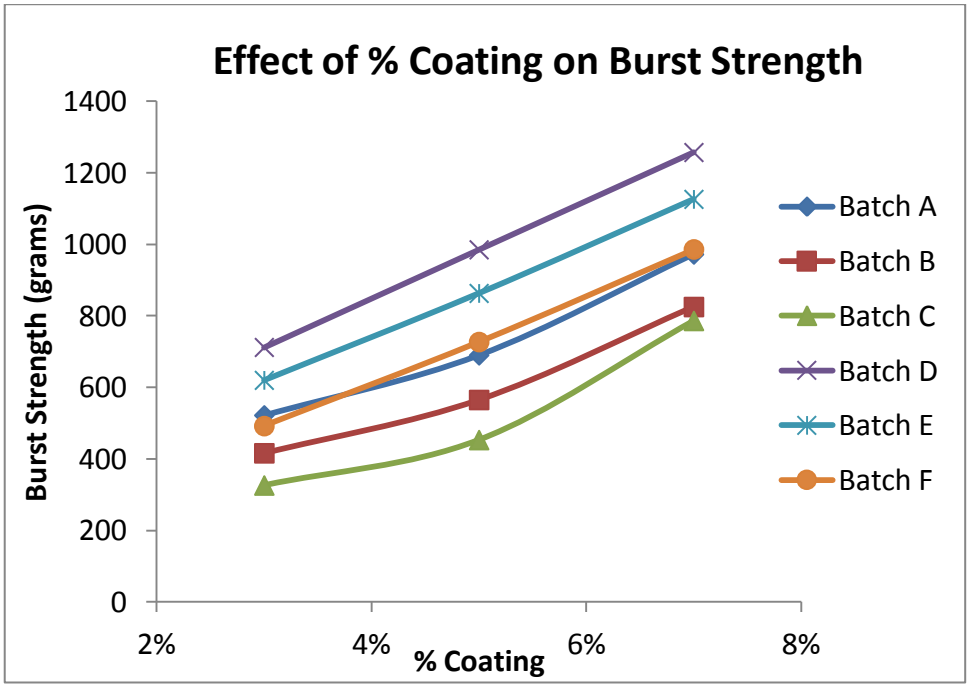


Figure 4.21: Study of Effect of % Coating on Burst Strength

Result: As the % coating increases, the burst strength increases. Hence, both are directly related.

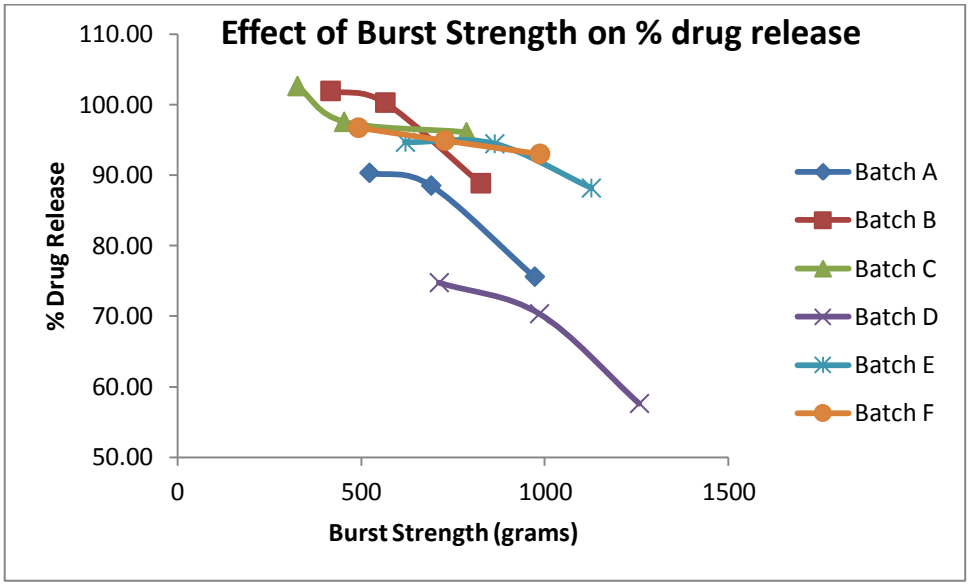


Figure 4.22: Study of Effect of Burst Strength on % drug release

Result: As the burst strength increases, the % drug release decreases in all the six batches. Hence, % drug release and burst strength are inversely related.

4.5.5. Introduction to Optimization Design [36, 40]

4.5.5.1. Introduction to Full Factorial design:

The design of an experiment can be simply defined as the statistical plan that governs the performance of an experiment, keeping in mind the pharmacist's choice of formulation components which can optimize one or more formulation attributes. It is the best interest of pharmaceutical scientist to understand the theoretical formulation and the target processing parameter in such a way that the formulation development can be done in the shortest possible time and with the use of minimum quantity of raw material. The developed formula is then tried at the pilot scale-up therefore, it is very essential to study the formulation from all the perspective at laboratory levels.

Factorial designs are used in experiments when the effects of different factors or conditions, on experiment results are to be elucidated. Factors may be qualitative or

quantitative. The levels of each factor are the value or designation assigned to combination of all levels of all factor. The effect of a factor is the change in response caused by varying the levels of the factor.

The objective of the factorial design is to characterize the effect of changing the levels of the factor or combination of factors on the response variable. Predictions based on the results of an undesired experiment will be more variable than those, which could be obtained in a designed experiment, in particular factorial design.

The optimization procedure is facilitated by construction of an equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed, where the coefficients in the equation are related to the effects and interaction of the factors. The equation 4.6 constructed form 3^n factorial experiment is in the following form.

$Y = BO + B1X1 + B2X2 \ldots\ldots BnXn + B12X1X2 + B1X12 + B22X22 \ldots BmnXn2$ (4.6)

Where,

Y= the measured response,

Xi = level of ith factor

Bi,Bj,Bij= the coefficients from the response of the formulation in design,

Bo= Intercept

The magnitudes of the coefficients represent the relative importance of each factor. Once the polynomial equation has been established, an optimum formulation can be found out by grid analysis. With the use of computer a grid method can be used to identify optimum regions, and response surfaces may be depicted. A computer can calculate the response based on equation at many combinations of factor levels. The formulation whose response has optimal characteristics based on the experimenter's specification is then chosen.

4.5.5.2. 3^2 FULL FACTORIAL DESIGNS [17]

The two- level design is written as a 3^2 factorial design. It means that 2 factors are considered, each at 3 levels which are usually referred to as low, medium and high levels. These levels are numerically expressed as -1, 0 and +1. The main advantage of three level design is that a three level for a factor facilitates investigation of a quadratic relationship between the response and each of the factors. The three-level full factorial design is prohibitive in terms of the number of runs, and thus in terms of cost and effort.

A design of experiments was generated between the factors and responses for determining the levels of factors, which yield optimum responses. A second order polynomial regression equation (Equation 4.7) that fitted to the data is as follows:

$$\mathbf{Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_{11}(X_1)^2 + B_{22}(X_2)^2 + B_{112}(X_1)^2(X2) + B_{221}(X_2)^2(X1)} \quad \mathbf{(4.7)}$$

Where, B_0 is the intercept representing the arithmetic averages of all the quantitative outcomes of eight experimental runs;

B1, B_2, B_{12}, B_{11}, B_{22}, B_{112} and B_{221} are the coefficients computed from the observed experimental values of Y; and X_1, X_2 are the coded levels of factors. $(X_1)^2$, $(X_2)^2$, $(X_1)^2(X_2)$ and $(X_2)^2(X_1)$ are known as the interaction terms which gives the interaction within the factors. If these interaction terms and the factors are significant, then the entire equation fits into the model and the model becomes significant.

The equation represents the quantitative effect of factors (X_1 and X_2) and also of the interaction terms (($(X_1)^2$, $(X_2)^2$, $(X_1)^2(X_2)$ and $(X_2)^2(X_1)$) upon each of the responses; Y_1 to Y_4. Coefficients with one factor represent the effect of that particular factor while the coefficients with more than one factor represent the interaction between those factors. A positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect of the factors. ANOVA was applied for estimating the significance of the model, at 5% significance level. A model is considered significant if the *p*-value is less than 0.05.

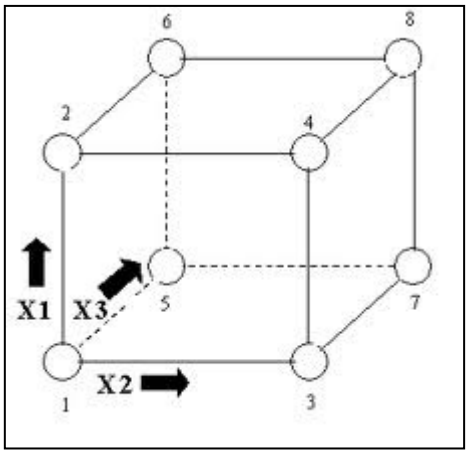


Figure 4.23: Schematic Diagram to show the Full Factorial Design

Advantages of factorial design:

1. Minimum number of trials per independent variable is required.
2. Factorial designs have maximum efficiency in estimating main effects.
3. They form the basis for several other designs (like fractional factorial, composite etc.)
4. More information is obtained with less work.
5. They can be used as building block to define a large response surface.
6. The effects are measured with maximum precision.
7. Both quantitative and qualitative variables can be examined and results can be easily interpreted.

Applications:

1. To help and interpret the mechanism of an experimental system.
2. To recommend or implement, a practical procedure or a set of condition, in an industrial manufacturing operation.
3. To provide guidance for further experimentations.

4.5.6. Evaluation of the optimized batches

4.5.6.1. Effect of pH

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies on optimized formulations were conducted in media at different pH, that is pH 1.2, pH 4.5 and pH 6.8 which can be mimicked by 0.1N Hydrochloric acid, Acetate buffer pH 4.5 and Phosphate buffer pH 6.8, respectively. USP Type II dissolution apparatus at 50 rpm and at a temperature of

37±0.5 °C was used. Samples of 5ml were withdrawn at predetermined intervals and analyzed in UV Spectrophotometer at λ_{max} 222nm. This study was conducted on the optimized batches containing sodium chloride (Batch B5) and potassium chloride (Batch E5). The results are shown in Tables 4.76 to 4.81:

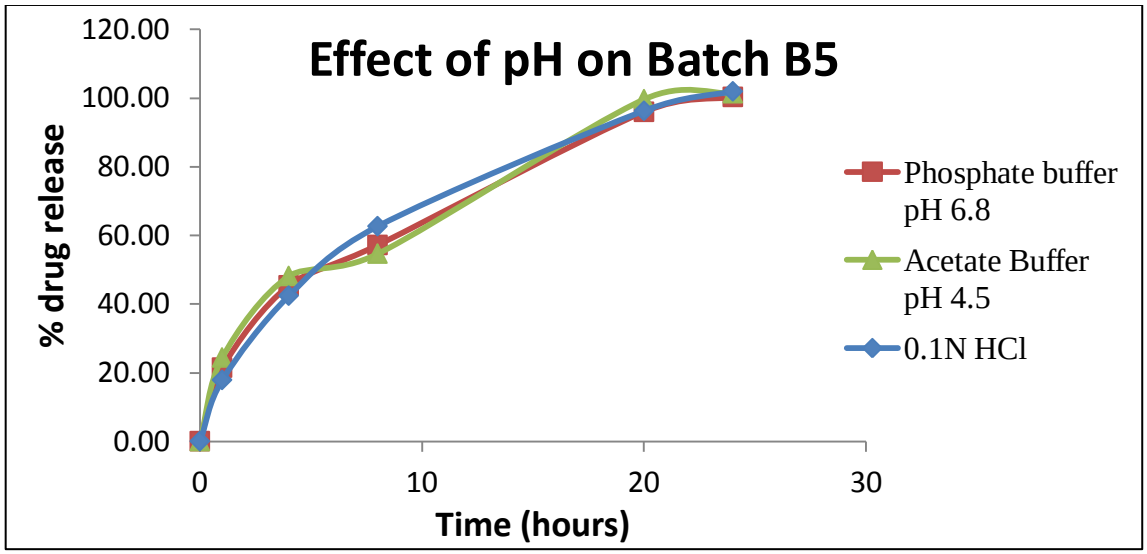


Figure 4.40: Effect of pH on Batch B5

Result: Batch B5 containing sodium chloride as osmogen, with 1:1 drug: osmogen ratio and 5% coating was evaluated at different pH range and it was found that there was no difference in drug release as the pH was changed.

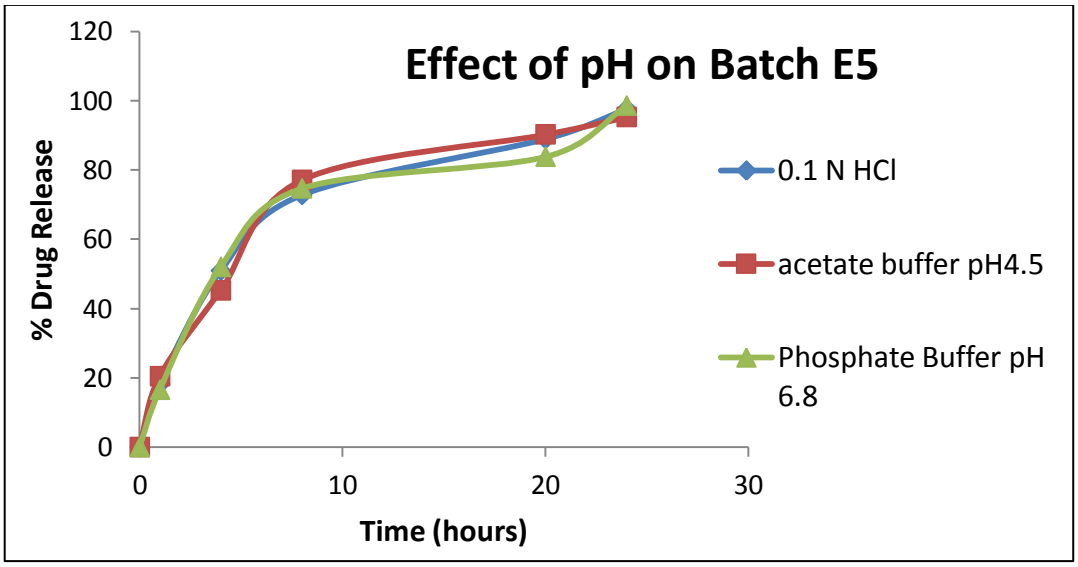


Figure 4.41: Effect of pH on Batch E5

Result: Batch E5 containing potassium chloride as osmogen, with 1:1 drug: osmogen ratio and 5% coating was evaluated at different pH range and it was found that there was no difference in drug release as the pH was changed.

4.5.6.2. Effect of Agitational Intensity

To study the effect of agitation intensity of release media and to assure a reliable performance of the developed formulations independent of agitational intensity, release studies of optimized formulation were carried out in dissolution apparatus at various rotational speeds. USP Type II dissolution apparatus was used at different rotational speeds of 25, 50, 75, 100 rpm and temperature 37±0.5°C was used. Samples of 5ml were withdrawn at predetermined intervals and analyzed in UV Spectrophotometer at λ_{max} 222nm. Fresh buffer solutions of volume 5ml were replenished. This study was conducted on the optimized batches containing sodium chloride (Batch B5) and potassium chloride (Batch E5). The results are shown in Tables 4.82 to 4.89:

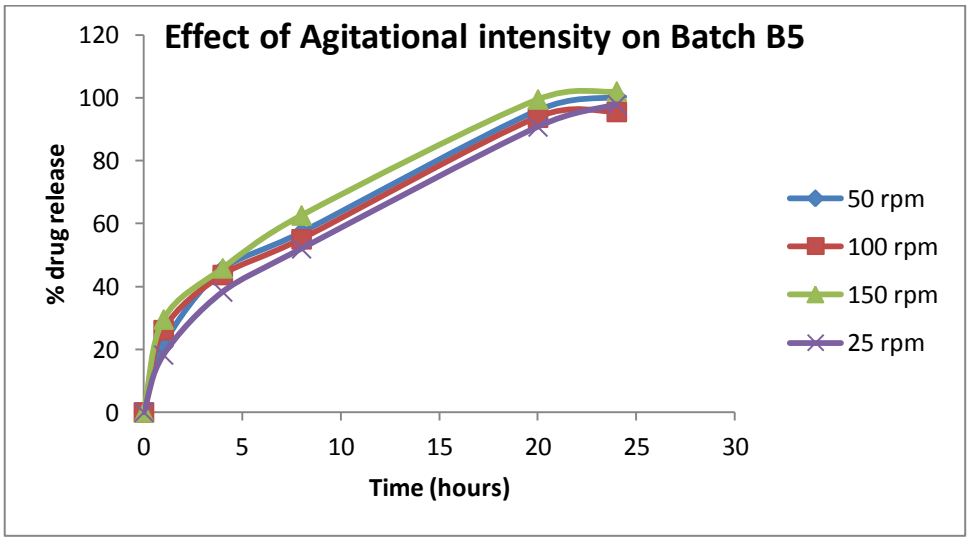


Figure 4.42: Effect of agitational intensity on Batch B5

Result: Effect of the agitational intensity on batch B5 containing sodium chloride as osmogen, with 1:1 drug: osmogen ratio and 5% coating was checked at different agitational intensity and it was found that no significant difference was found in the drug release when the intensity was changed from 25 rpm to 150 rpm.

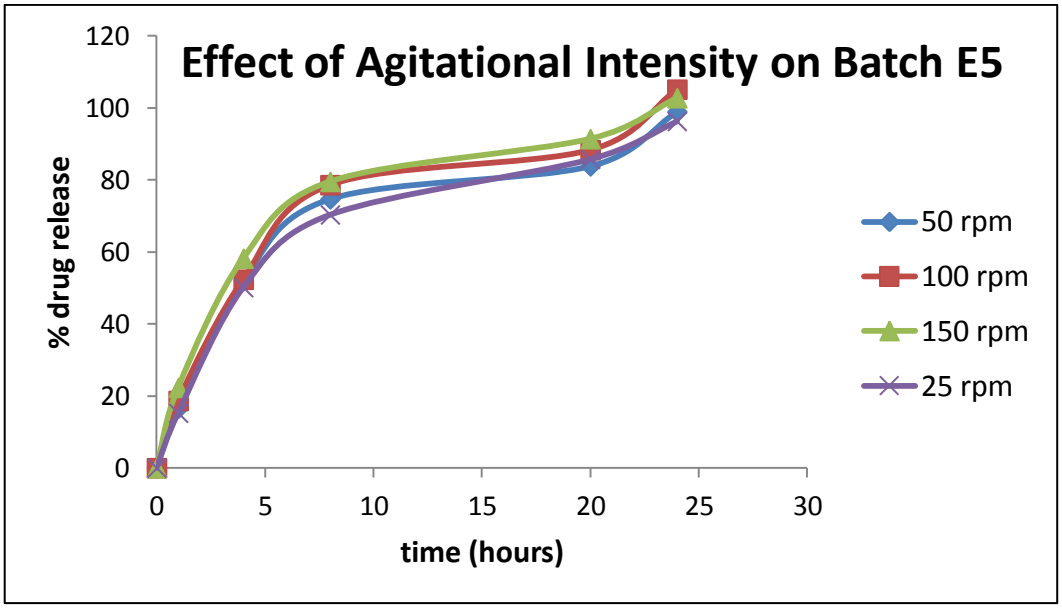


Figure 4.43: Effect of agitational intensity on Batch E5

Result: Effect of the agitational intensity on batch E5 containing potassium chloride as osmogen, with 1:1 drug: osmogen ratio and 5% coating was checked at different agitational intensity and it was found that no significant difference was found in the drug release when the intensity was changed from 25 rpm to 100 rpm.

4.5.7.3. Effect of Osmotic Pressure:

The effect of osmotic pressure is checked by adding different amount of an osmotic agent into the dissolution media. Different concentration (0.25%, 0.5%, 1% and 1.5%) of mannitol were added in Phosphate Buffer pH 6.8. USP Apparatus II is used for dissolution at 50 rpm and 37$\pm$0.5^{o}C. 5ml of samples were withdrawn at the predetermined intervals and the absorbance was checked by using UV Spectrophotometer at λ_{max} of 222nm. 5ml of fresh buffer was replenished in dissolution media. This study was conducted on the optimized batches containing sodium chloride (Batch B5) and potassium chloride (Batch E5). The results are shown in table 4.90 to 4.99.

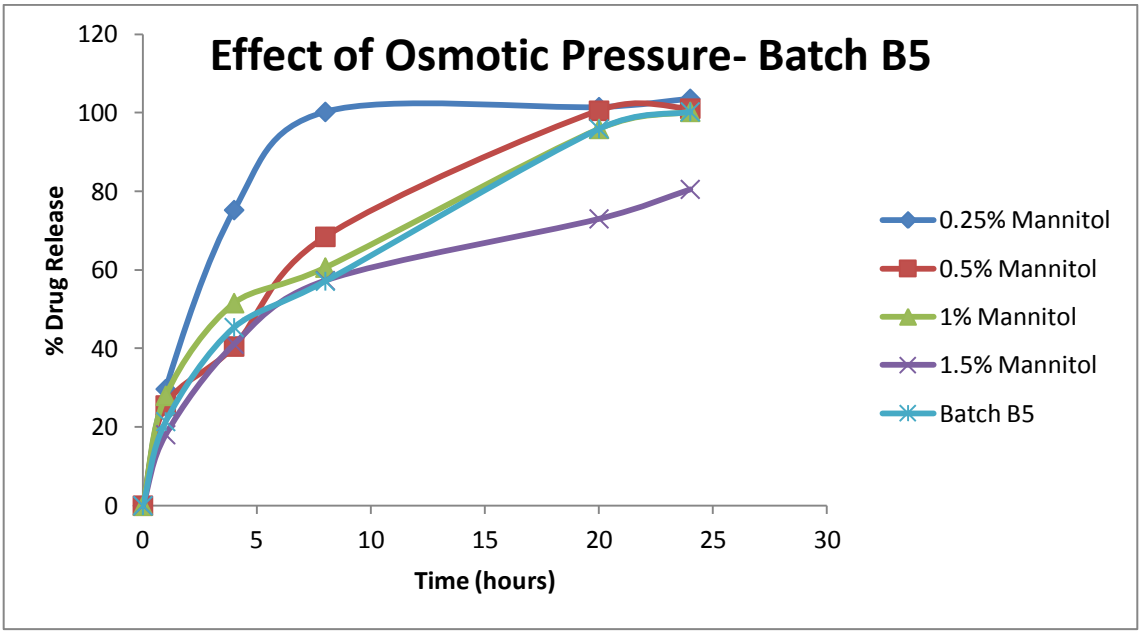


Figure 4.44: Effect of Osmotic Pressure on Batch B5

Conclusion: As the concentration of osmogen in the dissolution media is increased, the amount of drug release is decreased. This indicates that the release of the drug is inversely proportional to the amount of osmogen used. Hence, batch containing 0.25% of mannitol in the dissolution media releases maximum amount of drug and batch containing 1.5% of mannitol in the dissolution media releases the minimum amount of drug.

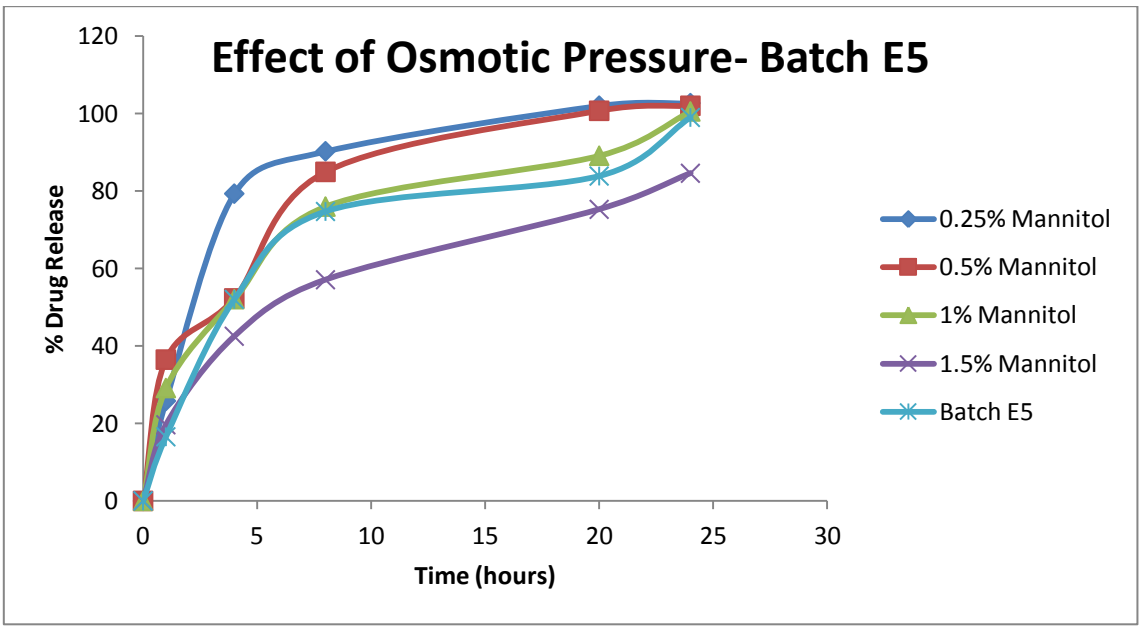


Figure 4.45: Effect of Osmotic Pressure on Batch E5

Conclusion: As the concentration of osmogen in the dissolution media is increased, the amount of drug release is decreased. This indicates that release of drug is inversely proportional to the amount of osmogen used. Hence, batch containing 0.25% of mannitol in the dissolution media releases maximum amount of drug and batch containing 1.5% of mannitol in the dissolution media releases the minimum amount of drug.

4.5.6.4. Comparative study of the optimized batches with batches containing same amount of different osmogens:

The comparative study of the optimized batches containing sodium chloride (Batch B5) and potassium chloride (Batch E5) in a drug: osmogen ratio of 1:1 and 5% coating of cellulose acetate was done with the batches containing the same amount of different osmogens like mannitol (Batch M5), dextrose (Batch N5) and sucrose (Batch O5) with 5% coating of cellulose acetate. The formulation of these batches is given in the Table 4.100.

Drug release study was carried out using USP apparatus II for dissolution at 50 rpm and $37\pm0.5^{o}C$ using Phosphate buffer pH 6.8 as dissolution media. The release of the drug from the CPOP tablets depends on the osmotic pressure of the osmogen incorporated in the formulation. As the amount of osmotic pressure increases, the amount of drug release also increases. The osmotic pressures of the osmogens used in this comparative study are given in the Table 4.101:

The details of the drug release profiles of the batches M5, N5, O5, B5 and E5are given in the Tables 4.102 to 4.106.

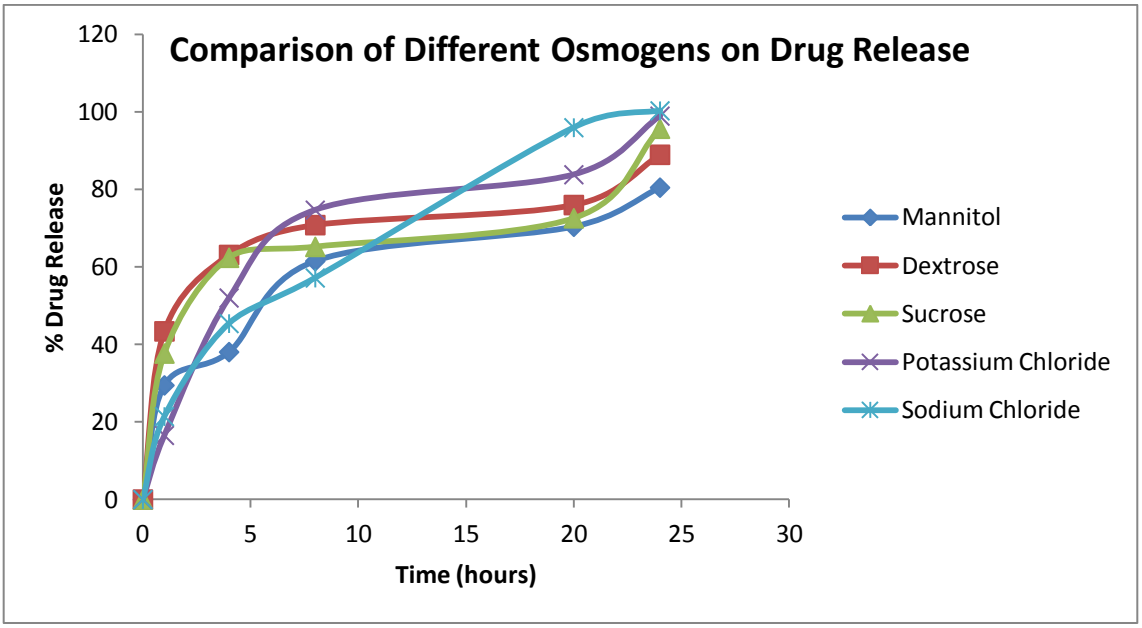


Figure 4.46: Comparison of different osmogens with the optimized batches

Result: The release of the drug is based on the type of osmogen and their osmotic pressure. As the osmotic pressure increases, the release of the drug increases. The drug release was least when mannitol (osmotic pressure: 38 atm) was used as osmogen and highest when sodium chloride (osmotic pressure: 356 atm) was used as osmogen.

Conclusion: On the basis of the drug dissolution profiles and the burst strength of the exhausted shells, two best batches of sodium chloride and potassium chloride each were found to be optimized. Different parameters like effect of pH, agitational intensity and osmogen were studied on both the optimized batches and the effect was studied. These parameters were also compared with the marketed product-Seloken $^{(R)}$. A comparison of the various osmotic agents like Mannitol, Sucrose, Dextrose, Potassium Chloride and Sodium Chloride was done and their drug release profiles were evaluated. From these studies, it was concluded that the batch carrying sodium chloride in drug: osmogen ratio of 1:1 with 5% semipermeable membrane coating was found to be the best formulation.

Chapter 5

SUMMARY

5. SUMMARY

Controlled Porosity Osmotic Pump drug delivery systems are the dosage forms which follow the zero order release and provide a controlled release for a long period of time. This makes it one of the most promising drug delivery systems in the recent times. Here, Metoprolol Succinate, a cardio selective β1-adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension is used as the drug of choice as it is BCS class I drug and it is practically soluble in almost all the solvents. The bioavailability of the drug is 50% as it undergoes the first pass metabolism. All these important properties of the drug necessitates for a twice daily dosage regimen which is inconvenient for maintenance therapy in asymptomatic patients. Thus, an alternative formulation of this drug, which was osmotically controlled oral drug delivery system was prepared and evaluated.

The rate of drug release from osmotic tablet depends on the drug solubility and the osmotic pressure of the osmogens. Here, core tablet was prepared by direct compression using 3% of Povidone (Kollidon 30) as a dry binder along with the other tablet diluents and lubricants. Effect of osmogens like Sodium Chloride and Potassium Chloride were studied. Drug/sodium chloride combination showed higher drug release in comparison to drug/potassium Chloride combination as the osmotic pressure of sodium chloride was 354 atm, while that of potassium chloride was 245 atm. Hence, it was understood that the osmotic pressures of these osmogens had a direct impact on the drug release.

Cellulose acetate was used as coating polymer to form semipermeable membrane around core tablet. Polyethylene Glycol-4000 (PEG 4000) was used as a plasticizer because it allows high permeability of the membrane compared to other plasticizers. Sorbitol was chosen as pore former at a concentration of 0.9%.

Drug release profiles of all the batches of coated tablets and the burst strength of the exhausted shells of the tablets were evaluated. A comparison of these parameters was done between all the batches of the tablets containing both the osmogens. The drug release profiles of all the batches were compared with the marketed product-Seloken $^{(R)}$.

Optimization of the batches was done separately for both the osmogens by using 3^2 Full Factorial Design using Statistica Software version 9.0. Response surface plots were generated. Dissolution data of optimized formulation was fitted and to various mathematical models to describe kinetics of drug release. Effect of pH, agitational intensity and osmotic pressure on in vitro release of drug from the optimized batch was studied. Drug release from optimized batch was found to be independent of pH and agitational intensity. The drug release profile of the CPOP was found to be dependent on the osmotic pressure of the osmotic agent present in the dissolution media. It was found that as the osmotic pressure in the media increases, the drug release decreases. A comparison of the various osmotic agents with the optimized batches was done. For this, same concentration of different osmotic agents like Mannitol, Sucrose, Dextrose, Potassium Chloride and Sodium Chloride were used in the formulation and their drug release profiles were studied. It was found that as the osmotic pressure of the formulation increases, the drug release of the dosage form also increases.

Thus, from the present investigation, it can be concluded that development of Controlled Porosity Osmotic Pump of Metoprolol Succinate will be an effective dosage form for the hypertensive patients as the antihypertensive effect can be seen for a prolonged duration of action within the therapeutic range as a result of which the adverse effects of the drug can be minimized and the patient compliance can be increased.

Chapter 6

REFERENCES

6. REFERENCES:

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