"FORMULATION AND OPTIMIZATION OF OSMOTICALLY CONTROLLED DRUG DELIVERY OF ANTIEPILEPTIC DRUG"

A Thesis Submitted to

NIRMA UNIVERSITY

in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

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21st, May 2019

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This is to certify that the dissertation work entitled "Formulation optimization of Osmotically Controlled Drug Delivery of Antiepileptic Drug" submitted by Ms. Hetal Panchal with Regn. No. (17MPH105) in partial fulfillment for the award of Master of Pharmacy in "Name of a Department" is a bonafide research work carried out by the candidate at the Department of Pharmaceutical Technology and Biopharmaceutics, 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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To Whom So Ever It May Concern

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Throughout her project she has shown full devotion in handling assignments entrusted upon her.

During her tenure with us, she was found to be sincere and focused.

We wish her all the best for her career.

For, Intas Pharmaceuticals Ltd.,

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CERTIFICATE OF ORIGINALITY OF WORK

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DECLARATION

I hereby declare that the dissertation entitled "Formulation and Optimization of Osmotically Controlled Drug Delivery of Antiepileptic Drug", is based on the original work carried out by me under the guidance of Dr. Tejal Mehta, Professor and Head, Department of Pharmaceutics, Institute of Pharmacy, Nirma University. 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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BCS	Biopharmaceutical Classification System
EOP	Elementary Osmotic Pump
CPOP	Controlled Porosity Osmotic Pump
PPOP	Push Pull Osmotic Pump
CDDS	Controlled Drug Delivery System
MSC	Maximum Safe Concentration
MEC	Maximum Effective Concentration
GIT	Gastrointestinal track
IVIVC	In-Vivo In-Vitro Correlation
BD	Bulk Density

TD	Tapped Density
CI	Carr's Index
HR	Hausner's Ratio
USP	United State Pharmacopeia
IP	Indian Pharmacopeia
CA	Cellulose Acetate
HPMC	Hydroxypropylmethylcellulose
HPC	Hydroxypropylcellulose
IPA	Isopropyl alcohol
EA	Ethyl alcohol
PEG	Polyethylglycol
SPM	Semipermeable membrane
NMT	Not More Than

FORMULATION AND OPTIMIZATION OF OSMOTICALLY CONTROLLED DRUG DELIVERY OF ANTIEPILEPTIC DRUG

Abstract

The aim of the project was to develop Elementary osmotic tablets to overcome the problems of conventional drug delivery system like, patient incompliance, require high drug loading, some GI irritation side effect pH. In this project prepared the antiepileptic drug for the treatment of the epilepsy. Drug had 6-7 half – life and 87% BA. It is poorly water soluble. There was not observed impurity in drug – exicepients compatibility study. There was

different factors amount of granulating agent, % coating affect the drug release. Batch F10 optimized with 160 ml of water as granulating agent and 4% coating gave better drug release and matched with innovator product. There was no effect of orifice size by mechanical drilling and laser drill on drug release. Optimized batch achieved zero order drug release with regression co-efficient value 0.994. The formulated optimized elementary osmotic batch matched with innovator product.

CHAPTER 1

INTRODUCTION

1. Introduction

1.1 Introduction of Controlled Drug Delivery System

Oral drug delivery system is most convenient route among all the routes like nasal, ophthalmic, rectal, transdermal and parenteral for administration of the drugs. Oral route have some advantages like, Patient acceptance, easy for administration. Generally Immediate and conventional drug delivery system given by oral routes, which are designed for rapid absorption. But they have limitations like, Drugs with shorter biological half-life that need frequent application of dose and possibly missing dose, fluctuations in dose. Developing CDDS to overcome the limitations of the conventional drug delivery system.

Controlled drug delivery system deliver drug at controlled level for certain period of time. They deliver drug constant at a zero order rate to locally or systematically. It is possible to achieve controlled drug delivery that controls drug delivery rates and effective concentration at the target site. This kind of results is a constant and predictable drug release leading to minimal side effects of the drug. They provide proper concentration of drug to the absorption site. The rate and extent of controlled drug delivery systems are independent of the various factors such as physiological properties of the drug, presence of exicepients, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility etc.[1] [2]

Advantages of CDDS over conventional delivery:

[1] Reduce the plasma level fluctuation.

[2] Reduce the side effects.

[3] Better patient comfort.

[4] Less require dose frequency.

[5] Maintain plasma concentration within therapeutic range.

[6] Reduce the toxicity

[7] Improve the bioavailability.

The concentration of the drug in the oral controlled system is maintained for a longer period of time between the maximum safe concentration (MSC) and minimum effective concentration (MEC), thus the pattern becomes sustained therapeutic action. [3]

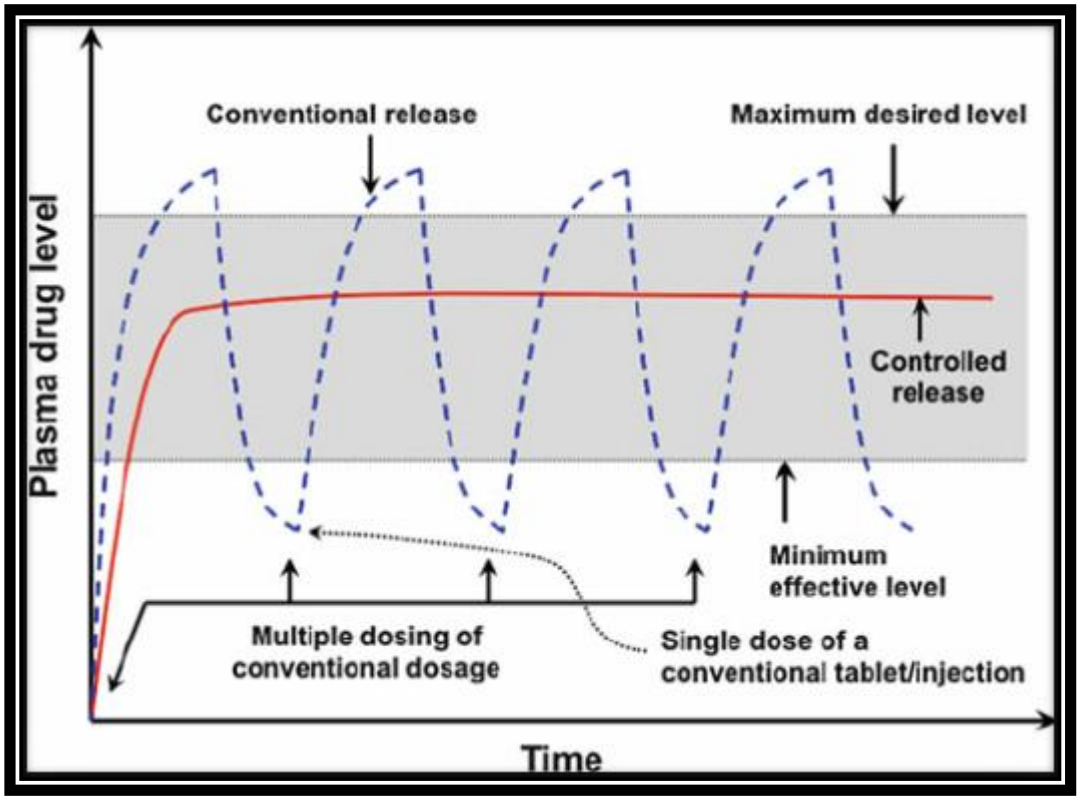


Figure 1.1 Plasma concentration for Controlled release dosage Form and Conventional release dosage form [3]

There are a number of design options available for controlling or modulating drug release from the matrix, reservoir and osmotic system dosage form.

In the matrix system, the drug is absorbed in polymer matrix and release occurs by dividing the drug into the polymer matrix and release medium, depending on rate of drug diffusion. Matrix system is easier to produce than reservoir system. But they are achieve zero order release.

The drug core is coated in reservoir system by controlling the membrane rate. Release rate is variable with various polymer type. Zero order release rate can be obtained by reservoir system. This device independent of pH and food presence.

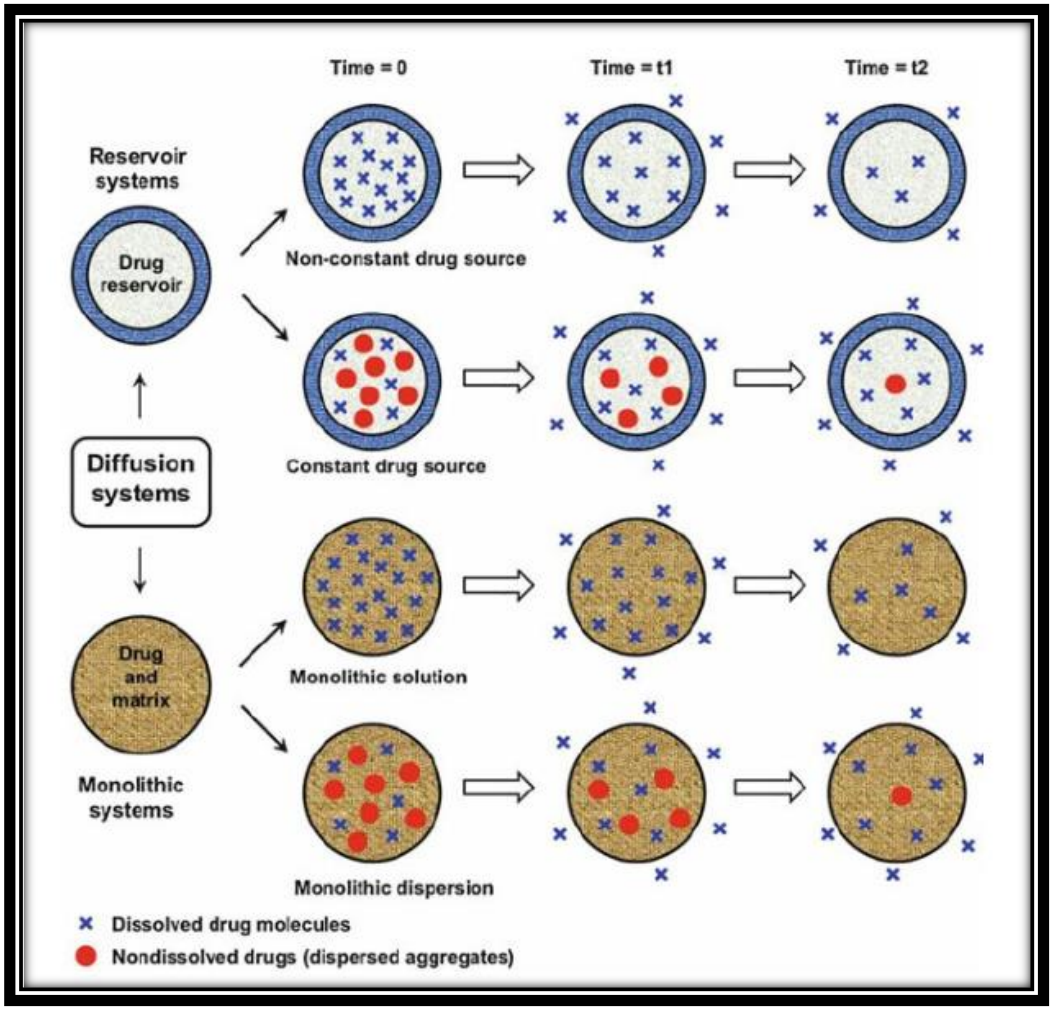


Figure 1.2 Schematic representation of Reservoir and Matrix diffusion controlled drug delivery system [3]

1.2 Introduction to Osmotically Controlled Drug Delivery System

1.2.1 Introduction

One of the most promising delivery system is osmotic drug delivery system, where osmotic hydrostatic pressure is used as energy source for controlled delivery of drugs. Many bioavailability fluctuations problems occurs due to gastric pH variations that are overcome by osmotic delivery system. This delivery system is not affected by gastric pH, physiological factors of GI tract, presence of food and GI motility, thermodynamics of dissolution medium. But affected by some pharmaceutical factors. There are osmotic core is coated with semipermeable membrane. Core formulation contain osmotic agent which produce osmotic pressure and water swellable polymers either in a solid or solution form. Due to the contact with external enviorment produce imbibition of water in the dosage form which regulate the drug delivery. The rate of water absorption depend on osmotic pressure. The delivery of osmotic drugs follows the zero order kinetic. [4] [5]

1.2.2 Advantages [6]

[1] Stable drug concentration

[2] Independent of pH, presence of food, reduce the chances of dose dumping.

[3] Reduce the dose administration frequency.

[4] Uniform drug effect and improved safety profile.

[5] Obtained high level of IVIVC.

[6] Provides a delivery rate at zero - order.

[7] Delivery of delayed or pulsed drugs is obtained.

[8] Delivery of drug takes place in the ready-to-absorb solution form, with osmotic pump simulating in-situ preparation as a liquid dosage form.

1.2.3 Disadvantages

[1] Dose dumping is occurs when film coating isn't controlled properly.

[2] Size of the orifice pore is critical

[3] Tablet couldn't be crushed or chewed that provide can cause to slow release of drug and produce toxicity.

[4] Food and gastric transit time may change the rate of drug release, resulting in differences can rise in the release rate between doses.

1.2.4 Principle of Osmosis

From lower concentration to higher concentration movement of solvent is called osmosis. In this process movement occur through semipermeable membrane which are control the drug delivery system. [7]

The drug's rate is directly proportional to the pressure of osmotic which are developed in osmotic pump. [8]

Osmotic pressure of an ideal solution with low concentration containing n moles of solvent particles in a volume V solution provided by the Van Hoff equation,

$$\pi V = nRT \quad \text{[1]}$$

Where,

Π = osmotic pressure

V = volume of solution (L)

n = number of moles

R = gas constant

T = absolute temperature

The osmotic water flows through membrane by this equation,

$$\frac{dv}{dt} = \frac{ALP\sigma(\Delta\pi - \Delta P)}{h} \quad \text{..... [2]}$$

Where,

dv/dt = water influx membrane

P = permeability

h = membrane thickness

$\Delta\pi$ = osmotic pressure

ΔP = Hydrostatic pressure

1.2.5 Parameters that affect Osmotic controlled drug delivery systems

[A] Orifice Size

Osmotic delivery is one option for delivery of drugs. Size will be optimized to control the release rate. Orifice size achieved the zero order kinetics. Orifice size required larger size than 0.075mm, if it is larger then produce solute diffusion from the device and smaller size than 0,274mm to minimize the diffusion rate of the drug delivery. If it is to smaller then affect the zero order release because of hydrostatic pressure in the core.

Orifice size drilled by two machine: Laser Drill and mechanical drill

Laser Drill: This technique is initiated to produce submilimeters size hole in tablets. Carbon dioxide lamp for drill. [9] [10]

[B] Drug Solubility

The release rate depends on the drug's solubility within the delivery device. So API have to be sufficient water solubility for release rate. Drugs which have highest solubility, they are poor agents for osmotic device. Drugs with low solubility that are enhanced by surfactants, cyclodextrin, salt form. Swellable polymers also increase the solubility of drugs. [11]

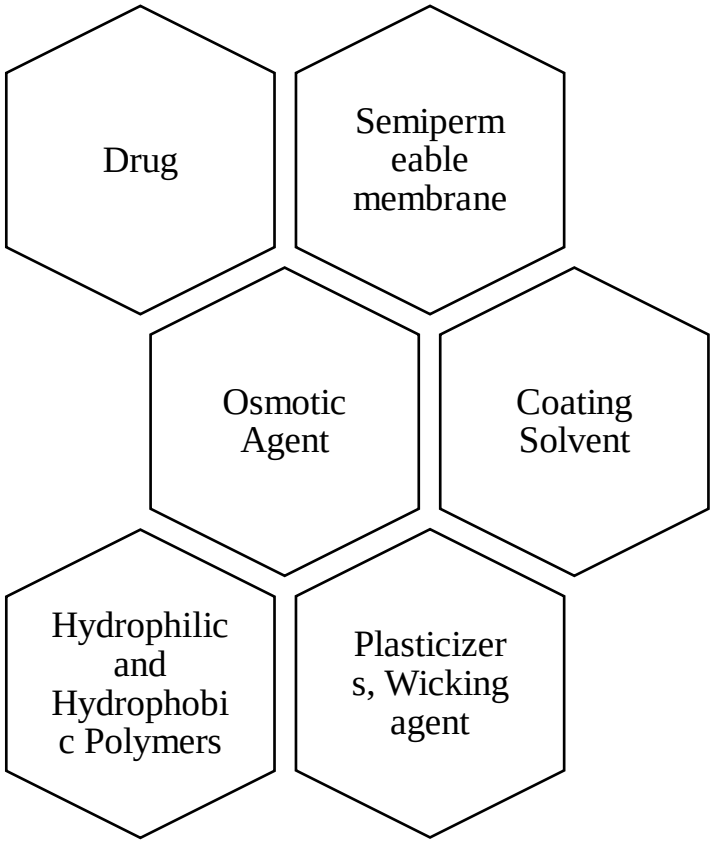
[C] Osmotic Pressure

This pressure π directly related with rate of release. Zero order achieved by osmotic pressure through saturated solution. The drug saturated solution formulate the osmotic pressure in device. In device if saturated solution have not enough osmotic pressure, they need to additional osmotic agents in formulation. Osmotic gradients maintain between in the delivery system and external enviorment for controlled release of drug. So there should require to maintain osmotic pressure.

[D] Semipermeable Membrane

Various types and nature of polymer used in membrane that effect the drug release. Thickness of membrane and other components which are present in membrane like plasticizers, solvents affect the release profile. Permeability of also change by proper selection of membrane additives. [12]

1.2.6 Basic components of osmotic systems



[1] Drug

Drugs which are soluble and insoluble used for this system, mostly preferred soluble drug. Short biological half-life less than 1 like furosemide and more than 12 such as, diazepam aren't used. A drug used to prolong disease relive is the perfect applicant for osmotic device.

- Shorter biological half-life (1-6 hrs)
- Potent in nature
- Extended release of drug should be required
- It should not have very low or high solubility

[2] Semipermeable membrane

Semipermeable membrane is important part of the osmotic device. This membrane penetrates into water but not ions, the drug's release rate is prerequisite not dependent on pH.

They should have some characteristics, such as:

- It shows sufficient water penetrability to retain the required range of water flux.
- It should be biocompatible.
- Materials that have enough wet strength and module to keep their dimensional integrity during the system's formulation.
- It can be used in osmotic pumps as a coating material polymer that absorb the H2O but is not permeable to solvent.
- They have ability to maintain its dimensional integrity therefor produce constant osmotic pressure during the delivery of drug release. [19]

This membrane made of cellulosic polymer like, cellulose ester, cellulose ether, esters like, CA, cellulose acetate butyrate and cellulose triacetate. Thickness of the membrane should be 200 - 300µm to withstand the osmotic pressure produce within the device.

[3] Osmotic Agent

They are also called osmogents. Osmogens are maintaining concentration gradients across the membrane which are used for formulating the osmotic tablet. Upon perforation of biological fluid by SPM into osmotic device. Osmotic pressure produces inside device when osmogents are diffuse in biological fluid. Drug is come out through orifice because of this pressure. Osmogents are increase the dissolution rate of low soluble drugs. [10] [20]

Osmotic agents are generally ionic compounds containing inorganic salts. Others are organic polymers, carbohydrates, amino acid, water soluble salts. [21]

Table 1.1 Types of Osmogens

Inorganic Salts	Sodium chloride, Sodium bicarbonate, magnesium chloride or sulphate
Organic Polymers	HPMC, HPC, Methyl cellulose
Carbohydrates	Glucose, Fructose, Lactose, Sucrose
Water soluble salt	Sodium & Potassium acetate

Table 1.2 Osmotic Pressure of osmogents

Osmogens	Osmotic Pressure
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.12H2O	36

[4] Coating Solvent

To make the polymeric solution for building of the walls of osmotic device coating solvents are used. For coating, organic as well as inorganic solvents are used. Methylene chloride, methylene alcohol, acetone, methanol, ethanol, IPA, cyclohexane, EA are used as solvent for coating.[23]

[5] Plasticizers

Plasticizers are different kind of plasticizers which are modify the properties of film forming variant polymers. They can switch the visco elastic behavior of polymeric agent and this diversity can affect the penetrability of the polymer film that will change release rate of drug. [24] Different types of diluent which have low molecular weight used for it. They can improve the physical property. Polymer's softer, more flexible properties formed by plasticizer. [25]

Table 1.3 Examples of Plasticizers [26]

Ethylene glycol diacetate	Ethylene glycol monoacetate
PEG – 200	Diethyl tartarate
PEG – 600	Triacetin

[6] Wicking Agent

It has swelling property. In nature, they can be swellable or non-swellable. It has ability to withstand force upon contact with aqueous fluid. Force of Vander Waals between the surface of the wicking agent and absorbed molecule formed that produces solvent molecule on the surface. They develop the contact surface area of area when it come in contact with water and they intensify the dissolution rate delivery of tablet. [27]

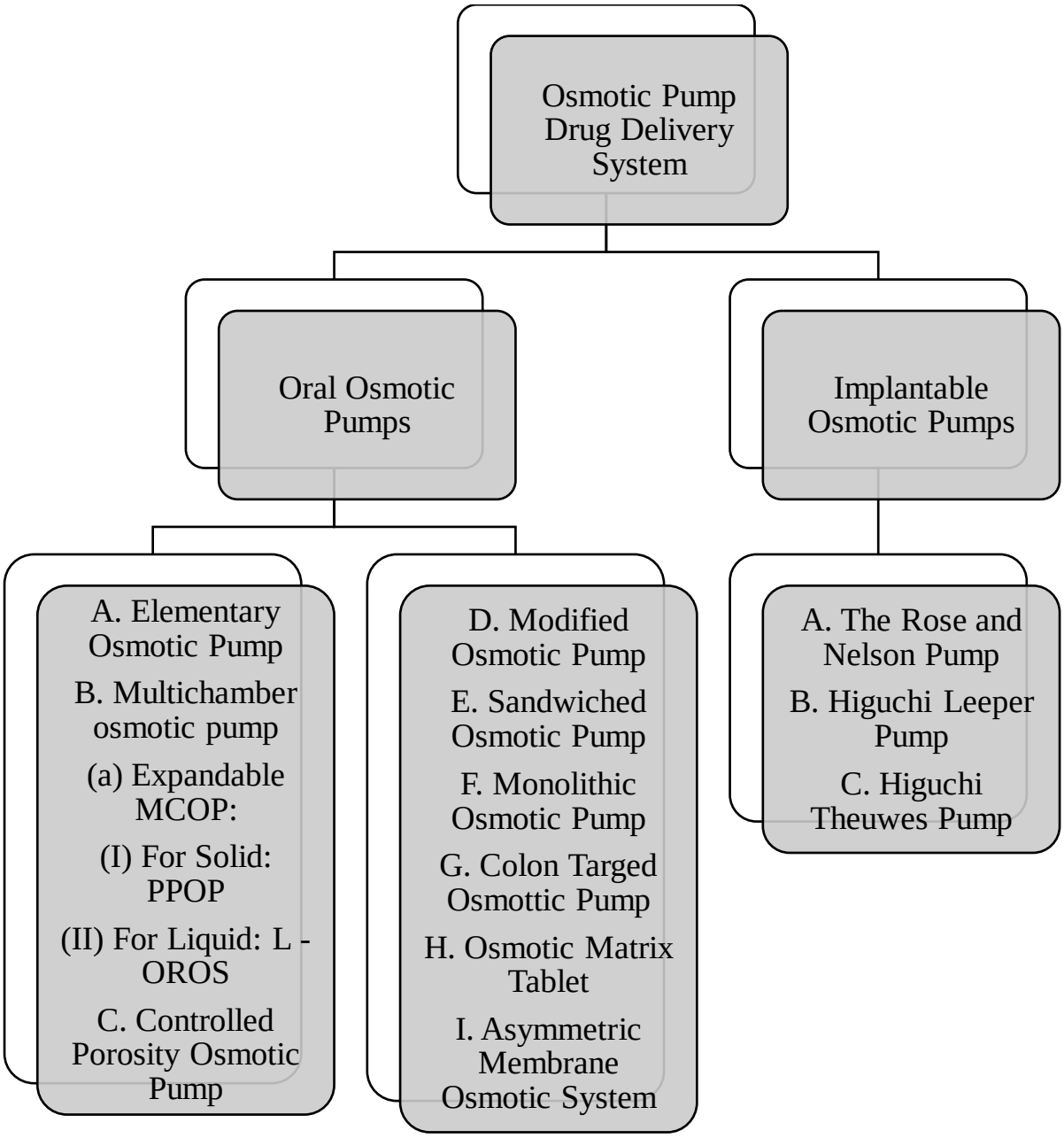
Table 1.4 Examples of wicking agents

Silicon Dioxide	Poly Vinyl Pyrrolidone
Kaolin	Bentonite
Sodium Lauryl Sulphate	Aluminium Silicate

[7] Hydrophilic and Hydrophobic Polymers

Polymers are used to formulate matrix form of osmotic tablet core part. There are hydrophobic polymers are used for highly water soluble compounds and develop matrix of tablet. Hdrophilic polymers used for generally moderately water soluble compound. Both polymer mixture used in development of water soluble drugs osmotic pumps.

1.3 Types of Osmotic Pumps



1.3.1 Implantable Osmotic Pumps

[1] Rose - Nelson Pump

Implantable pumps developed in 1955. By this system drug deliver to the sheep and cattle gut. There are total three compartment:

- The first is drug chamber which are drilled with orifice
- The second compartment is solid chamber which containing solid salt
- The third is water compartment

Semipermeable membrane separate the drug and water chamber which made of cellulose acetate. From aqueous to salt compartment water pass due to the osmotic pressure. Flow of water swell the salt chamber, which expand the elastic diaphragm apart the drug and salt chamber that are drug throughout by orifice. There are some disadvantages of rose- nelson pump. [27]

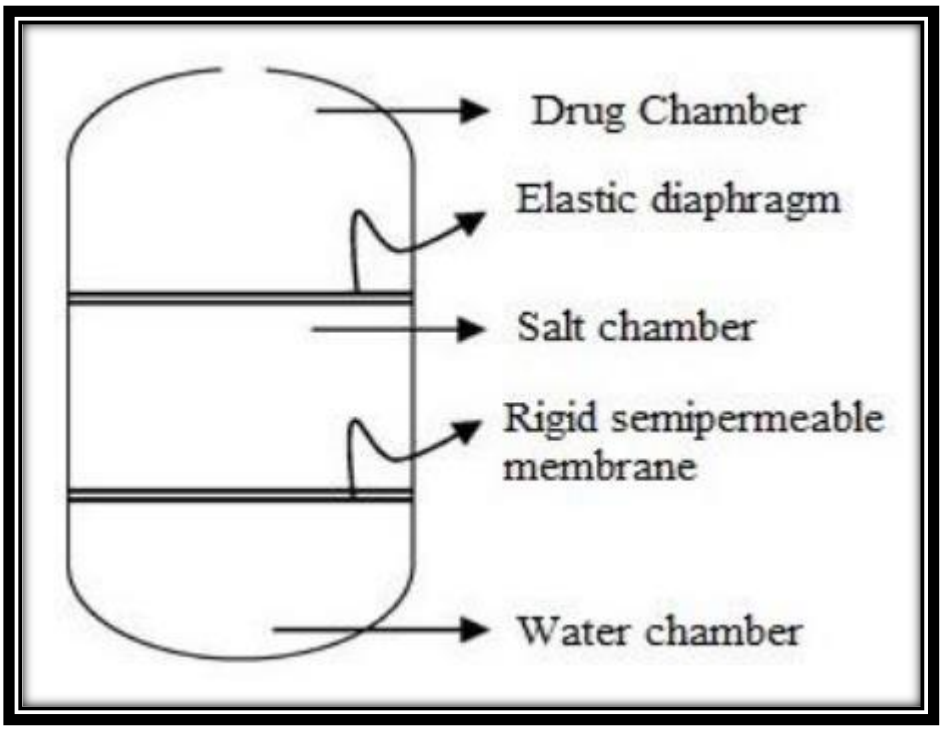


Figure 1.3 The Rose-Nelson Pump [27]

[2] Higuchi Leeper Pump

The problems of rose nelson pump overcome by higuchi leeper which is remodel version. There are only two chamber, water chamber is absent. They imbibe the water from aqueous enviorment and contain in salt chamber. Fluid solution with solid salt activate the pump. There are movable separator instead of elastic membrane which separate the salt and drug compartment. Porous membrane support developed by rigid housing and SPM containing pump. This pump loaded with drug after it prepared and then use after few weeks or months. Modify form of higuchi leeper pump allows the pulsatile drug delivery. [28]

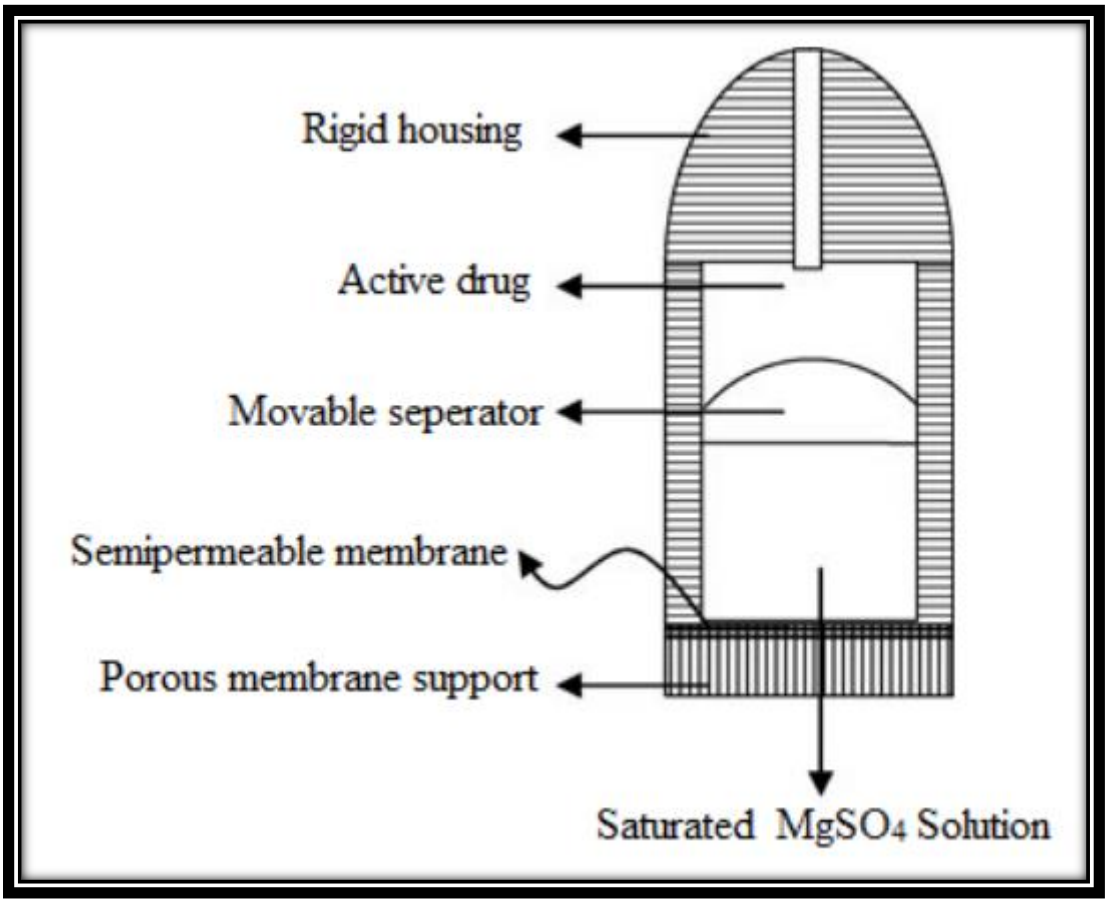


Figure 1.4 Higuchi Leeper Pump [28]

[3] Higuchi Theeuwes Pump

This pump is developed in 1970. It is uncomplicated variant of Rose Nelson device. In this system, outer membrane composed of SPM. When this device put in aqueous enviorment that imbibe the water from external. The drug is filled in the pump initial to its requisition. Salt chamber containing salt set the time course of drug release and penetration of the outer membrane coating. [29]

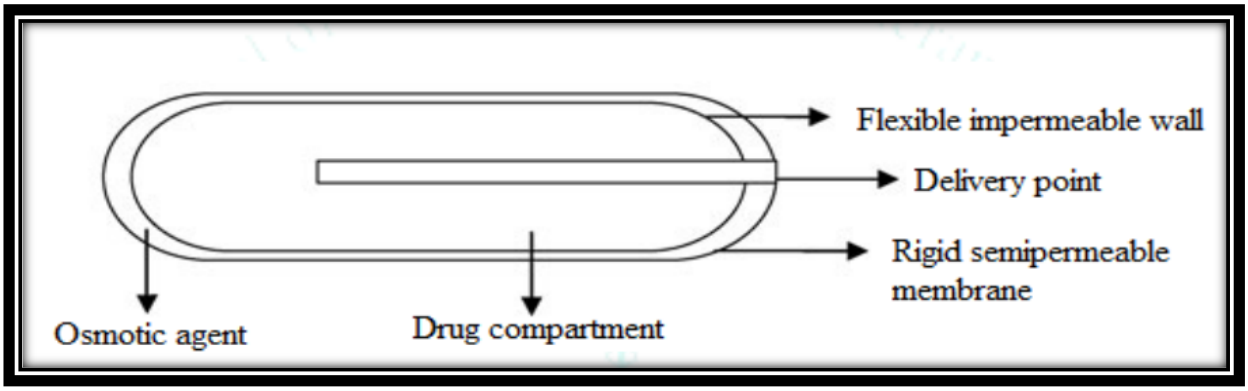


Figure 1.5 Higuchi Theeuwes Pump [29]

1.3.2 Oral Osmotic Pump

[1] Elementary osmotic pump

An EOP is single chamber osmotic pump. It consisted of an active agent that ingredients have suitable osmotic pressure and deliver at a controlled rate. This device has two parts core and coated. Core of the tablet consist of swellable polymer and coated with semipermeable membrane. The drug come out through orifice which is created in membrane. [30]

When coated tablet come in contact with an aqueous enviorment, the drug's osmotic pressure inside the tablet drew water and osmotic agent swelling occurs and the drug's saturated aqueous solution is formed inside the device. [31]

Because of non-extensible nature of membrane that increases in volume due to water immersion that occurs because of hydrostatic pressure that leads to active agent out of the device through aperture which is drilled by laser or mechanical high speed drill. [32]

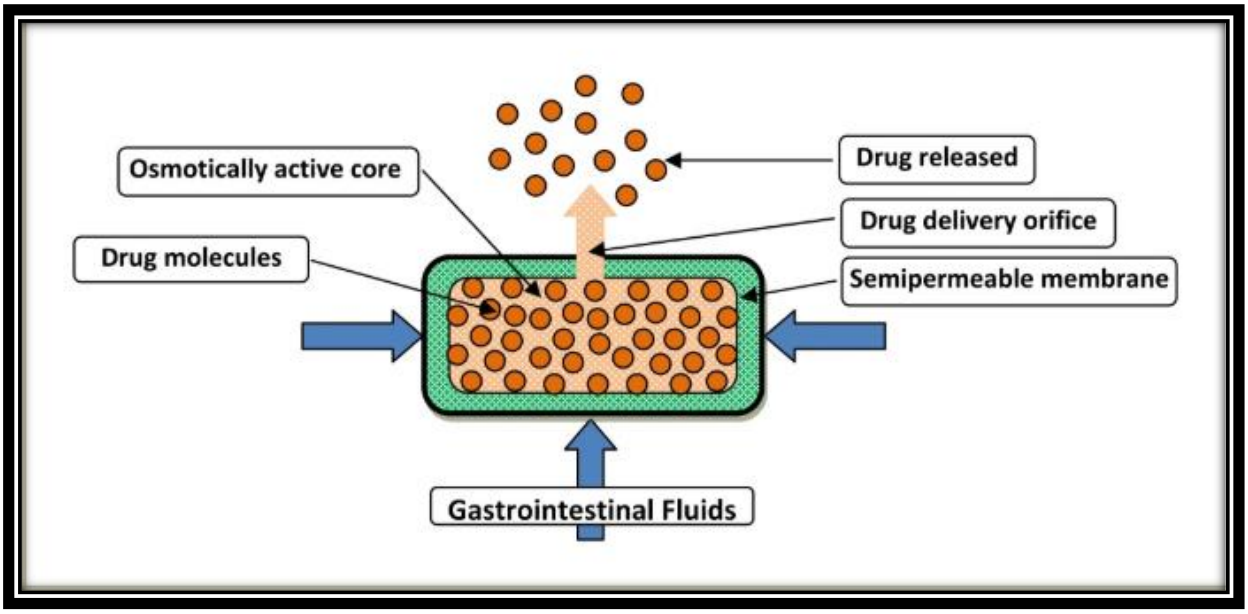


Table 1.6 Elementary Osmotic Pump [31]

[2] Controlled Porosity Osmotic Pump

In this osmotic system, semipermeable membrane contains water soluble pore formers that are soluble in water that producing forces and forming holes. Drug solubility, level of lixiviating pore forming agent and osmotic pressure that all are factors affect the drug release of CPOP tablet. The microporous membrane is penetrable to both water and dissolved solutes. The pore size generally 10A - 100µm can be used. [6]

In this device after dissolution the hydrostatic pressure deliver the drug from core of the tablet and diffusion through channeling agents. These microporous pores are differentiate the CPOP from elementary pump. [33] [34]

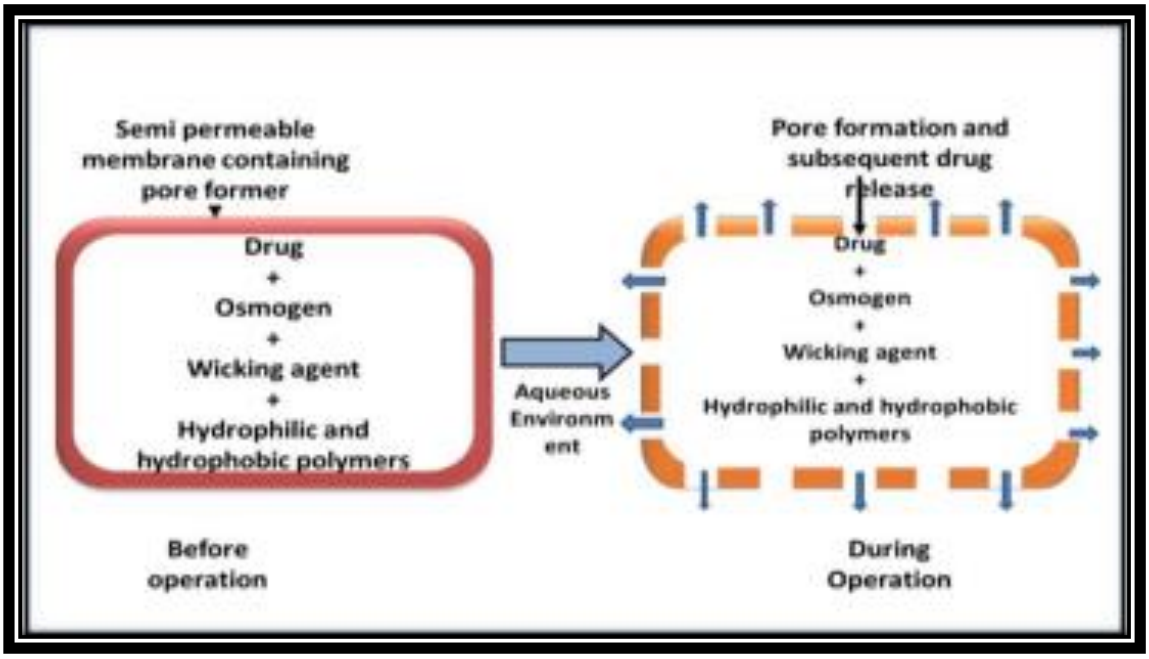


Table 1.7 CPOP Pump [34]

[3] Push Pull Osmotic Pump

EOP's modified version is push pull osmotic tablet. Low water solubility and high water soluble drugs can delivered by PPOP at constant rate. It's a bilayer compartment. Drug and osmogen formulated in upper layer and swellable polymers present in lower layer. They have semipermeable membrane coating. Both layers separated by elastic diaphragm. [35]

Fine dispersion of drug formed when gastric fluid or water contact with drug. Drug is pulled out through centered orifice by forcing of osmotic agent.

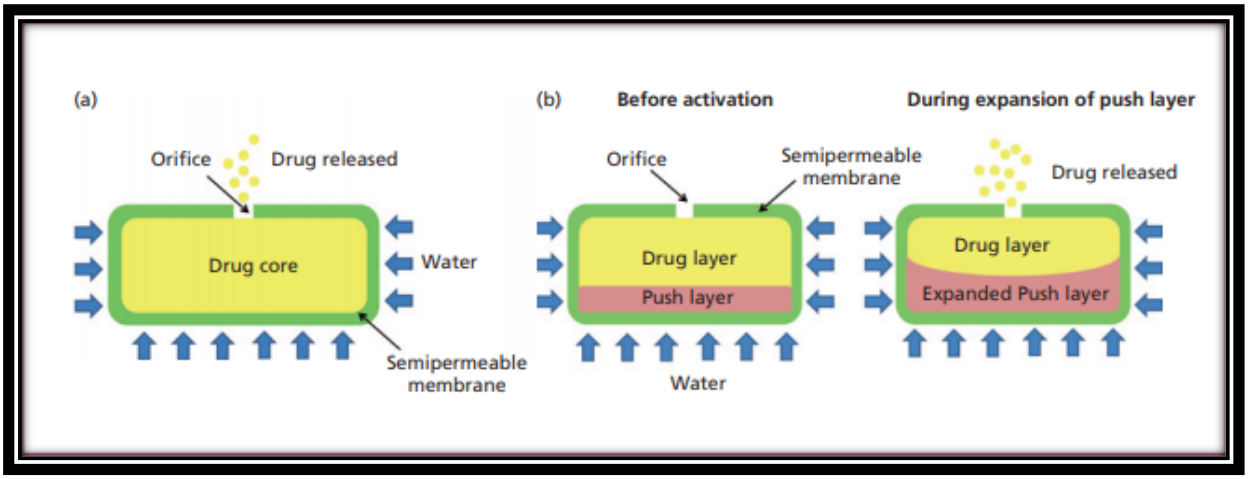


Figure 1.8 PPOP Pump [35]

[4] Sandwiched Osmotic Tablets

It is designed with two orifices. Push layer sandwiched by two attached drug layers that core layer with cellulose acetate membrane. Polymeric push layer contain osmotic agents. Push layer swell when come in contact with water. Decrease the irritation of mucosa by this SOTs is one of the advantage. [36] [37]

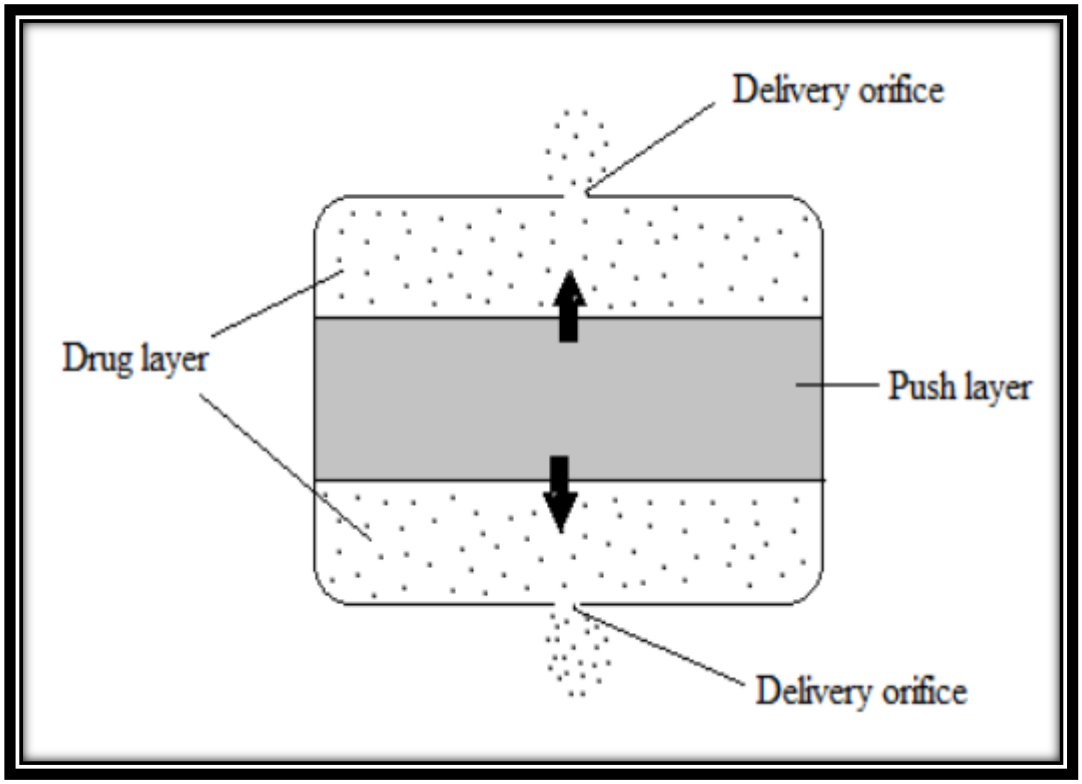


Figure 1.9 Sandwiched Osmotic System [37]

[5] Colon targeted Oral Osmotic System

Five to six PPO units containing OROS-CT filled in gelatin capsules for the targeted drug delivery system. This formulation generally used once or two times in a day. Hard gelatin capsules dissolves in presence of gastric fluids. Fluids which are come from stomach stopped to enter in system by enteric coating. [38] Enteric coating dissolves when system contact with small intestine. Water is absorbed in core and push compartment swell and formed gel flowable in drug layer that come out by orifice. [39]

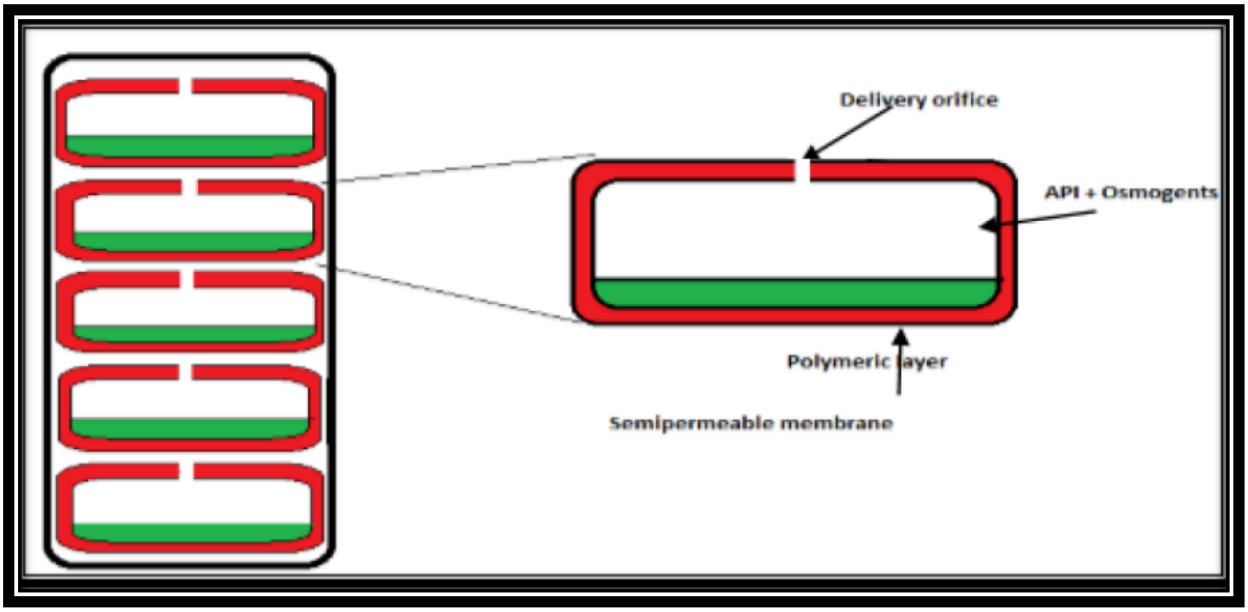


Figure 1.10 Colon targeted oral osmotic system [38]

[6] Modified Osmotic Pump

Elastic semipermeable film coated surrounded by osmotic agent particles. Then insoluble drugs properly mixed with these particles and compressed in tablet.

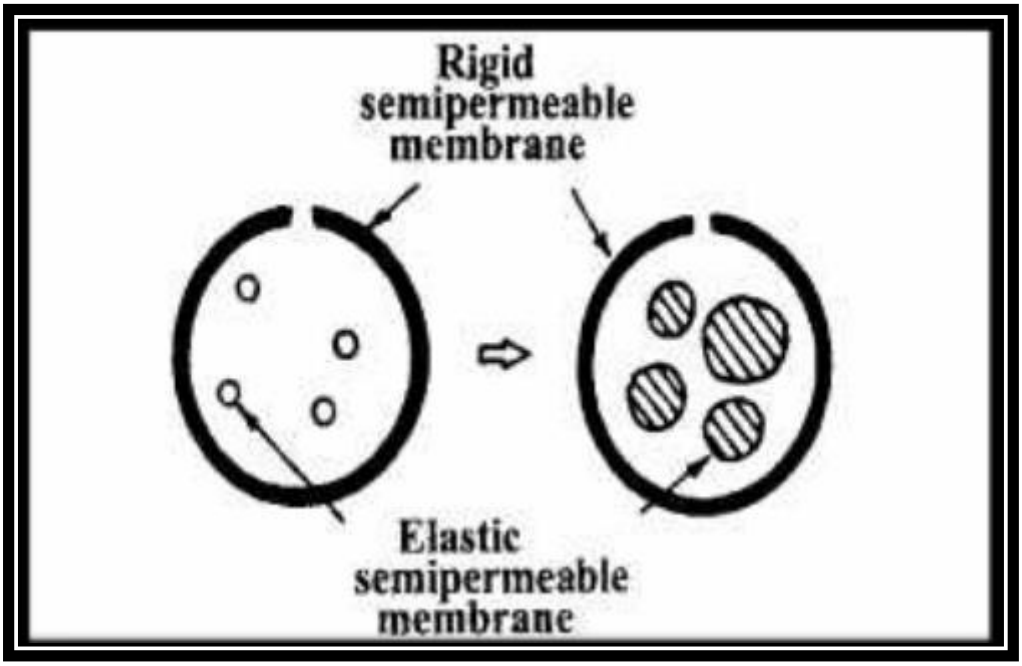


Figure 1.11 Modified Osmotic Pump

[7] Liquid Oral Osmotic System

For low soluble drugs and macromolecules liquid formulation formulated by this pump system and have benefit of extended release. Liquid drug continuously delivered by a delayed liquid bolus system, Hardcap and softcap of L-OROS. This system coated with semipermeable membrane containing liquid drug layer. [6] The osmotic layer is activated when water diffuse through the rate controlling membrane, which is occurs due to system enter in aqueous compartment. The enlargement of osmotic layer produce hydrostatic pressure within the system. They are designed by liquid drug, push layer, placebo delay layer and SPM. This is formulated in capsule shaped device and orifice placed on the placebo layer which is release first and drug release delayed from 1 to 10 hr. Drug release depends on the thickness of SPM. [10] [38]

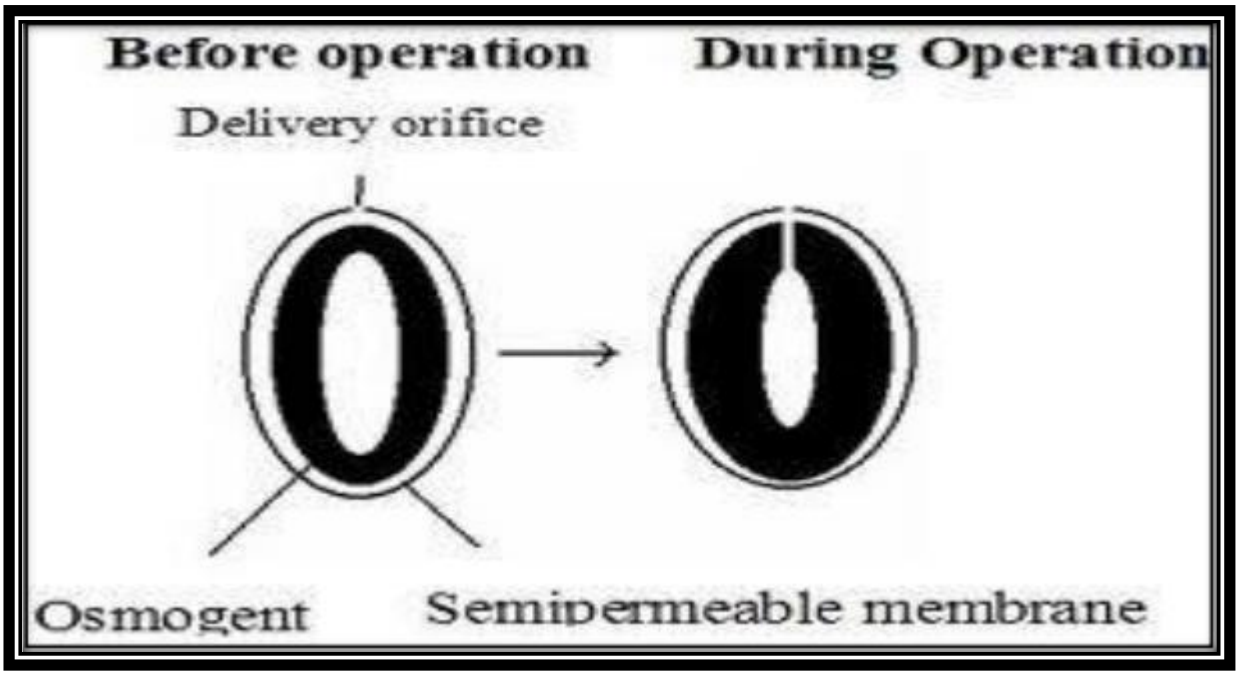
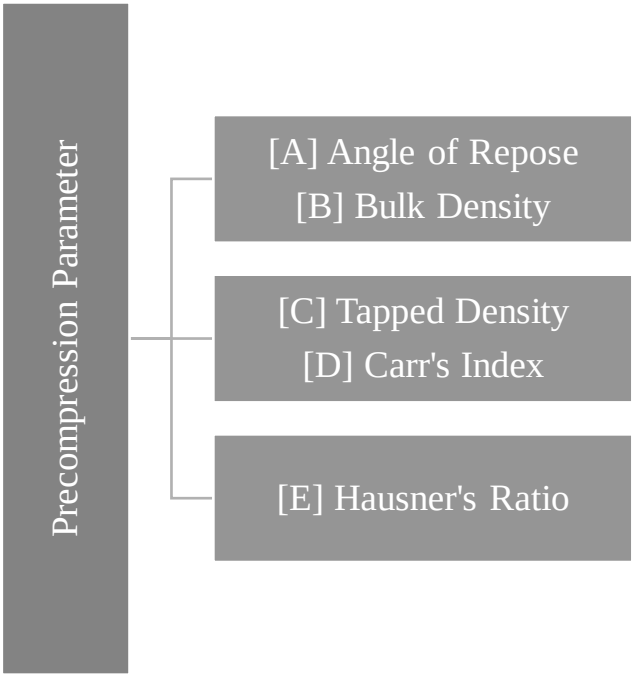


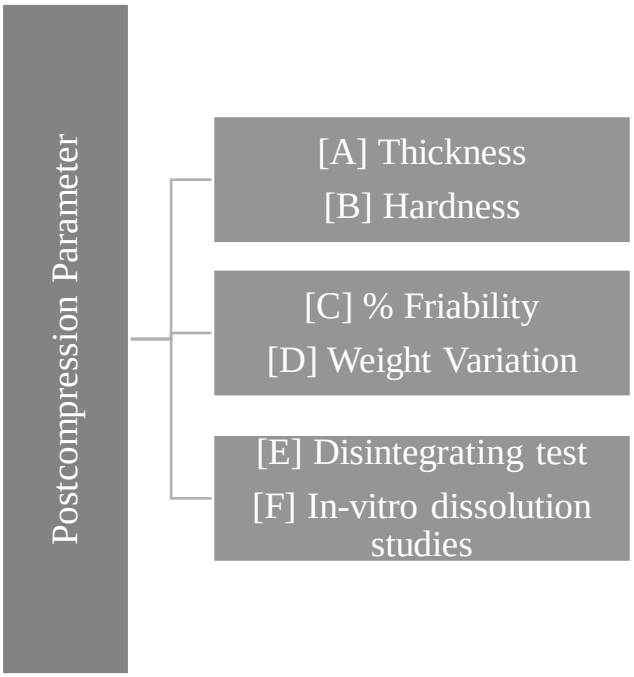
Figure 1.12 Liquid Oral Osmotic System [38]

[8] Monolithic Osmotic System

It's easy to disperse. In this system, there are polymer matrix which contain water soluble agent. This matrix capsule ruptures surrounding the agent and liberated when contact with water. At the outer environment of polymer matrix that occurs. If this device containing 20 to 30% active agent then it becomes fail. Because high level of agent produce leaching of the substance.

1.4 Evaluation of Osmotic Pump Tablets





[1] Precompression Evaluation Parameters

[A] Angle of Repose

Flow property of powder is discovered by angle of repose. It is the maximum angle between a powder pile's surface and the horizontal plane.

Table 1.5 Types of AOR

AOR Type	Method of Measurement
Static	Fixed horizontal cone, Fixed base cone, Tiling table
Dynamic	Rotating cylinder, Rotating drum
Drained	Ledge type, crater type, platform type

This equation used to measure angle of repose.

$$\emptyset = \tan -1 \frac{h}{r} \quad \text{..... [3]}$$

Where, $\emptyset$ = angle of repose

h = height of heap

r = Radius

Table 1.6 Types of Flow with value

AOR	Type of Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
>40	Very Poor

[B] Bulk Density

By adding granules to the graduated measuring cylinder, BD is evaluated. The mass and bulk volume of granules are measured. Following formula showed the % BD. [13]

$$\% \text{ Bulk Density} = \frac{Mass\ Volume}{Bulk\ Volume} \quad \text{..... [4]}$$

[C] Tapped Density

Tapped density measuring by granules containing cylinder which is tapped 1000 times at fixed rate. Minimum volume obtained after tapped (Vt) and weight of granules (m) are calculated. Formula for this:

$$\text{TD} = \frac{Mass\ of\ Granules}{Tapped\ volume\ of\ Granules} \quad \text{..... [5]}$$

[D] Carr's Index [14]

$$\% \text{ Carr's Index} = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} * 100 \quad \text{..... [6]}$$

Table 1.7 Types of flow of % CI

% Compressibility	Type of Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
> 35	Very Poor

[E] Hausner's Ratio

$$HR = \frac{Tapped\ Density}{Bulk\ Density} \quad \text{..... [7]}$$

Table 1.8 Types of flow of HR

HR	Type of Flow
< 1.25	Good
1.25 – 1.5	Moderate
> 1.5	Poor

[2] Postcompression Evaluation Parameters

[A] Thickness

The dimensional variable related with process is thickness parameter of tablet. Variation of thickness is depend on die fill and compression load. It should be controlled as standard value within a variation of ±5 percent. Accurate measurement of Individual tablet's thickness evaluate by Vernier caliper. Unit for parameter is mm. [15]

[B] Hardness

The force needed in a diametric compression test to break a tablet is hardness. There are different tester used for evaluation of hardness. [16]

Table 1.9 Types of Hardness Tester

Sr. No	Tester Name	Principle
1	Monsanto	Compressible spring between 2 plungers
2	Strong – cobb	By Hydraulic Pressure
3	Pfizer	Mechanical principle using a pair of pliers.
4	Erweka	Same mechanical principle vertically
5	Schleuniger	Operate in horizontal position

Generally Monsanto hardness is used for it and unit is kg/cm2.

[C] Friability

It is combined effect of abrasion and shock. It is defined as the tendency of tablet to crucible. Lab tester – Roche Friabilator used a plastic chamber that revolves at 25rpm, dropping tablets with each revolution at a distance of 6 inches. Preweighted tablets at 100 revolution. Tablets are then dusted and reweighted. [17]

Acceptable weight loss: < 0.5 – 1% of weight of tablet

$$\%F = \frac{Weight\ loss\ of\ Tablets}{Original\ weight\ of\ tablets} * 100 \quad \text{[8]}$$

$$\%F = \frac{1-W}{W0} * 100 \quad \text{[9]}$$

Where, W0= Original weight of tablets

W = Final weight of tablets

% of moisture content affects the hardness and friability

[D] Weight variation

Satisfactory method to determine tablet uniformity in drug content. Doesn't apply to layered/ enteric coated tablets.

Weight 20 tablets individually on the basis of the USP weight variation test and calculate average weight. Compare individual weight with it. Tablets meet limits if, ≥ 2 tablets outside limit and number of tablets differ by more than 2 times the percentage limit.

USP % weight difference tolerance for uncoated tablets.

Table 1.10 Limits of weight variation of USP

Average Weight (mg)	Maximum % difference allowed
≤ 130	10
130 – 324	7.5
>324	5

Table 1.11 Limits of Weight Variation of IP

Average Weight (mg)	Maximum % difference allowed
≤ 80	10
80 – 250	7.5
> 250	5

[E] Disintegrating test [5]

It is a process of breakdown tablets into small particles or granules. Venderkamp disintegrating tester is used.

USP device uses 6 glass tubes 3 inch long, open at the top and held at the bottom of the basket rack against a 10 – mesh screen. 1 tablet in 1L beaker of water stimulated gastric fluid/ SIF at 37° ± 2° C in each tube basket position.

Tablet remains 2.5cm below the liquid surface when moving upwards and not nearly 2.5cm below the beaker's bottom. A motor driven device, at a frequency of 28-32 cycles per

minute moves the basket up and down by 5-6 cm. Perforated plastic disks on the top of tablets give abrasive action.

USP standards: Tablet has to disintegrate and in the specified time particles have to pass through 10# mesh sieve. [17]

[F] In-vitro dissolution

In-vitro test, for indirect bioavailability measurement. Results of in-vitro test plotted as concentration vs time. There are seven types of dissolution apparatus. Generally USP type I Basket apparatus is used. There are temperature maintained 37 ± 5°C and volume of media like 0.1 N hydrochloride or phosphate buffer 900ml in apparatus with stirrer rotating at a specific RPM. At different time interval take out 10 ml solution and replaced it with media solution. This solution analyzed by UV for estimation of concentration of absorbance and then calculate the drug release. [18]

1.5 Identification of Drug

Table 1.12 Drug A Profile

Characteristics	Observation
Appearance	Off- White to White
State	Solid
BCS class	Class II
Solubility	Soluble in Chloroform, Acetone, PG, Dimethylformamide; Practically insoluble in water
Melting Point	204-206°C

Route of Administration	Oral
Mechanism of Action	It is an anticonvulsant. It is an inhibitor of sodium channel protein type 5 subunit alpha. It blocks synaptic transmission in the trigeminal nucleus.
Absorption	Completely absorbed in GIT. Extended Release tablet slower than conventional Relative Bioavailability : 89%(For ER) Time to peak concentration: 4-5 h (conventional) & 3-12 h (ER Tablet)
Metabolism	Hepatic. CYP3A4 is main for metabolism of drug. In younger patient more metabolite than adults.
Distribution	Plasma Protein Binding: 76%
Elimination	Completely eliminated in 24 hrs with 72% of dose recovered in urine and 28% recovered in feces.
Indication	Indicate to improve epilepsy and reduce the pain of true trigeminal neuralgia.
Drug Interaction	Interacts with alcohol, phenobarbital, primidone and phenytoin.

1.6 Excipients and Polymers Profile

1.6.1 Hydroxypropyl methyl cellulose (HPMC E3 LV)

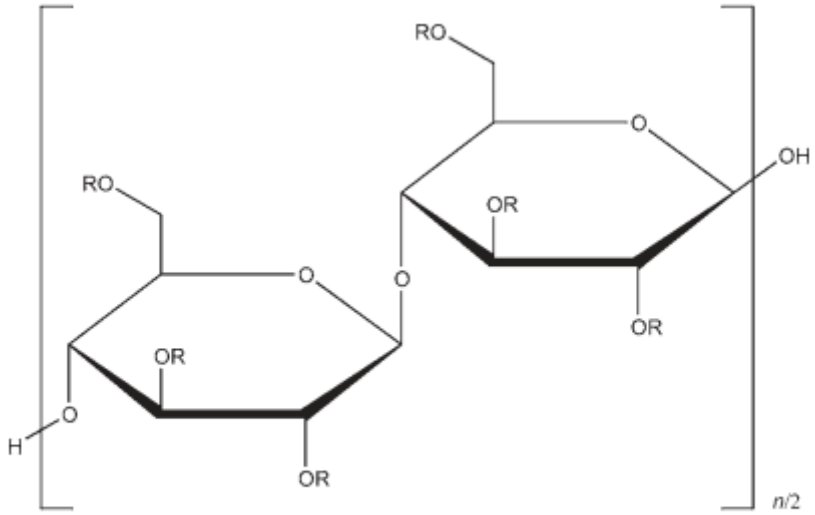
Nonproprietary Name

Hypromellose

Synonyms

Methocel, hypromellosum, methylcellulose propylene glycol ether, hydroxypropylcellulose.

Structure Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Molecular weight

10,000 – 15,00,000 gm/mole

Fuctional Category

Bioadhesive agent, Coating material, solubilizer, dissolution enhancer, extended release, controlled release material, emulsifying agent, binding agent, thickness enhancer and viscosity enhancer.

Description

Creamy – white powder that is fibrous or granular. It's tasteless and odourless.

Application

- HPMC used in oral, topical, nasal, ophthalmic preparation.
- In oral formulation, used as a binder in tablet preparation in wet and dry granulation. They also used in coating solution as film thickening agent.
- In extended release formulation used as matrix agent.
- In topical formulation used as stabilizing agent, suspending and emulsifying agent.

- Low HPMC viscosity grades used in preparation of aqueous film coating and high level of viscosity grades used with organic solution.

HPMC Grades

Table 1.13 Grades of HPMC

Methocel K3 Premium LV	Methocel K100 Premium LVEP
Methocel K4M Premium	Methocel K100M Premium
Methocel K15M Premium	Methocel E4M Premium LV
Methocel E3 Premium LV	Methocel F4M Premium
Methocel E15 Premium LV	Methocel F50 Premium

1.6.2 Hydroxy ethyl cellulose (HEC 250L & HEC 250HX)

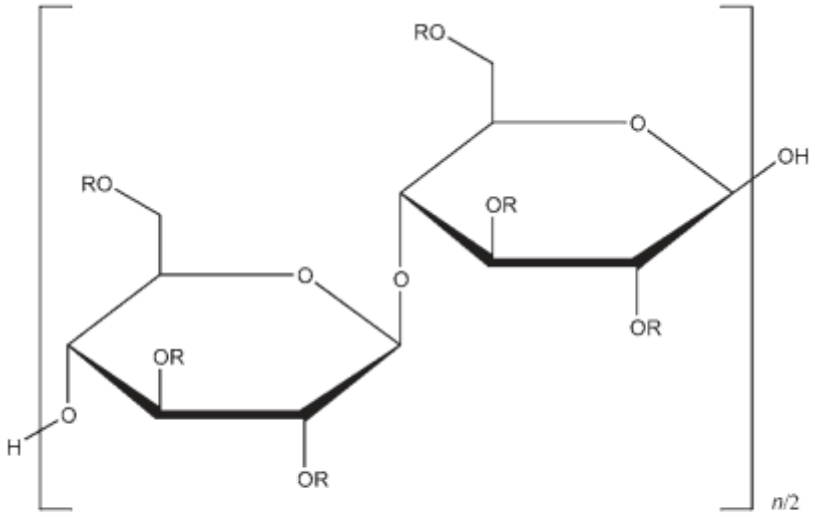
Nonproprietary Name

Hydroxy ethyl cellulose

Synonyms

Cellulose hydroxyethyl ether, cellulose hydroxyethylate, ethylhydroxy cellulose, Natrosol.

Structure Formula



R is H or $[—CH_2CH_2O—]_mH$ where m is a common integral number of cellulose derivatives.

Fuctional Category

Viscosity enhancer, suspending agent, Thickening agent, Binder.

Description

Odorless, tasteless, white, yellowish – white, hygroscopic powder.

Application

- It is used as a film coating agent and binging agent in oral, topical pharmaceutical formulations.
- Natrosol 250 L and Natrosol 250 HX are viscosity grade of hydroxyethyl cellulose.

1.6.3 Mannitol (Pearlitol) 50C

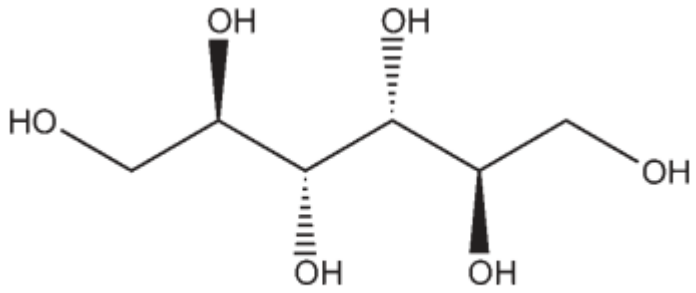
Nonproprietary Name

D – Mannitol

Synonyms

Pearlitol, mannite, mannitolum.

Structure formula



Molecular weight

182.17 gm/mole

Functional category

Sweetener, plasticizer, diluent

Description

White, Odorless, sweet taste, free flowing and crystalline granules.

Application

- Mannitol mainly used in food industry as sweeting agent. It is used as a diluent for DC and wet granulation.
- It is used as a thickening agent in suspension formulation.

1.6.4 Emdex (Dextrates hydrated)

Nonproprietary Name

Dextrates

Synonyms

Emdex, Candex

Fuctional Category

Binder and Diluent

Description

Dextrates is spheres which are white, free flowing anhydrous or hydrated and formed crystalline particles.

It is odorless and sweet in taste because of saccharides which are form from the hydrolysis of starch.

Application

- In the formulation of chewable, non-chewable, effervescent and dispersible tablets used as a diluent.
- It is free flowing powder. So, it is used as a glidant and also used as lubricant with Mg stearate.

1.6.5 Iron oxide yellow and Iron oxide Red

Synonyms

Iron oxide red, yellow monohydrate, brown, black.

Molecular weight

231.54 gm/mole

Functional category

Colorant

Description

The color form of red, yellow, brown, black which is depend on particle size, shape and crystal form.

Application

It is mainly used in food and cosmetics industry as a coloring agent. They are used in their limited color range.

1.6.6 Sodium lauryl sulphate

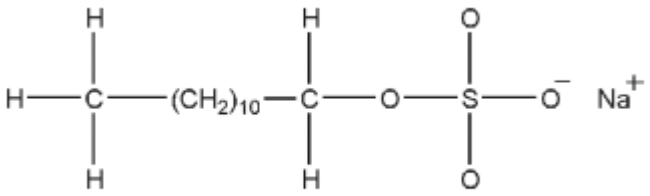
Nonproprietary Name

Sodium lauryl sulphate

Synonyms

Dodecyl sodium sulfate, dodecylsulfate sodium salt, monodecyl sodium sulfate.

Structure formula



Fuctional category

Surfactant, emulsifying agent, wetting agent.

Description

White or cream to pale yellow color, bitter taste, faint odor.

Application

SLS is anionic surfactant used as detergent, wetting agent, in cosmetic preparation.

1.6.7 Cellulose acetate 320S & Cellulose acetate 398/10

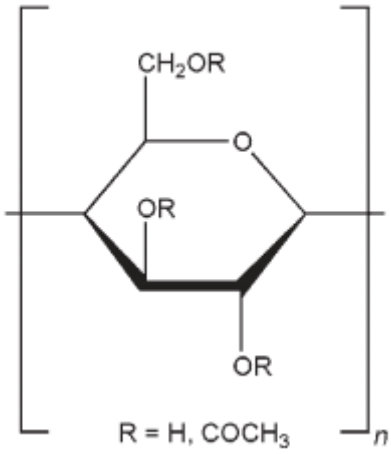
Nonproprietary Name

Cellulose acetate

Synonyms

Acetyl cellulose, cellulose diacetate, cellulose triacetate, acetic acid

Structure formula



Fuctional category

Film coating material, ER agent, diluent.

Description

White to off white color, tasteless, odorless or slightly smelling of acetic acid, free flowing but hygroscopic powder.

Application

- It is used as a semipermeable membrane in osmotic tablets as controlled release or extended release formulation.
- In transdermal drug delivery system used as film coating material.
- Other grades of cellulose acetate- 320S, 398-3, 398-6, 398-10, 394-60S.

1.6.7 PEG 8000

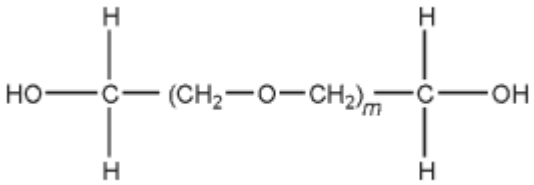
Nonproprietary Name

Macrogols

Synonyms

Carbowax, lipoxol, lutrol E

Structure Formula



Molecular weight

PEG 8000 – 7000- 9000 gm/mole

Fuctional category

Plasticizer, Coating solvent, ointment base, lubricant in capsule.

Description

It is mixture of ethylene oxide and water. There are different grades in the form of solid and liquids. Viscosity range of 200 - 600 are liquids and 1000 and above grades are solids.

Liquids grades are colorless, slightly yellow colored, clear or viscous form and bitter in taste.

Solids are white to off white, faint, sweet color and free flowing powder.

Application

- It is used in topical, oral, parenteral, ophthalmic formulation.
- As a matrix material used in controlled release formulation.
- It is easily removed from the skin because of water soluble material, so used in ointment base.
- Aqueous solution used in suspension because of its stability. They are adjust the viscosity of formulation.
- In film coating of tablets used as plasticizer.
- It is also used in preparation of hydrogels as controlled release formulation.
- In Bioadhesive CR formulation used with poly (methacrylic acid).

1.7 Marketed Products of Osmotic Pump Drug Delivery System

Sr. No	Brand Name	Active ingredient	Design	Purpose
1	Acutrim	Phenylpropanolamine	EOP	For the treatment the congestion associated with allergies, hay fever, sinus irritation, and the common cold.
2	Alpress LP	Prazosin	PPOP	For treatment of hypertension
3	Cardura XL	Doxazosin	PPOP	For treatment of hypertension
4	Covera HS	Verapamil	PPOP	For the management of hypertension and Angina
5	EÒdac 24	Pseudoephiderine	EOP	Temporary relief of stuffy nose and sinus pain/ pressure caused by infection
6	Viadur	Leuprolide acetate	Implantable osmotic system	For treatment of prostate cancer and breast Cancer
7	Tegretol XR	Carbamazepine	Implantable osmotic systems	For use as an anticonvulsant drug

CHAPTER 2

AIM OF INVESTIGATION

2. Aim of the Investigation

The problems associated with conventional drug delivery system is solved by formulating the controlled drug delivery system. These delivery system control the concentration of drug at effective level. They offered some benefits like, patient acceptance, minimize drug accumulation, employs low amount of drug, reduce the local side effects.

Osmotic system promotes the osmosis principle for drug delivery which is independent of physiological enviorment of GIT, pH and food effects. They deliver water soluble as well water insoluble drugs. Semi permeable membrane and osmogents modulate the drug release from this system. By modulating formulation properties zero order release rate achieved to determine drug release.

Drug A is used in the treatment of epilepsy and trigeminal neuralgia. Relative bioavailability is 89% and 6-7 hrs is average terminal half-life of drug. Drug A is poorly water soluble. To reduce the frequency of daily dosing and make better patient compliance these factors are required for development of an alternative formulation. So, it is determined to formulate osmotic tablets of drug A for once a day with zero order drug release and compared with the innovator product ER tablets for twice in a day.

The aim of present work was to develop an osmotic formulation with elementary osmotic pump technique which is single layer tablet to achieve zero order kinetics. There are various formulation parameters influencing dissolution profile drug like, rate controlling membrane, granulating agent and concentration of coating. Based on the dissolution profile optimized formulation is selected.

CHAPTER 3

LITERATURE REVIEW

3. Literature Review

[1] Wen – Jin Xu developed controlled porosity Salvianolic acid B osmotic tablets. This preparation optimized by Artificial neutral network experimental design. They studied that ANN have better output than other optimized design. This controlled release tablet achieved zero order kinetic release. Screening and optimization of formulation by ANN optimized three different factors for drug release of drug.

There are three level weight of coating, concentration of PEG400 in coating solution and different ratio of drug and osmotic agent. Osmogents have main factor for release of drug. If increase in weight of osmotic agent, they increase osmotic pressure which enhance the drug release form the formulation. In this study, the variation of hardness not more affect release profile of drug. Drug release rate of drug affected by coating weight and plasticizer of coating solution. At the zero order rate drug release will be obtained for 12 h. This study showed the obtained result was more applicable than the uniform design.[40]

[2] Hadjira Rabti developed extended release elementary osmotic carbamazepine tablet. In this formulation carbamazepine antiepileptic poorly water soluble drug, there are solubility enhanced by solubility enhancers - surfactant SLS. They improve the dissolution rate of the formulation. Swellable polymers with EOP tablet reduce the side effect and improve the drug profile rate. The variable of different factors core components and coated was optimized by single parameter Taguchi orthogonal design with ANOVA. From this optimization design showed that the solubility of drug increase by sodium lauryl sulfate and little amount of PVP K30. Zero order rate more affected by coating materials than core.

There are four factors optimized – Plasticizer type, amount of plasticizer, Semipermeable membrane thickness, size of orifice. In coating of the core tablets by cellulose acetate and acetone that rupture the surface of the core tablets. So, there was use plasticizer that affect the drug release and permeability of polymers. More viscosity grade increase the release rate. Thickness of the SPM affect the diffusion rate and dissolution medium of drug. Orifice size had not significant change in the formulation. Drug release rate of carbamazepine tablet compared with innovator product Tegretol CR 200 tablets. Drug release of Carbamazepine achieved 80% at zero order in 12 h. [41]

[3] Zhi – hong Zhang developed pull-push osmotic pump tablets and delevop design expert system of formulation. Expert system is generally related to the artificial intelligence. PPOP generally used for poorly water soluble drugs or water-insoluble drugs. In this PPOP formulation drug layer contain famotidine API, osmotic agent, PVP as a binder and push layer contain NaCl or KCl, osmotic agent, PEO and ferric oxide. Core tablets coated with semipermeable membrane, pore former. Release behaviour of model predicted by artificial neural network system. There are many formulations predicted by ANN system. [42]

[4] Vincent Malaterre designed pull - push pumps. The aim of the investigation was drug release affected by which factors in drug delivery system. There are two drugs used – Isradipine and Chlorpheniramine.

There are some factors that affect the drug delivery like surface area of tablets, the ratio of PEG in SPM, amount of osmogents and polymeric grade in drug layer. Size of pores are depend on ratio of polyethylene glycol and cellulose acetate. Membrane thickness and PEG type affect the lag time. If molecular weight of PEG increase then lag time also increased.

PPOP achieved zero order kinetics for prolonged period of time. They also checked drug release rate with osmotic agent and without osmotic agent. Without NaCl osmogents affect the dissolution of the drug. Experimental design optimized the parameters which are affect the drug delivery system. [43]

[5] Li Yuenan developed double layered osmotic controlled tablet. There was use actarit drug which is used in rheumatoid arthritis. There was developed this formulation to overcome some disadvantages like short biological half-life and in plasma concentration occurs large fluctuations.

There was above layer containing drug and below layer contained expanding agents. Core layer coated with semipermeable membrane. Below layer hydrated and swollen that are help to release drug.

The factors were optimized by single factor experiment. The effect of PEO on drug layer was that low molecular weight decrease the release rate. They used some penetration enhancers like NaCl, lactose, mannitol. From these NaCl had more release rate than others. They also observed drug loading with different concentration of dose of actarit. PEO act as swelling agent in push layer. Pore former also affect the release profile that are depend on

the plasticizers. Different viscosity grades were used as pore former. Form PEG 200/400/4000, PEG 4000 had fast release rate. They completely dissolved in coating film. They optimized the three factors; amount of the NaCl in pull layer (above), amount of the plasticizer PEG 4000 in coating solvent and weight gain of coating layer. Observed their release rate effect. [44]

[6] Elbary AA, Tadros MI and Eldin AA developed etodolac loading controlled porosity osmotic pump. a) osmogent types (sodium chloride, mannitol), (b) ratio of drug-osmogent, (c) composition of coating solution, (d) weight gain% these variables influencing design were investigated. Drug release were estimated by Statistical analysis and kinetics models. From the result of design determine that fructose was more significant ($P<0.5$) in core tablets for drug release rates. Coating weight gain achieved with 4% W/W a mixture of CA- SPM, diethyl phthalate and Polyethyleneglycol- 400 on core tablets to enabled zero order sustained release over 24h. Optimized batch showed enhancement of bioavailabilty and plasma concentration of etodolac CPOP tablets when compared with immediate release Napilac capsules. [45]

[7] Sinchaipanid developed Propranolol hydrochloride loaded drug with PVP as pore formers in preparation of micro/nanoporous containing osmotic pump tablets which coated by CA. Two level and two factor containing central composite design optimized the formulation. Pore former and coating level were variables. Pore former's molecular weight effect determined. Drug release increased If M.W increased. By statistical software founded the responses of variables with drug release. From results founded that drug release profile depend on molecular weight and concentration of PVP. Optimized concentration of PVP-K30 containing batch showed acceptable 12h drug release with membrane thickness. However 24h drug release estimated with PVP-K30 and PVP-K90 containing membrane. [46]

[8] Vyas SP et al formulated and evaluated Diltiazem hydrochloride containing elementary osmotic pump with high drug release rate. Drug release can reduce by incorporation of various polymer and drug entrapment in matrix. By this research hydrophilic polymer's effect on release profile was searched. Ingredients parameters like amount of osmotic agent and ratio of drug and polymer were optimized for to obtained desire release. Two formulation were optimized and evaluated. Release rate optimized by theoretical and

compared. Different dissolution models were applied. By sum of squared residuals kinetics model is selected. [47]

[9] Han Pan, Hengpan Jing designed Elementary Osmotic Pump that consist of metformin hydrochloride and glipizide for synchronized and controlled release. There are elementary osmotic pump compared with conventional tablet for estimation of controlled release of the drug. There was metformin hydrochloride has high solubility and glipizide with low solubility. Elementary osmotic pump generally more suitable for high solubility drugs. But here, metformin was also act as an osmogent which helped to release glipizide through orifice. Because of low solubility of glipizide sodium hydrogen carbonate used as a pH modifier for better release of drug. Metformin's burst release decreased by ethyl cellulose which is act as release preventers. These formulation optimized by FCCD to determined various effect of the factors on drug release. EOP tablets prepared with sodium hydrogen, PVP K-90, ethyl cellulose and coated with cellulose acetate and polyethylene glycol. In FCCD, there were optimized two factor and three level. Factors: Ratio of CA:PEG and Weight gain. There was optimized % release of both drugs in 12h. There was different impact of factors of pore forming agents on release profile. In this study, there was PEG-400, PEG-1500, PEG-4000. MTF and GLZ had increase in release rate in 4h with rise in level of PEG-1500. If weight gain of membrane coating is increase then drug release rate decrease. For increase the release rete of drug weight gain of coating decrease, so penetration of water across membrane increase which help to core of tablet dissolve faster. The optimize formulation was validated by in vivo and in vitro study. The zero order drug release rate optimized by in vitro and in vivo study determined the Plasma concentration-time profile. [48]

[10] Naushad Alam and Sarwar Beg developed trimetazidine hydrochloride mucoadhesive elementary osmotic tablet, which are improve the oral absorption and achieved the controlled release rate. There was some factors affect the EOP tablets, like thickness of coating, solubility of drug, level of leachable components in coating solution. Elementary osmotic pump also improve poor oral absorption with bioavailability. In core tablets they used different osmogents like sodium chloride, mannitol, sodium bicarbonate; binders-PVP K-30; channeling agent like HPMC and in coating of core tablets with various concentration of ethyl cellulose (5%, 10%, 12%, 15%), HPMC, different concentration of

plasticizers. 10% plasticizers have good surface property in tablet coating formulation. In coating HPMC act as a pore former which is release drug faster. They are also compared with marketed formulation like, Vastarel-MR. Proper selection of HPMC and ethyl cellulose showed better controlled release of drug and mucoadhesive strength. [49]

[11] Zentner GM et al investigated the controlled porosity walls containing active water soluble agents of osmotic tablets with zero order release. Sponge like appearance of walls and it was penetrate to aqueous and dissolved solutes. Thickness of wall, amount of leachable additives and permeability of polymer components of wall, core tablet's solubility, concentration of drug and osmotic difference over the wall affect the release rate. Release was not affected by pH and degree of agitation. Release was basically related with the osmosis mechanism. Permeability of water and solute to the walls steady state release calculated and compared with actual device formulation. An equivalent mass per unit surface area basis was demonstrated by osmotic delivery theory and extended release of multiparticulate dosage form. [50]

[12] Kumaravelrajan et al designed Nifedipine and Metoprolol containing controlled porosity osmotic tablets to achieve controlled release. Tablets were prepared by core containing drug and coated with various polymers (Polyvinylpyrolidone, PEG - 400, HPMC), different concentration (30, 40 and 50% of CA) of pore former with increase in weight 8, 12 and 15%. Type and amount of pore former and % weight gain of membrane all were formulation factors which were observed to affect the release rate. Membrane weight was indirectly proportional to the drug but opposite of the pore former. Burst strength of exhausted shell was reversely related to the level of pore former, but affected by membrane weight. Drug release from the pores which is showed by SEM study. Drug release kinetics mechanism determine by dissolution models which was applied to release data. For the determination of in vivo of formulated batch estimated by in vitro release kinetics which was subjected to superposition method. Controlled release of optimized batch containing both drugs is successfully showed effect in hypertension multi-drug therapy. [51]

[13] Gupta BP et al investigated that conventional drug delivery system. At the target site this system have slight or no control with effective concentration over their drug release. There may continuously changing on the dosing pattern. By controlling the delivery

system, drug can be applied for long term in a controlled manner. By controlled delivery administer oral, transdermal and parenteral dosage. Poor solubility and permeability containing molecules have low oral bioavailability. Formulation of an extended delivery also necessitate reasonable absorption in GIT. To enhance the drug's bioavailability osmotic drug delivery system is the most appropriate from all the delivery system. These delivery system is independent from the concentration and physiological factors related to GIT and achieved release of drug at zero order kinetics. [52]

[14] Rajewski RA et al investigated a controlled porosity osmotic pump tablet with 7m-beta-CD as solubiling agent and an osmogens for poor soluble drugs with different physiological properties. Study of drugs and 7m-beta-CD release from the OPTs found from Japanese Pharmacopoeia dissolution method and determined by HPLC. Proper ratio of 7m-β-CD to drug at which release the drug from OPTs was achieved. It was not dependent on pH of GI tract estimated for each drug. When took release of OPTs for 2 hrs, the ACR values correlate to the drug concentration in core tablets. The release profile of prednisolone and sodium chloride from the OPTs were almost similar to 7m-beta-CD. The present study results confirmed that as solubility enhancer and as an osmotic agent 7m-beta-CD used and release rate of both water soluble and water insoluble drugs can be achieved. [53]

CHAPTER 4

EXPERIMENTAL SECTION

4. Experimental Section

4.1 Materials

Table 4.1 List of Material used

Exicepients	Company	Use
Drug A	-	API
HPMC E3 LV	Dow Chemical	Binder
HEC 250 L	Ashland Pharm	Rate controlling Polymer
HEC 250 HX	Ashland Pharm	Rate Controlling Polymer
Mannitol 50 C	Roquette	Osmogent
Dextrates emdex	Evonik Industries	Osmogent
SLS	FMC Bipolymer, Bangalore, India	Solubilizing agent
Iron Oxide Red	Colorcon Pharma, Verna, Goa	Colorant
Iron Oxide Yellow	Colorcon Pharma, Verma, Goa	Colorant
Magnesium Stearate	-	Lubricant
Cellulose acetate 320S	Rotuba, USA	Semipermeable agent
CA – 398/10	Rotuba, USA	Semipermeable agent
HPMC 15 cps	BASF Industries, Germany	Binder
PEG 8000	Dow Chemicals	Plasticizer
Methyl Alcohol	ACS Chemicals	Coating solvent
Methylene chloride	Fischer Scientific India Pvt Ltd, Mumbai	Coating solvent

4.2 Instrumentation

Table 4.2 List of Instrument used

Instrument	Company
Digital_weighing balance	Mettler Toledo, Mumbai, India
Tablet compression machine	Korsch, silverwater, Australia
Hardness tester	Dr. Schleuniger Pharmatron, Switzerland
Vernier calipers	Dr.Schleunigre pharmatron
Tablet coating machine	Ganson, Thane, India
Friabilator	Labindia
Density tester	Labindia, Thane, India
Dissolution apparatus	Shanghai, Chaina

4.3 Identification of API

4.3.1 Evaluation of Melting Point

At a temperature, substance's solid and liquid phases become equilibrium with specific pressure is called melting point. For estimation liquid paraffin used.

4.3.2 Maximum UV absorption of Drug A

By using ultraviolet-visible spectrometer, 100µg/ml concentration containing drug in methanol solution was measured the spectra at 200-400nm wavelength.

4.4 Estimation of Drug A

4.4.1 Preparation of Calibration Curve

Method to prepare Stock Solution

For preparation of 1000µg/ml solution, in 50ml containing volumetric flask took 50mg Drug A and dissolved in mixture of methanol and distilled water.

Determination of Standard Curve

From 1000µg/ml stock solution 2, 4, 6, 8, 10, 12 and 14 µg/ml concentration of drug A containing serial dilution were made in 10 ml volumetric flask. The absorption of dilution was measured at 284nm three times by UV. By using average absorbance and concentration graph was plotted.

4.5 Compatibility study of Drug A and excipients

By analysis of binary mixtures of excipients and API compatibility study was determined in open container at 40°C/ 75 RH for 1 month. The excipients which have functioning as filler, lubricants, disintegrates were evaluated by this study.

Table 4.3 Binary mixture and their ratio with API

Binary Mixture of Ingredients	Ratio with API
API + HPMC E3 LV	1 : 0.1
API + HEC 250 L	1 : 0.1
API + Mannitol	1 : 1
API + HEC 250 HX	1 : 0.1
API + Dextrates	1 : 1
API + Magnesium stearate	1 : 0.1
API + Ferric Oxide	1 : 0.01
API + CA-320S	1 : 0.1
API + CA-398/10	1 : 0.1

4.5.1 Excipient- Excipients compatibility study

Here, Compatibility study of excipients at initial stage, in open container at 40°C – 75%RH for 4 weeks and 50° C with moisture after 4 week was evaluated.

4.6 Characterization of Innovator Product

4.6.1 Physical Property Characterization

By osmotica pharmaceuticals innovator product of drug A USP is manufactured. This elementary antiepileptic tablets are available in 100mg, 200mg and 400mg tablets strengths in US market.

4.6.2 Innovator Product's chemical property estimation

4.6.2.1 Assay of product

As shown in USP monograph method, innovator product's assay was performed and 92% obtained.

4.6.2.2 Determination of Related substances

As mentioned in USP monograph, analytical method of drug's relative substances were performed.

4.6.2.3 Dissolution Profile

By using USP apparatus I basket dissolution profile of innovator product was measured in purified water at 100 RPM.

4.7 Formulation of Osmotic Controlled Tablets

4.7.1 Formula of Elementary Osmotic Tablet of Drug A

Table 4.4 Core Tablet formula of EOP Tablets

Serial. No	Materials	Qty %	Application
1	Drug A	53.33	API
2	HPMC E3 LV	5.33	Binder

3	HEC 250 L	1.33	Rate Controlling Polymer
4	HEC 250 HX	5.33	Rate Controlling Polymer
5	Mannitol 50 C	14.47	Osmogent & Diluent
6	Dextrates Emdex	14.47	Osmogent
7	SLS	0.67	Surfactant
8	Iron Oxide Yellow	0.15	Colorant
9	Iron Oxide Red	0.85	Colorant
10	Magnesium Stearate	0.93	Lubricant
11	Purified Water	q.s	Granulating Agent

Table 4.5 Coated tablet formula of EOP Tablets

Sr. No	Ingredients	Qty%	Application
1	Cellulose Acetate 320S	2.92	Semipermeable Agent
2	Cellulose Acetate 398/10	0.44	Semipermeable Agent
3	PEG 8000	0.32	Plasticizer
4	Methocel E15 premium LV	0.32	Coating Polymer
5	Methyl Alcohol	q.s.	Coating Solvent

4.7.2 Preparation Producer of EOP Tablet of Drug A

Following steps are performed in preparation of each elementary antiepileptic tablets of Drug A.

STEP 1: Shifting of Materials

Drug A shifted through 20# sieve, HPMC E3 LV, HEC 250 L, HEC 250 HX, Mannitol 50C, Emdex shifted through 40# sieve and Iron oxide yellow and Iron oxide red shifted through 30# sieve.

STEP 2: Dry Mixing

All material taken in Rapid Mixture granulator and mixed for 15min with slow impeller speed.

STEP 3: Granulation

All dry mix material granulated using purified water for 2 minutes. Kneading for 1 minute with impeller and chopper slow speed.

STEP 4: Drying

Granulated mixture dried in rapid fluid bed dryer at 45°C (LOD NMT 3%W/W).

STEP 5: Milling

Dry mixture shifted through 20# sieve and oversized milled through 1.5mm screen.

STEP 6: Blending

At 24 rpm, shifted materials mixed in blender for 10 mins.

STEP 7: Lubrication

Magnesium stearate added in blending material after passing through 40# sieve and at 24 rpm blend for 8 mins.

STEP 8: Compression

In 18 stations tablet compression machine compression of lubricated blend was carried out by 11.80 mm round plain of both sides.

STEP 9: Semipermeable Membrane

Cellulose acetate 320S and cellulose acetate 398/10 were dissolved in methyl chloride and PEG 8000 dissolved in methyl alcohol. Then mix the both solution and coating was done by coating machine, Ganscoater which had 3kg coating pan capacity at 10rpm. Spray rate of coating was fixed at 1.4 – 1.8g/min. Inlet temperature was 55±10°C and exhaust temperature was kept between 35 - 40°C. Coating of the tablet was continued until proper weight of the tablets were achieved.

STEP 10: Orifice Drilling

Orifice drilling of tablet was done by mechanical drilling machine and laser drilling machine.

4.8 Formulation trials of EOP tablets of Antiepileptic Drug

In formulation of EOP tablets wet granulation was performed as above method and lubricated blend was evaluated in density tester.

4.8.1 Preliminary Trials

The core and coated batches was prepared in line of innovator product. Trial batches showed table 4.6.

Table 4.6 Formula of Core Tablet F1 Batch

Sr. No	Ingredients	Qty (mg) / tablet
1	Drug A	400
2	HPMC E3 LV	40
3	HEC 250 L	10
4	HEC 250 HX	20
5	Mannitol 50C	108.5
6	Dextrates Emdex	108.5
7	SLS	5
8	Iron Oxide Yellow	0.15
9	Iron Oxide Red	0.85

10	Magnesium Stearate	7

Table 4.7 Semiperable Membrane Coating Formula

Sr. No	Ingredients	Qty (mg) / tablet
1	Cellulose acetate 320 S	18.25
2	Cellulose acetate 320/10	2.75
3	PEG 8000	2.0
4	Methocel E15	2.0

4.8.2 Optimization of Rate controlling Polymer

Trial batches of core tablets with different concentration of rate controlling polymer HEC 250HX was given in following table 4.8.

Table 4.8 Formula of core tablets for batch F2 and F3

Sr. No	Ingredients	F2	F3
1	Drug A	400	400
2	HPMC E3 LV	40	40
3	HEC 250L	10	10
4	HEC 250HX	**30**	**40**
5	Mannitol 50C	108.5	108.5
6	Dextrates Emdex	108.5	108.5
7	SLS	5	5
8	Iron Oxide Yellow	0.15	0.15
9	Iron Oxide Red	0.85	0.85
10	Magnesium Stearate	7	7

Table 4.9 Formula of coated tablets for batch F2 and F3

Sr. No	Ingredients	F2	F3
1	Cellulose acetate 320S	18.25	18.25
2	Cellulose acetate 320/10	2.75	2.75
3	PEG 8000	2.0	2.0
4	Methocel E15	2.0	2.0

4.8.3 Optimization of Granulating Agent

In granulation part purified water used as granulating agent in formulation of EOP tablets and quantity of water which was affect the dissolution release profile. Different amount of water was used in these batches F4 to F8.

Table 4.10 Formula of Core EOP tablets of batch F4, F5, F6, F7 and F8

Sr. No	Ingredients	F4	F5	F6	F7	F8
1	Drug A	400	400	400	400	400
2	HPMC E3 LV	40	40	40	40	40
3	HEC 250L	10	10	10	10	10
4	HEC 250 HX	40	40	40	40	40
5	Mannitol 5OC	108.5	108.5	108.5	108.5	108.5
6	Dextrates Emdex	108.5	108.5	108.5	108.5	108.5
7	SLS	5	5	5	5	5
8	Iron oxide yellow	0.15	0.15	0.15	0.15	0.15
9	Iron oxide red	0.85	0.85	0.85	0.85	0.85
10	Purified Water	**80**	**120**	**160**	**200**	**240**

11	Magnesium Stearate	7	7	7	7	7

Table 4.11 Coated tablet formula

Sr. No	Ingredients	F4	F5	F6	F7	F8
1	Cellulose acetate 320S	18.25	18.25	18.25	18.25	18.25
2	Cellulose acetate 398/10	2.75	2.75	2.75	2.75	2.75
3	PEG 8000	2.0	2.0	2.0	2.0	2.0
4	Methocel E15	2.0	2.0	2.0	2.0	2.0

Table 4.12 Optimized Core Tablet Batch F6

Ingredients	Optimized Core F6 Batch (mg)
Drug A	400
HPMC E3 LV	40
HEC 250L	10
HEC 250HX	40
Mannitol 50C	108.5
Dextrates Emdex	108.5
SLS	5
Iron Oxide Yellow	0.15
Iron Oxide Red	0.85
Magnesium Stearate	7

4.8.4 Optimization of different Variation of % Coating

In the optimization of % coating five batches core tablets were prepared as above optimized formula. After done with different % coating trial, core tablets of EOP's evaluation parameters obtained in acceptable range.

Table 4.13 Formula of different % of coating of batch F8, F9

Sr. No	Ingredients	F8 (3%)	F9 (3.5%)
1	Cellulose Acetate – 320S	14.6	18.25
2	Cellulose Acetate – 398/10	2.20	2.75
3	PEG 8000	1.60	2.0
4	Methocel E15	1.60	2.0

Table 4.14 Trial Batches of Different %Coating of F10, F11and F12

Sr. No	Ingredients	F10 (4%)	F11 (4.4%)	F12 (4.6%)
1	CA – 320S	21.9	24	24.82
2	CA – 398/10	3.3	4.16	3.74
3	PEG 8000	2.4	1.92	2.72
4	Methocel E15	2.4	1,92	2.72

4.8.5 Optimization of Orifice Size by different Drilling Machine

Optimized core and coated tablets batch formulated above formula and then optimized the different size of the orifice by two machine mechanical drilling and laser drilling and evaluate the effect on dissolution profile.

Table 4.15 Different Orifice size by Mechanical drilling of batch F12 and F13

Sr. No		Innovator	Mechanical Drilling	
		F11	F12	F13
1	Drill Diameter	0.8	0.8	0.8
2	Depth Diameter	1.1	1.25	0.8
3	F2 wrt Innovator	-	62	60
4	F2 wrt IH	-	60	70

Table 4.16 Different Orifice size by Laser Drilling of batch F14 and F15

Sr. No		Innovator	Laser Drilling	
		F11	F14	F15
1	Drill Diameter	0.8	0.8	0.8
2	Depth Diameter	1.1	0.9	1.1
3	F2 wrt Innovator	-	62	62
4	F2 wrt IH	-	79	80

4.9 Statistical analysis of Optimize Formulation

Similarity factor (F2), statistical derived mathematical parameter used to predict in vitro release profile. It was calculated by comparing release profile of optimized batch with innovator product.

The equation of similarity factor is:

$$f_2 = 50 * \log \{[\, 1 + \frac{1}{n} \times \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where,

R_t and T_t = % drug release of test and reference product at time

n = Dissolution Sample number

t = sample index time

f_2 value is 100, if two profiles are identical. $f_2 \geq 50$ value which indicate similarity of two product test and reference dissolution profiles.

4.10 Model fitting to evaluate the Mechanism of Drug Release

There are various models fit to the optimized batch for determination of drug release.

4.10.1 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

Where, k = Zero-order rate constant

M = % drug unreleased (or released) at t time

The plot of % drug unreleased versus time is linear

4.10.2 First – Order Model

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

Where, a = intercept

b = slope

It assumes that a drug molecule diffuses out through a gel like layer formed around drug during dissolution process. A plot of log cumulative % drug remaining versus time is linear.

4.10.3 Higuchi Model

A 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.

$$M = (100-q)* \text{ square root of time}$$

Where, q = Higuchi constant (% per square root of time)

A plot of % drug unreleased versus square root of time is linear

4.10.4 Korsmeyer – Peppas Model

$$Mt/M = k*tn$$

Where, Mt/M = the fraction of drug released at time t‘.

n = diffusion exponential

If n = 1, the release is of zero order; 0.5<n<1, release is through anomalous 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.

4.10.5 Hixon Crowell Model

$$M = (1001/3 – (k*t))3$$

Where, k = Hixon crowell constant

A plot the graph of % drug unreleased versus cube root of time is linear

CHAPTER 5

RESULTS & DISCUSSIONS

5. Results and Discussion

5.1 Results of API

5.1.1 Melting Point

Melting point of drug was given in following table.

Table 5.1 Melting point of API

Reported Melting Point	Observed Melting Point
204 - 206°C	204°C

Result: API's melting point was obtained 205°C corresponding to the theoretical value.

Conclusion: The drug's determined M.P was found to be the same as reported value.

5.1.2 Maxima absorption of Drug A

In following figure showed maximum absorbance of drug.

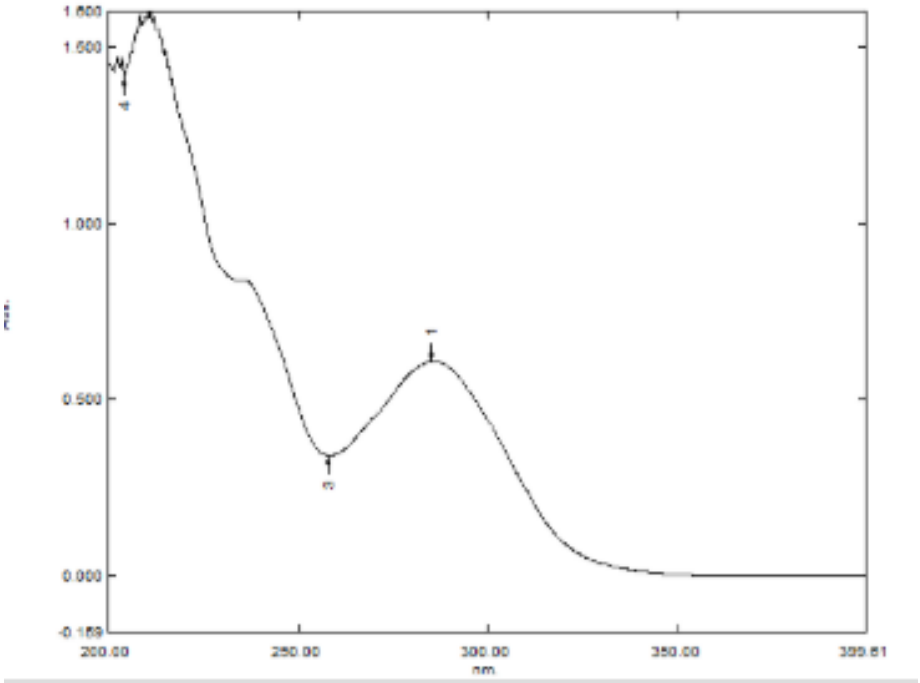


Figure 5.1 Absorption maxima of Drug A

Conclusion

A maximum absorption of drug A was determined at 284nm that matched drug A's standard absorption. Therefore it can be concluded that the sample being procured is identify.

5.2 Evaluation of absorbance of Drug A

Table 5.2 Absorbance of drug A

Concentration	Absorbance
0	0
2	0.132
4	0.231
6	0.353
8	0.471
10	0.592
12	0.701
14	0.824

Result

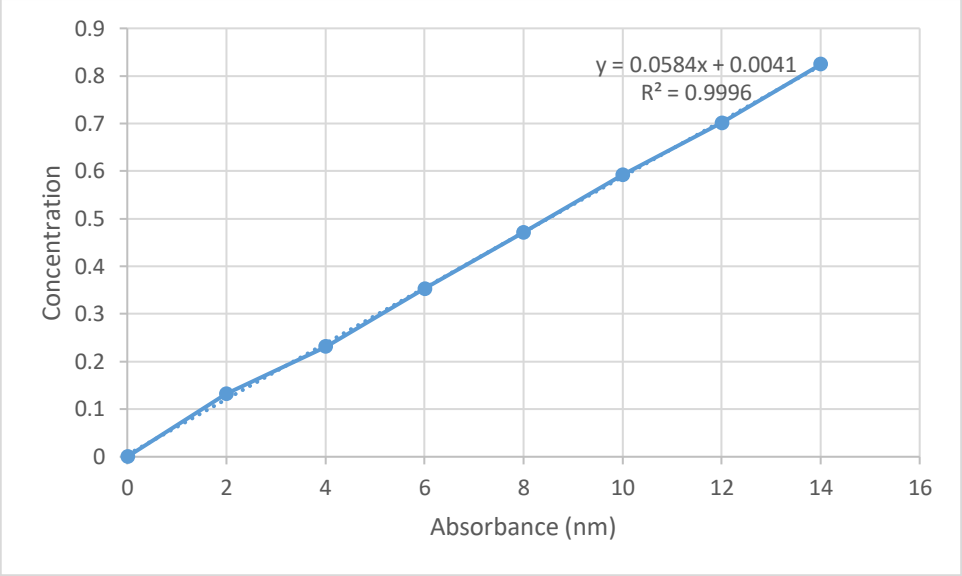


Figure 5.2 Standard curve of Drug A

Table 5.3 Regression Parameter of Drug Standard curve

Regression Parameters	Value
Correlation Coefficient	0.9996
Slope	0.0584
Intercept	0.0041

Discussion: Coefficient of correlation close to 1.

5.3 Determination of Drug-Excipients Compatibility Study

Result of impurities of API with excipients at different stages.

Table 5.4 Results of API related substance with Excipients

Impurities	Initial	After 4 weeks	Specification
Descyclohexanol Impurity	0.01	0.02	NMT 0.20
Relative Compound A	0.01	0.02	NMT 0.20
Max. Unknown Impurity	0.04	0.04	NMT 0.20
Total Impurities	0.06	0.08	NMT 1.0

Table 5.5 Assay of Drug A with Excipients

Time Period	Assay%	Specification
At Initial Stage	98	90-110%
After 4 weeks	99	90-110%

Table 5.6 %Water Content of Drug A

Time Period	Water content%	Specification
At Initial Stage	4.3	NMT 8.0
After 4 weeks	5.2	NMT 8.0

Discussion: No change in the percentage of water content was determined in open container for one month at 40°C / 75% RH in binary mixtures. There was no degradation that desired compatibility of API and excipients.

5.3.1 Determine Excipient-Excipient Study

Result of impurities study of excipient-excipient at different condition given in following table.

Table 5.7 Result of Relative substance of excipients at Initial stage

Excipients	At Initial Stage		
	Any Individual unspecified impurity in Procedure 1 NMT 0.2%	Any Individual unspecified impurity in Procedure 2 NMT 0.2%	Total Procedure 1 + Procedure 2 NMT 0.5%
HPMC ELV	0.02	0.02	0.06
HEC 250 L	0.02	0.02	0.05
HEC 250 HX	0.02	0.02	0.06
Mannitol	0.02	0.02	0.06
Emdex	0.02	0.02	0.07
Iron Oxide	0.02	0.02	0.07
SLS	0.02	0.02	0.07
Magnesium Stearate	0.02	0.02	0.09
Cellulose Acetate	0.02	0.02	0.06

Table 5.8 Result of Relative substance of excipients at 50° C with moisture after 4 weeks

At 50°C with moisture after 4 weeks			
Excipients	Any Individual unspecified impurity in Procedure 1 NMT 0.2%	Any Individual unspecified impurity in Procedure 2 NMT 0.2%	Total Procedure 1 + Procedure 2 NMT 0.5%
HPMC E3 LV	0.03	0.02	0.08
HEC 250 L	0.03	0.02	0.07
HEC 250 HX	0.03	0.02	0.07
Mannitol	0.03	0.02	0.08
Emdex	0.03	0.02	0.08
Iron Oxide	0.03	0.02	0.07
SLS	0.03	0.02	0.08
Magnesium Stearate	0.03	0.02	0.08
Cellulose Acetate	0.03	0.02	0.07

Table 5.9 Result of Relative substance of excipients at 40°C – 75% RH after 4 weeks in open container

At 40° C – 75% RH after 4 weeks in open container			
Excipients	Any Individual unspecified impurity in Procedure 1 NMT 0.2%	Any Individual unspecified impurity in Procedure 2 NMT 0.2%	Total Procedure 1 + Procedure 2 NMT 0.5%
HPMC E3 LV	0.03	0.02	0.09

HEC 250 L	0.03	0.02	0.08
HEC 250 HX	0.03	0.02	0.08
Mannitol	0.03	0.02	0.09
Emdex	0.03	0.02	0.08
Iron Oxide	0.03	0.02	0.08
SLS	0.03	0.02	0.09
Magnesium Stearate	0.03	0.02	0.08
Cellulose Acetate	0.03	0.02	0.08

Table 5.10 %Assay of Excipients

Time Period	Assay%	Specifications
At Initial Stage	97	90 – 110%
After 4 Weeks	96	90 – 110%

Table 5.11 %Water Content of Excipients

Time Period	% Water Content	Specifications
At Initial Stage	4.3%	NMT 8.0%
After 4 Weeks	5.0%	NMT 8.0%

Discussion: No significance changes in the levels of impurities in above blends. There are impurities of drug excipients not more than 0.5% in the total procedure. So, all excipients are compatible with drug. There are excipients stable with drug, because there was not observed degradation at initial stage and after 4 weeks.

5.4 Characterization of Marketed Innovator Product

5.4.1 Physiological Properties

Table 5.12 Description of Innovator Product

Sr. No	Description	Innovator Product
1	Manufactured By	Osmotica Pharmaceutical
2	Shape	Round
3	Colour	Brown
4	Average weight of Core Tablet (mg)	687 mg
5	% Coating	4.19 %
6	Coating (mg)	34 mg
7	Average weight of coating (mg)	722.8 mg
8	Diameter (mm)	12.08 mm
9	Thickness	6.49
10	Ingredients	HPMC E3 LV, HEC, Mannitol, Dextrates Emdex, SLS, Cellulose acetate, Iron oxide, Mg Stearate. PEG 8000, Methocel.

5.4.2 Chemical Property

Table 5.13 Determination of Impurities of Relative Substances

Initial Stage Impurities	0.02 %
50C with moisture after 4 weeks	0.03 %
45C -75 %RH after 4 weeks open vial	0.03 %
Total Impurities	0.09%

In – Vitro Release of Innovator Product

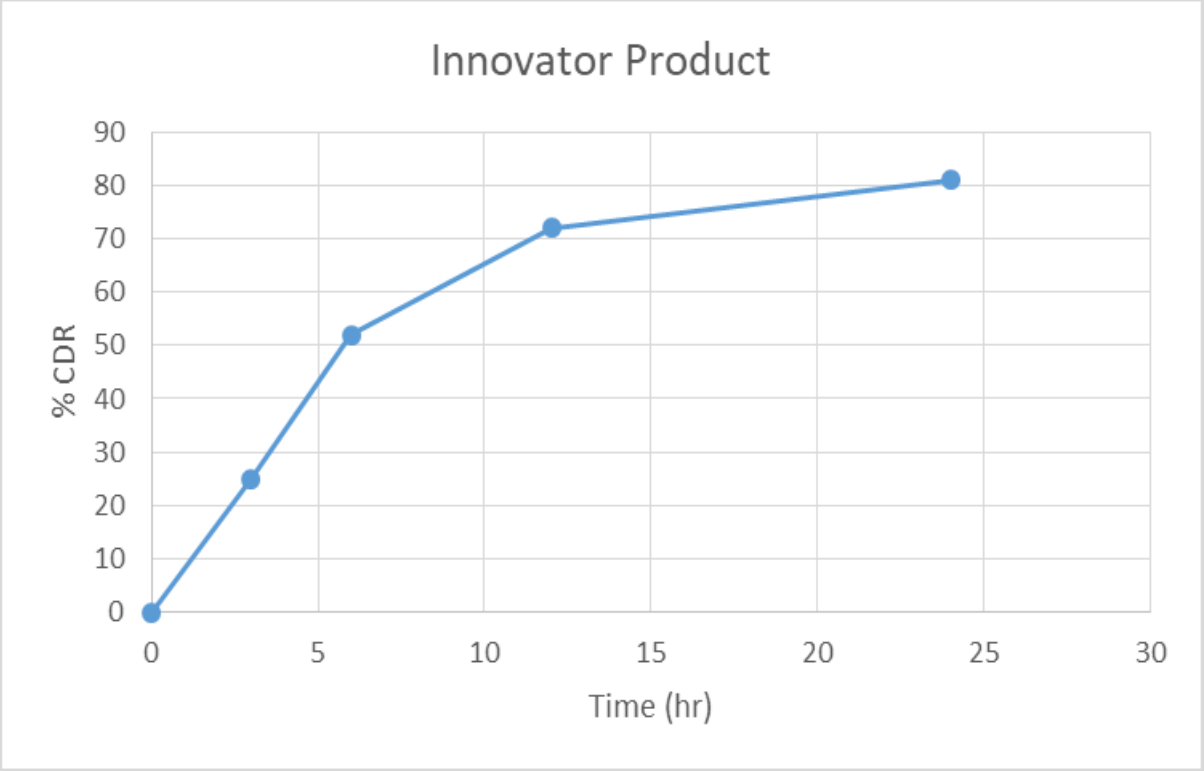


Figure 5.3 %CDR of Innovator Product

Conclusion: It can be concluded from the above results that the innovator product shows up to 24 hrs of maximum cumulative drug release.

5.5 Evaluation of Trial Batches of Elementary Osmotic Tablets

5.5.1 Preliminary determination of Blend

Table 5.14 Flow Properties of Lubricated Blend

Bulk Density	0.73
Tapped Density	0.85
Carr's Index	14.68
Hausner's Ratio	1.17
Angle of Repose	22.68

Discussion: For the formulation of EOP tablet blend had uniform flow properties. Because after wet granulation lubricated blend passed desirable range of flow properties.

5.5.2 Results of Trial Batches of Osmotic Tablets

Evaluate the core and coating parameters of first trial batch F1 and performed dissolution and compare with innovator product.

Table 5.15 Evaluation of Core Tablets of Batch F1

Parameters	Result
Average Weight (mg)	698-700
Hardness (N)	19.5 – 23.5
Friability (%)	0.07
Thickness (mm)	6.47 – 6.59

Table 5.16 Evaluation of Coated Tablets of Batch F1

Parameters	Result
Average Weight (mg)	725 – 730
Thickness (mm)	6.34 – 6.42
Hardness (N)	29 – 30

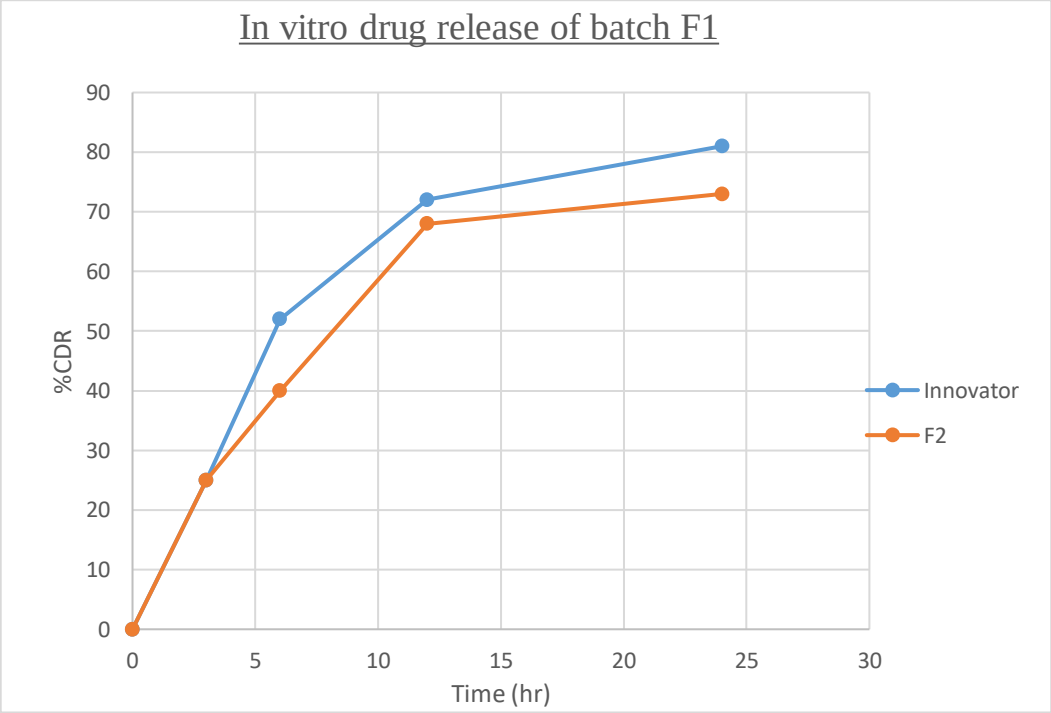


Figure 5.4 In – vitro drug release of Batch F1

Discussion: As per as innovator product weight and thickness of tablets were not achieved within limits. Dissolution not obtained by 2.6% rate controlling polymer that were not matched with innovator release profile.

5.5.3 Results of different concentration of HEC 250HX

In batch F2 and F3 with different concentration of HEC 250 HX evaluate the parameters and drug release.

Table 5.17 Evaluation of batch of core tablets F2 and F3

Parameters	F2	F3
Average Weight (mg)	707-710	723-728
Hardness (N)	18.8-24.6	19.9-23.9
Friability%	0.08	0.04
Thickness (nm)	6.49-6.69	6.89-6.93

Table 5.18 Evaluation of coating Tablets of batch F2 and F3

Parameters	F2	F3
Average Weight (mg)	734 – 740	745 – 750
Hardness (N)	6.40 – 6.94	6.45 – 7
Thickness (mm)	29 – 32	30 – 35.4

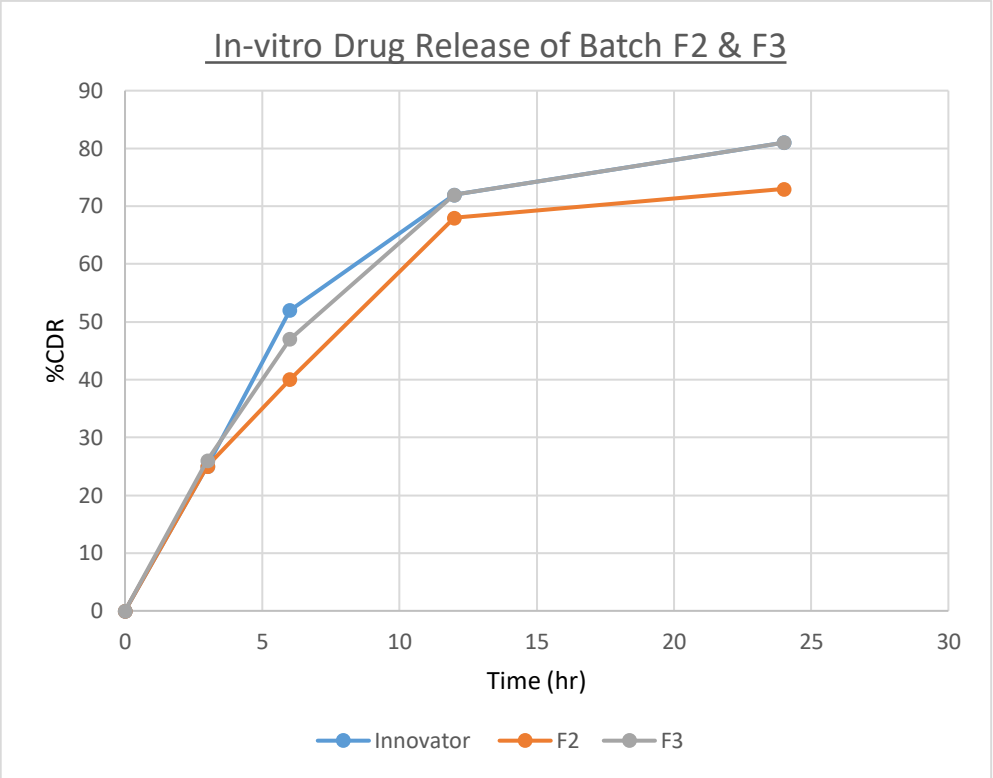


Figure 5.5 In-vitro Drug Release of F2 & F3 Batches

Discussion: Batch F3 gave faster drug release compared to batch F1 and F2, because of high concentration of high viscosity grade HEC polymer. F3 batch's dissolution profile matched with innovator product. Hardness, thickness, % friability were good of batches.

5.5.4 Results of Different amount of Water as Granulating Agent

Evaluation parameters of core and coating tablets given in following table.

Table 5.19 Evaluation of core tablets of batch F4, F5, F6, F7 and F8

Parameter	F4	F5	F6	F7	F8
Average Weight (mg)	722-728	723-729	724-730	723-729	722-729
Hardness (N)	19.5-23.7	19.4-23.1	19.9-23.6	18.9-23.5	19.5-23.9

Friability (%)	0.06	0.05	0.06	0.06	0.08
Thickness (mm)	6.46-6.59	6.49-6.58	6.47-6.57	6.48-6.58	6.46-6.59

Table 5.20 Evaluation of Coated tablets of Batch F4, F5, F6, F7 and F8

Parameter	F4	F5	F6	F7	F8
Average Weight (mg)	744.1-746.4	745.4-748.1	745.3-747.1	745.2-746.5	745.3-747.3
Hardness (N)	30-35.6	30.1-35	31.1-34.9	31.2-35.1	32.2-35.6
Thickness (mm)	6.48-7.15	6.49-7.13	6.47-7.12	6.44-7.11	6.47-7.14

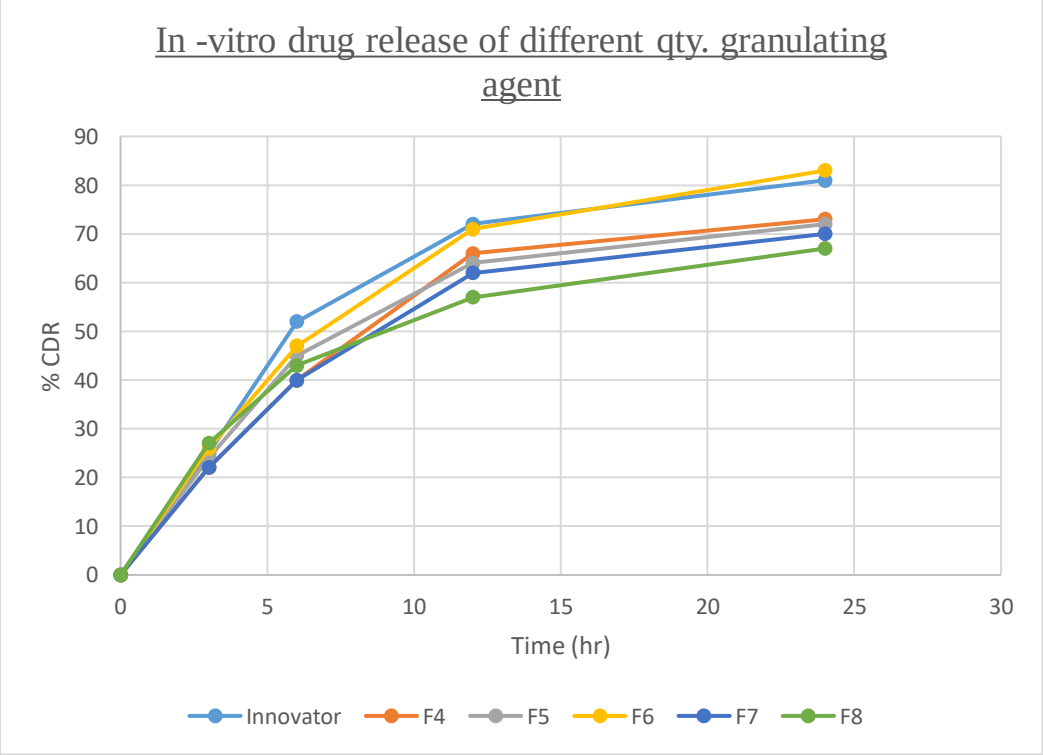


Figure 5.6 In-vitro Drug Release of Batches F4, F5, F6, F7 and F8

Discussion: Batch F4 and F5 containing 80 and 120ml water respectively that producing granules with large lumps compared to batch F6. Batch F7 and F8 had formed hard granules. Evaluation parameters of Batch F7 and Batch F8 had more hardness compared to other batches and innovator product. Batch F6 has granules with good properties so it matched with innovator's dissolution profile. Optimized core tablet batch were optimized with different % of coating.

5.5.5 Determination of Different Concentration of Coating

Result of different concentration containing batches given in following table.

Table 5.21 Evaluation of coated tablet of batch F8, F9, F10, F11 and F12

Parameter	F8	F9	F10	F11	F12
Average Weight (mg)	740.1-744.1	745.2-747.3	749.1-750.4	752.3-753.9	754.6-755.9
Thickness (mm)	19.5-23.5	25.1-29.8	30-35.6	32.4-35.9	34.4-36.8
Hardness (N)	4.55-5.1	5.15-5.95	6.48-7.15	6.92-7.25	7.12-7.65

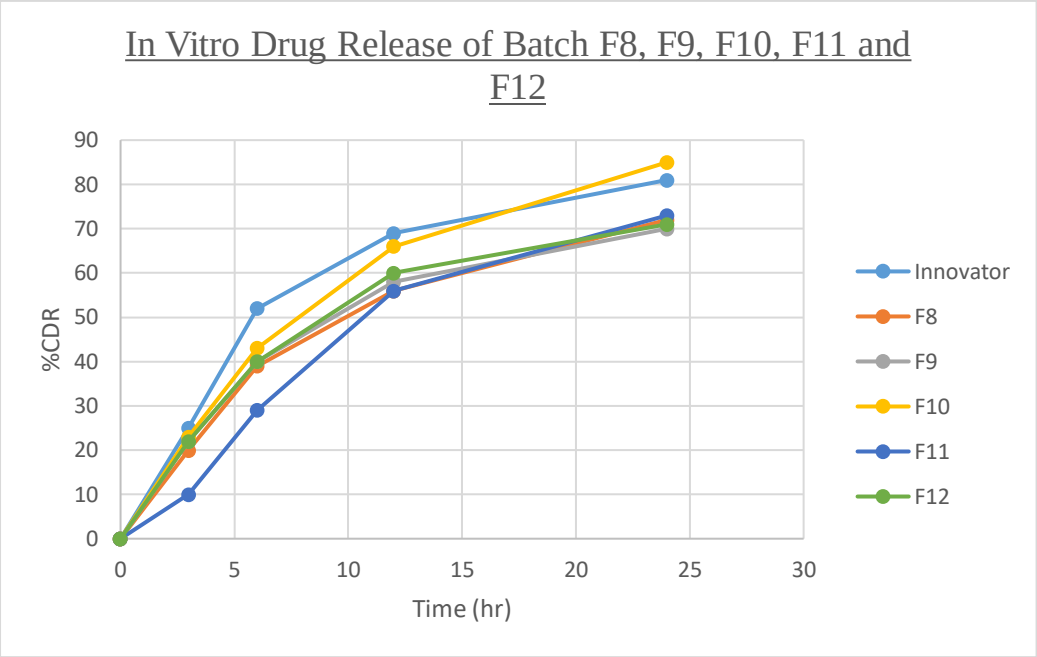


Figure 5.7 In vitro drug release of batch F8, F9, F10, F11 and F12

Discussion: Dissolution rate was delayed if % coating increased. In the batch F10 4% weight gain which was matched with innovator drug product which was evaluated that dissolution release rate depend on the % of coating as the weight of coating increase that increase the thickness of tablets. Thickness of tablets affect the drug release rate. Zero release of batch F10 matched with innovator product so it was optimized.

Optimized Elementary osmotic tablet batch given in following table 5.22.

Table 5.22 Optimized Elementary Osmotic Tablet Batch

Ingredients	Qty (mg)	Qty (%)
Core Tablet		
Drug A	400	53.33
HPMC E3LV	40	5.33
HEC 250L	10	1.33
HEC 250HX	40	5.33
Mannitol 50C	108.5	14.47
Dextrates Emdex	108.5	14.47

SLS	5	0.67
Iron Oxide Yellow	0.15	0.02
Iron Oxide Red	0.85	0.11
Magnesium Stearate	7	0.93
Coated Tablet		
CA – 320S	21.9	2.92
CA – 398/10	3.3	0.44
PEG 8000	2.4	0.32
Methocel E3 LV	2.4	0.32
Total	750	100

5.5.6 Release Profile of mechanical drilling containing Batches

Optimized batch drilled with different size by mechanical drilling. Release rate of this batch was showed and calculate similarity factor.

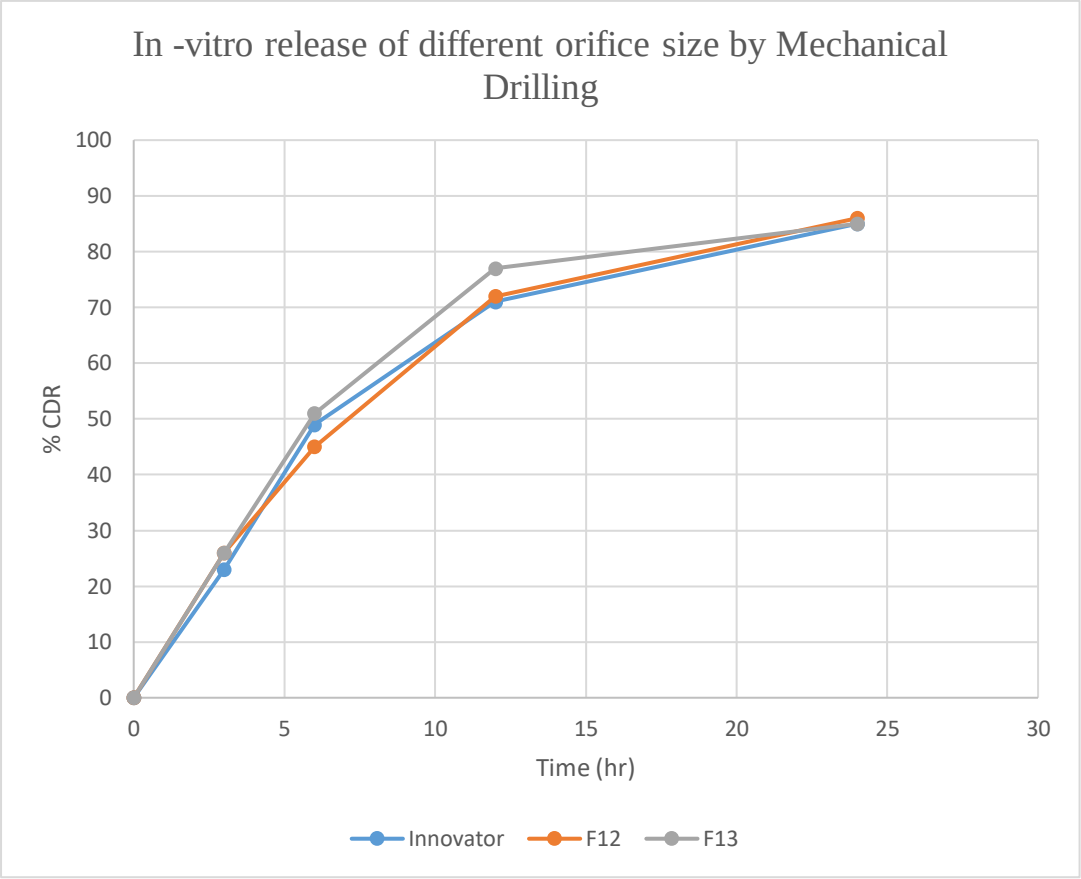


Figure 5.8 In- vitro drug release of F12 & F13 Batches

Discussion: In batch F12 and F13 formulated with different size of drill depth and drill diameter by mechanical drilling machine. But there was not obtained major difference in dissolution rate. Both batch F12 and F13 matched with innovator release profile and f_2 value obtained ≥ 50.

5.5.7 Release Profile of Laser Drilling containing Batches

Release rate of optimized with laser drilling showed in following figure 5.9.

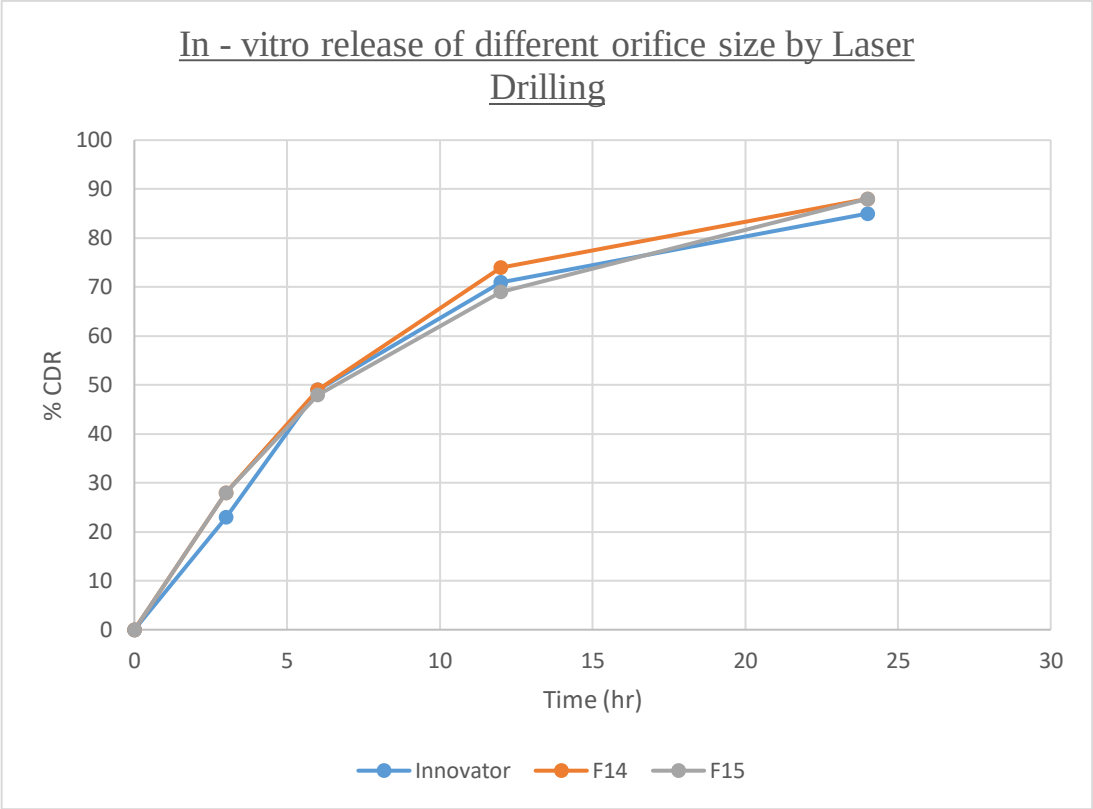


Figure 5.9 In-vitro Drug Release of F14 & F15 Batches

Discussion: Batch F14 and F15 formulated as above optimized batch with different drill depth and drill diameter by laser drilling machine. We had concluded that there was dissolution matched with innovator product. So we evaluated that laser drilling and mechanical drilling.

5.6 Result of Model fitting to evaluate the mechanism of drug release

5.6.1 Zero Order Model

Optimized batch fitted in zero order, first – order, Higuchi, Kors-peppas model and Hixon crowell model for determination of drug release. The graph showed R^2 value in figure 5.10.

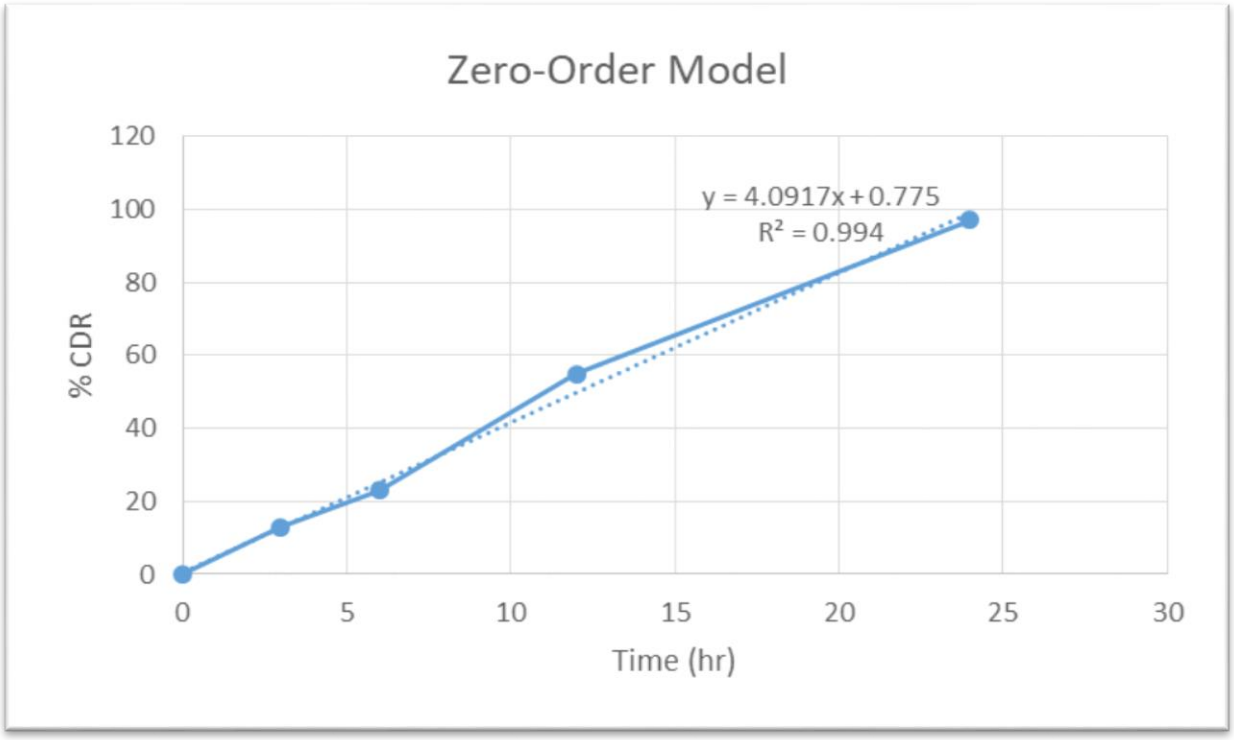


Figure 5.10 Zero – Order Model

5.6.2 First Order Model

Optimized batch of EOP fitted in first – order model and graph showed in figure 5.11.

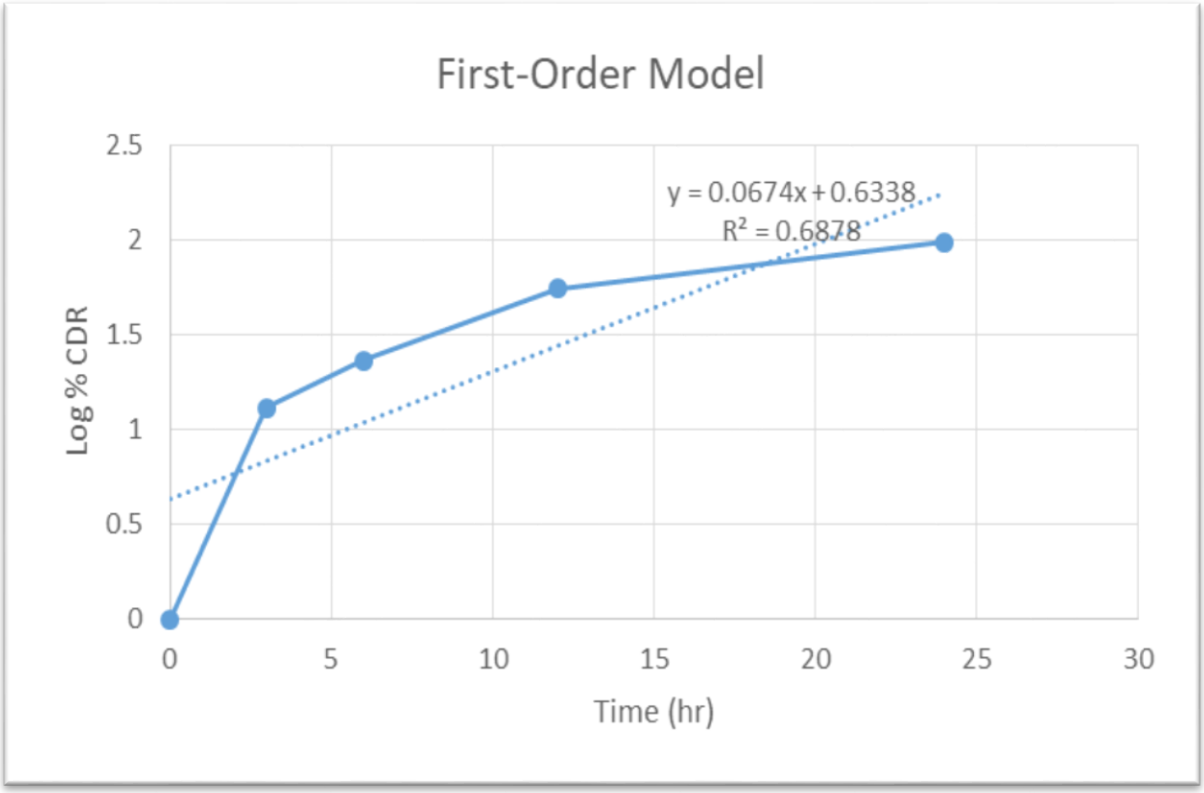


Figure 5.11 First – Order Model

5.6.3 Higuchi Model

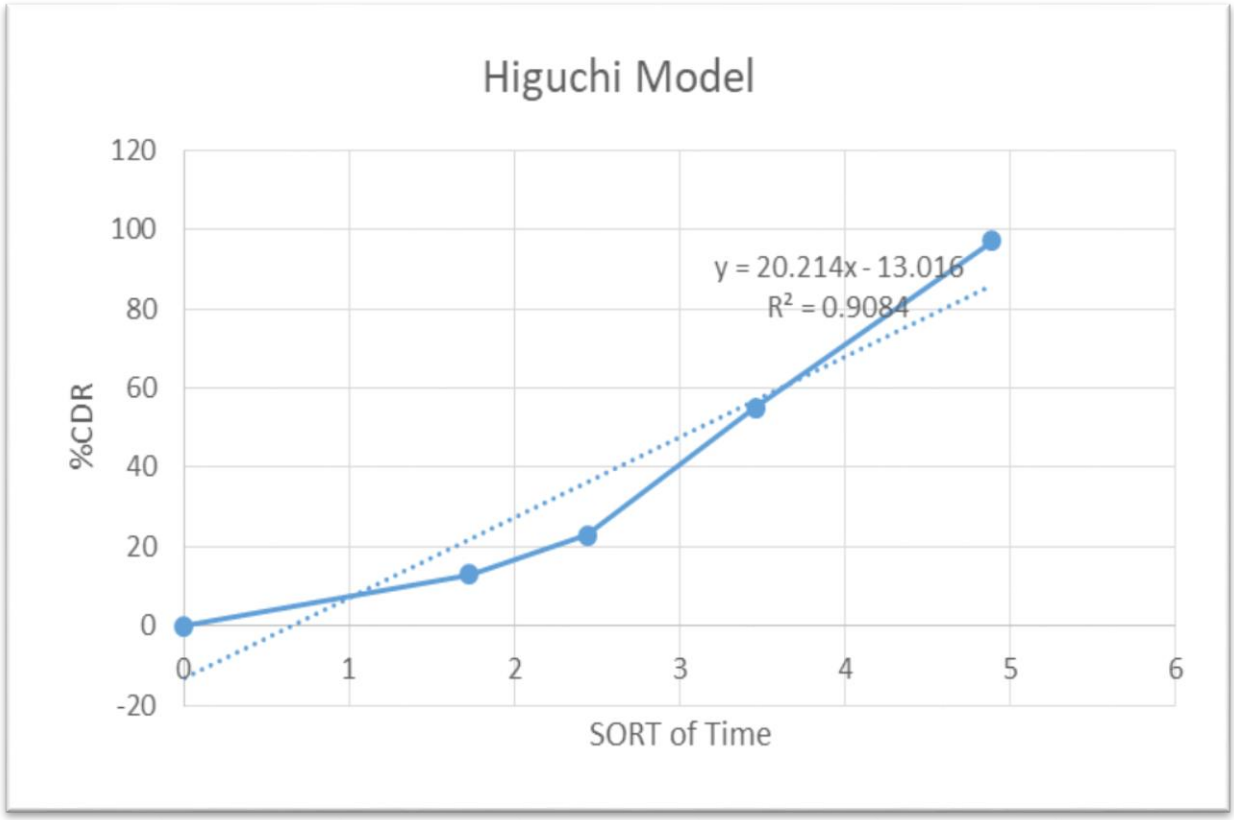


Figure 5.12 Higuchi Model

5.6.4 Kors – Peppass Model

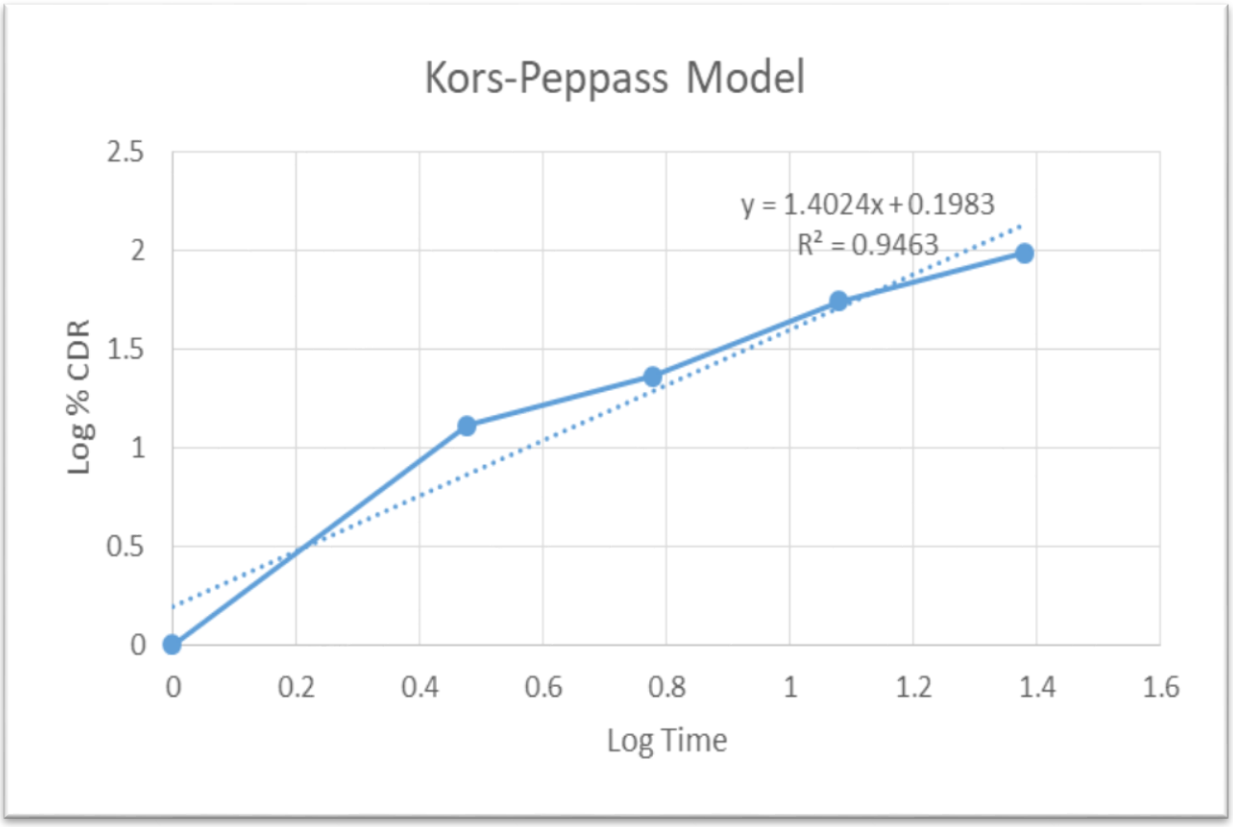


Figure 5.13 Kors – Peppass Model

5.6.5 Hixon Crowell Model

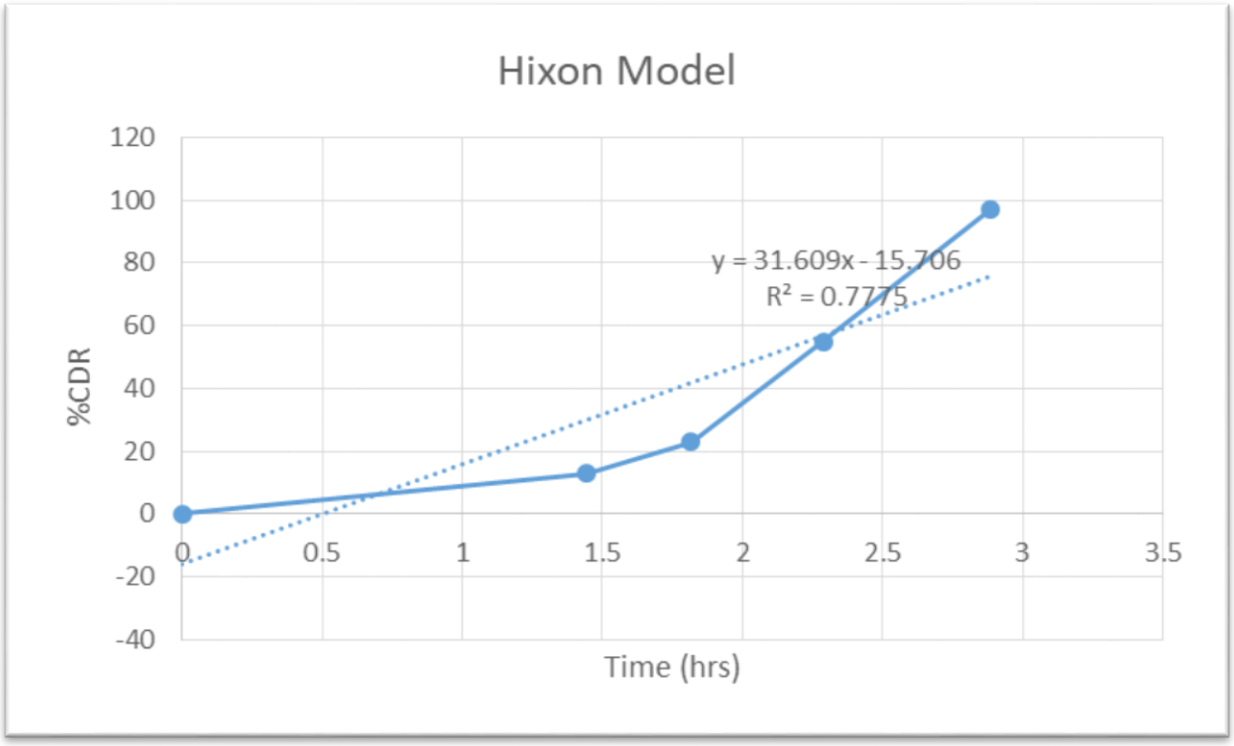


Figure 5.14 Hixon Model

Result

Table 5.24 R square value of Models

Sr. No	Model	R Square Value
1	Zero Order	0.994
2	First Order	0.687
3	Higuchi	0.908
4	Kors-Peppas	0.946
5	Hixon	0.777

Discussion

Out of all the models applied, the best fitting model was zero order for optimized batch. R2 value of zero order was also somehow nearest to 1. Therefore, the Zero order Model was significant model for this formulation. The formulation follows Zero order kinetics. Zero order is apparently independent of the reactant concentration. Other models First order, Higuchi, Hixon Crowell and Kors – peppas had not achieved R^2 value near to 1.

CHAPTER 6

CONCLUSION

6. Conclusion

Zero order drug release kinetics followed by osmotic pump drug delivery systems and achieve controlled release for long term of time. This drug delivery system has been one of the most optimistic in recent times. Here, Drug A used to control seizures. It is BCS class II drug and soluble in alcohol, acetone, propylene glycol and its relative BA is 89% as it undergoes the first pass metabolism with half-life 6-7hrs. Twice daily dose is inconvenient for maintenance of therapy in patient which necessitates by drug's properties. Therefore, once a daily dose of EOP was prepared and evaluated.

Present project work was aimed to achieve zero – order kinetics and formulate drug delivery of osmotic tablets to provide extended release in controlled manner and evaluated the formulation. In my project work. Elementary osmotic delivery was performed and it shows the desired drug release within 24 hrs. Drug-Excipients compatibility study revealed that there was no impurities. The optimized batch was having good flow properties with optimize amount of granulating agent. Thickness, hardness, % friability, weight variation evaluation parameters of tablets were given satisfactory results. Core tablet batch optimized with different amount of water as granulating agent. Batch F6 was giving good result of core tablets. Then batch F6 was shows better drug release profile in 24 hrs which follows zero order. There was no effect on dissolution profile with variation of different orifice size by laser and mechanical drilling. The developed optimize formulation of elementary osmotic tablets matched with the innovator product profile.

CHAPTER 7

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