Formulation, Development and Optimization of Controlled Release Osmotic Tablets of Venlafaxine Hydrochloride

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NIRMA UNIVERSITY

In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY & BIOPHARMACEUTICS

BY

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May 2014

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This is to certify that the dissertation work entitled ***"Formulation, Development and Optimization of Controlled Release Osmotic Tablets of Venlafaxine Hydrochloride" submitted by Ms. Sapna Sharma with Reg. no (12MPH114)*** *in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" 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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TO WHOMSOEVER IT MAY CONCERN

This is to acknowledge that **Ms. Sapna Laxmandev Sharma** has done her dissertation in **"FORMULATION DEVELOPMENT AND OPTIMIZATION OF CONROLLED RELEASE OSMOTIC TABLETS OF VENLAFAXINE HYDROCHLORIDE."** during 01/11/2013 to 30/05/2014 as a part of her study assigned by her Institute of Pharmacy, Nirma University, Ahmedabad.

During her training she has been found to be sincere and committed. We wish her all the very best for her bright future.

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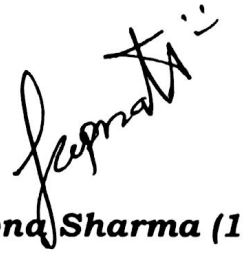
The Care Continues...

DECLARATION

I hereby declare that the dissertation entitled "Formulation, Development and Optimization of Controlled Release Osmotic Tablets of Venlafaxine Hydrochloride" is based on the original work carried out by me under the guidance of Dr. Tejal Mehta, Professor and Head, Department Of Pharmaceutics and Pharmaceutical Technology, Institute of Pharmacy, Nirma University. and Industrial Guide Mr. Narendra Patel Deputy Manager (ANDA Group) in Formulation & Development Department at Cadila Pharmaceuticals Pvt. Ltd. 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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Formulation, Development and Optimization of Controlled Release Osmotic Tablets of Venlafaxine Hydrochloride

Abstract

Osmotic drug delivery system is a dosage form which follows a zero order release and provides controlled release for longer time in sustained manner. Venlafaxine Hydrochloride an anti depressant BCS class I drug and having bioavailability 45% it undergoes the first pass metabolism. Half life of Venlafaxine HCl is 5 hours so it necessitates for a twice daily dosage regimen which is inconvenient for maintenance therapy in patients. Therefore once a day osmotic tablets formulated and evaluated by using two different coating methods as EOP and Asymmetric membrane coating and done comparative study between EOP and Asymmetric membrane coating. In this study core tablets were formulated with two different osmogens PEG-400 and Mannitol at three level of concentration. Tablets were formulated at different process parameters like concentration of binder solution, different granulation parameters and amount of granulating agent. EOP coating was done with Cellulose Acetate and PEG 400 and while in Asymmetric membrane coating Glycerol was used as a pore forming agent with Cellulose Acetate. Drug release profile of the batches was evaluated for the optimization of osmotic pressure, concentration of coating, permeability of membrane, and concentration of plasticizer. Optimized formulations were studied for the effect of agitation intensity and osmotic pressure. The drug release profiles of all the batches were compared with marketed product Venlafaxine Hydrochloride ER tablets. In comparative study between EOP and Asymmetric membrane coating found that EOP coating was better as compared to asymmetric membrane coating. A Box-Behnken design using statistical software version 7.0 was applied on the batches to get the optimized result. Model fitting of optimized batch confirmed zero order drug release.

CHAPTER 1- AIM OF INVESTIGATION

1. AIM OF INVESTIGATION

Controlled release drug delivery systems are developed to overcome the limitation of the conventional 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.

Osmotic system utilizes the principle of osmosis for drug delivery of advantageous that independent of physiological environment of GIT, food effects and pH. Osmotic drug delivery system can be used for the delivery of water soluble as well as water insoluble drugs. Semipermeable membrane and osmotic agents modulate drug release from this system. Drug release can be optimized to zero order release rate by modifying formulation properties.

Venlafaxine Hydrochloride (VFX HCl), an antidepressant agent structurally unrelated to other antidepressants, is used to treat, generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder, and hot flashes in breast cancer survivors. Absolute bioavailability is 45% and average terminal half-life of Venlafaxine HCl is 5 hours. Venlafaxine Hydrochloride is highly water soluble drug (570mg/ml), so incorporation of release retardant polymers may modify release pattern for longer duration of release. These factors necessitate the development of an alternative formulation of Venlafaxine Hydrochloride in order to reduce the frequency of daily dosing and improve the patient compliance. Hence, decided to formulate zero order drug release osmotic tablets of VFX HCl for once a day formulation and compared with the market product of Venlaflaxine ER tablets.

The aim of the present work was to develop controlled osmotic formulation with two different coating techniques as EOP and Asymmetric Membrane coated tablets. EOP is the orifice drilled method into the tablets while in the asymmetric membrane coating

having in-situ pore forming region in the coating surface so no need to drill into the tablets. These two techniques were compared with each other. A Box-Behnken design with statistical software version 7.0 was 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. Effect of the agitation rate on optimized batch was also evaluated. Kinetic model fitting study was also done and proved the zero order released pattern in developed formulation.

CHAPTER 2- INTRODUCTION

2. INTRODUCTION [1]

2.1 Introduction of Controlled Drug Delivery System

Conventional oral drug delivery systems are used for immediate release of drug, in which release of the drug cannot control at the desirable site for prolonged period of time. In conventional drug delivery oral bioavailability is very low because of food, pH of the GIT, degradation by enzymes, and change in GI motility. Controlled dosage forms offer many advantages, such as reduction in dose of drug, constant drug release at the site of action, reduced dosage frequency, prevention of peak-valley fluctuations, reduce side effects, and improved surpass patient compliance.

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

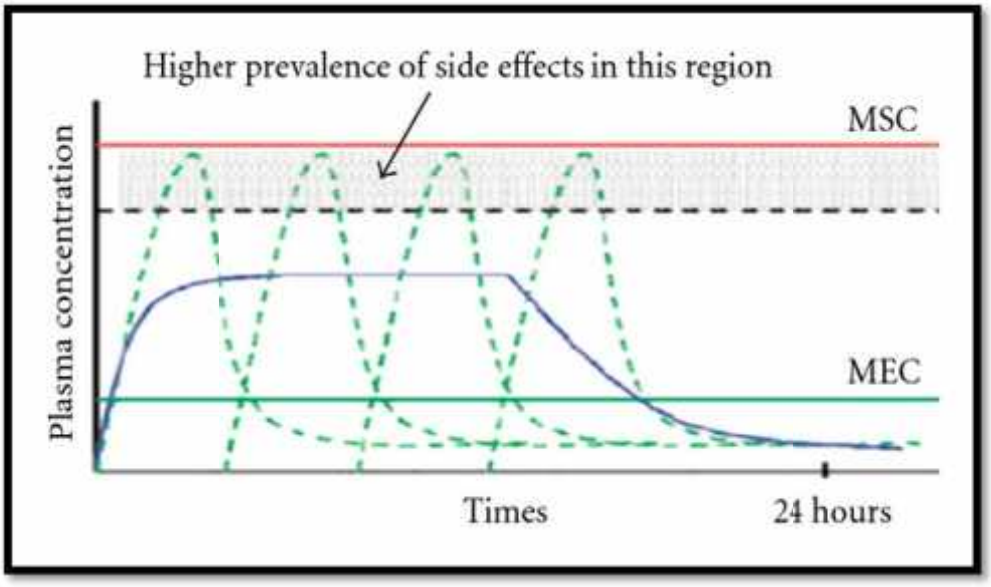


Figure 2.1 *Plasma concentration: For controlled release dosage form (—) and for conventional dosage form (- - -)*

Various designs are there for modulate the drug release from a dosage form, which are matrix, reservoir and osmotic system. In the matrix system, the drug is immersed in polymer matrix and the release occurs by taking part of drug into the release medium and the polymer matrix. In detail, reservoir systems drug core is coated by the rate

controlling membrane. However factors like, presence of food and pH condition can affect drug release from traditional controlled release systems.

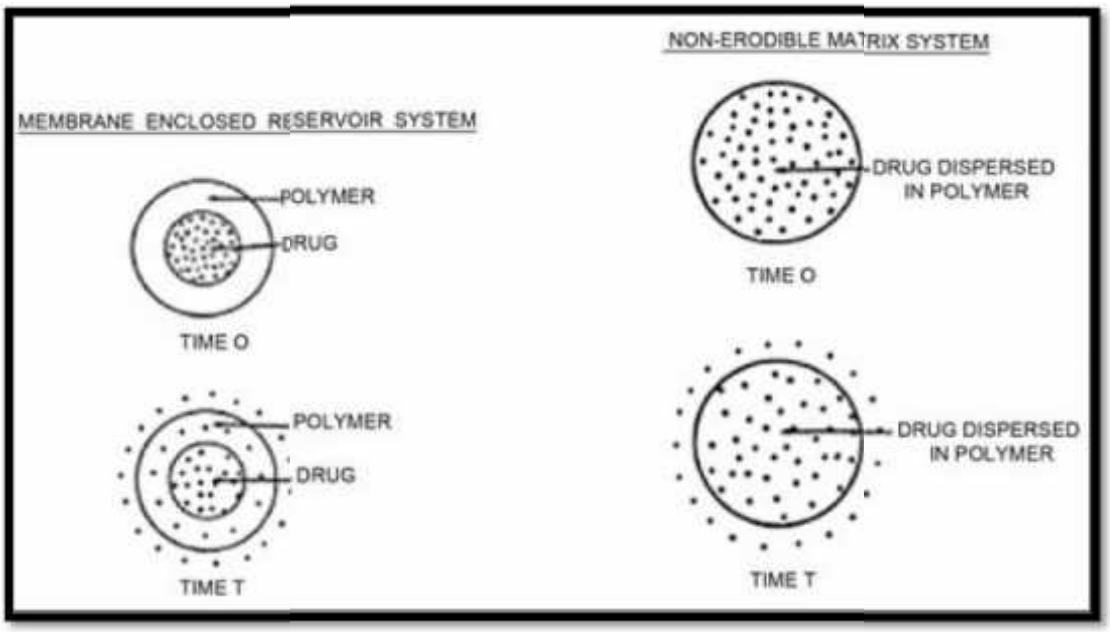


Figure 2.2 *Schematic Representation of of Reservoir and Matrix Diffusion Controlled Drug Delivery Systems.*

2.2. Osmotic Drug Delivery Systems [2][3][4]

Osmotic drug-delivery system contains a compressed core tablet which coated with semipermeable membrane coating. Semipermeable coating has one or more special laser-drilled delivery orifice through which a suspension of the drug is released at constant time. The core involves drug formulation that contains an osmotic agent and a water swellable polymer which can be either a solution or a solid formulation. The rate of water absorbance depends upon the osmotic pressure created by the core elements and coating. As the core absorbs water, it increases in volume, which pushes the drug solution to out of the tablet.

These systems can be used for all two route of administration, that are oral and implantation. Osmotic pump comes up with many advantages over other controlled drug delivery systems, like they are simple and easy in use, improved patient compliance with overcoming number of doses and prolonged therapeutic effect with uniform blood

concentration and more consistence. Moreover they are cheap and its production set up is easy.

2.2.1. Principle of Osmosis [5] [13]

The drug release from the osmotic system across the semi permeable membrane, which depends upon the water influx in core tablet, that can be describe as,

$$dv/dt = \frac{A\ LP\ \sigma\ (\Delta\Pi - \Delta P)}{h} \quad \textbf{(2.1)}$$

Where dv/dt= water influx

A = membrane area

h = membrane thickness

P = mechanical permeability

ΔΠ = osmotic pressure

ΔP = hydrostatic pressure difference between inside and outside the system

σ = describes the leakages of solute through the membrane.

The general expression for the solute delivery rate, dM/dt calculated by pumping from the orifice of the reservoir is given by,

$$dM/dt = dV/dt\ \ C \quad \textbf{(2.2)}$$

where C is concentration of solute if dispersed fluid.

2.2.2. Advantages [5]

- Osmotic drug delivery system is differing from the other technologies used in controlled-release formulations like release drug at a rate which is not dependent on pH and external dissolution medium.

- The result is a vigorous dosage form for which the in vivo rate of drug release is comparable to the in vitro rate, producing an excellent in vitro/in vivo correlation.
- Provides Zero-order delivery rate.
- Another key advantage of the present osmotic systems is that they are applicable to drugs with a large range of aqueous solubilities.
- The rate of delivery is significantly larger than that attainable with diffusion based system of comparable size.
- Delivery rate is independent of agitation rate, including GI motility.
- Release rate is highly predictable and programmable.
- The device is really simple to join using conventional pharmaceutical manufacturing equipment.

2.2.3. Limitations [5]

- Special equipments are needed for making an orifice in the system.
- The time of residence of the system in the body changes with the food intake and gastric motility.
- It may cause irritation or ulcer because of release of saturated solution of drug or dose dumping.

2.2.4. Types of Osmotic Drug Delivery Systems [2] [6] [7]

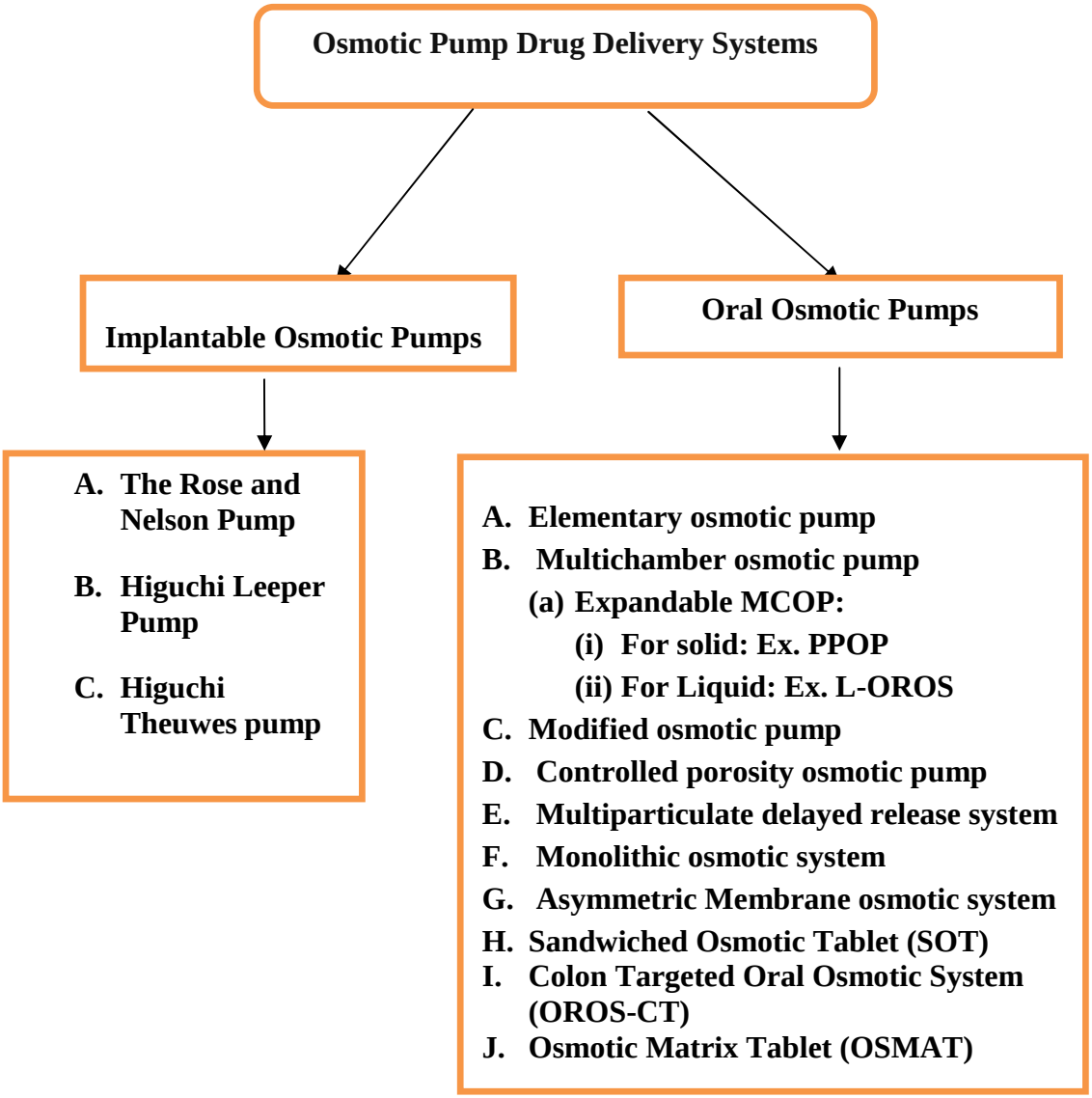


Figure 2.3 *Classification of osmotic drug delivery system*

2.2.4.1. Implantable Osmotic Pump

A. Rose-Nelson Pump

Rose and Nelson, were founders of osmotic drug delivery system. In 1955, they had developed an implantable pump for the delivery of drugs to the cattle gut and sheep. This pump is composed of three chambers: drug chamber, salt chamber holding solid salt, and water chamber. A semipermeable membrane works as separator for salt from

water chamber. When water push from the water chamber to salt chamber is change by difference in osmotic pressure over the membrane. When, volume of salt chamber raises because of water influx, and drug is come out (pumped) of the device.

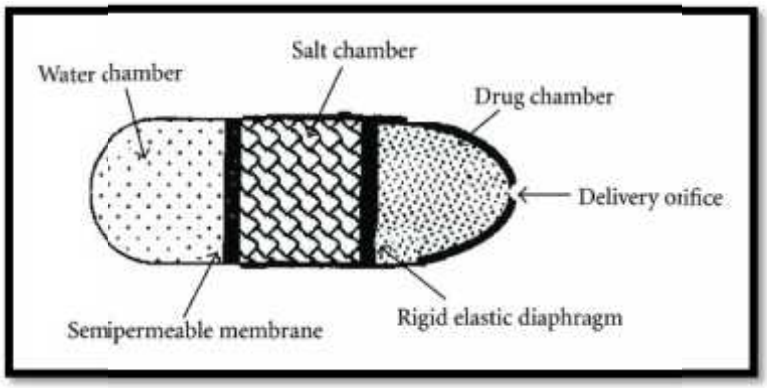


Figure 2.4 *Rose Nelson Pump System.*

The main problem with Rose-Nelson pumps was that the osmotic activity began when water comes in contact to the semipermeable membrane. It needs water to be loaded in advance to use.

B. Higuchi-Leeper Osmotic Pump

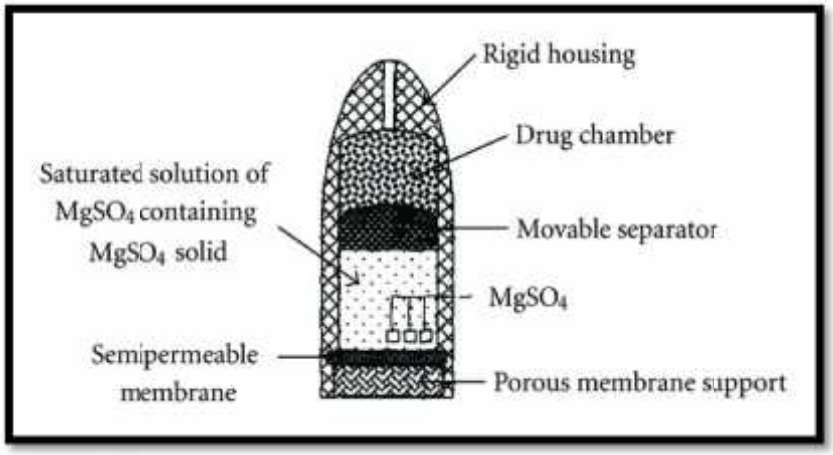


Figure 2.5 Higuchi-leeper osmotic pump

The Higuchi-Leeper pump has no water chamber, that contains a semi permeable membrane and a rigid housing, and salt chamber contains a fluid solution with an excess of solid salt is mostly present in such pump types.

Upon implantation, biological fluid penetrates into the device from porous membrane and dissolves the $MgSO_4$, creating osmotic pressure inside the device that pushes drug chamber to remove drug outside the device. It is largely employed for veterinary usage. This pump type is implanted in the body of an animal for growth hormones or delivery of antibiotics to animals.

C. Higuchi-Theeuwes Osmotic Pump [16] [17]

In early 1970s Higuchi and Theeuwes developed another version of the Rose-Nelson pump, even simple than the Higuchi-Leeper pump. This device is shown in figure.

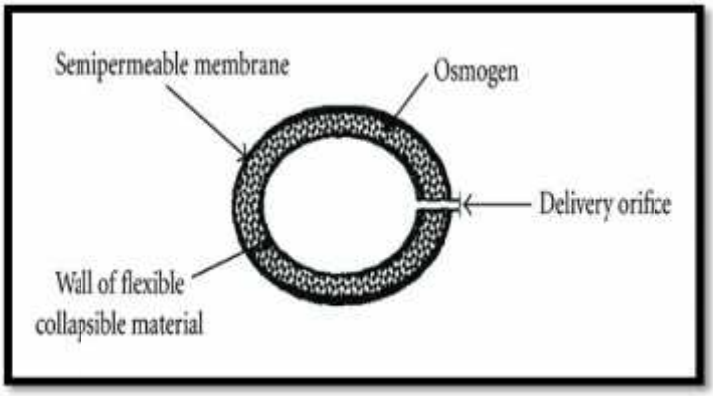


Figure 2.6 *Higuchi Theeuwes Pump.*

In this device, consisted of a semipermeable membrane. This membrane developed pressure inside the device due to imbibitions of water. The drug release from the device is governed by the salt used in the salt chamber and the permeability characteristics of the outer membrane. E.g. Alzet pump.

2.2.4.2. Oral Osmotic Pumps

A. Elementary Osmotic Pump (EOP) [16]

Elementary osmotic pump contains an active agent have a perfect osmotic pressure; it is fabricated as a tablet covered with semi permeable membrane, normally cellulose acetate. A small orifice is drilled from the membrane covering.

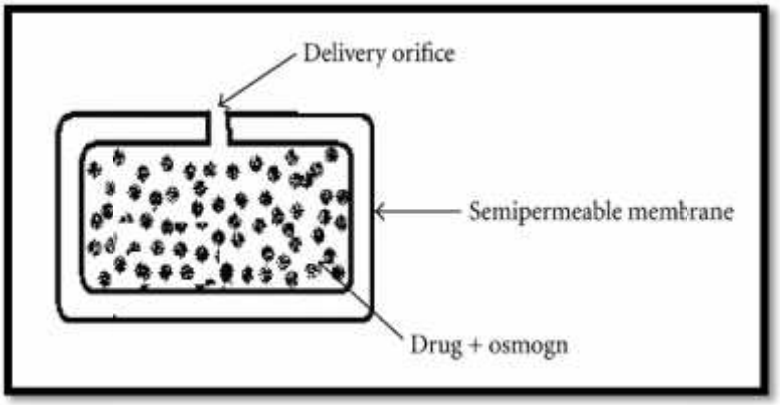


Figure2.7 *The elementary osmotic pump*

When this coated tablet is open to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water from the semi permeable coating and a saturated aqueous solution of drug is formed inside the device. The membrane is nonextensible and the increase in volume because of imbibitions of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through a small orifice.

B. Multi Chamber Osmotic Pump

I. Expandable MCOP for solid osmotic system

- **Push-Pull Osmotic Pump (PPOP)**

Push-pull osmotic pump is a modification of EOP. Push-pull osmotic pump is delivered both poorly water soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (the upper layer) contains drug in a formulation of polymeric, osmotic agent, and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semipermeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment, water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the

compartment to form in situ a suspension of drug. The osmotic agent in the nondrug layer simultaneously attracts water into that compartment, causing it to expand volumetrically, and the expansion of nondrug layer pushes the drug suspension out of the delivery orifice.

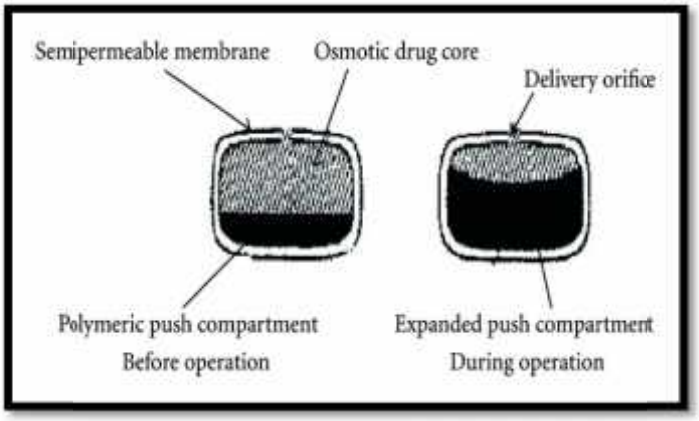


Figure 2.8 *The push-pull osmotic pump (PPOP).*

In this formulation upper compartment contain drug with or without osmogent (drug compartment nearly 60 – 80 %) and lower compartment (Push compartment) contain Osmogent at 20 – 40 %. Example like ProcardiaXL is for Nifedipine [19]

II. Expandable MCOP for liquid osmotic system [20]

This liquid formulation is use for delivering insoluble drugs and macromolecules. Such molecules require external liquid components to assist in solubilization, dispersion, protection from enzymatic degradation and promotion of gastrointestinal absorption. Thus the L-OROS system was designed for continuous delivery of liquid drug.

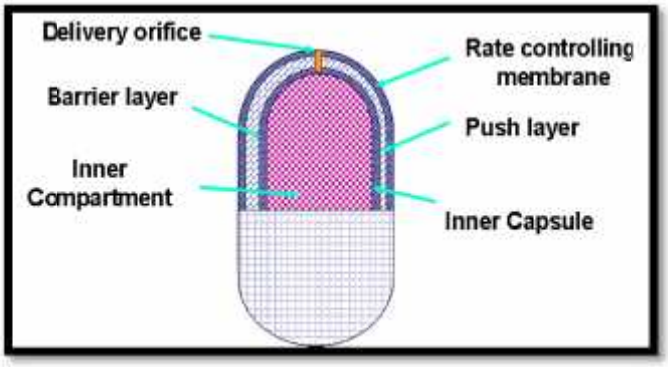


Figure 2.9 L-OROS system

The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered at the delivery orifice. Whereas L-OROS hardcap and L-OROS softcap systems are designed to provide continuous drug delivery, the L-OROS delayed liquid bolus delivery system is designed to deliver a pulse of liquid drug. [21]

C. Modified osmotic pump

Particles of osmotic agent are coated with an elastic semipermeable film. These particles are then mixed with the insoluble drug and compressed in the form of a tablet.

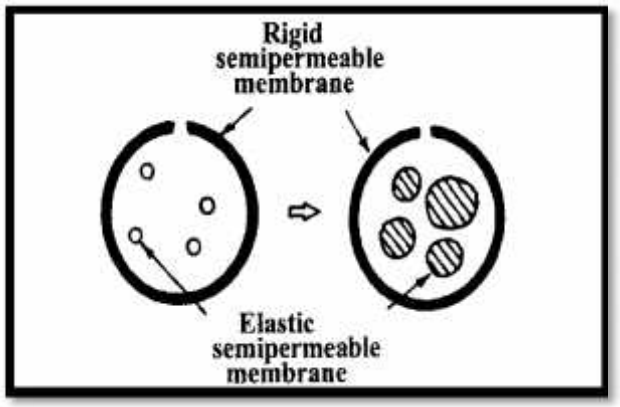


***Figure 2.10** Modified osmotic pump*

D. Controlled Porosity Osmotic Pump (CPOP) [24]

The controlled porosity osmotic pump (CPOP) is an osmotic tablet wherein the delivery orifices (holes) are formed in situ through leaching of water soluble pore-forming agents incorporated in semipermeable membrane (e.g., urea, nicotinamide, sorbitol, etc.) [25] Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane.

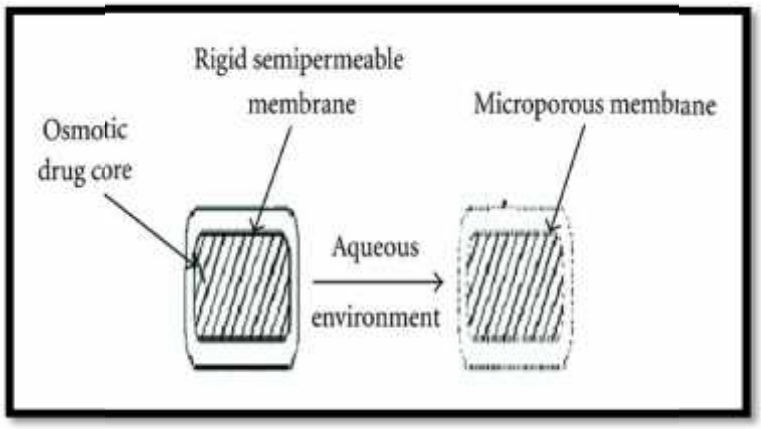


Figure 2.11 *CPOP system*

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

E. 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.

F. Monolithic Osmotic System

It constitutes a simple dispersion of a water-soluble agent in a polymeric matrix. When this system comes in contact with the aqueous environment, water imbibitions 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.

G. Asymmetric Membrane Coated Tablets [32]

In asymmetric membrane system coatings have an asymmetric structure, similar to control pore forming membranes made for reverse osmosis or ultra filtration, in that the coating consists of a porous substrate with a thin outer membrane skin.

Asymmetric tablet coating possesses some unique characteristics, they are as:

- High water fluxes can be achieved.
- The permeability of the coating to water can be adjusted by controlling the membrane structure.
- The porosity of the membrane can be controlled to minimize the time lag before drug delivery begins and allowing the drug to be released from large number of delivery ports.

H. Sandwiched Osmotic Tablet (SOT) [36]

Sandwiched osmotic tablet is made up by polymeric push layer sandwiched between two drug layers with two delivery orifices. When they are placed in the aqueous environment, the middle push layer which contain the swelling agents it swells and the drug is released from the two orifices, so thus sandwiched osmotic tablets (SOTS) can be the most suitable for drugs prone to cause local irritation of the gastric mucosa.

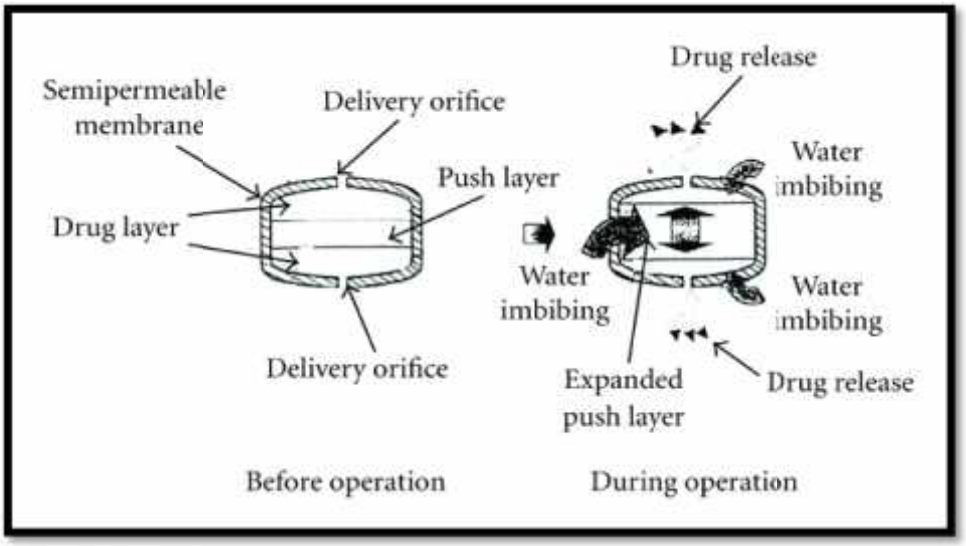


Figure 2.12 *Sandwiched osmotic pump prior and during the operation.*

I. Colon Targeted Oral Osmotic System (OROS-CT) [26]

OROS-CT is used as once or twice in a day formulation for targeted delivery of drugs to the colon. It is a system with five or six enteric-covered push-pull osmotic units filled in hard gelatin capsule for targeted colonic drug delivery. After being in contact with GI fluids, the gelatin capsule dissolves and the enteric coating resist 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.

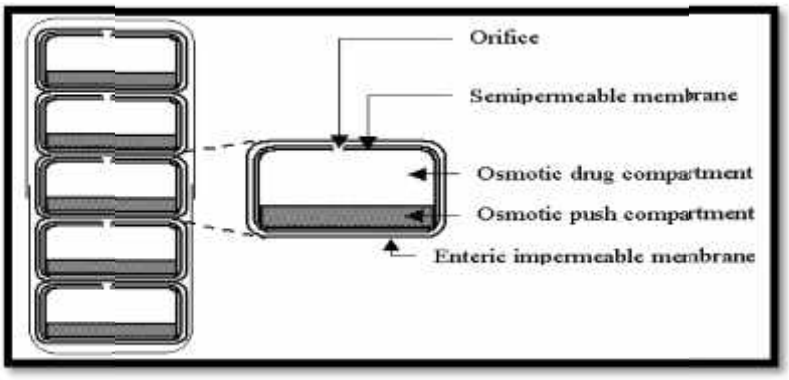


Figure 2.13 *Colon Targeted Oral Osmotic System.*

J. 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 osmogensts also. 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.

2.2.5. Materials Used in Formulation of Osmotic Pumps

The following are the materials used in formulation of osmotically regulated system.

(1) Semipermeable Membrane

Since the membrane in osmotic systems is semipermeable membrane that is permeable to water but impermeable to solute can be selected. Cellulose acetate is a commonly employed semipermeable polymer for the preparation of osmotic pumps. It is available in different acetyl content grades. Some of the polymers that can be used for semipermiable membrane include cellulose esters such as cellulose-diacetate, cellulose-triacetate, cellulose- propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose. Apart from cellulose derivatives, some other polymers such as agar acetate, amylose triacetate, betaglucan acetate, poly(vinyl methyl) ether copolymers, poly(orthoesters), poly acetals and selectively permeable poly(glycolic acid), poly(lactic acid) derivatives, and Eudragits can be used as semipermeable film-forming materials. The permeability is the important criteria for the selection of semipermeable polymers.

(2) Hydrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The highly water soluble compounds can be co-entrapped in hydrophobic matrices and moderately water soluble compounds can be co-entrapped in hydrophilic matrices to obtain more controlled release. Generally, mixtures of both hydrophilic and hydrophobic polymers have been used in the development of osmotic pumps of water-soluble drugs.

Hydrophilic polymers such as hydroxyethyl cellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, high-molecular-weight poly(vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose.

(3) Wicking Agents

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. The use of the wicking agent helps to enhance the rate of drug released from the orifice of the drug. A wicking agent is of either swellable or nonswellable 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 Van der 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. The examples are colloidal silicon dioxide, PVP and Sodium lauryl sulfate.

(4) Solubilizing Agents

For osmotic drug delivery system, highly water-soluble drugs would demonstrate a high release rate that would be of zero order. Thus, many drugs with low intrinsic water solubility are poor candidates for osmotic delivery. However, it is possible to modulate the solubility of drugs within the core. Addition of solubilizing agents into the core tablet dramatically increases the drug solubility.

Nonswellable solubilizing agents are classified into three groups:

i. Agents that inhibit crystal formation of the drugs or otherwise act by complexation with the drugs (e.g., PVP, poly ethylene glycol, PEG 8000 and β-cyclodextrin).
ii. Micelle-forming surfactant with high HLB value, particularly nonionic surfactants (e.g., Tween 20, 60, and 80, polyoxyethylene or poly ethylene containing surfactants and other long-chain anionic surfactants such as SLS).

iii. Citrate esters (e.g., alkyl esters particularly triethyl citrate) and their combinations with anionic surfactants. The combinations of complexing agents such as polyvinyl pyrrolidone (PVP) and poly (ethylene glycol) with anionic surfactants such as SLS are mostly preferred.

(5) Osmogens

Osmogens are essential ingredient of the osmotic formulations. Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure build up inside the pump and pushes medicament outside the pump through delivery orifice. They include inorganic salts and carbohydrates. Mostly, potassium chloride, sodium chloride, and Mannitol used as osmogens. Generally combinations of osmogens are used to achieve optimum osmotic pressure inside the system.

Category of osmogens

- **Water-soluble salts of inorganic acids** Magnesium chloride or sulfate, lithium, sodium, or potassium chloride; lithium, sodium, or potassium sulfate; sodium or potassium hydrogen phosphate.
- **Water-soluble salts of organic acids** Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate, etc.
- **Water-soluble amino acids** Glycine, leucine, alanine, methionine, etc.
- **Carbohydrates** Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, mannitol.
- **Organic polymeric osmagents** Sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linked PVP, polyethylene oxide, carbopols, polyacrylamides,

(6) Surfactants

Surfactants are particularly useful when added to wall-forming material. The surfactants act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. Typical surfactants such as poly-oxyethylenatedglyceryl-recinoleate, poly-

oxyethylenated castor oil having ethylene oxide, glyceryl laurates, and glycerol are incorporated into the formulation.

(7) Coating Solvents

Solvents are used for manufacturing the wall or semipermiable membrane of the osmotic device includes inert inorganic and organic solvents that do not adversely harm the core and other materials of osmotic device. The typical solvents include isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexanemethylene chloride, acetone, methanol, ethanol, carbon tetrachloride, and water. The mixtures of different solvents such as acetone-methanol (80 : 20), acetone-ethanol (80 : 20), acetone-water (90 : 10), methylenechloride-methanol (79 : 21), methylenechloride-methanol-water (75 : 22 : 3) can be used.

(8) Plasticizers

In coatings, plasticizers, or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change viscous elastic behavior of polymers significantly. Plasticizers lower the temperature of the second order-phase transition of the wall and increase the workability, flexibility, and permeability of the coating solvents. Generally from 0.001 to 30 parts of a plasticizer or a mixture of plasticizers are incorporated into 100 parts of costing materials. PEG-600, PEG-200, PEG-400, Triacetin(TA), Dibutylsebacate, Ethyleneglycol- monoacetate, Ethylene glycol diacetate, Triethyl phosphate, and Diethyl tartrate used as plasticizer in formulation of semipermeable membrane.

(9) Pore-Forming Agents

These agents are mainly used for poorly water-soluble drugs and in the development of controlled porosity and asymmetric membrane osmotic drug delivery system. These agents cause the formation of microporous membrane. 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, and alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and

mannitol. Triethyl citrate (TEC), Glycerol and triacetin (TA) are also used to create pore in the membrane. Membrane permeability to the drug is further increased addition of HPMC or sucrose.

2.2.6. Factors Affecting Release of Drug From Osmotic DDS

1) Solubility
2) Osmotic pressure
3) Delivery orifice
4) Membrane type
5) Membrane thickness
6) Type and amount of plasticizer

1. Solubility

Kinetic of drug released by osmotic system is directly related to the drug solubility. The drug release with zero order kinetic is given by this formula

$$F(z) = 1 - \frac{S}{P} \qquad \textbf{(2.1)}$$

Where F (z): drug release by zero order

S: solubility

P: density of core tablet.

Drug with density of unity and solubility less than 0.05g/cm3 would release greater than or equals to 95 % by zero order kinetics. Drug with density less than or equals to 0.3g/cm3 solubility would demonstrate with higher release rate $\geq$ 70 % by zero order. Both highly soluble and poorly soluble drugs are not good candidates for osmotic drug delivery.

2. Osmotic pressure

Osmotic pressure must be maintained between inside the compartment and the external environment. The simplest way to achieve a constant osmotic pressure is to maintain a

saturated solution of osmotic agent in the core compartment. The release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation.

Table 1

List of various osmogens with their osmotic pressure [32, 34].

Osmotic pressures of saturated solution of commonly used osmogens	Osmotic pressure (atm)
Sodium chloride	356
Fructose 3	55
Potassium chloride	245
Sucrose	150
Xylitol	104
Sorbitol	84
Dextrose	82
Citric acid	69
Tartaric acid	67
Mannitol	38
Potassium sulphate	39
Lactose	22

Figure 2.15 *various osmogens with their osmotic pressure.*

3. Delivery Orifice

Osmotic delivery systems contain delivery orifice in the semipermeable membrane for drug release. The size of delivery orifice affects on control of drug release from osmotic systems. If size of delivery orifice too large diffusion from the orifice may take place so fast and if the size of orifice is too small, zero-order delivery will be affected because of development of low hydrostatic pressure within the core, thereby resulting in unpredictable drug delivery. Optimum orifice diameter is in the range of 0.075–0.5 mm.

Techniques for orifice drilling

1) Laser drilling
2) Systems with passage way formed in situ
3) Use of modified punches
4) Use of pore formers

Laser drilling is one of the most commonly used techniques for drilling of orifice in the osmotic tablet. In laser beam drilling, surface of the tablet absorbs the energy of beam and gets heated and causing piercing of wall and forming orifice. In some osmotic systems, there is in-situ orifice. In this system pore-forming agents incorporated into the coating solution. Pore-forming agents are water soluble, so when they contact with the aqueous solution, they dissolve in it and leach out from membrane, creating orifice.

4. Membrane types and characteristics

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. Drug release from osmotic systems is independent of the pH and agitational intensity of the GI tract to a large extent. This is because of selectively water permeable membrane and isolation of dissolution process from the gut environment. To ensure that the coating is able to resist the pressure within the device, thickness of membrane is usually kept between 200 and 300 mm.

Selecting membranes that are having high water permeabilities can be a solution to this problem. One approach that can be utilized is by using composite walls .The tablet cores are coated with a membrane that has a passageway through the wall for releasing the agent. The wall is formed of various types of materials like CA, HPMC or hydroxyl butyl methylcellulose.

5. Membrane thickness

Thickness of the membrane has a profound effect on the drug release from osmotic systems. On studying the release as a function of coating thickness, it was found that as the coating thickness increased from 9 to 50 mm, the drug release decreased in an inversely proportional manner. On the other hand, thickness of the membrane in case of asymmetric coating was found to have insignificant effect on drug release.

6. Type and amount of plasticizer

Plasticizers or low molecular weight diluents are modifier for the physical properties and improve film-forming characteristics of polymers. Plasticizers can change viscous and elastic behavior of polymers significantly. The water permeability of CA films was

found to decrease with increasing plasticizer concentration to a minimum and then increases with higher concentration of plasticizer. Low plasticizer concentrations were found to decrease water permeability by their antiplasticization effect. This antiplasticization effect could be because of interaction between the polymer and the plasticizer molecules that decreased the molecular mobility of the polymer.

2.2.7. In -vitro Evaluation of Osmotic Drug Delivery System

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

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

2. **Inspection**: Visual inspection of the film of tablets for smoothness, uniformity of coating, edge coverage and luster.

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

4. **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.

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

2.2.8. In Vivo Evaluation of Osmotic Drug Delivery Systems

The intestinal tract of the dog is quite similar to that of the human beings in terms of pH and motility, so dogs have widely been used for in vivo delivery rate measurement for oral osmotic drug delivery systems and also to establish in vitro in vivo correlation (IVIVC). In vivo evaluation of osmotic tablets can also be performed in healthy human

volunteers. Various pharmacokinetic parameters (Cmax, Tmax, AUC and MRT) and relative bioavailability are calculated.

2.3. Introduction of Experimental Design

It is the methodology of how to conduct and plan experiments in order to extract the maximum amount of information in the fewest number of runs.

2.3.1. Types of Experimental Design

Choice of experiments depends on level of knowledge before experiments, resource available and objectives of the experiments.

Discovering important process factors

- Placket-Burman
- Fractional Factorial

Estimating the effect and interaction of several factors

- Full Fractional
- Fractional Factorial

For optimization

- Central composite
- Simplex lattice
- D-optimal
- Box Behnken

2.3.2. Box-Behnken Design

The Box-Behnken design is an independent quadratic design in that does not contain an surrounded factorial or fractional factorial design. In this design the treatment combinations are at the midpoints of edges of the process space and at the center. These designs are rotatable (or near rotatable) and require 3 levels of each factor.

Features of Box-Behnken Design

- Box-Behnken designs are response surface designs, specially made to require only 3 levels, coded as -1, 0, and +1.

- Box-Behnken designs are available for 3 to 10 factors. It is formed by combining two-level factorial designs with incomplete block designs.

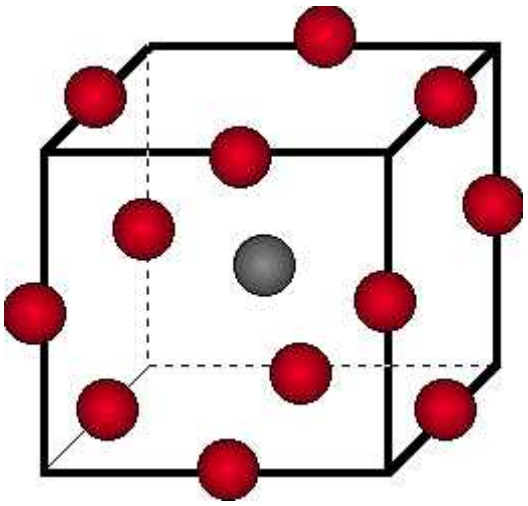


Figure 2.16 *Box-Behnken designs*

- This procedure creates designs with desirable statistical properties but, most importantly, with only a fraction of the experimental trials required for a three-level factorial. Because there are only three levels, the quadratic model was found to be appropriate.

Table 2.1 Box-Behnken design levels

Box-Behnken			
Rep	**X1**	**X2**	**X3**
1	-1	-1	0
1	+1	-1	0
1	-1	+1	0
1	+1	+1	0
1	-1	0	-1
1	+1	0	-1
1	-1	0	+1
1	+1	0	+1
1	0	-1	-1
1	0	+1	-1

1	0	-1	+1
1	0	+1	+1
3	0	0	0
Total Runs		15	

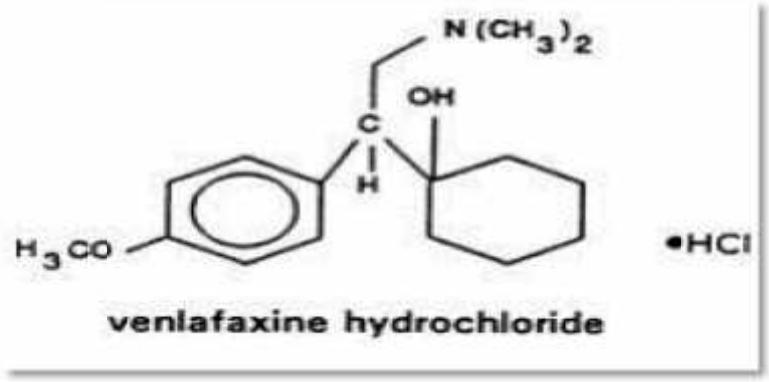
- In this design three factors were evaluated, each at three levels, and experiment design were carried out at all seventeen possible combinations.

2.4. Introduction of Drug

2.4.1. VFX HCl

Chemical formula: C17H27NO2

Chemical structure



Chemical name: 1-[2-dimethylamino 1(4methoxyphenyl)ethyl]cyclohexan-1-ol

Average molecular weight: 277.401

State: Solid

Melting point: 215-217°C (Hydrochloride salt)

Experimental water solubility: 572 mg/ml (Hydrochloride salt)

Pharmacology: An antidepressant agent, structurally unrelated to other antidepressants, is used to treat melancholia, generalized anxiety disorder (GAD), panic disorder, post-traumatic stress disorder, and hot flashes in breast cancer survivors

Mechanism of action

VFX and its active metabolite, O-desmethylVFX(ODV), inhibit the reuptake of both serotonin and norepinephrine with a potency greater for the 5-HT than for the NE reuptake process. Both VFX and the ODV metabolite have weak inhibitory effects on the reuptake of dopamine but, unlike the tricyclics and similar to SSRIs, they are not active at histaminergic, muscarinic, or alpha(1)-adrenergic receptors.

Pharmacokinetics

Absorption

Absolute bioavailability is 45% and a single oral dose is well absorbed (at least 92%).

Steady-state concentrations of VFX and O-desmethylVFX (ODV) in plasma are attained within 3 days of oral dosing. Exhibits linear kinetics over dose range of 75 to 450_mg/day. For ER, C max is 150 ng/mL (260 ng/mL for ODV) and T max is 5.5 h (9 h for ODV).

Distribution

Vd is 7.5 L/kg (5.7 L/kg for ODV); 27% of VFX and 30% of ODV is protein bound.

Metabolism

Extensively metabolized in the liver. The only major metabolite is ODV, which is active.

Elimination

Renal elimination of VFX and its metabolite is the primary route of excretion.

Within 48 h, 87% is recovered in urine. Elimination half-life is 5 h (11 h for ODV).

Indications and usage

ER capsules, ER tablets, immediate-release tablets

Treatment of major depressive disorder (MDD).

ER capsules, ER tablets

Treatment of social anxiety disorder.

ER capsules

Generalized anxiety disorder, panic disorder.

Contraindications

Concomitant use with MAOIs; hypersensitivity to VFX or any component in the formulation.

Dosage and administration

Adults (immediate-release)

PO 75 mg/day in 2 or 3 divided doses; titrate to clinical effect, adding up to 75 mg/day at intervals of at least 4 days (max, 375 mg/day).

Adults (ER capsules, ER tablets)

PO 75 mg/day administered as single dose either in the morning or evening at approximately same time once daily. Some patients may need to start at 37.5 mg/day for 4 to 7 days before increasing to 75 mg/day. Titrate to clinical effect in increments of up to 75 mg/day at intervals of no less than 4 days (max, 375 mg/day).

Generalized Anxiety Disorder Adults (ER capsules)

PO 75 mg/day administered as single dose either in the morning or evening at approximately same time once daily. Some patients may need to start at 37.5 mg/day for 4 to 7 days before increasing to 75 mg/day. Titrate to clinical effect in increments of up to 75 mg/day at intervals of no less than 4 days (max, 225 mg/day).

General advice

- Administer with food.
- It is generally agreed that acute episodes of MDD require several months or longer with sustained pharmacological therapy beyond response to the acute episode.
- Swallow VFX ER capsules or tablets whole. Do not divide, crush, chew, or place in water.
- For patients who have difficulty swallowing VFX ER capsules whole, the capsules may be opened and the contents sprinkled on a spoonful of applesauce.

The drug/applesauce mixture should be swallowed immediately without chewing and followed with a glass of water. Do not prepare the mixture ahead of time and store.

Drug interactions

- **Aspirin, NSAIDs** The risk of GI bleeding may be increased.
- **Azole antifungal agents (eg, ketoconazole)** VFX plasma levels may be elevated, increasing the risk of adverse reactions.
- **Cimetidine** VFX plasma concentrations may be increased. Caution is advised in patients with hypertension or hepatic function impairment.
- **Clozapine** Plasma levels of clozapine may be increased.
- **CNS-active drugs (eg, serotonin reuptake inhibitors (eg, fluoxetine, lithium)**
- Because this interaction has not been studied, caution is warranted when coadministering these agents with VFX.
- **CYP3A4 inhibitors** VFX plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions; use with caution.
- **Cyproheptadine** Decreased pharmacologic effects of VFX may occur.
- **Desipramine, haloperidol** Plasma levels of these drugs may be elevated by VFX, increasing the risk of adverse reactions.
- **Indinavir** Plasma concentrations may be decreased by VFX.
- **Linezolid, lithium, methylene blue, metoclopramide, selective 5-HT 1 receptor agonists (eg, sumatriptan), sibutramine, SNRIs, SSRIs, tramadol, trazodone** Serotonin syndrome, including irritability, increased muscle tone, shivering, myoclonus, and altered consciousness, may occur.

Adverse reactions

Cardiovascular: Vasodilatation (6%); hypertension (5%); palpitation (3%); tachycardia (2%); postural hypotension (1%); deep vein thrombophlebitis, ECG abnormalities (eg, QT prolongation), cardiac arrhythmias (including atrial fibrillation, torsades de pointes)
(post marketing).

CNS: Headache (38%); somnolence (26%); dizziness, insomnia (24%); nervousness (21%); asthenia (19%); anxiety (11%); tremor (10%); abnormal dreams (7%); agitation (5%);depression, hypertonia, paresthesia, twitching (3%); abnormal thinking, confusion (2%); amnesia, hypesthesia, migraine, trismus, vertigo (at least 1%); depersonalization (1%); catatonia, delirium, extrapyramidal symptoms, impaired coordination and balance, involuntary movements, NMS-like events, panic, serotonin syndrome, shock-like electrical sensations (postmarketing).

Dermatologic: Sweating (19%); rash (3%); pruritus (1%); erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (postmarketing).

GI: Nausea (58%); dry mouth (22%); anorexia (20%); constipation (15%); abdominal pain, diarrhea, vomiting (8%); dyspepsia (7%); flatulence (4%); eructation (2%); increased appetite (at least 1%); GI bleeding (postmarketing).

Precautions

Warnings

Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD and other psychiatric disorders. Appropriately monitor patients of all ages who are started on antidepressant therapy and observe them closely for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with their prescriber.

Monitor: Monitor patients for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of therapy or at times of dose changes, either increases or decreases, and during discontinuation of therapy. Monitor serum cholesterol levels in patients receiving long-term therapy. Monitor BP and heart rate at regular intervals. Periodically reassess patient to determine need for maintenance treatment and the appropriate dose for such treatment.

Pregnancy: Category C. Neonates exposed to VFX late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding.

Lactation: Excreted in breast milk.

Children: Safety and efficacy not established. Not approved for use in children. Growth rate reduction and weight loss may occur.

Abnormal bleeding: Risk of bleeding events, ranging from ecchymosis to life-threatening hemorrhages, may be increased.

Blood pressure: Dose-related increases in supine systolic and diastolic BP may occur.

Seizures: Use with caution in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Discontinue use if seizures occur.

Weight changes: A loss of 5% or more of body weight has been reported in about 7% of patients.

Marketed products

Effexor

- Tablets 25 mg
- Tablets 37.5 mg
- Tablets 50 mg
- Tablets 75 mg
- Tablets 100 mg

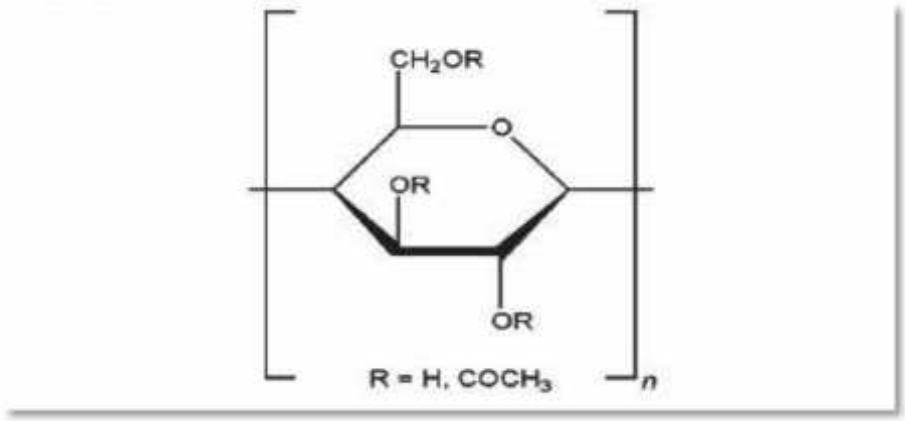
Effexor XR

- Capsules, ER 37.5 mg
- Capsules, ER 75 mg
- Capsules, ER 150 mg

2.5. Introduction of Polymers

2.5.1. 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 : 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.

Table 2.2.Comparison of Different Types of Cellulose Acetate

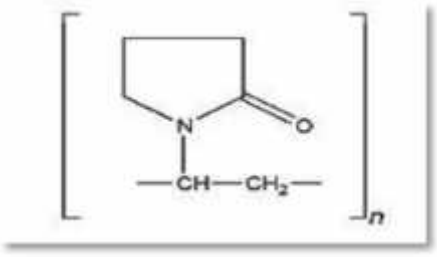
Comparison of different types of cellulose acetate							
Type	Acetyl (%)	Viscosity (mPa s)	Hydroxyl (%)	Melting range (°C)	T_g (°C)	Density (g/cm^3)	MWn
CA-320S	32.0	210.0	8.7	230–250	180	0.1	38 000
CA-398-3	39.8	11.1	3.5	230–250	180	0.1	30 000
CA-398-6	39.8	22.8	3.5	230–250	182	0.1	35 000
CA-398-10NF	39.8	38.0	3.5	230–250	185	0.1	40 000
CA-398-30	39.7	114.0	3.5	230–250	189	0.1	50 000
CA-394-60S	39.5	228.0	1.0	240–260	186	—	60 000
CA-135-75	13.5	—	0.9	280–300	185	0.7	122 000

Applications

- Cellulose acetate is widely used in pharmaceutical formulations both in sustainedrelease 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.

2.5.2. Polyethylene Glycol 400

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.

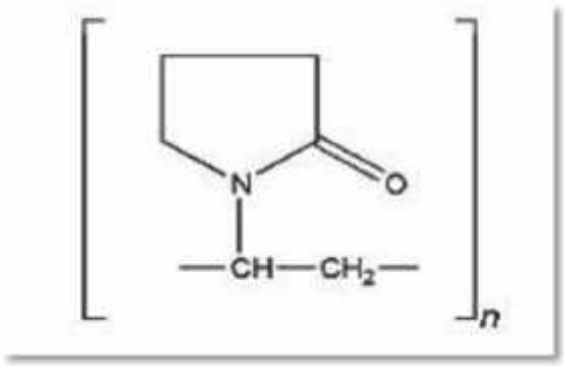
Applications

- 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

2.5.3. Povidone (Kollidon 30)

Structural formula



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

Table 2.3 Uses of Povidone K 30

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

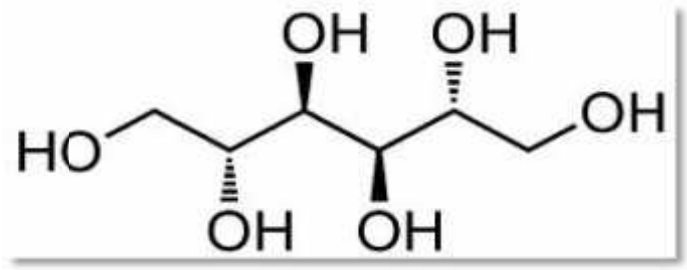
2.5.4. Mannitol

Synonyms: Cordycepic acid; C*PharmMannidex; E421; Emprove; manna sugar; D-mannite; mannite; mannitolum; Mannogem; Pearlitol.

Formula: C6H14O6

Molecular weight: 182.17

Structural formula



Functional category: Diluent; plasticizer, sweetening agent, tablet and capsule diluents, therapeutic agent, tonicity agent.

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or freeflowing granules. It has a sweet, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Applications

- Mannitol is widely used in pharmaceutical formulations and food products.
- In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.
- Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouthfeel'.

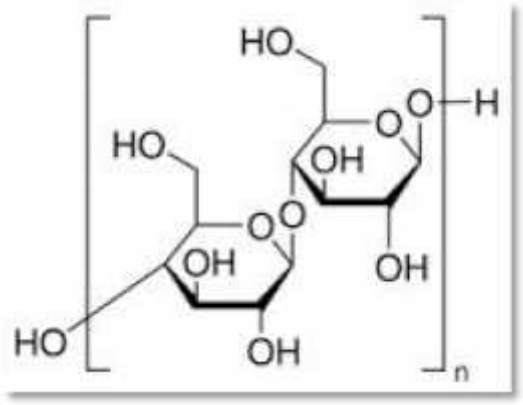
- In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use. Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers.
- It is also used as a diluent in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent.
- Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure.

2.5.5. Avicel PH-101

Formula: (C6H10O5)n, where n 220.

Molecular weight: 36 000

Structural formula



Functional category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Description: Microcrystalline cellulose is a purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Applications

- Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.
- In addition to its use as a binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tabletting.

Stability and storage conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

2.5.6. Colloidal Silicon Dioxide (Aerosil 200)

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

Table 2.4: Uses of Colloidal Silicon Dioxide

Use	Concentration (%)
Aerosols	0.5–2.0
Suspending and thickening	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 25oC (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.

2.5.7. 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.

CHAPTER 3 – LITERATURE REVIEW

3. LITERATURE REVIEW

3.1. Literature review of 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.

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.

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.

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.

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.

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.

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. This review mainly focuses on performance of these technologies, 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.

Edavalath S. et al designed the 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.

Vavia PR et al described an asymmetric membrane osmotic pump-based drug delivery system by the use of different channeling 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.

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.

Choudhury Pratim K et al formulated an asymmetric membrane capsule of cellulose acetate for osmotic delivery of flurbiprofen and influence of osmogents and solubilizing agent on in vitro drug release were evaluated. The capsule membrane was prepared by the phase inversion technique. To ensure the osmotic delivery of drug, two approaches were adopted: (i) the drug was encapsulated with osmogents like sodium chloride and mannitol to increase the osmotic pressure of the core, and (ii) the drug was encapsulated with sodium lauryl sulfate in the core of the formulation to increase the solubility and thus its osmotic pressure. Scanning electron microscopy of the membrane confirmed its porous, dense asymmetric nature. Dye test revealed in situ pore formation. The in vitro release study showed that as the proportion of osmogent and solubilizing agent was increased the release rate also increased. A good correlation was observed between the zero-order rate constant and the amount of the osmogent and solubilizing agent used.

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.

3.2. Literature review of Venlafaxine Hydrochloride formulations

Gohel M C et al. prepare novel modified release press coated tablets of Venlafaxine Hydrochloride. HPMC K4M and HPMC K100M were used as release modifier in core and coat, respectively. A 3^2 full factorial design was adopted in the optimization study. The drug to polymer ratio in core and coat were chosen as independent variables. The drug release in the first hour and drug release rate between 1 and 12 h were chosen as dependent variables. The tablets were characterized for dimension analysis, crushing strength, friability and in vitro drug release. A check point batch, containing 1:2.6 and 1:5.4 drug to polymer in core and coat respectively, was prepared. The tablets of check point batch were subjected to in vitro drug release in dissolution media with pH 5, 7.2 and distilled water. The kinetics of drug release was best explained by Korsmeyer and Peppas model (anomalous non-Fickian diffusion).

Baria S H et al. have developed Venlafaxine hydrochloride-coated and layered matrix tablets using hypromellose adopting wet granulation technique. The granules and the tablets were characterized. The monolithic tablets were coated with different ratios of ethyl cellulose and hypromellose. The in vitro dissolution study was performed in distilled water. In the layered tablets, the middle layer containing drug was covered with barrier layers containing high viscosity grade hypromellose. Simplex lattice design was

used for formulating the layered tablets. The dissolution study of the optimized batches and a reference product was carried out in 0.1 N HCl, phosphate buffer and hydro alcoholic solution. Burst drug release was exhibited by the uncoated tablets, probably due to high aqueous solubility of venlafaxine HCl. The coated tablets showed sustained drug release without burst effect. The drug release was best explained by weibull model. A unified Weibull equation was evolved to express drug release from the coated tablets. The layered tablets also exhibited sustained release without burst effect due to effective area reduction. The optimized batches showed identical drug release in 0.1 N HCl, phosphate buffer and 10% v/v aqueous alcohol. Layered tablets may well be adopted by the industry due to the possibility of achieving a high production rate.

Feleder E C et al. have invented osmotic device including single core comprising a salt, wherein the drug salt and the osmotic salt have a common ion. The release rate of the active drug was reduced and the release profile of the active drug was modified, from a first order release profile to a zero order, pseudo-zero order or sigmoidal release profile, by increasing the amount of the sodium chloride in the core of the device of Venlafaxine hydrochloride.

Sherman D M et al. have invented 24 hrs extended release dosage form and unit dosage form of venlafaxine hydrochloride , which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and fiber provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally HPMC coated with a mixture of ethyl cellulose and HPMC.

CHAPTER 4- EXPERIMENTAL WORK

4. EXPERIMENTAL WORK

4.1 Materials and Equipments Used

Table 4.1: List of materials used

Materials	Company
VFX HCl (VFX HCl)	Cadila Pharmaceuticals Pvt Ltd Ankleshavar
PVP K 90	BASF Industries, Mumbai
Avicel PH 101	FMC Bipolymer, Mumbai
PEG-400	Clariant, Chennai
Mannitol	Roquette Freres, France
Aerosil 200	Evonik Degussa Industries, Germany
Magnesium Stearate	Ferro, USA
Cellulose acetate 320-5	Rotuba, USA
Cellulose acetate 398-10	Rotuba, USA
Acetone	Fischer Scientific India Pvt. Ltd, Mumbai
Opadry Y 30 18037	Colorcon Asia Pvt Ltd, Goa

Table 4.2: List of equipments used

Equipments	Company name
18 station tablet punching machine	Karnavati, Gujarat, India
Cage Bin Blender	Karnavati, Gujarat, India
Coating pan Ganscoater	Silverwater, Australia Thane, India
Disintegration apparatus USP	Shanghai, China
Electronic Weighing Balance	Mettler Toledo, Mumbai, India
Hardness Tester	Dr. Schleuniger Pharmatron, Switzerland
Moisture analyzer	Mettler Toledo, Mumbai, India
Rapid Mixer Granulator Ganson,	Karnavati, kadi, Gujarat, India
Roche Friabilator	Labindia, Thane, India
Sieve Shaker	Retsch GmbH, Germany
Tap density tester	Labindia, Thane, India
USP dissolution apparatus-I	Labindia, Thane, India
UV Spectrophotometer Shimadzu	Shanghai, China

4.2 Identification of VFX HCl

4.2.1 Melting Point Determination [22]

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.

Table 4.3: Melting point of VFX HCl

Actual melting point	Observed melting point
217- 215°C	215-217°C

Result

The melting point of VFX Hydrochloride was found 215°C which matched with the theoretical value.

Conclusion: The observed melting point of drug was found similar as reported value of melting point, which confirmed the identity of drug.

4.2.2 Fourier Transform-Infra Red (FT-IR) Spectroscopy

Sample was prepared by triturating the sample with KBr (Spectroscopic grade). The samples were scanned from 4000 to 400 cm^{-1} using FTIR (Jasco FTIR 6100 TYPE A) observed FTIR spectra were shown in figure no 4.1.

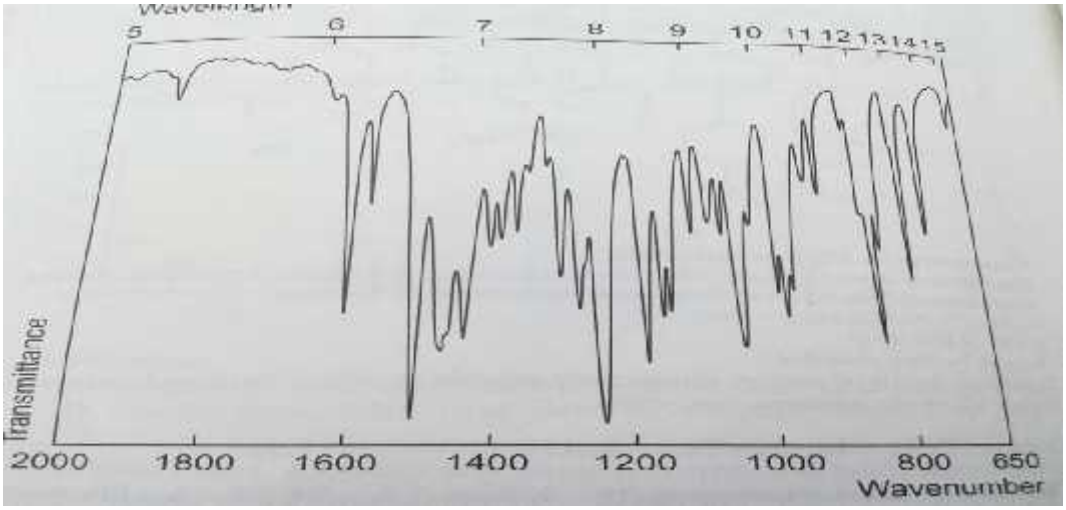


Figure4.1. *Standard FTIR of VFX HCl* [39]

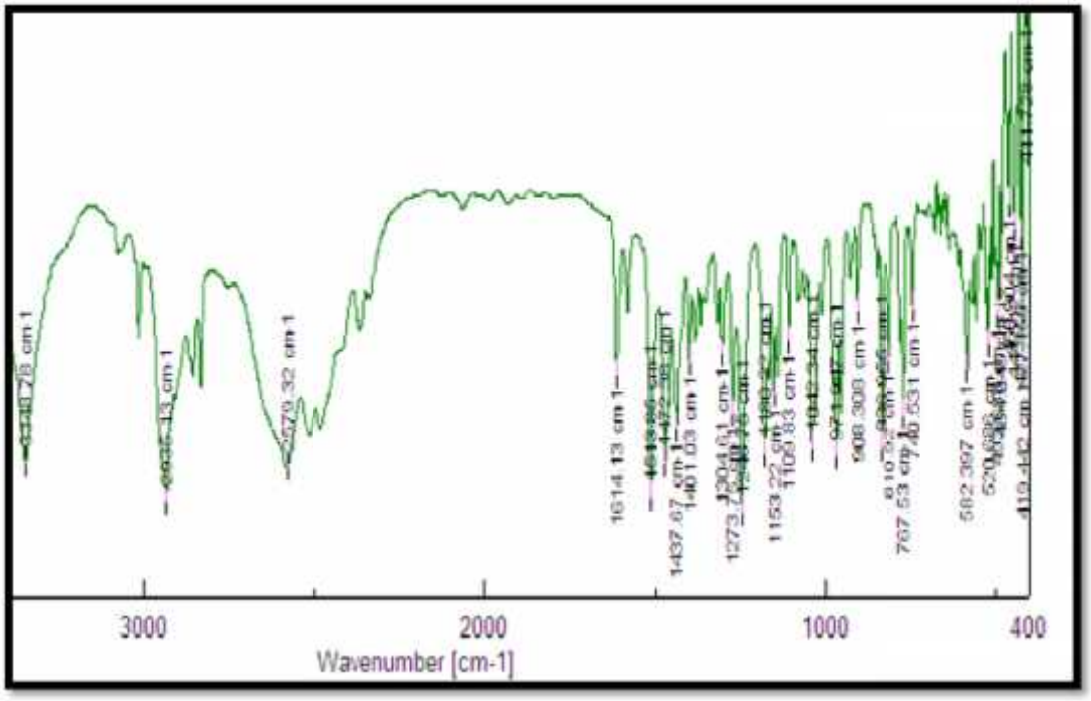


Figure4.2. *FTIR Spectra of VFX HCl*

Table 4.4: Observations of FTIR

Functional group	Standard Frequency (cm^{-1})	Observed frequency (cm^{-1})
OH-Stretch	3300	3348
C-O Stretch	1300	1273.75
C-C aromatic	1614	1614.13

Conclusion: According to assigned functional group in molecular structure of VFX HCl, observed peaks were obtained at the relevant peaks. This concluded the identity of drug.

4.2.3 U.V Absorption Maxima of VFX HCl

UV spectra of 50 µg/ml drug solution in distilled water was examined between the 200-400 nm using double beam UV/Visible spectrophotometer.

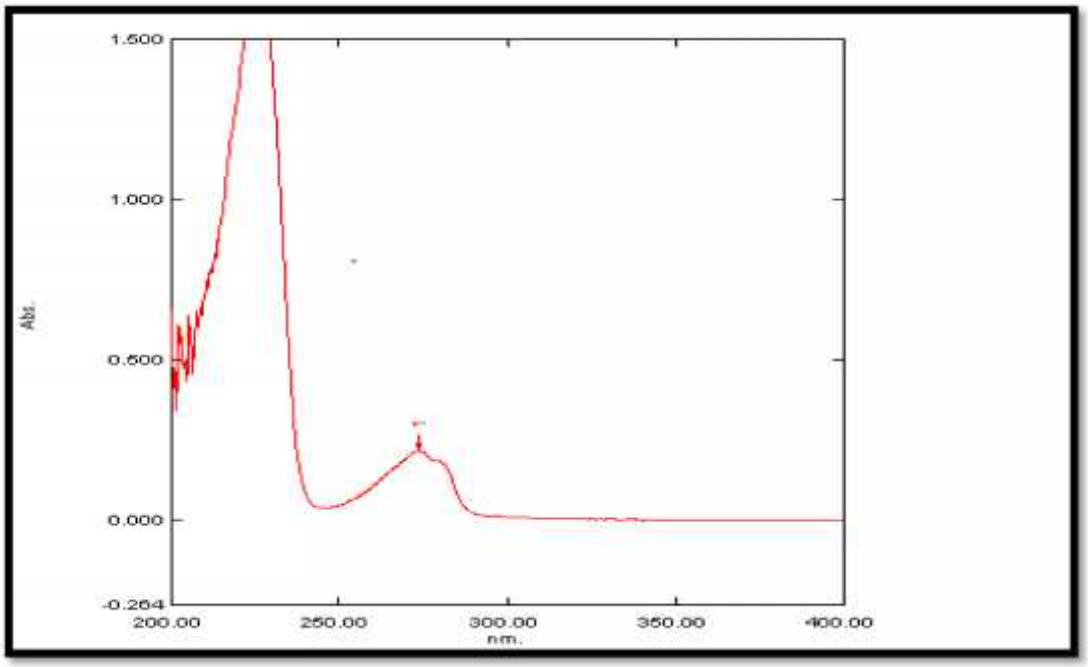


Figure 4.3 *Absorption maxima of VFX HCl*

Conclusion: An Absorption maximum of VFX HCl was found at 274 nm which matched with the standard absorption maxima of VFX HCl. Hence it can be concluded the identity of procured sample.

4.3 Estimation of VFX HCl

4.3.1 Preparation of Calibration Curve of VFX HCl

Preparation of stock solution

VFX HCl 100 mg was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in distilled water and volume was made up to get 1000µg/ml solution.

Preparation of standard curve

From the stock solution (1000 µg/ml), serial dilutions were made in 10 ml volumetric flask with distilled water to obtain 50, 75, 100, 125, 150, 175, 200 and 225µg/ml concentration of VFX HCl. The absorbances of dilutions were measured at 274 nm using double beam UV/Visible spectrophotometer in triplicate and the graph was plotted between average absorbance vs. concentration.

Table 4.5: Absorbance of VFX HCl

Concentration (µg/ml)	Absorbance (n=3)
0	0
25	0.0939
50	0.1879
75	0.2758
100	0.3721
125	0.5381
150	0.6296
175	0.7265
200	0.8411

Results

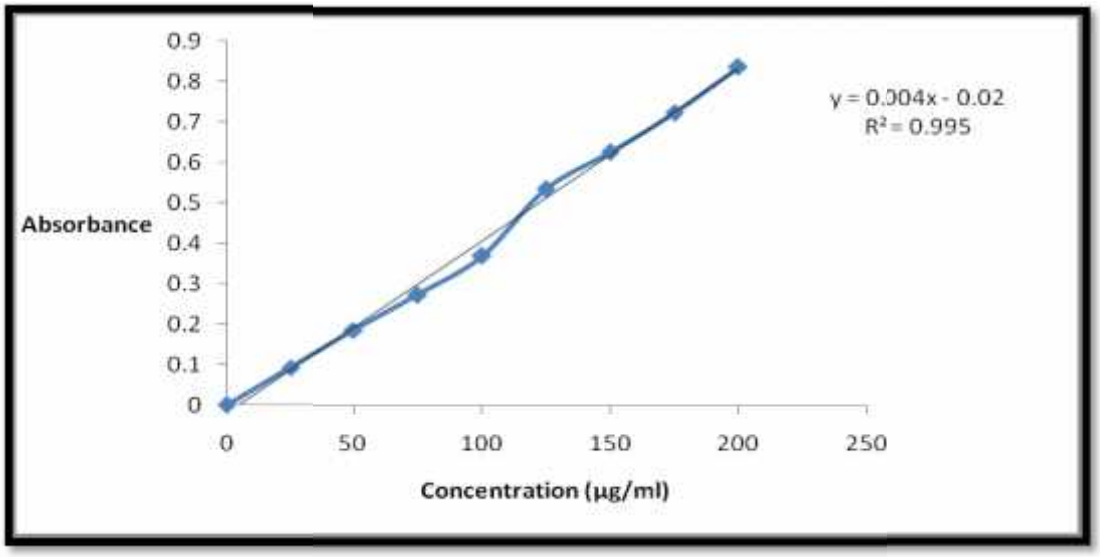


Figure 4.4 *Standard curve of VFX HCl*

Table 4.6: Regression Analysis for Standard Curve of VFX HCl

Regression parameter	Value
Correlation coefficient	0.995
Slope	0.004
Intercept	-0.02

Discussion: Correlation coefficient value was near to 1 and according to Beer-Lambert's law linearity was found 0 to 225µg/ml.

4.4 Preformulation Study of API

4.4.1 Physical Appearance

White to off white crystalline powder.

4.4.2 Solubility Study

Solubility of VFX HCl was determined at different pH conditions and mentioned in table no. 4.7

Results

Table 4.7: Solubility of VFX HCl in different pH

pH	Solubility (g/L)
1	999
2	999
3	999
4	999
5	999
6	670
7	260
8	31
9	5
10	2.4

Discussion: From the above result it can be concluded that VFX HCl is highly soluble in the acid condition as compared to basic pH.

4.4.3 Particle size analysis

The particle size distribution study of procured VFX HCl sample was carried out using Malvern particle size analyzer. Standard specification for particle size of VFX HCl is mentioned in table no. 4.8

Table 4.8: Standard specification for particle size

	Specification
Particle Size	d(10%) : Not more than 20µ
	d(50%) : Between 40 and 80µ
	d(90%) : Between 160 and 210µ

Results

Table 4.9: Particle Size in «m (% of particles under size)

Sr. no	API Lot no.	10%	50%	90%
1	2VN 003	13.7	56.9	141
2	2VN 004	17.7	64.7	142.4
3	2VN 005	18.1	64.8	140.2

Discussion: In the all three lots of the VFX HCl the particle size complied with the standard requirements. Thus it can be concluded that API lots were matched with the standard values of particle size.

4.4.4 Determination of Flow Properties of API

Different flow properties of VFX HCl was determined in the Density Tester and found results were tabulated in the table no. 4.10

Results

Table 4.10: Flow properties of VFX HCl

Bulk density	0.476 g/cc
Tapped density	0.689 g/cc
Carr's index	30.91%
Hausner's ratio	1.44

Discussion: From the above table it can be concluded that VFX HCl exhibits poor flow so different diluents and fillers were decided in the formulation of VFX HCl tablets.

4.4.5 Chemical Stability of API

Stress testing (force degradation) was carried out on VFX HCl to study its impurity profile, degradation pathway and facilitate the development of stability indicating method. Analytical method was developed in the HPLC and impurities

were found on the basis of HPLC chromatograph. Different stress conditions were applied on the sample and mentioned in the tablet 4.11. As per the USP monograph of VFX HCl, impurities should NMT 1.0% in stress conditions..

Result

Table 4.11: VFX HCl in different stress conditions

Test	Purity %	Degradation %
As such	99.18	Nil
UV Degradation	98.99	0.19
Thermal Degradation	98.81	0.37
Sunlight Degradation	98.43	0.75
Acid Hydrolysis	78.04	21.14
Alkali Hydrolysis	92.95	6.23
Oxidative Degradation	80.31	18.87

Discussion: From the above results of stress analysis, it can be concluded that in UV, white light and heating condition, sample was stable while significant degradation was observed in acid, alkali and oxidative conditions therefore these conditions were avoided during storage condition.

4.4.6 Compatibility Studies of VFX HCl with Excipients

The compatibility was assessed through analysis of binary mixtures of excipients and drug substance of VFX HCl at a 40^0 C/75 % RH in an open container for 1 month. Common excipients functioning as fillers, disintegrates and lubricants were evaluated in excipients compatibility studies. The ratio of VFX HCl with all excipients taken as per the formula were shown in the table no. 4.12

Table 4.12: Binary mixture of VFX HCl with excipients

Binary mixture of Ingredients	Ratio with VFX HCl
VFX HCl	-
VFX HCl + Avicel PH 101	1:0.5
VFX HCl + PEG 400	1:1
VFX HCl + Mannitol	1:0.5
VFX HCl + Aerosil	1:0.5
VFX HCl + Magnesium Stearate	1:0.1
VFX HCl + CA 320-5	1:0.1
VFX HCl + CA 398-10	1:0.1
VFX HCl + Opadry	1:0.1

Results

Table 4.13: Results of Relative Substances of VFX HCl with Excipients

Impurities	At Initial stage %	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 4.14: Results of Assay of VFX HCl with Excipients

Time period	Assay %	Specification
At initial stage	98	90-110%
After 4 weeks	99	90-110%

Table 4.15: Results of Water Content of VFX HCl with Excipients

Time period	water content %	Specification %
At initial stage	4.2	NMT 8.0
After 4 weeks	5.1	NMT 8.0

Discussion: No change in water content was observed in any of binary mixtures at 40^0 C/75 % RH in open container for 1 month. No degradation was found which indicated compatibility of drug and excipients.

4.4.6 Excipients Excipients Compatibility Study

Here, mixture of the drug and excipients were prepared. First mix the drug and all excipients in the ratio of representative of the finished product formulation. In subsequent sets, one excipient was removed at a time, these mixture were stored in vials at 40^0 C/75 % RH in an open container for 1 month and checked the relative substances at initial and after 1 month.

Results

Table 4.16: Result of Relative Substances of Excipients at initial stage

Initial stage	Descyclohexanol Impurity %	Relative compound A %	Any Unspecified Degraded Product %	Total Impurities %
Drug with all excipients	0.01	0.01	0.04	0.06%

All excipients without Avicel PH 101	0.01	0.01	0.04	0.07%
All excipients without PEG 400	0.01	0.01	0.04	0.06
All excipients Without Mannitol	0.01	0.02	0.04	0.07
All excipients without Aerosil	0.01	Nil	0.02	0.03
All Excipients Without Magnesium Stearate	0.01	0.01	Nil	0.02
All excipients without CA 320-5	0.01	0.01	0.04	0.06
All excipients without CA 398-10	0.01	Nil	0.04	0.03
All excipients without Opadry	0.01	Nil	0.04	0.05
Specification %	**NMT 0.20**	**NMT 0.20**	**NMT 0.20**	**NMT 1.0**

Table 4.17: Result of Relative Substances of excipients after 4 weeks

After 4 Weeks	Descyclohexn-ol impurity %	Relative compound A %	Any Unspecified degraded product %	Total Impurities %
Drug with all excipients	0.02	0.02	0.04	0.08
All excipients without Avicel PH 101	0.02	0.02	0.04	0.08
All excipients without PEG 400	0.02	0.02	0.04	0.08
All excipients without Mannitol	0.02	0.02	0.04	0.08
All excipients without Aerosil	0.02	0.01	0.04	0.07
All excipients without Magnesium Stearate	0.02	0.02	0.04	0.08
All excipients without CA 320-5	0.02	0.02	0.04	0.08
All excipients without CA 398-10	0.02	0.01	0.05	0.08
All excipients without Opadry	0.02	0.01	0.04	0.07
Specification %	**NMT 0.20**	**NMT 0.20**	**NMT 0.20**	**NMT 2.0**

Table 4.18: Result of Assay of Excipients

Time period	Assay %	Specifications
At initial stage	97	90-110%
After 4 weeks	95	90-110%

Table 4.19: Result of water content of excipients

Time period	% water content	Specifications
At initial stage	4.2%	NMT 8.0%
After 4 weeks	5.0%	NMT 8.0%

Discussion: No degradation was observed at initial and after 4 weeks that indicating excipients are stable with drug.

4.4.7 Drug Excipients Compatibility Study with FTIR

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectra of pure drug and physical mixture of drug and excipients were studied by making KBr disc. The characteristic absorption peaks of VFX Hydrochloride were obtained with mixture of excipients**.**

Results

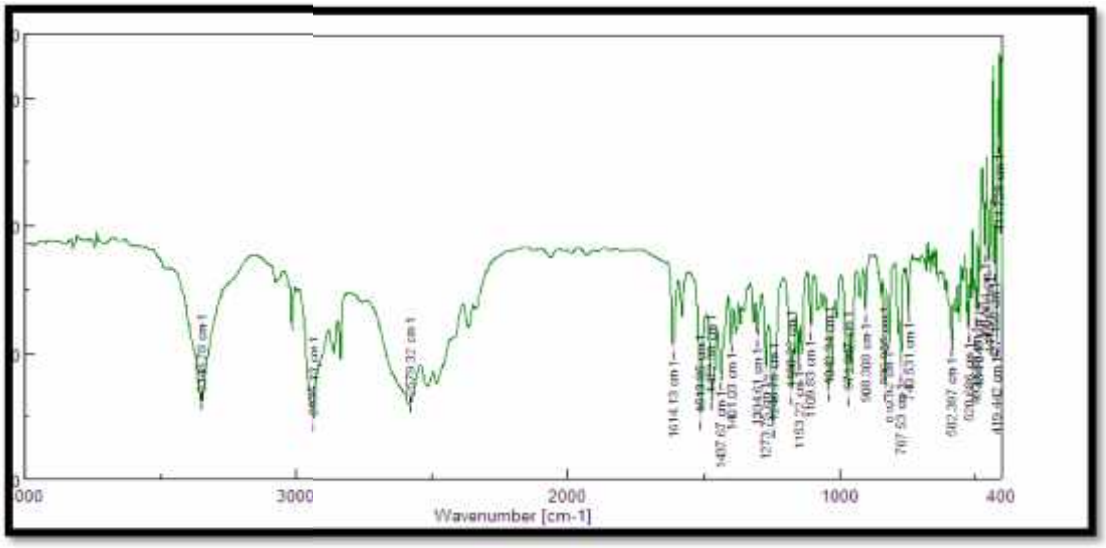


Figure 4.5: *FTIR spectra of VFX HCl*

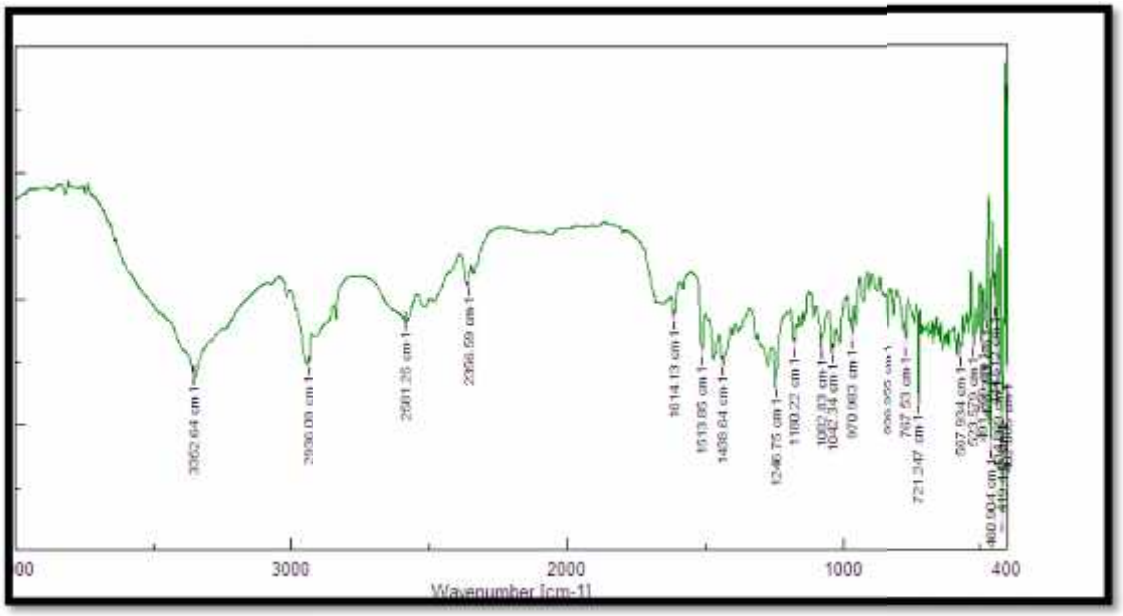


Figure 4.6 *FTIR spectra of VFX HCl with excipients*

Table 4.20: Observations of FTIR of VFX HCl and Excipients

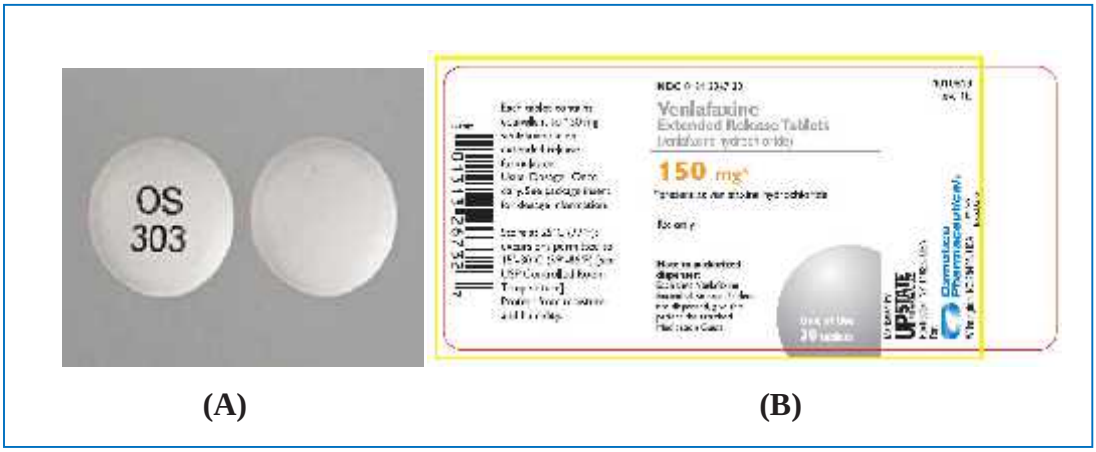
Principle Peaks (cm-1)	Observed peaks (cm-1)
1513	1513
1243	1273
1179	1180

Discussion: VFX Hydrochloride and excipients mixtures were showed the respective characteristic principle peaks of VFX HCl at 1513, 1243 and 1179 cm^{1}. The results confirmed that there was no chemical interaction between drug and excipients. The principle peaks correlates well with the observed peaks of drug spectra. This indicates that the drug is compatible with the excipients.

4.5 Innovator Product Characterization [37]

4.5.1 Physical Characterization

The reference product VFX Hydrochloride ER tablets USP is manufactured by osmotica pharmaceuticals. VFX Hydrochloride ER tablets are available in 37.5 mg, 75mg and 150 mg tablets strengths in US market.



(A) **(B)**

Figure 4.7 A. Imprinted Innovator. **B.** Label of innovator product

Table 4.21: Description of Innovator Product

Sr. No	Description	VFX Hydrochloride ER tablets (150mg)
1	Manufactured by: (Name and Address)	Osmotica Pharmaceutical Corp. Wilmington, NC 28405, USA
2	Average weight	400 mg
3	Ingredients	Mannitol , Povidone, Microcrystallinecellulose Polyethylene glycol, Colloidal silicon dioxide Magnesium stearate, Cellulose acetate, Hypromellose, Lactose, Titanium dioxide, Triacetin, Black iron oxide Propylene glycol.

4	Appearance	Round, biconvex, white coated tablets with OS303 printed on one side.
5	Thickness	4.2-4.5 mm
6	Hardness	80-90 N
7	Friability	NIL

4.5.2 Chemical Characterization of Innovator Product

4.5.2.1 Assay

Assay of innovator product was done as per the method mentioned in the USP monograph of VFX HCl and found **90%**

4.5.2.2 Related substances

Relative substances were also checked as per analytical method which were mentioned in the USP monograph of VFX HCl. [36]

Table 4.22: Result of Related Substances of Innovator Product

Descyclohexanol impurity	0.03%
Relative compound A	0.03%
Max. Unknown Impurity	0.04%
Total Impurities	0.10%

4.5.3 Dissolution Profile

The Innovator product was evaluated for dissolution profile in OGD media using developed method. Dissolution profile of VFX hydrochloride tablet 150 mg was carried out in purified water 900 ml in USP dissolution Apparatus I (Basket) at 100 RPM.

Result

Table 4.23: % CDR of Innovator Product

Sr. no	Time (Hours)	Cumulative drug dissolved (%)
1	0	0
2	3	20
3	6	42
4	16	75
5	24	99

In-Vitro Drug Release of Innovator Product

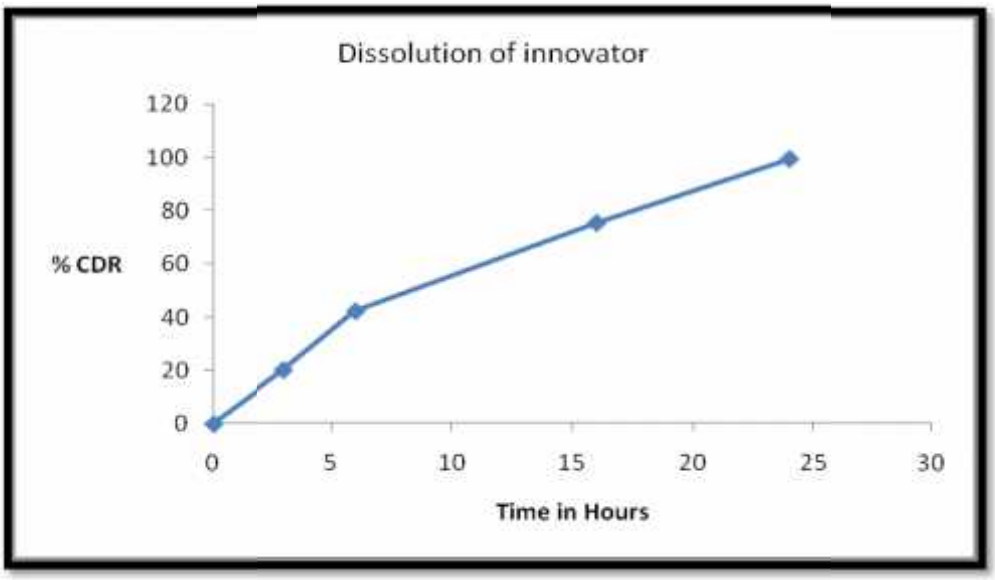


***Figure 4.6** % CDR of innovator product*

Conclusion: From the above results it can be concluded that innovator product shows the maximum cumulative drug release upto the 24 hours.

4.6 Formulation Development of Osmotic Tablets

4.6.1 General Formula for EOP Tablet of VFX HCl

Table 4.24: Formula of core tablet of EOP Tablets

Sr. no	Ingredients	Quantity %	Use
1	VFX HCl	26.5 - 47.1	Drug
2	PVP K 90	3-6	Binder
3	Avicel PH 101	35-62	Filler
4	PEG-400	3-5	Osmotic agent-1
5	Mannitol	3-6	Osmotic agent-2
6	Aerosil	0.5-1.5	Glidant
7	Magnesium Stearate	0.5-1.5	Lubricant
8	Purified water	q.s	Granulating agent

Table 4.25: Formula for semipermiable membrane

Ingredients	Quantity %	Use
Cellulose acetate 320-5	50-56	Film forming polymer
Cellulose acetate 398-10	39-44	Film forming polymer
PEG-400	4-6	Plasticizer
Acetone	q.s	Coating solvent

Table 4.26: Formula for external coating

Ingredients	Quantity %	Use
Opadry Y 30 18037	9-10	External color coat
Purified water	q.s.	Coating solvent

4.6.2 Formulation Method of EOP Tablet of VFX HCl

In the formulation of EOP tablets of VFX HCl following steps are repeated in development of each batch.

STEP 1: Sifting of ingredients: Drug and all excipients were shifted in # 30 sieve and magnesium stearate through # 60 sieve.

STEP 2: Wet Granulation: Wet granulation was done in the 2kg rapid mixture granulator (RMG). Binder solution of PVP K 90 and PEG 400 were added in intragranular materials. After the drying of the granules sizing the granules was done by the sifting of the granules from #30 sieve.

STEP 3: Mixing: Mixing was carried out in the cage bin mixture at 10$\pm$ 2 rpm for the 10 minutes.

STEP 4: Lubrication: Lubrication of above mixture was done with half quantity of the aerosil and magnesium stearate in cage bin mixture for 5 minutes at 10 rpm.

STEP 5: Compression: Compression of lubricated blend was carried out in 18 stations tablet compression machine by type B rounded punch upper and lower size 10.31 mm.

STEP 6: Semipermiable Membrane Coating: Cellulose acetate was dissolved in acetone while PEG 400 was dissolved in the purified water. After the both solution mixed then coating was carried out in the coating machine, Ganscoater with a capacity of coating pan as 3 kilogram at 10 rpm. The spray rate was fixed at 1.4-1.8g/min. Inlet temperature was kept between 60$\pm$10^{o}C and exhaust temperature was kept between 35-40^{o}C. The bed temperature was maintained at 35-40^{o}C while atomization speed was fixed at 1kg/cm^2 and fan speed was set at 0.8-1.0 kg/cm^2. Coating was continued till the desirable weight of tablets were achieved.

STEP 7: Orifice Drilling into Tablet: Orifice drilled into tablets by the standard niddle kit and 0.5 mm hole drilled into tablets.

STEP 8: External Coating: External coating carried out in the Ganscoater by the Opadry Y solution at the above coating parameters.

4.6.3 Evaluations of EOP tablets

4.6.3.1 Precompression Parameters

The flow properties of the prepared blend were evaluated by determining the bulk density, tapped density, compressibility index (carr's index) and Hausner's ratio.

a) Bulk density (BD)

Bulk Density was determined by accurately weighed the blend and then poured into 25ml measuring cylinder and the volume was noted. Bulk Density was obtained from the following formula:

$$\text{Bulk density} = \frac{\text{weight of powder taken}}{\text{Bulk Volume}} \qquad \textbf{(4.1)}$$

b) Tapped Density (TD)

Tapped Density was determined by tapping the above weighed blend for 500 taps in 25ml measuring cylinder and volume was noted after the tapping process. Tapped Density was obtained from the following formula

$$\text{Tapped density} = \frac{\text{Weight of powder taken}}{\text{Tapped Volume}} \qquad \textbf{(4.2)}$$

c) Carr's index

Carr's index which is used to predict the compressibility and ease of flow of the blend was calculated from the following formula

$$\text{Carr's index: } \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ X100} \qquad \textbf{(4.3)}$$

d) Hausner's ratio

Hausner's ratio which indicates the flow property of the blend was calculated from the following formula:

$$\text{Tapped density} = \frac{\text{Tapped density}}{\text{Bulk density}} \qquad \textbf{(4.4)}$$

4.6.3.2 In-Vitro Drug Release Test

Dissolution of VFX hydrochloride tablet 150 mg carried out in purified water 900 ml in USP dissolution Apparatus I (Basket) at 100 RPM

4.7 Formulation trials of EOP of VFX HCl

Wet Granulation method described as above was used in the formulation of the EOP tablets of VFX HCl and evaluated lubricated blend's flow properties in the Density Tester. The flow proprietors of blend is mentioned in the table 4.27

Table 4.27: Flow Properties of Lubricated Blend

Bulk Density	0.75
Tapped Density	0.89
Carr's Index	14.73

Hausner's Ratio:	1.18
Angle of Repose	22.78

Discussion: After the wet granulation, flow properties of lubricated blend passed the all desirable rang of flow properties, so it can be concluded that blend having desirable flow for the formulation of EOP tablets. Lubricated blend was compressed and then coated with semipermiable membrane.

4.7.1 Preliminary Trials

Preliminary trial of EOP tablets of VFX HCl was formulated by the using the as per of the general formula of the EOP tablets mentioned in table no 4.24. After the evaluations of the compressed core tablet was coated with the semipermiable membrane and using coating formula mentioned in table no. 4.29 and this formula repeated till the coating parameters were optimized.

Table 4.28: Formula of Core Tablet F1 Batch

Sr. no	Ingredients	Qty (mg) / tablet
1	VFX HCl	169.72
2	PVP K 90	14
3	Avicel PH 101	140.68
4	PEG-400	10
5	Mannitol	20
6	Aerosil	2
7	Magnesium Stearate	3.60
Total		360 mg

Table 4.29: Semipermiable Membrane Coating Formula

Ingredients	mg/tab.
Cellulose acetate 320-5	11.25
Cellulose acetate 398-10	12.50
PEG-400	1.25
Acetone	430ml
Purified Water	76ml

Results

Table 4.30: Evaluations of Core Tablets of Batch F1

Average weight (mg)	351.2
Hardness (N)	69-73
Friability (%)	0.07
Thickness (mm)	3.61-3.79
Diameters (mm)	10.30

Table 4.31: Evaluations after Coated Tablets of Batch F1

Parameters	F1
Average weight (mg)	374.4
Thickness (mm)	3.72-3.82
Diameter (mm)	10.34

In- Vitro Drug Release of Preliminary Batch F1

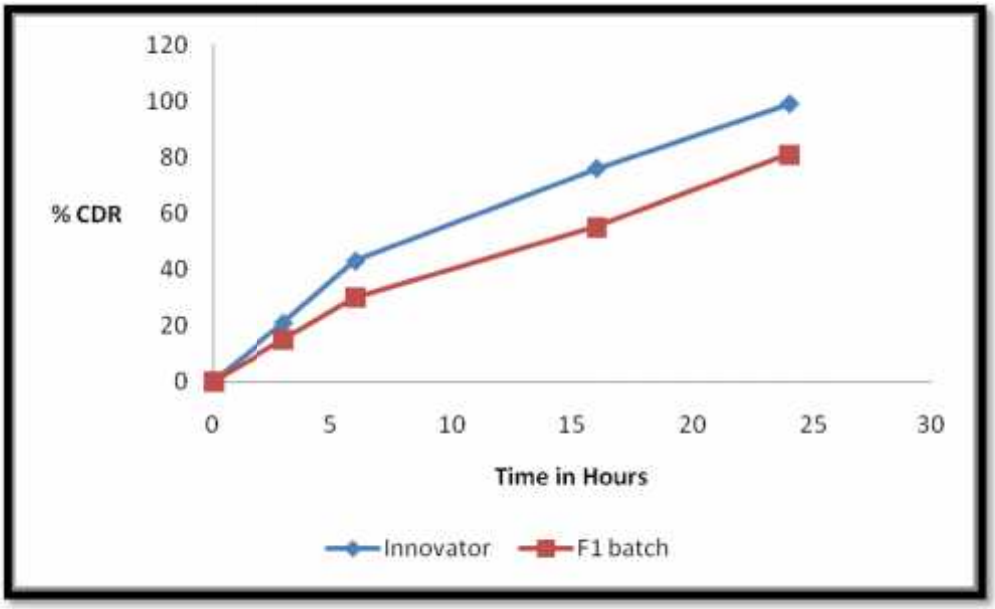


Figure 4.8 *In- Vitro Drug Release of Preliminary Batch F1*

Discussion: Weight and thickness were not achieved as per the innovator product in preliminary batch and dissolution was also not obtained within limits. At 4 % of binder solution hardness was not found as per innovator so further study was carried out for optimization of binder solution to get sufficient hardness, weight, thickness and dissolution as the innovator product.

4.7.2 Optimization of Binder Solution

Table 4.32: Formula of core tablet for batch F2, F3 and F4

Sr. no	Ingredients	F2	F3	F4
		Qty (mg) / tablet	Qty (mg) / tablet	Qty (mg) / tablet
1	VFX HCl	169.72	169.72	169.72
2	**PVP K 90**	**12**	**16**	**20**

3	**Avicel PH 101**	**142.68**	**138.68**	**134.68**
4	PEG-400	10	10	10
5	Mannitol	20	20	20
6	Aerosil	2	2	2
7	Magnesium Stearate	3.6	3.6	3.6
8	Total	360 mg	360 mg	360 mg

Results

Table 4.33: Evaluations of Core Tablets of Batch F2, F3 and F4

Parameters	F2	F3	F4
Weight (mg)	357.6	355.2	360.2
Hardness (N)	73-80	68-73	75-90
Friability (%)	0.07	0.04	0.03
Thickness (mm)	3.64-3.75	3.62-3.73	3.68-3.72
Diameters (mm)	10.31	10.31	10.32

Table 4.34: Evaluations of Coated Tablets of Batch F2, F3 And F4

Parameters	F2	F3	F4
Average weight (mg)	384.2	385.4	387.7
Thickness (mm)	3.82-3.91	3.70-3.85	3.82-3.87

Diameter (mm)	10.34	10.34	10.36

In-Vitro Drug Release of Batch F2, F3 and F4

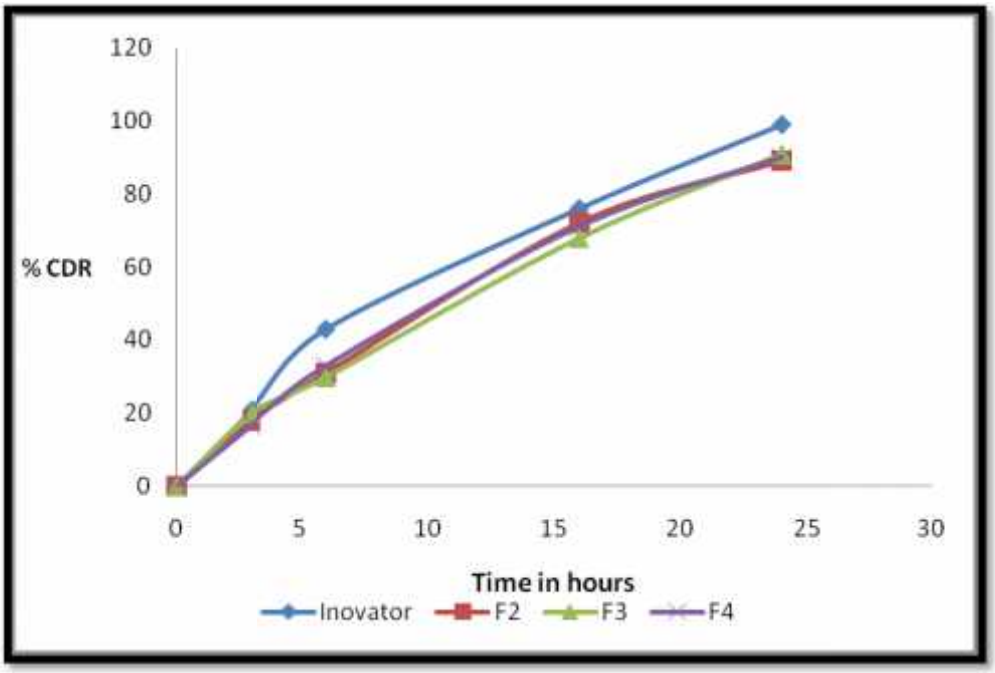


***Figure 4.9**. In- Vitro Drug Release of Preliminary batch F2, F3 and F4*

Discussion: In all above batches dissolution profiles were not matched with the innovator profile. Batch F4 with 6% of binder solution matched with desirable hardness. From the above batches, it can be concluded that as the quantity of binder solution increased it affected on the hardness of the tablets. For improvement of physical properties of tablets, further study was carried out for the optimization of granulation parameters.

4.7.3 Optimization of Granulation Parameters

Table 4.35: Granulation Parameters

Parameters	F5	F6	F7
Binder Adding time	**1 min**	**2 min**	**3 min**
Kneading time	1 min	1 min	1 min
RPM	1500	1700	1900
Drying after Granulation	Up to LOD NLT 2%	Up to LOD NLT 2%	Up to LOD NLT 2%

Results

Table 4.36: Evaluations of Core Tablets of Batch F5, F6 and F7

Parameters	F5	F6	F7
Average Weight(mg)	357.6	355.2	360.2
Hardness (N)	86-98	78-93	65-82
Friability (%)	0.07	0.04	0.03
Thickness (mm)	3.64-3.75 mm	3.98-4.03	3.68-3.72
Diameters (mm)	10.31 mm	10.31 mm	10.32 mm

Table 4.37: Evaluation after Coated Tablets of Batch F5, F6 and F7

Parameters	F5	F6	F7
Average weight (mg)	389.2	398.7	385.4
Thickness	3.83-3.89	4.21-4.47	3.82-3.87
Diameter	10.34	10.36	10.33

In-Vitro drug relesed of batch F5, F6 and F7

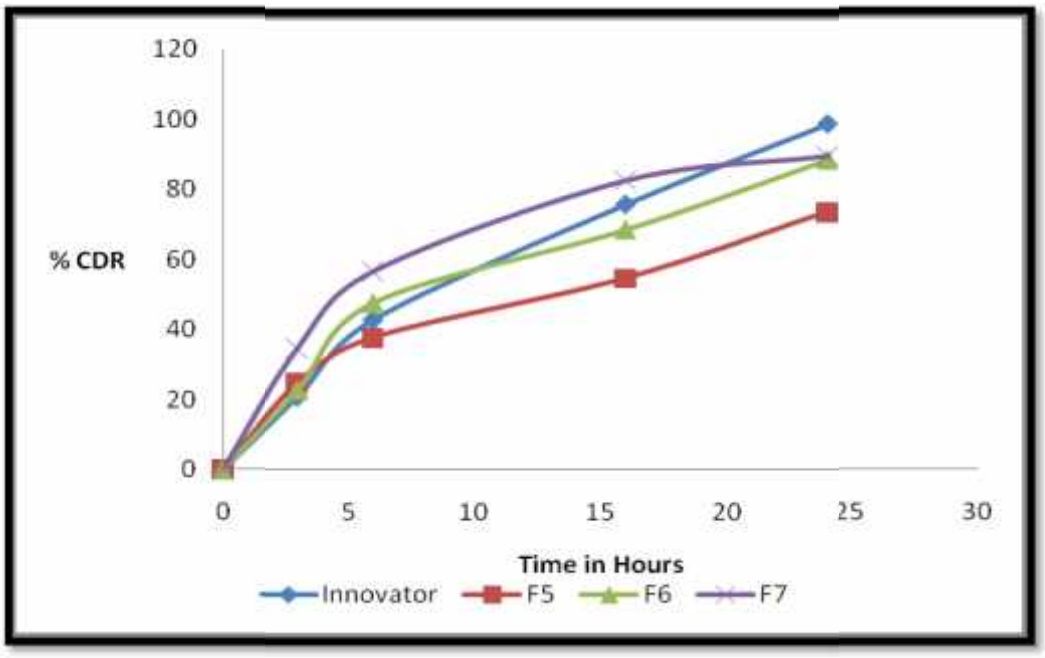


Figure 4.10. *In-Vitro drug relesed of batch F5, F6 and F7*

Discussion: As the binder solution adding time was increased, the granules were decreased in size in above batches. Batch no. F6 in which the binder adding time was 2 minutes that matched average weight and thickness with the innovator but dissolution profile was not matched. As the binder solution adding time affected

in the physical properties of tablets, granulating solution's amount also affects on the dissolution profile. Therefore in the further study amount of water as the granulating agent was optimized.

4.7.4. Optimization of Granulating Agent

In wet granulation of EOP tablets, water was used as the granulating agent, and amount of granulating agents affects on the dissolution profile, different level of granulating agent was used in following Batch F8, F9 and F10

Table 4.38: Formula for core tablet of batch F8, F9 and F10

Sr. no	Ingredients	F8	F9	F10
		Qty (mg) / tablet	Qty (mg) / tablet	Qty (mg) / tablet
1	VFX HCl	169.72	169.72	169.72
2	PVP K 90	20	20	20
3	Avicel PH 101	134.68	134.68	134.68
4	PEG-400	10	10	10
5	Mannitol	20	20	20
6	Aerosil	2	2	2
7	Magnesium Stearate	3.6	3.6	3.6
8	Water (For 1000 tablets)	**Upto 50 ml**	**Upto 100 ml**	**Upto 150 ml**
9	Total	360 mg	360 mg	360 mg

Results

Table 4.39: Evaluations of Core Tablets of Batch F8, F9 and F10

Parameters	F8	F9	F10
Average Weight(mg)	357.6	355.2	360.2
Hardness (N)	88-95	78-91	69-87
Friability	0.04 %	0.03 %	0.04 %
Thickness (mm)	3.74-3.75 mm	3.72-3.93	3.88-3.92
Diameters (mm)	10.31 mm	10.31 mm	10.32 mm

Table 4.40: Evaluations of Coated Tablets of Batch F8, F9 and F10

Parameters	F8	F9	F10
Average weight (mg)	385.4	390.2	386.8
Thickness (mm)	3.83-3.91	4.21-4.45	4.2-4.7
Diameter (mm)	10.34	10.36	10.35

In-vitro drug release of batch F8, F9 and F10

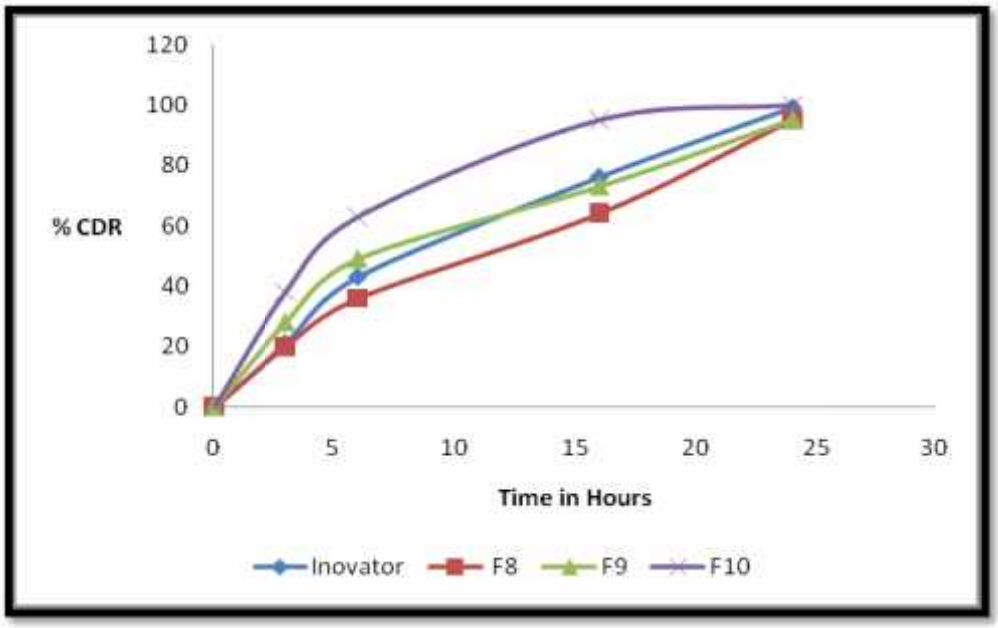


Figure 4.11. *In-vitro drug release of batch F8, F9 and F10*

Discussion: Batch F8 which containing 50 ml amount of water for 1000 tablets that formed the large size lumps of granules as compared to batch F9. In batch F10 more amount of water decreased the granules size that increased dissolution rate. Batch F9 matched the dissolution profile because of good properties of the granules. Optimized core tablets of VFX HCl further were optimized with the different coating parameters.

4.7.5 Optimization of Weight Gain % After Coating

In the optimization of the weight gain three batches were prepared as per the above batches, after the evaluations of the core tablets which found in acceptable range, coating was done at different weight level were mentioned in the following table.

Table 4.41: Formula of different coating parameters of batch F11, F12 and F14

Ingredients	F 11(mg/tab.)	F12 (mg/tab.)	F13 (mg/tab.)
Weight gain after coating A	12 mg	18 mg	25 mg
Weight gain after coating B	8 mg	10 mg	15 mg
Total weight gain after coating	20 mg	28 mg	40 mg
Percentage weight gain	**5%**	**7%**	**10%**

Results

Table 4.42: Evaluation after coating of batch F11, F12 and F14

Parameters	F11	F12	F13
Average weight (mg)	393.4	393.2	394.8
Thickness (mm)	3.18-3.30	4.13-4.27	4.21-4.38
Diameter(mm)	10.35	10.34	10.37

In-vitro drug release of batch F11, F12 and F13

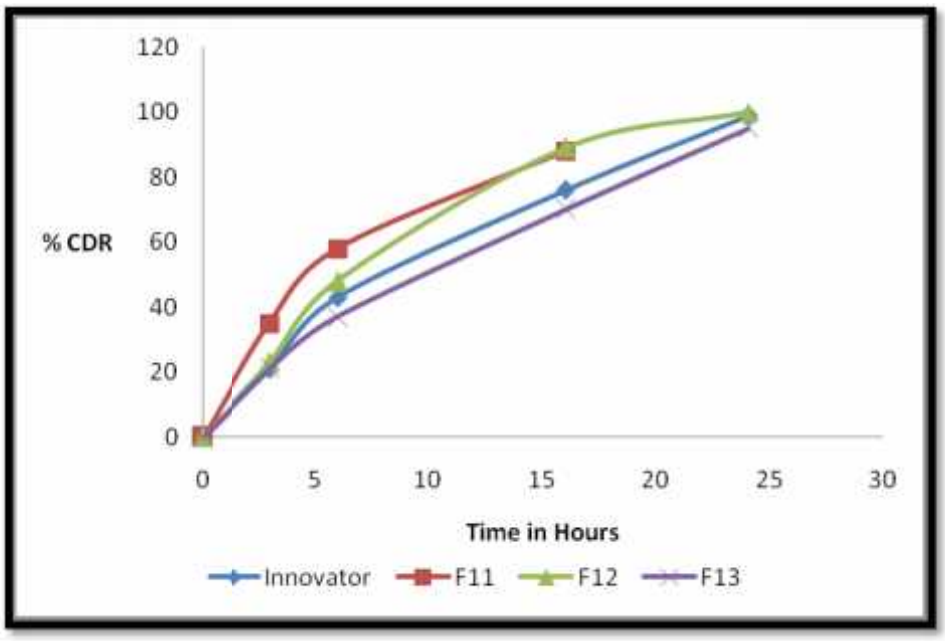


Figure 4.12. *In-vitro drug release of batch F11, F12 and F13*

Discussion: As coating percentages increased the dissolution rate of tablets were delayed. In batch F13 10% weight gain matched with the innovator tablets so it can be concluded that dissolution rate depended on the thickness of the coating as the thickness of the tablet increased the dissolution rate was delayed. The zero order drug release of batch F13 was similar to the innovator product. So batch F13 was considered as optimized batch. Thus, this batch was subjected for stability study.

4.8. Statistical Analysis of the Optimized Formulation

Release profile of optimized batch of EOP and Innovator product were compared by calculating statistically derived mathematical parameter, "similarity factor" (f_2), using predicted in vitro release profile as the reference.

The equation of similarity factor is:

$$f_2 = 50 * \log \{ [1 + \frac{1}{n} \times \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100 \} \quad (4.5)$$

where,

R_t and T_t = percent Drug AST04 dissolved at each time point for the reference and test product,

n = number of dissolution sample times,

t = time sample index.

If the two profiles are identical, f_2 is 100. Values of $f_2 \geq 50$ indicate similarity of two dissolution profiles.

Conclusion

Similarity factor (f_2) values for optimized batch and Innovator product when compared with predicted release profile is **65.95**. Ideally the f_2 values must fall in the range of 50-100. Thus, it can be concluded, the release profile of the developed formulation was similar to the innovator product release profile.

4.9 Stability Study of Optimized Batch

In the stability study, tablets of batch F14 were stored at 40^0 C/75 % RH for 1 month and 3 months with the silica gel desiccant in the HDPE bottles and checked the following parameters at the initial stage, after 1 month and after 3 months.

Table 4.43: Stability study of optimized batch

Sr no.	Tests	Specification	40°C / 75 % RH		
			Initial	1M	3M
1	Description	White colored round biconvex coated tablets plain on both sides.	White colored round biconvex coated tablets plain on both sides.	White colored round biconvex coated tablets plain on both sides.	White colored round biconvex coated tablets plain on both sides.

2	Assay	90-110%	98.9	98.8	98.5
3	**Related Substances**				
	Related Compound A	NMT 0.20%	0.09	0.10	0.10
	Decyclohexanol impurity	NMT 0.20%	0.03	0.03	0.04
	Max. unknown impurities	NMT 0.20%	0.08	0.11	0.13
	Total impurities	NMT 1.0%	0.20	0.24	0.27
4	Loss on drying (%)	NMT 8%	4.2	3.83	3.71
5	Thickness	3.9-4.5	4.0	4.3	4.5
6	Hardness	80-90 N	83N	82N	81N
7	Dissolution	NLT 85% in 24 H	87%	88%	88%

In-vitro drug release of optimized batch at different conditions

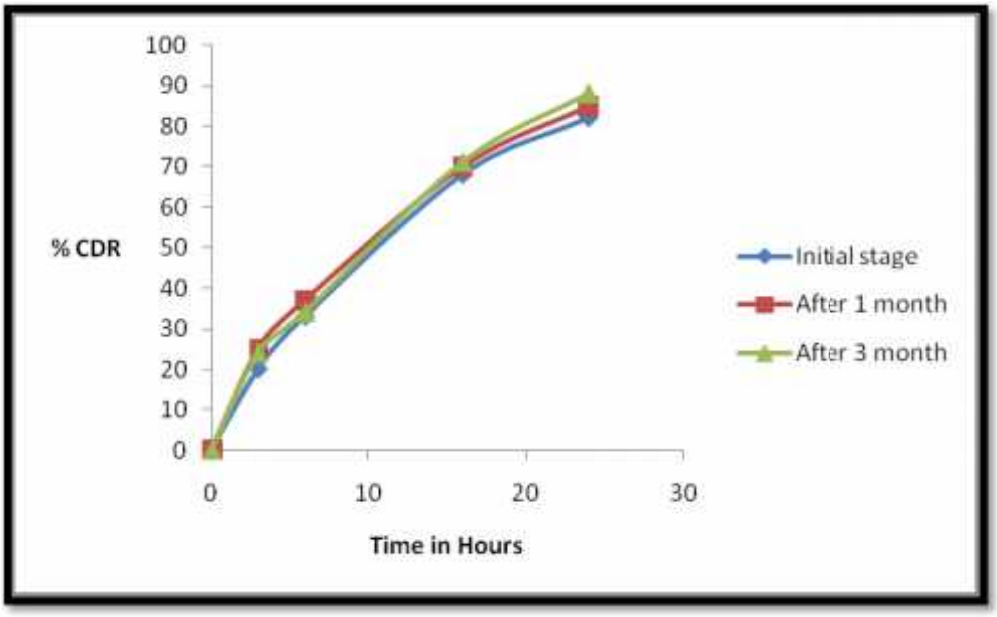


Figure 4.13. *In-vitro drug release of optimized batch at different conditions*

Discussion: Batch F13 shows the similar properties till the three months so concluded that developed product was stable for longer time.

- The EOP formulations were shown zero order drug release upto 24 hours. To find out the potentiality of developed technology of VFX HCl another approach was selected which was asymmetric membrane technology. So further tablets were prepared by using Asymmetric technology.

4.10 Asymmetric Membrane Technology [33] [34]

Asymmetric membrane tablets are osmotic system with in-situ pore formation that consist of a drug containing core portion surrounded by a membrane which has an asymmetric structure that has a porous region. In the asymmetric membrane system no need to drill into the tablets.

Advantages of Asymmetric Membrane Technology

- High water fluxes can be achieved.
- The permeability of the coating to water can be adjusted by controlling the membrane structure.

- The porosity of the membrane can be controlled to minimize the time lag before drug delivery begins and allowing the drug to be released from large number of delivery ports.

4.10.1 Method of Preparation of Asymmetric Membrane Tablets

4.10.1.1 Preparation of Core tablet: Based on optimized formula of EOP, fewer trials were carried out using asymmetric membrane technique. The different ratio of osmotic agent was taken in following batches.

Table 4.44: Formula of Core Tablets of Asymmetric Membrane Technology

		A1	A2	A3
Sr. no	**Ingredients**	**Qty (mg) / tablet**	**Qty (mg) / tablet**	**Qty (mg) / tablet**
1	VFX HCl	169.72	169.72	169.72
2	PVP K 90	20	20	20
3	Avicel PH 101	134.68	134.68	134.68
4	PEG-400	10	15	20
5	Mannitol	20	15	10
6	Aerosil	2	2	2
7	Magnesium Stearate	3.60	3.60	3.60
Total		360 mg	360 mg	360 mg

Preparation of Coating solution

- Cellulose acetate (CA) solution (5% m/V) was prepared in an acetone/water (90/10 V/V) solvent system.
- Accurately weighed quantity of CA was added to acetone/water and the resulting mixture was stirred in a well-closed beaker to obtain an aqueous solution.

- The required quantity of the pore forming agent glycerol (10 g) and coloring agent were also added to the solution under stirring till the clear solution was obtained.
- Coating was done manually upto the 10% weight gain.

Results

Table 4.45: Evaluations of core tablets of batch A1, A2 and A3

	A1	**A2**	**A3**
Weight (mg)	360.2	360.5	360.7
Hardness (N)	80-92	72-82	72-77
Friability	0.02 %	0.04 %	0.04 %
Thickness (mm)	5.09-5.14	5.09-5.12	5.05-5.13
Diameters (mm)	9.41	9.41	9.41

Table 4.46: Evaluations of coated tablets of batch A1, A2 and A3

Parameters	**A1**	**A2**	**A3**
Average weight (mg)	403.04	405.08	402.06
Thickness(mm)	5.21-5.30	5.13-5.23	5.23-5.30
Diameter(mm)	9.64mm	9.64mm	9.64mm

In-Vitro drug release of batch A1, A2 and A3

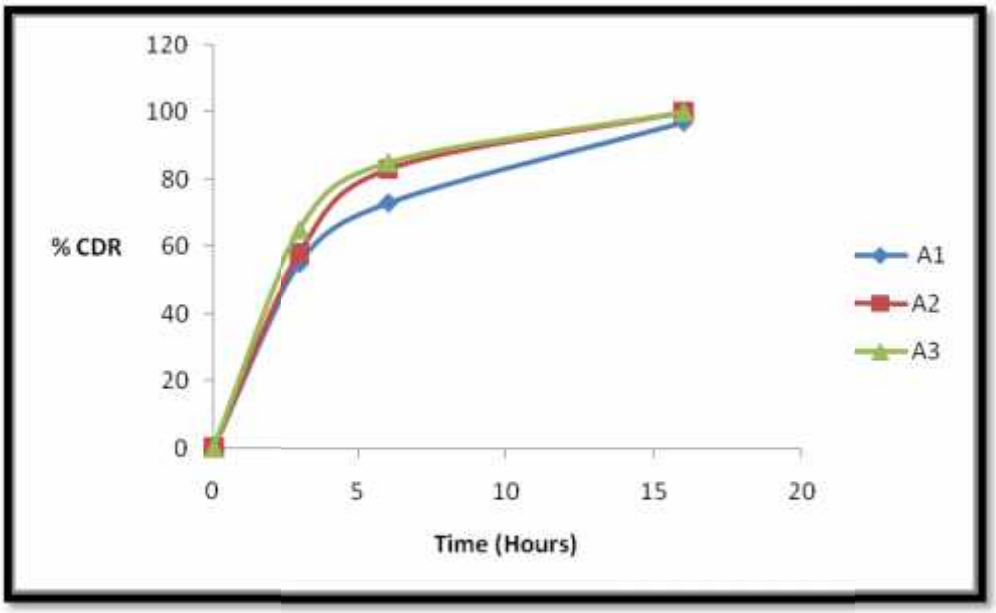


Figure 4.14: *In-Vitro drug release of batch A1, A2 and A3*

Discussion: In the above batches, Batch A1 was found better as compared to other batches because of lower osmotic agent ratio and that created lower osmotic pressure in the core tablets resulting in delayed drug release. But batch A1 did not show release profile up to 24 hours.

4.10.2 Comparison of Optimized EOP Tablets with Tablet Prepared Using Asymmetric Membrane Technology

Dissolution was conducted of asymmetric membrane and EOP tablets were carried out in USP type paddle II and I dissolution apparatus.

Results

- **Dissolution of Asymmetric membrane Tablet & EOP in Type I Dissolution Apparatus**

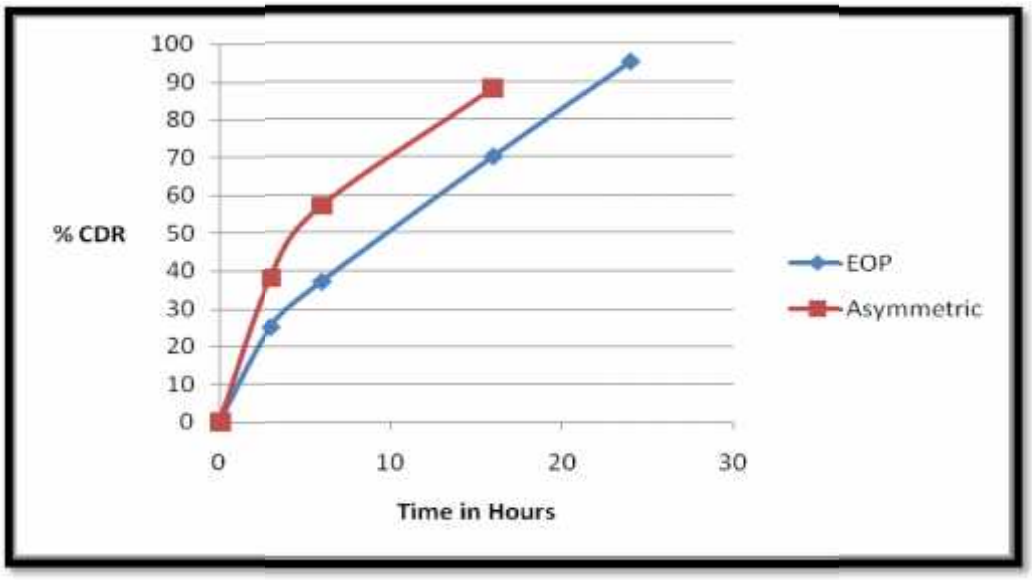


Figure 4.15 *Dissolution of Asymmetric membrane Tablet & EOP in Type II dissolution apparatus.*

- **Dissolution of Asymmetric membrane Tablet & EOP in Type I Dissolution Apparatus**

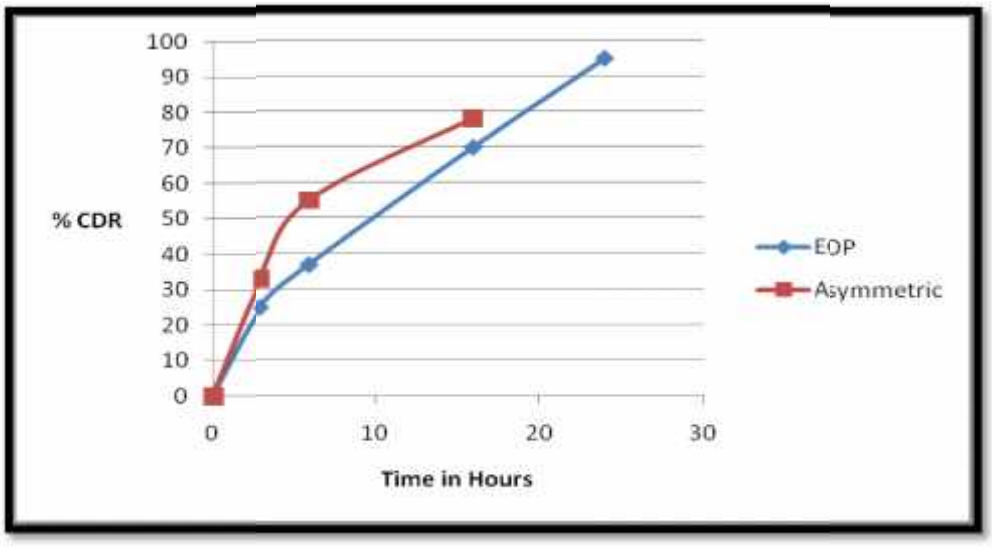


Figure 4.16 *Dissolution of Asymmetric membrane Tablet & EOP in Type I dissolution apparatus.*

Discussion: Asymmetric membrane osmotic tablets of batch A1 were found to give slower drug release in both the dissolution apparatus. Thus it can be concluded that VFX HCl prepared by EOP technology was found to be more suitable as once a day formulation.

4.11 Effect of Agitation on EOP Tablets of VFX HCl

EOP tablets of VFX HCl were also checked for its independence towards agitational rate at 50 and 100 RPM in USP dissolution apparatus type I. The comparative dissolution profile was shown in figure 4.18

Results

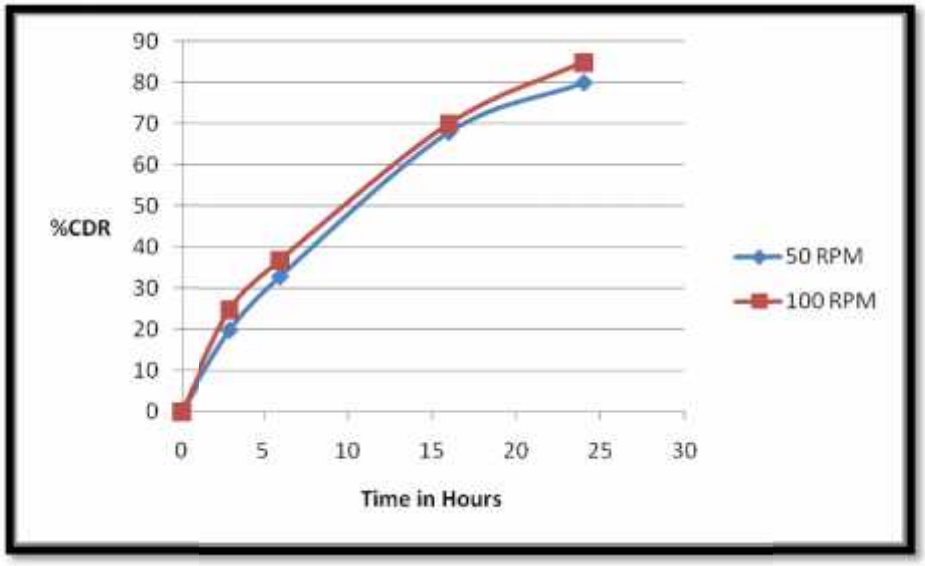


Figure 4.17 *At 50 and 100 RPM dissolution of the EOP tablets*

Discussion: At 50 and 100 RPM dissolution rate was found similar to each other, so there is no significant effect of agitation on the EOP tablets. Similarity factor was also applied as per formula mentioned in the equation 4.5 and (f_2) values was found **56.88**. This indicates that developed tablets prepared by EOP technology were independent of agitation.

4.12 Box Behnken Design [36]

A three-factor, three level, Box Behnken Design was applied to assess the simultaneous effect of all the three factors for their optimization. This design is suitable for the exploration of quadratic response surfaces and constructs a second order polynomial model, thus helping in optimization a process with small number of experimental runs.

All the batches were prepared with the same method as described above and all the factors as shown in table were evaluated statistically by using Design Expert 7.0 Trial Version.

Dependable Variable: T 85 (Time required for 85 % Drug Release)

Table 4.47: Independent variables of design

Independent variables	Design level	
	Coded level	Uncoded level
1. Osmotic Agents Ratio (PEG-400 : Mannitol)	-1	(1:2)
	0	(1:1)
	+1	(2:1)
2. Concentration Coating (%) (Cellulose Acetate)	-1	3%
	0	4%
	+1	5%
3. Plasticizer % (PEG-400)	-1	5%
	0	10%
	+1	15%

Results

Table 4.48: Responses of design batches

Batches	X1	X2	X3	T85 (hrs)
F1	-1	-1	0	18.19
F2	+1	-1	0	14.96
F3	-1	+1	0	20.94
F4	+1	+1	0	14.76
F5	-1	0	-1	19.31
F6	+1	0	-1	16.19
F7	-1	0	+1	21.35
F8	+1	0	+1	16.61
F9	0	-1	-1	16.73
F10	0	+1	-1	19.42
F11	0	-1	+1	17.28
F12	0	+1	+1	16.87
F13	0	0	0	17.32
F14	0	0	0	17.43
F15	0	0	0	17.07

In-Vitro Drug Release of Design Batches

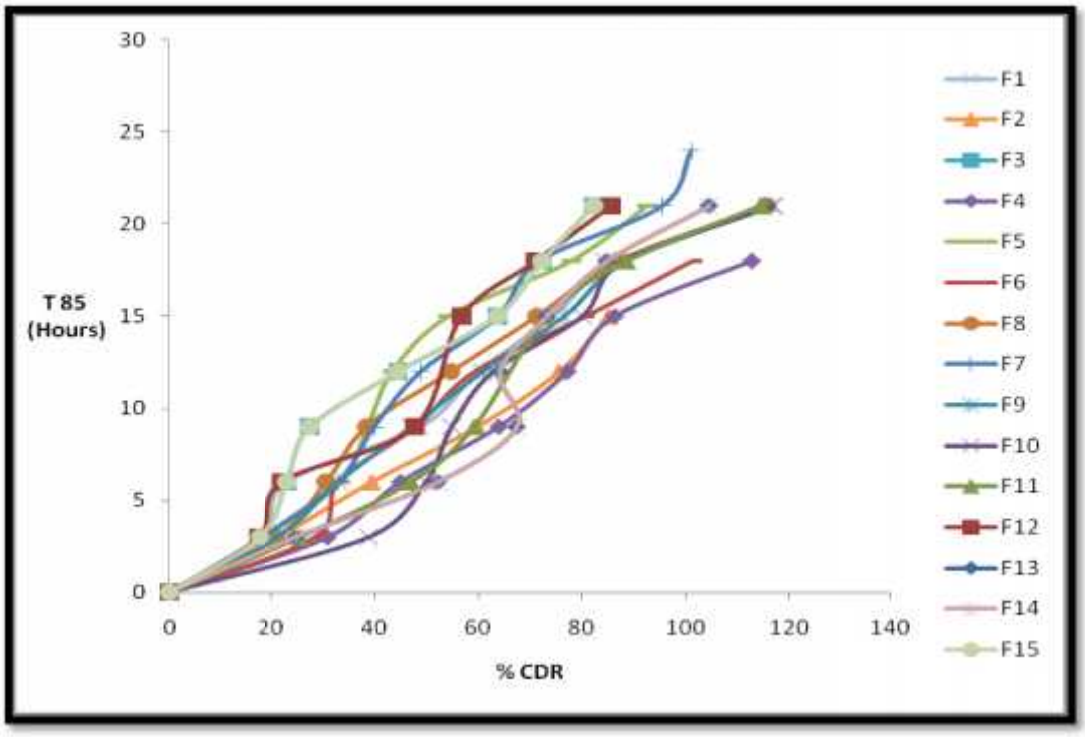


Figure 4.18 *Responses of design batches*

T85 for Design Batch

Figure 4.19 *Responses of design batches*

4.12.1 Statistical Analysis of ANOVA of Response T 85

In regression analysis of ANOVA model was found significant and other parameters mentioned in the following table.

Table 4.49: Regression analysis and ANOVA for T85

Intercept	17.27
R-Squared	0.9445
Adj R-Squared	0.8445
Standard Error	0.44

Table 4.50: ANOVA Responses for T85

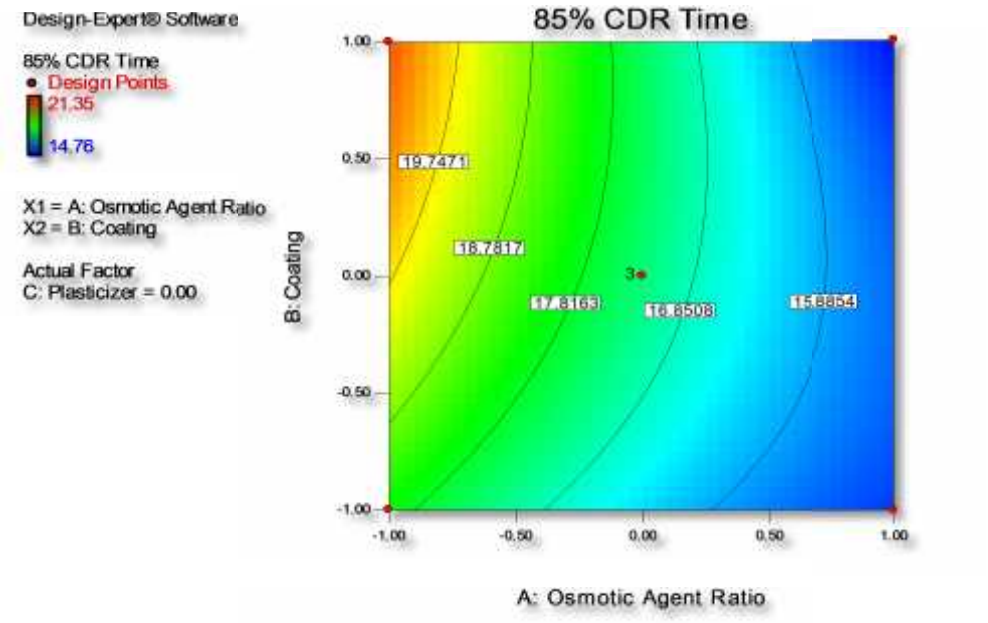
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	48.71	9	5.41	9.45	0.0118
A-Osmotic Agent Ratio	37.28	1	37.28	65.09	0.005
B-Coating	2.98	1	2.98	5.09	0.0737
C-Plasticizer	0.026	1	0.026	0.046	0.8383
AB	2.18	1	2.18	3.80	0.1088
AC	0.66	1	0.66	1.15	0.3334
BC	2.40	1	2.40	4.19	0.0959

A^2	0.49	1	0.49	0.86	0.3471
B^2	0.67	1	0.67	1.17	0.3294
C^2	1.95	1	1.95	3.41	0.1242
Residual	2.86	5	0.57		
Cor Total	51.57	14			

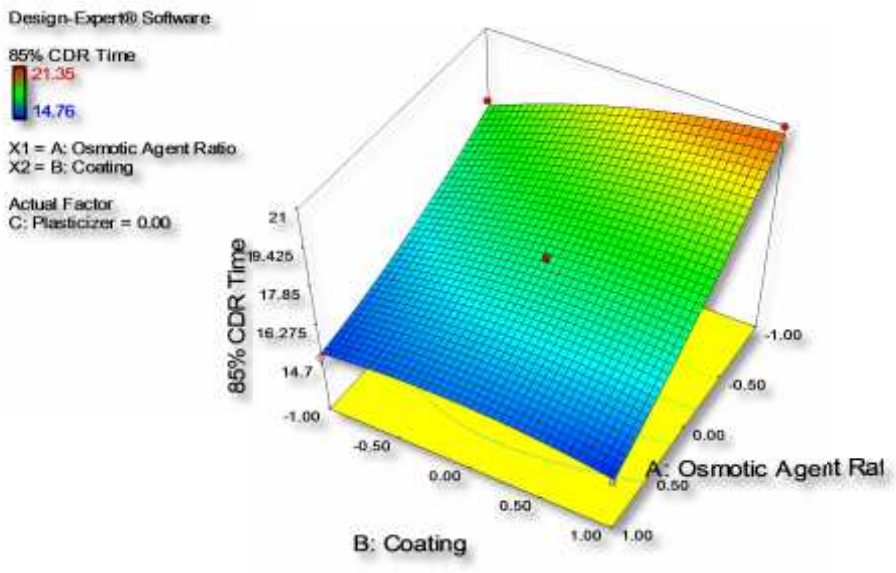
Polynomial Equation

Final Equation in Terms of Coded Factors:

T 85 CDR = +17.27 -2.16* A+0.60* B+0.058* C-0.74* A * B-0.41* A * C-0.78* B * C+0.36* A^2 -0.43* B^2 +0.73* C^2

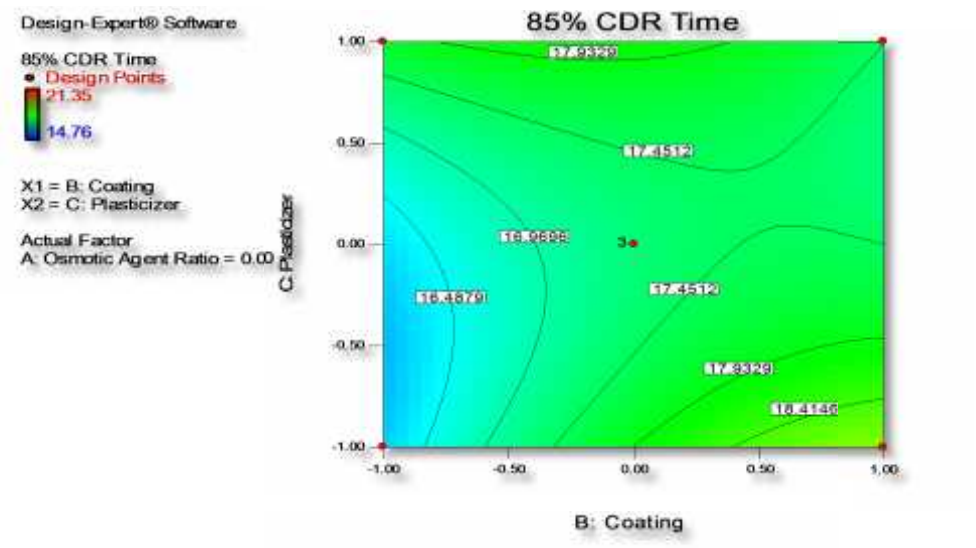


a) ***Figure 4.20:*** *Contour Plot for Response of Osmotic agent ratio and Plasticizer*

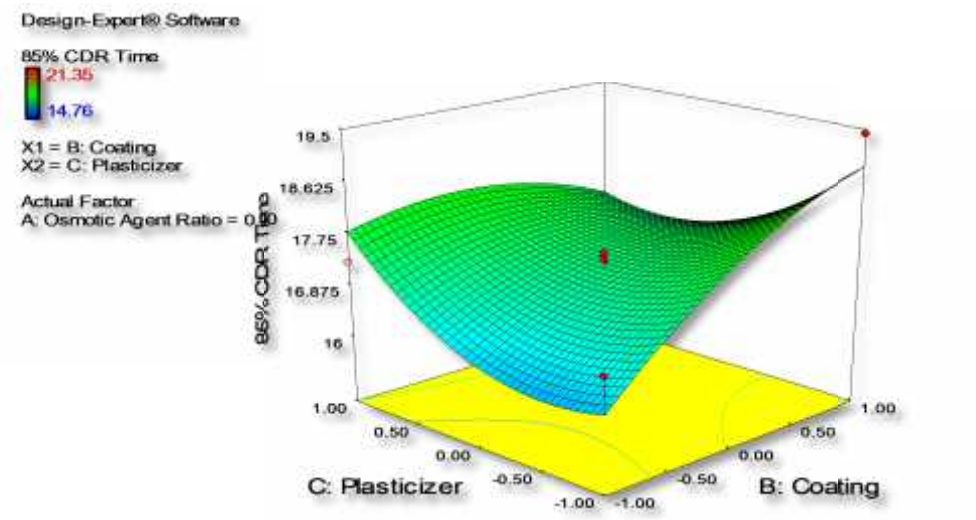


b) Figure: 4.21 *3D Plot for Response of Osmotic agent ratio and coating*

Discussion: T85 of all batches were found to be in between 14.96 to 21.35. From the polynomial equation it was concluded that X1 had negative effect on T85 that indicates, when osmotic agent ratio was increased time required for 85% drug release was decreasing. Result revealed that X2 had positive effect on T85 and it did not show any significant effect on time required for 85% of drug released.

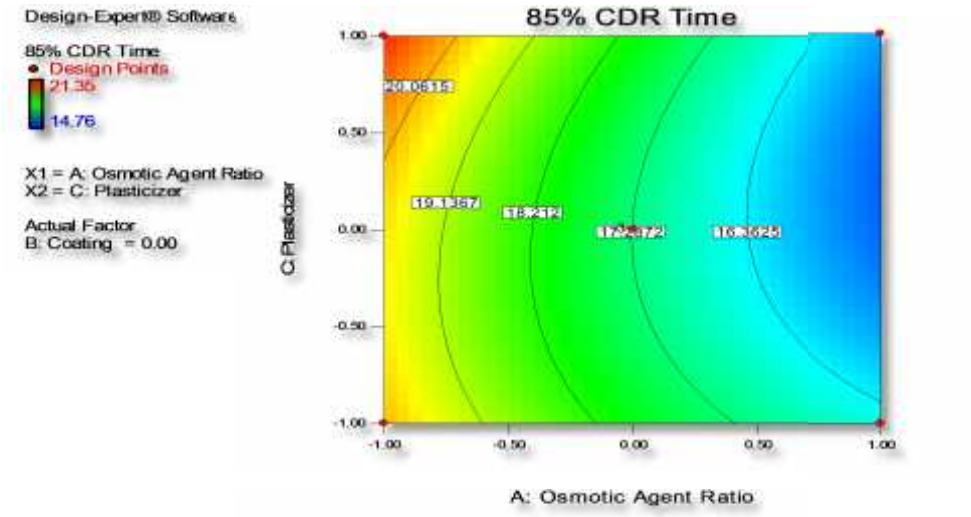


c) ***Figure 4.22:*** *Contour Plot for Response of coating and Plasticizer*

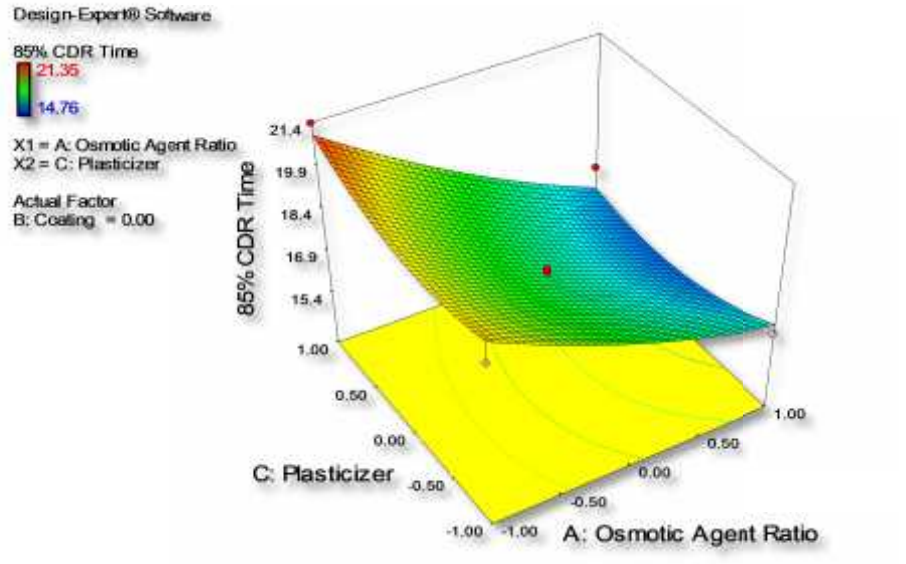


d) ***Figure 4.23:*** *3D Plot for Response of coating and Plasticizer*

Discussion: From the polynomial equation it was concluded that X3 had positive effect on T85 that indicates, when plasticizer percentages was increased time required for 85% drug release was increased. But X2 and X3 did not show any significant effect on time required for 85% of drug released as compared to X1.



e) ***Figure 4.24*** *Contour Plot for Response of osmotic agent ratio and Plasticizer*



f) ***Figure 4.25*** *3D Plot for Response of osmotic agent ratio and Plasticizer*

Discussion: X1 had positive effect on T85 that indicates, when osmotic agent ratio was increased time required for 85% drug release was decreased. But X3 did not show any significant effect on time required for 85% of drug released as compared to X1. That means mainly osmotic agent ratio affected on the T85.

Check point batches

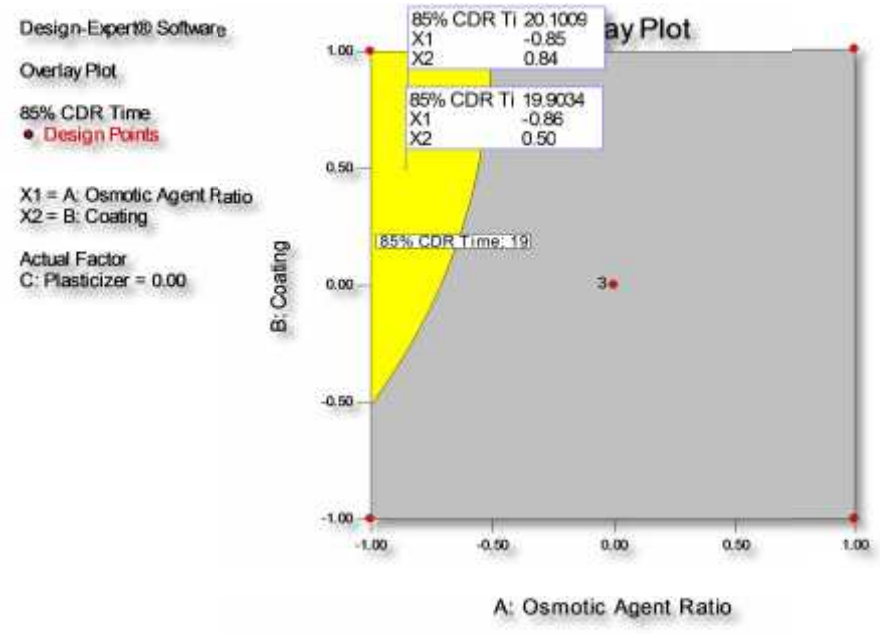


Figure 4.26 *Check point batches*

4.12.2. Formulation of check point batches

Table 4.51: Observation of check point batch

Batch	X1	X2	X3	Theoretical T85	Experimental T85
B1	-0.85	0.92	0	20.10	20.03
B2	-0.85	0.57	0	19.90	19.93

Discussion: In the optimization study effect of osmogens like Mannitol and PEG-400 were studied and 1:2 ratio of Mannitol/ PEG-400 showed highest sustained drug release compared to 1:1 and 2:1 ratio. Osmotic pressure of PEG-400 was 133 atm, while Mannitol was 38 atm hence lower amount of PEG 400 and higher amount of Mannitol had a direct impact on the drug release. Therefore, it was understood that the osmotic pressures of these osmogens affected on drug release. Batch F7 that had optimum concentration of PEG-400 and Mannitol gives desired dissolution rate, thus it was considered as the best batch. From the ANOVA results it shows that model which was significant and R_2 value is also desirable. From the check point batch in can be concluded that observed values are similar that to expected value. Thus the mathematical model which selected for study was validated.

4.13. Model Fitting To Evaluate Mechanism Of Drug Release [41]

Various models were tried to fit the optimized batch to determine the mechanism of drug release. Different models for drug release mentioned in following.

4.13.1. Zero Order Model

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

$$M = k*t \qquad (4.6)$$

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.

4.13.2. First order model:

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

$$M = e_a * e^{-bt} \quad (4.7)$$

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.

4.13.3. 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.

$$M = (100-q) * \text{sqrt of time} \quad (4.8)$$

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.

4.13.4. Korsmeyer-Peppas model

$$M_t/M = k*t_n \quad (4.9)$$

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.

4.13.5. 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.

$$M = (100^{1/3} - (k*t))^3 \quad (4.10)$$

Where,

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

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

Results

Table 4.52: Kinetic models value for optimized batch

Model name	R Square	SSR	Fischer Ratio
Zero order	0.9734	124.2158	15.5270
First order	0.9589	6182.6854	772.8357
Higuchi	0.9841	336.9744	42.1218
Korsmeyer - peppas	0.9881	7444.3217	1063.4745
Weibull model	0.9705	6819.8117	974.2588
Hixson - crowell	0.9389	27194.4123	3884.9160

Discussion: Out of all the models applied, the best fitting model was zero order for optimized batch. In zero order model R^2 value was nearest to 1 that means optimized batch follows the zero order drug release.

CHAPTER 5 - SUMMARY

5. SUMMARY

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, Venlafaxine HCl, anti depressant drug used for the management of major depressive disorder (MDD), generalized anxiety disorder (GAD) and social anxiety disorder (social phobia). Venlafaxine HCl is BCS class I drug and it is practically soluble in almost all the solvents. The bioavailability of the drug is 45% as it undergoes the first pass metabolism with half life 5 hours. All these important properties of the drug necessitates for a twice daily dosage regimen which is inconvenient for maintenance therapy in patients. Thus, once a day 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 wet granulation using PVP K 90 as a binder along with the osmotic agent PEG-400. In this study two different coating methods as EOP and Asymmetric membrane coating were compared and Cellulose acetate was used as coating polymer in both of coating methods to form semipermeable membrane around core tablet. In EOP tablets with Cellulose Acetate, Polyethylene Glycol-400 (PEG 400) was used as a plasticizer because it allows high permeability of the membrane compared to other plasticizers. In asymmetric membrane coating Glycerol was chosen as pore former with Cellulose Acetate. Drug release profiles of all the batches of coated tablets were evaluated and compared with the marketed product-Venlafaxine HCl ER tablets®.

In comparative study of EOP and Asymmetric membrane coating it was found that EOP coating was better as compared to asymmetric membrane coating. Optimization of the EOP batches was done by Box-behnken design with statistical software version 7.0. In the optimization study effect of osmogens like Mannitol and PEG-400 were studied and 1:2 ratio of Mannitol/ PEG-400 showed highest sustained drug release in comparison to 1:1 and 2:1 ratio. Osmotic pressure of PEG-400 was 133 atm, while Mannitol was 38 atm hence lower amount of PEG 400 and higher amount of Mannitol had a direct impact on the drug release. Therefore, it was understood that the osmotic pressures of these osmogens affected on drug release.

Dissolution data of optimized formulation was fitted to various mathematical models to describe kinetics of drug release. Effect of 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 agitational intensity and dependent on the osmotic pressure of the osmotic agents present in the core tablets. 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 osmotic tablets of Venlafaxine Hydrochloride will be an effective dosage form for the management of major depressive disorder (MDD), generalized anxiety disorder (GAD) and social anxiety disorder (social phobia) patients as the antidepressant effect can be seen for a prolonged duration of action with once a day formulation and the patient compliance can be increased.

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CHAPTER 7 - ANNEXURE

ANNEXURE

Development of Nicardipine Hydrochloride Osmotic Tablet Using an Asymmetric Membrane Technique

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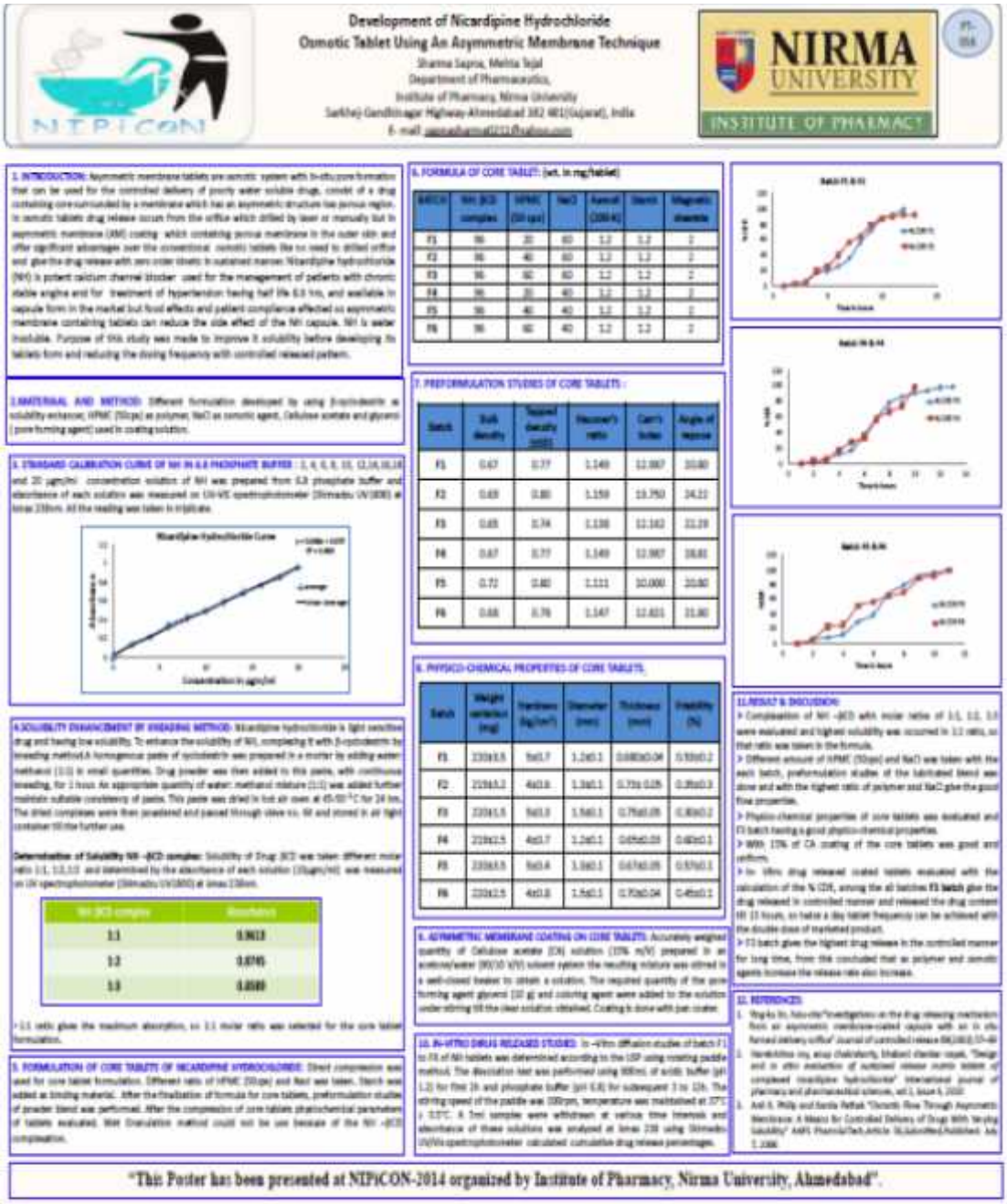
Osmotic drug delivery is one of the controlled drug release technology having membrane coating with semipermeable membrance. The drug release occurs from the orifice which drilled by laser or manually. The aim of present study was to develop asymmetric membrane (AM) coating which containing porous membrane in the outer skin and offer significant advantages over the conventional osmotic tablets like no need to drilled orifice and give the drug release with zero order kinetic in sustained manner. Nicardipine hydrochloride (NH) is potent calcium channel blocker used for the management of patients with chronic stable angina and for treatment of hypertension having half life 8.6 hrs, and available in capsule form in the market but food effects and patient compliance affected so asymmetric membrane containing tablets can reduce the side effect of the NH capsule. NH is water insoluble Thus, attempts were made to improve it solubility before developing its OCDDS. The complexation using β-CD was utilized to improve its solubility. This inclusion complex was used in formulation of core tablets that coated with the asymmetric membrane. Core tablets were prepared using, HPMC (50cps) as carrier NaCl as osmogent. Asymmetric membrane coating was obtained by use of cellulose acetate in acetone/water solvent and glycerol as pore forming agent also added. The results of optimized batch shown zero order drug release. Further, drug release was also found independent of pH, food effects, agitation etc. The study indicated that development of NH tablets using asymmetric membrane approach is advantageous than conventional osmotic tablets.



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1. INTRODUCTION: Asymmetric membrane tablets are osmotic system with in-situ pore formation that can be used for the controlled delivery of poorly water soluble drugs, consist of a drug containing core surrounded by a membrane which has an asymmetric structure like porous region. In osmotic tablets drug release occurs from the orifice which drilled by laser or manually but in asymmetric membrane (AM) coating which containing porous membrane in the outer skin and offer significant advantages over the conventional osmotic tablets like no need to drilled orifice and give the drug release with zero order kinetic In sustained manner. Nitendipine hydrochloride (NH) is potent calcium channel blocker used for the management of patients with chronic stable angina and for treatment of hypertension having half life 8.6 hrs, and available in capsule form in the market but food effects and patient compliance affected so asymmetric membrane containing tablets can reduce the side effect of the NH capsule. NH is water insoluble. Purpose of this study was made to improve it solubility before developing its tablets form and reducing the dosing frequency with controlled released pattern.

2.MATERIAL AND METHOD: Different formulation developed by using β-cyclodextrin as solubility enhancer, HPMC (50cps) as polymer, NaCl as osmotic agent, Cellulose acetate and glycerol (pore forming agent) used in coating solution.

3. STANDARD CALIBRATION CURVE OF NH IN 6.8 PHOSPHATE BUFFER : 2, 4, 6, 8, 10, 12,14,16,18 and 20 µgm/ml concentration solution of NH was prepared from 6.8 phosphate buffer and absorbance of each solution was measured on UV-VIS spectrophotometer (Shimadzu UV1800) at λmax 238nm. All the reading was taken in triplicate.

4.SOLUBILITY ENHANCEMENT BY KNEADING METHOD: Nicardipine hydrochloride is light sensitive drug and having low solubility. To enhance the solubility of NH, complexing it with β-cyclodextrin by kneading method.A homogenous paste of cyclodextrin was prepared in a mortar by adding water: methanol (1:1) in small quantities. Drug powder was then added to this paste, with continuous kneading, for 1 hours An appropriate quantity of water: methanol mixture (1:1) was added further maintain suitable consistency of paste. This paste was dried in hot air oven at 45-50 °C for 24 hrs. The dried complexes were then powdered and passed through sieve no. 60 and stored in air tight container till the further use.

Determination of Solubility NH –βCD complex: Solubility of Drug: βCD was taken different molar ratio 1:1, 1:2,1:3 and determined by the absorbance of each solution (10µgm/ml) was measured on UV spectrophotometer (Shimadzu UV1800) at λmax 238nm.

NH:βCD complex	Absorbance
1:1	0.903
1:2	0.870
1:3	0.859

> 1:1 ratio give the maximum absorption, so 1:1 molar ratio was selected for the core tablet formulation.

5. FORMULATION OF CORE TABLETS OF NICARDIPINE HYDROCHLORIDE: Direct compression was used for core tablet formulation. Different ratio of HPMC (50cps) and NaCl was taken. Starch was added as binding material. After the finalization of formula for core tablets, preformulation studies of powder blend was performed. After the compression of core tablets physicochemical parameters of tablets evaluated. Wet Granulation method could not be use because of the NH –βCD complexation.

6. FORMULA OF CORE TABLET: (wt. in mg/tablet)

Batch	NH: βCD complex	HPMC (50 cps)	NaCl	Aerosil (200 #)	Starch	Magnesium stearate
F1	90	20	60	1.2	1.2	2
F2	90	40	60	1.2	1.2	2
F3	90	60	60	1.2	1.2	2
F4	90	20	40	1.2	1.2	2
F5	90	40	40	1.2	1.2	2
F6	90	60	40	1.2	1.2	2

7. PREFORMULATION STUDIES OF CORE TABLETS :

Batch	Bulk density	Tapped density (gm/cc)	Hausner's ratio	Carr's Index	Angle of repose
F1	0.67	0.77	1.149	12.987	20.80
F2	0.69	0.80	1.159	13.750	24.21
F3	0.65	0.74	1.138	12.162	21.29
F4	0.67	0.77	1.149	12.987	18.81
F5	0.72	0.80	1.111	10.000	20.80
F6	0.68	0.76	1.147	12.821	21.80

8. PHYSICO-CHEMICAL PROPERTIES OF CORE TABLETS:

Batch	Weight variation (mg)	Hardness (kg/cm²)	Diameter (mm)	Thickness (mm)	Friability (%)
F1	220±3.5	5±0.7	1.2±0.1	0.68±0.04	0.93±0.2
F2	219±3.2	4±0.8	1.3±0.1	0.70± 0.05	0.95±0.3
F3	220±3.5	5±0.3	1.5±0.1	0.75±0.05	0.80±0.2
F4	219±2.5	4±0.7	1.2±0.1	0.65±0.03	0.60±0.1
F5	220±3.5	5±0.4	1.3±0.1	0.67±0.05	0.93±0.1
F6	220±2.5	4±0.8	1.4±0.1	0.70±0.04	0.45±0.1

9. ASYMMETRIC MEMBRANE COATING ON CORE TABLETS: Accurately weighed quantity of Cellulose acetate (CA) solution (10% m/V) prepared in an acetone/water (80:20 v/v) solvent system the resulting mixture was stirred to a well-closed beaker to obtain a solution. The required quantity of the pore forming agent glycerol (10 g) and coloring agent were added to the solution under stirring till the clear solution obtained. Coating is done with pan coater.

10. IN-VITRO DRUG RELEASE STUDIES: In -vitro diffusion studies of batch F1 to F6 of NH tablets was determined according to the USP using rotating paddle method. The dissolution test was performed using 900mL of acidic buffer (pH 1.2) for first 2h and phosphate buffer (pH 6.8) for subsequent 3 to 12h. The stirring speed of the paddle was 100rpm, temperature was maintained at 37°C ± 0.5°C. 5 5ml sample were withdrawn at various time intervals and absorbance of these solutions was analyzed at λmax 238 using Shimadzu UV/Vis spectrophotometer calculated cumulative drug release percentages.

11.RESULT & DISCUSSION:

> Complexation of NH –βCD with molar ratio of 1:1, 1:2, 1:3 were evaluated and highest solubility was occurred in 1:1 ratio, so that ratio was taken in the formula.

> Different amount of HPMC (50cps) and NaCl was taken with the each batch, preformulation studies of the lubricated blend was done and with the highest ratio of polymer and NaCl give the good flow properties.

> Physico-chemical properties of core tablets was evaluated and F3 batch having a good physico-chemical properties.

> With 15% of CA coating of the core tablets was good and uniform.

> In- Vitro drug released coated tablets evaluated with the calculation of the % CDR, among the all batches **F3 batch** give the drug released in controlled manner and released the drug content till 12 hours, so twice a day tablet frequency can be achieved with the double dose of marketed product.

> F3 batch gives the highest drug release in the controlled manner for long time, from this concluded that as polymer and osmotic agents increase the release rate also increase.

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