"DESIGN DEVELOPMENT AND CHARACTERIZATION OF CONTROLLED POROSITY OSMOTIC TABLET OF A CALCIUM CHANNEL BLOCKER"

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BY

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CERTIFICATE

This is to certify that **Mr. TEJAS PATEL** *have prepared the thesis entitled "DESIGN DEVELOPMENT AND CHARACTERIZATION OF CONTROLLED POROSITY OSMOTIC TABLET OF A CALCIUM CHANNEL BLOCKER", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. They have carried out the work at the Department of Pharmaceutics & pharmaceutical technology, Institute of Pharmacy, Nirma University.*

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DECLARATION

We declare that the thesis "DESIGN DEVELOPMENT AND CHARACTERIZATION OF CONTROLLED POROSITY OSMOTIC TABLET OF A CALCIUM CHANNEL BLOCKER", have been prepared by us under the guidance of Dr.Tejal A. Mehta, Professor & Head, Department of Pharmaceutics And Pharmaceutical Technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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LIST OF ABBREVIATION

Short name	Abbreviation
IP	India Pharmacopoeia
BP	British Pharmacopoeia
USP	United States Pharmacopeia
PhEur	European Pharmacopoeia
USPNF	United States Pharmacopoeia National Formulary
FTIR	Fourier Transfer Infra Red
UV	Ultra Violet
CA	Cellulose acetate
DEP	Diethyl phthalate
DBP	Dibutyl phthalate
NaCl	Sodium chloride
KCl	Potassium chloride
PEG-400	Poly Ethylene Glycol 400
NDDS	Novel drug delivery system
PVP	Poly vinyl Pyrrolidone
GI	Gastro intestinal
β-CD	β cyclodextrin
EOP	Elementary osmotic pump
PPOP	Push Pull Osmotic Pump
L-OROS	Liquid Oral Osmotic System
SOTS	Sandwiched Osmotic Tablets
OROS-CT	Colon Targeted Oral Osmotic System
OSMAT	Osmotic Matrix Tablet
KBr	Potassium Bromide
CPOP	Controlled Porosity Osmotic Tablet
°C	Degree centigrade
Conc.	Concentration
CPR	Cumulative Percentage Release
µg	Microgram
RH	Relative Humidity
SD	Standard Deviation
Avg.	Average
Hr	Hour
min	Minute
W/w	Weight by weight
W/v	Weight by volume
atm	Atmospheric pressure

Chapter 1

Aim of present investigation

1 AIM OF PRESENT INVESTIGATION

Oral drug delivery has been extensively used for both local and systemic effect. Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dosage required, higher frequency of administration, uncontrolled release of drug, lower effectiveness, toxicity and adverse side effects. Ideal drug delivery should deliver the drug in controlled and reproducible manner. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession. These systems can be characterized as controlled drug release systems and targeted drug delivery systems.

Controlled release drug delivery system attempts to sustain drug blood concentration 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, employ less total drug, improve patient compliance, and minimize local and systemic side effects

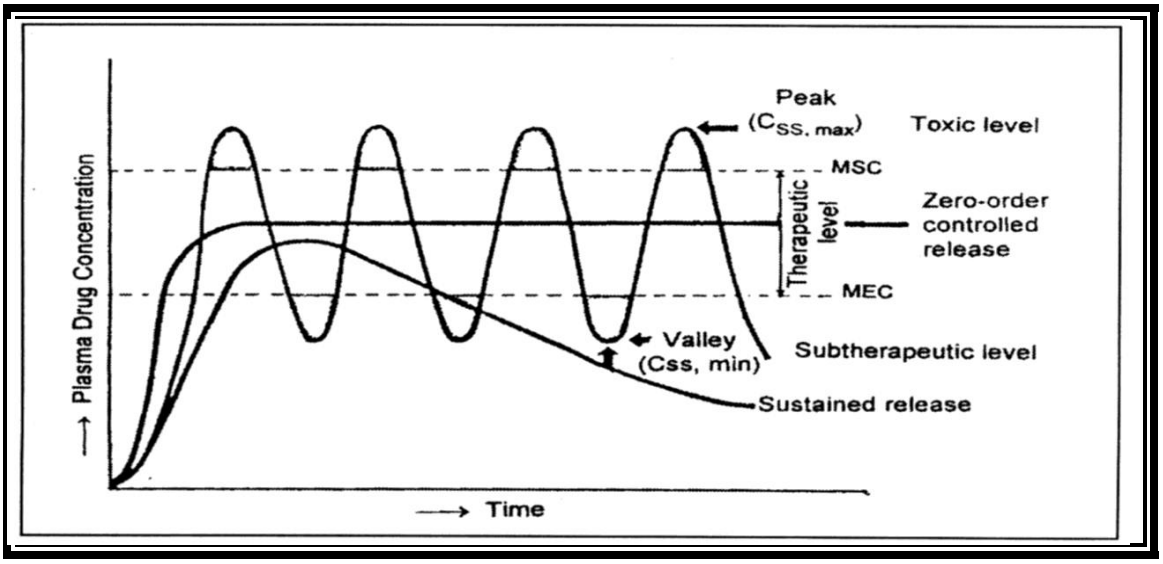


Figure1.1 PLASMA LEVEL PROFILES FOLLOWING CONVENTIONAL AND CONTROLLED RELEASE DOSING.

A significant milestone in oral NDDS is the development of the osmotic drug delivery system, an innovative and highly versatile drug delivery system. Osmotic drug delivery systems utilize the principle of osmotic pressure, as an energy source, for the delivery of drugs. Oral osmotic drug delivery systems with their versatility and their highly predictable drug release rates offer various biomedical advantages. Osmosis is an aristocratic phenomenon that seizes the attention for its exploitation in zero-order drug delivery systems. The drug delivered from these systems is independent of pH and the physiological conditions. Optimizing semipermeable membrane and the osmotic agents can modulate drug release from the system.

Nisoldipine is 3-methyl-5-(2-methylpropyl) ester-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid and a dihydropyridine calcium-channel blocker, used in the treatment of cardiovascular disorders, such as hypertension, angina, and cardiac arrhythmia. The average terminal half-life of nisoldipine is 7 to 12 hours. The standard formulation undergoes rapid absorption and extensive hepatic biotransformation. This necessitates a twice daily dosage regimen which is inconvenient for maintenance therapy in asymptomatic patients [4]. An alternative formulation of nisoldipine has been needed to develop in an attempt to reduce the frequency of daily dosing.

Thus osmotic formulation of Nisoldipine was decided to prepare which provides zero order drug release up to 24 hours and there by helpful in chronic cardio vascular disease.

The controlled porosity osmotic pump (CPOP) formulations provide following advantages over other approaches for oral controlled drug delivery such as:

1. CPOP is Easy to formulate and simple in operation.
2. It is possible to attain better release rates than those obtained with conventional diffusion based controlled drug delivery systems.
3. Cost for manufacturing is low compare to other approaches.

Thus in present work attempt has been made to design, develop and characterisation of OCDDS formulation of Nisoldipine.

The design of experiment approach was also utilized to optimize systematically the formulation & process parameters influencing drug release.

The optimized batches was selected on the basis of

I. 10 % drug should release at 1st hour.
II. 30 % drug should release at 6 th hour.
III. 50 % drug should release at 12 th hour.
IV. 100 % drug should release at 24 th hour.
V. It should follow zero order kinetic for drug release.

Chapter 2

Introduction

2. INTRODUCTION

2.1 Introduction to osmotically controlled drug delivery system (OCDDS)

2.1.1 Introduction [42]

A number of design options are available to control or modulate the drug release from a dosage form. Majority of oral dosage form fall in the category of matrix, reservoir or osmotic system. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded\coated by the rate controlling membrane. However factors like pH, presence of food and other physiological condition may affect drug release from conventional controlled release systems.

Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semipermeable membrane coat.

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property of a solution and dependent on the solubility and molecular weight and activity coefficient of the solute (osmogent).

Van't Hoff and Morse equation describing osmotic pressure:

$$\prod V = nRT$$

Where, $\prod$ - osmotic pressure in atmosphere.

V - Volume of solution in liters

n - Number of moles of solute

R - Gas constant, (0.082 Latm/molK)

T - Absolute temperature in K

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

$$dv/dt = A Q \Delta \pi / L$$

Where, dv\dt - water flow across the membrane of area A in cm^2,

L - Thickness,

Q - Permeability

$\Delta \pi$ - The osmotic pressure difference between the two solutions on either Side of the membrane.

2.1.2 Advantages

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

2.1.3 Key parameters that influence the design of osmotic controlled drug delivery systems [42]

a) Orifice size

b) Solubility of drugs

c) Osmotic pressure

d) Semipermeable membrane

a) Orifice size

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice.

Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure build up in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values [29, 30]

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

- **Mechanical drill**
- **Laser drill:** This technology is well established for producing sub-millimetre size hole in tablets. Normally, CO_2 laser beam (with output wavelength of 10.6µ) is used for drilling purpose, which offers excellent reliability characteristics at low costs.
- **Indentation that is not covered during the coating process:** Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.

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

b) Solubility of drug

The release rate depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery.

In the case of low solubility compounds, the approaches can be divided into two categories.

- Swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension.
- The drug solubility can be modified employing different methods such as co compression of the drug with other excipients, which improve the solubility
  For example, cyclodextrin can be included in the formulation to enhance drug solubility. Additionally, alternative salt forms of the drug can be employed to modulate solubility.

c) Osmotic pressure

The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure.

d) Semipermeable membrane

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

2.1.4 Basic components of osmotic systems

a) Drug

b) Semipermeable membrane

c) Osmotic agent

d) Flux regulating agent

e) Wicking agent

f) Pore forming agent

g) Coating solvent

h) Plasticizers

a) Drug

Having short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems.

b) Semipermeable membrane

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation.

The membrane should possess certain characteristics, such as

1. The material must posses sufficient wet strength (-105) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
2. The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
3. The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
4. The membrane should also be biocompatible.
5. Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. E.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits.

c) Osmotic agent

Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers.

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

TABLE 2.1 OSMOTIC PRESSURES OF SATURATED SOLUTION OF COMMONLY USED OSMOGENTS [3]

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

d) Flux regulating agent

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux. Hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate) tend to decrease the flux.

e) Wicking agent

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area.

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

f) Pore forming agent

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These pore forming agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore-former by its leaching during the operation of the system.The pore formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose,

mannose, lactose, sorbitol, mannitol and, diols and polyols such as poly hyric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

g) Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials.

The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohal, butyl alcohal, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc.

h) Plasticizer

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change viscoelastic behaviour of polymers and these changes may affect the permeability of the polymeric films.

Some of the plasticizers used are polyethylene glycols ethylene glycol monoacetate, and diacetate, tri ethyl citrate, diethyl tartarate.

2.1.3 Osmotically controlled drug delivery can be developed by various approaches such as:

- Elementary osmotic pump (EOP)
- Push Pull Osmotic Pump (PPOP)
- Controlled Porosity Osmotic Pump (CPOP)
- Osmotic Bursting Osmotic Pump
- Liquid Oral Osmotic System (L-OROS)
- Sandwiched Osmotic Tablets (SOTS)
- Multiparticulate Delayed-Release System
- Monolithic Osmotic System
- Colon Targeted Oral Osmotic System (OROS-CT)
- Osmotic Matrix Tablet (OSMAT)

Elementary osmotic pump (EOP)[1][2][3]:

An EOP is the most basic device made up of a compressed tablet. The EOP consists of an osmotic core with the drug, surrounded by a semipermeable membrane. The semipermeable membrane is provided with a hole for the controlled delivery of the saturated solution of the drug formed as a result of imbibition of water whose rate is determined by the fluid permeability of the membrane and the osmotic pressure of the compressed tablet when the dosage form is placed in the aqueous environment. Though 60% to 80% of drug is released at a constant rate from EOP, a lag time of 30 to 60 minutes is observed in most of the cases as the system hydrates before zero-order delivery from the system begins

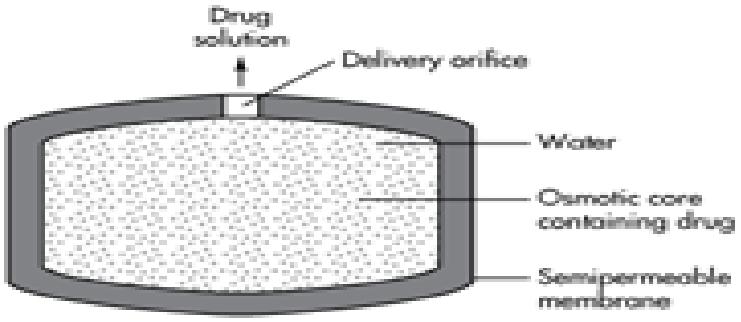


Figure2.1 ELEMENTARY OSMOTIC PUMP TABLET

Push-Pull Osmotic Pump (PPOP) [1][2][3]:

It is a bilayer tablet coated with semi permeable membrane. The PPOP system consists of two compartments separated usually by an elastic diaphragm. The upper compartment contains the drug and is connected to the outside environment via a small delivery orifice a swellable polymer osmotic agent is present in the lower compartment, accounting for around 20-40 per cent of the tablet. The upper layer consists of drug and the delivery orifice, and accounts for 60-80 per cent of tablet weight. PPOP can be used to deliver drugs with extremes of water solubility.

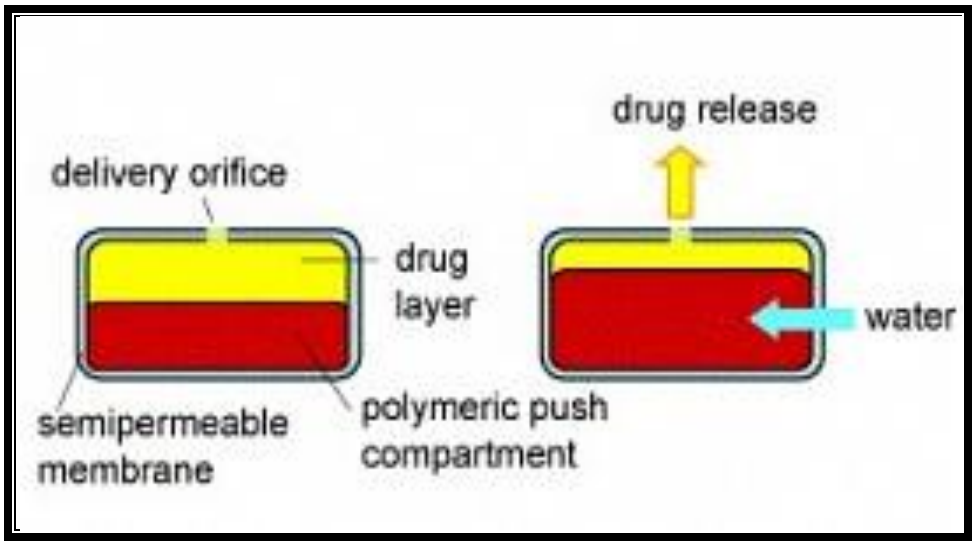


Figure2.2 PUSH-PULL OSMOTIC PUMP TABLET

Controlled Porosity Osmotic Pump (CPOP) [1][2][3]:

A controlled porosity osmotic pump-based drug delivery system 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, controlled porosity of the membrane is accomplished by the use of different channeling agents in the coating.

The CPOP contains water soluble additives in coating membrane, which after coming in contact with water; dissolve resulting in an in-situ formation of a microporous membrane. Generally, materials producing from 5 to 95% pores with a pore size from 10A - 100µm can be used. Then the resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role.

Drug delivery from asymmetric membrane capsule is principally controlled by the osmotic pressure of the core formation. In-situ formed delivery orifice in the asymmetric membrane in mainly responsible for the solubilization in the core for a drug with poor water solubility.

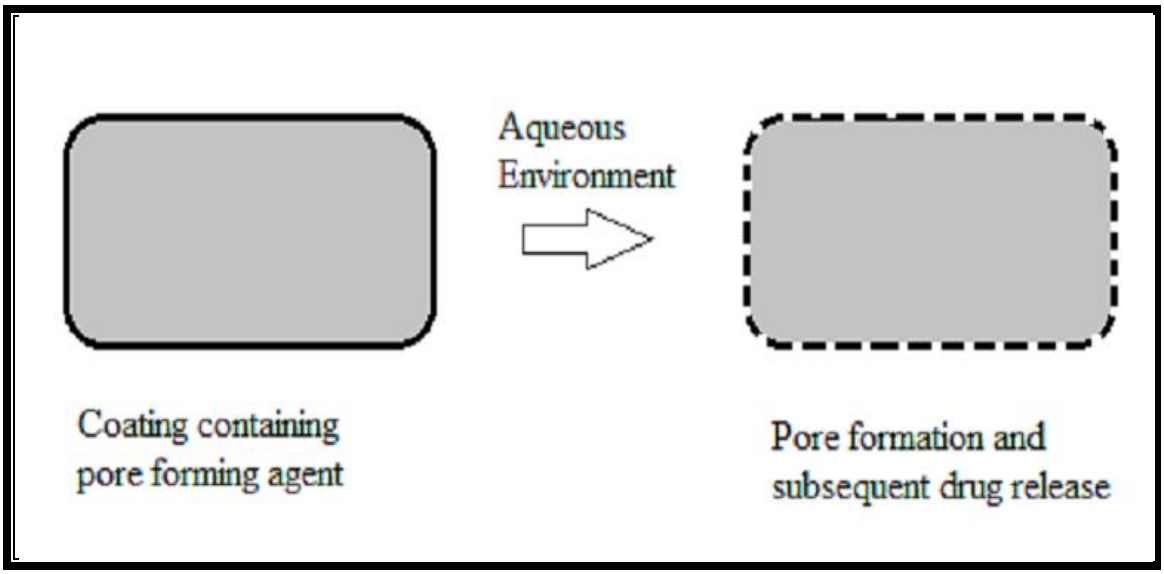
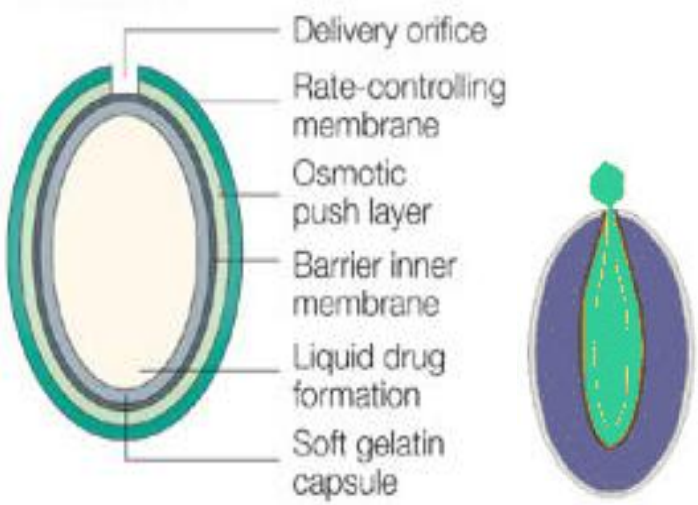


Figure2.3 CONTROLLED POROSITY OSMOTIC PUMP TABLET.

Osmotic Bursting Osmotic Pump [1][2][3]: This system is similar to an EOP expect delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release.

Liquid Oral Osmotic System (L-OROS) [1][2][3]:

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



Before Operation **During Operation**

Figure2.4 LIQUID ORAL OSMOTIC SYSTEM.

Sandwiched Osmotic Tablets (SOTS) [1][2][3]:

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

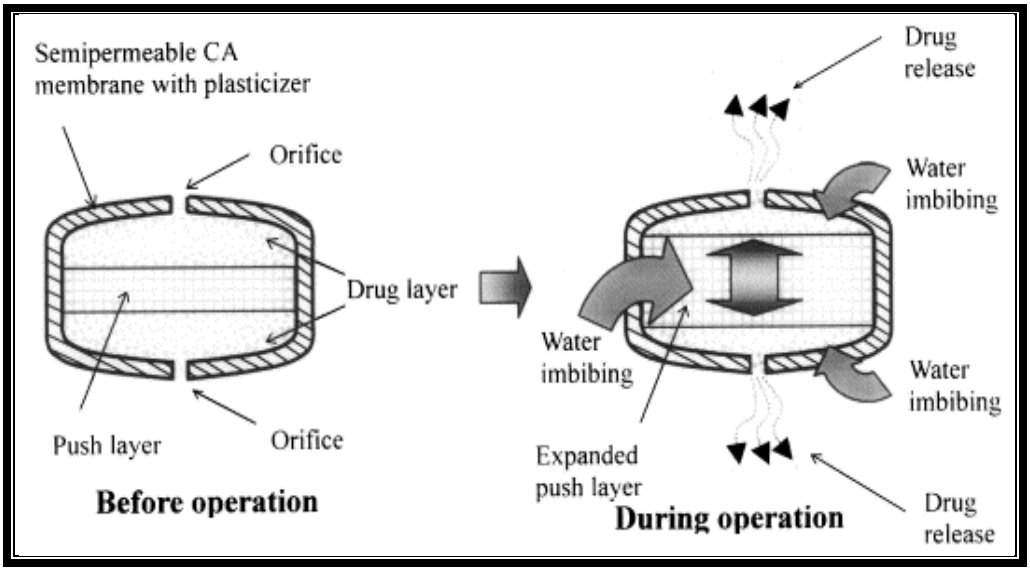


Figure2.5 SANDWICHED OSMOTIC TABLETS.

Multiparticulate Delayed-Release System [1][2][3]:

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.

Monolithic Osmotic System [1][2][3]:

It constitutes a simple dispersion of a water-soluble agent in a polymeric matrix. When the system comes in contact with the aqueous environment, water imbibitions by the active agent takes place rupturing the polymeric matrix capsule surrounding the drug, thus liberating 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.

Colon Targeted Oral Osmotic System (OROS-CT) [1][2][3]:

OROS-CT is used as once or twice a day formulation for targeted delivery of drugs to the colon. It is a system with 5-6 enteric-coated push-pull osmotic units filled in hard gelatin capsule for targeted colonic drug delivery. After coming in contact with GI fluids, the gelatin capsule dissolves and the enteric coating prevents the entry of fluids from stomach into the system As the OROS-CT system enters into the small intestine, the enteric coating dissolves and water is imbibed into the core, thereby causing the push compartment to swell. At the same time, flow-able gel is formed in the drug compartment, which is pushed out of the orifice at the rate precisely controlled by the rate of water transport across the semi-permeable membrane. About 80% of the drug is delivered to the large intestine by OROS-CT.

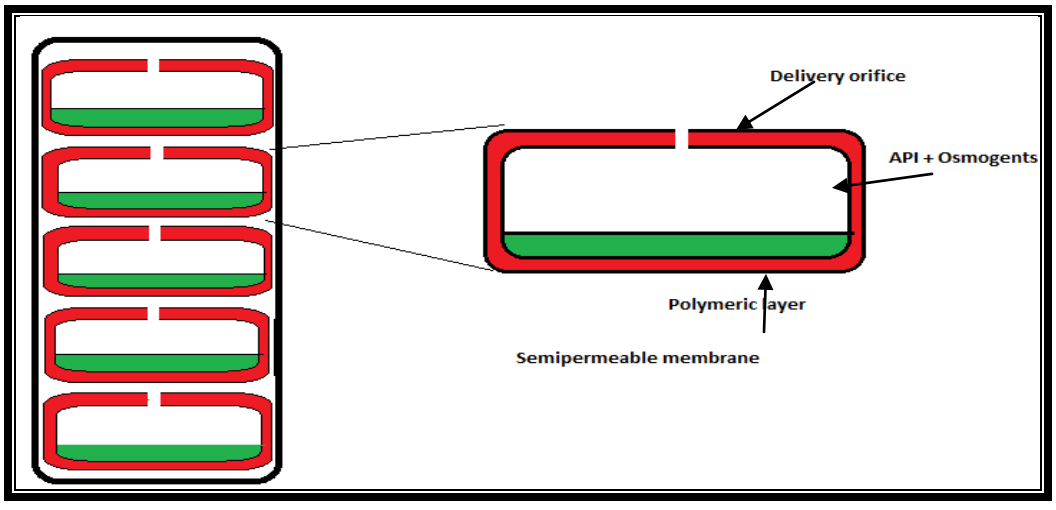


Figure2.6 COLON TARGETED ORAL OSMOTIC SYSTEM.

Osmotic Matrix Tablet (OSMAT) [1][2][3]:

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

2.1.4 Evaluation

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

A. In Vitro Evaluation

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

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

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

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

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

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

.

B. In Vivo Evaluation

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

2.2 INTRODUCTIONS TO DISSOLUTION ENHANCEMENT

2.2.1 INTRODUCTION

When the osmotic tablet comes in contact with gastrointestinal tract, fluid enters into the preparation and dissolves the active material in the core. Thus, the pressure formed in the preparation induces a release of the solution at a slow but continuous rate. To ensure the delivery of drug from the osmotic system, osmotically active agents called osmogents are used for drugs with low osmotic pressure and solubilizing agents for the drugs having low solubility.[20]

Nisoldipine is practically in soluble in water so solubility of drug should be increased for successful delivery of drug by CPOP.

Enhancement of solubility, dissolution rate and bioavailability of drug is a very challenging task in drug development, nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the in vivo efficacy. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility and dissolution properties of drugs play an important role in the process of formulation development. Problem of solubility is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work.

2.2.2 TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are [21]

1) PHYSICAL MODIFICATIONS

Particle size reduction

- Micronization
- Nanosuspension
- Sonocrystalisation
- Supercritical fluid process

Modification of the crystal habit

- Polymorphs
- Pseudopolymorphs

Drug dispersion in carriers

- Eutectic mixtures
- Solid dispersions
- Solid solutions

Complexation

- Use of complexing agents

Solubilization by surfactants:

- Microemulsions
- Self microemulsifying drug delivery systems

2) CHEMICAL MODIFICATIONS

3) OTHER METHODS

- Cocrystalisation
- Cosolvency
- Hydrotrophy
- Solvent deposition
- Selective adsorption on insoluble carrier
- Use of soluble prodrug
- Functional polymer technology
- Porous microparticle technology
- Nanotechnology approaches

COMPLEXATION

Complexation is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

Inclusion complexation: [22]

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced. Cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability. Cyclodextrins are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Cyclodextrin molecules are relatively large with a number of hydrogen donors and acceptors and, thus, in general they do not permeate lipophilic membranes.

Structure of cyclodexrine[22]

Cyclodextrine are a group of structurally related natural products formed during bacterial digestion of cellulose. These cyclic oligosaccharides consist of (α-1, 4)-linked α-D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface. Due to the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders. The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl Cyclodextrins groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity is lined by the skeletal carbons and ethereal oxygens of the glucose residues, which gives it a lipophilic character. The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution. The natural α-, β- and γ-Cyclodextrin consist of six, seven, and eight glucopyranose units, respectively. The natural Cyclodextrins, in particular β-

Cyclodextrin, are of limited aqueous solubility meaning that complexes resulting from interaction of lipophiles with these Cyclodextrin can be of limited solubility resulting in precipitation of solid Cyclodextrin complexes from water and other aqueous systems. In fact, the aqueous solubility of the natural Cyclodextrins is much lower than that of comparable acyclic saccharides. This is thought to be due to relatively strong intermolecular hydrogen bonding in the crystal state. Substitution of any of the hydrogen bond forming hydroxyl groups, even by lipophilic methoxy functions, results in dramatic improvement in their aqueous solubility. Cyclodextrin derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β- and γ-Cyclodextrin, the randomly methylated β-Cyclodextrin, sulfobutylether β-Cyclodextrin, and the so-called branched Cyclodextrins such as glucosyl-β-cCclodextrin.

TABLE 2.2 CHARACTERISTIC OF CYCLODEXTRINS

Characteristics	**α**	**β**	**γ**	**δ**
Number of glucopyranose unit	6	7	8	9
Molecular weight	92	1135	1297	1459
Central cavity diameter	4.7 – 5.3	6.0 – 6.5	7.5 – 8.3	10.3 – 11.2
Water solubility	14.5	1.85	23.2	8.19

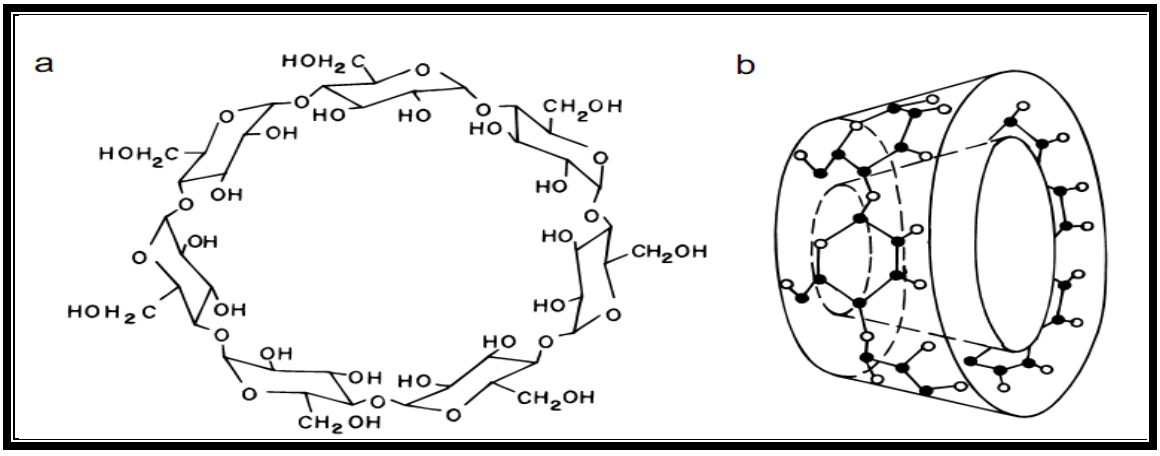


Figure2.7 (a) THE CHEMICAL STRUCTURE AND (b) THE TOROIDAL SHAPE OF THE β-CYCLODEXTRINE MOLECULE.

APPROACHES FOR MAKING INCLUSION COMPLEXES

Physical blending method:

A solid physical mixture of drug and Cyclodextrin are prepared simply by mechanical trituration. In laboratory scale Cyclodextrin and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product.

Kneading method: [23]

This method is based on impregnating the Cyclodextrin with little amount of water or hydroalcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required.

Co-precipitation technique: [24]

This method involves the co-precipitation of drug and Cyclodextrin in a complex. In this method, required amount of drug is added to the solution of Cyclodextrin. The system is kept under magnetic agitation with controlled process parameters and the content is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

Solution/solvent evaporation method: [25]

This method involves dissolving of the drug and Cyclodextrin separately in to two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid powdered inclusion compound. Generally, the aqueous solution of Cyclodextrin is simply added to the alcoholic solution of drugs. The resulting mixture is stirred for 24 hours and evaporated under vacuum at 45 °C. The dried mass was pulverized and passed through a 60-mesh sieve. This method is quite simple and economic both on laboratory and large scale production and is considered alternative to the spray drying technique.

Neutralization precipitation method: [26]

This method is based on the precipitation of inclusion compounds by neutralization technique and consists of dissolving the drug in alkaline solutions like sodium/ammonium hydroxide and mixing with an aqueous solution of Cyclodextrin. The resultant clear solution is then neutralized under agitation using HCl solution till reaching the equivalence point. A white precipitate is being formed at this moment, corresponding to the formation of the inclusion compound. This precipitate is filtered and dried.

Atomization/Spray drying method: [27] Spray-drying is a common technique used in pharmaceuticals to produce a dry powder from a liquid phase. Another application is its use as a preservation method, increasing the storage stability due to the water elimination. This method represents one of the most employed methods to produce the inclusion complex starting from a solution. The mixture pass to a fast elimination system propitiate solvent and shows a high efficiency in forming complex. Besides, the product obtained by this method yield the particles in the controlled manner which in turn improves the dissolution rate of drug in complex form.

Lyophilization/ Freeze drying technique: [28] In order to get a porous, amorphous powder with high degree of interaction between drug & Cyclodextrin, lyophilization/ freeze drying technique is considered as a suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & Cyclodextrin at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique are considered as an alternative to solvent evaporation and involve molecular mixing of drug
and carrier in a common solvent.

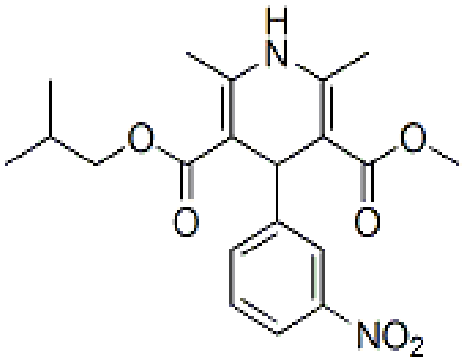
2.3 Introduction to Nisoldipine

2.3.1 Introduction

IUPAC Name: 3-methyl-5-(2-methylpropyl) ester-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)- 3,5-pyridinedicarboxylic acid

Empirical formula: $C_{20}H_{21}D_3N_2O_6$

Structural formula:



Molecular Weight: 388.414 g/mol

Brands: Sular

Melting point: 150 -155 ^{0}C

Solubility: Freely soluble- ethanol

Slightly soluble- n-butanol, acetone, 0.01M potassium dihydrogen phosphate.

2.3.2 Pharmacology

Mechanism of action:

Nisoldipine is a member of the dihydropyridine class of calcium channel antagonists (calcium ion antagonists or slow channel blockers) that inhibit the transmembrane influx of calcium into vascular smooth muscle and cardiac muscle. It reversibly competes with other dihydropyridines for binding to the calcium channel. Because the contractile process of vascular smooth muscle is dependent upon the movement of extracellular calcium into the muscle through specific ion channels, inhibition of the calcium channel results in dilation of the arterioles. In vitro studies show that the effects of nisoldipine on contractile processes are selective, with greater potency on vascular smooth muscle than on cardiac muscle. Although, like other dihydropyridine calcium channel blockers, nisoldipine has negative inotropic effects in vitro. The effect of nisoldipine on blood pressure is principally a consequence of a dose related decrease of peripheral vascular resistance. While nisoldipine, like other dihydropyridines, exhibits a mild diuretic effect, most of the antihypertensive activity is attributed to its effect on peripheral vascular resistance, studies conducted in intact anesthetized animals have shown that the vasodilating effect occurs as doses lower than those that affect cardiac contractility

Pharmacodynamics:

Administration of a single dose of nisoldipine leads to decreased systemic vascular resistance and blood pressure with a transient increase in heart rate. The change in heart rate is greater with immediate release nisoldipine preparations. The effect on blood pressure is directly related to the initial degree of elevation above normal. Chronic administration of nisoldipine results in a sustained decrease in vascular resistance and small increases in stroke index and left ventricular ejection fraction. A study of the immediate release formulation showed no effect of nisoldipine on the renin-angiotensin-aldosterone system or on plasma norepinephrine concentration in normals.

Nisoldipine does not appear to have significant negative inotropic activity in intact animals or humans, and did not lead to worsening of clinical heart failure in three small studies of patients with asymptomatic and symptomatic left ventricular dysfunction.

Pharmacokinetics

Absorption

Bioavailability

Relatively well absorbed from the GI tract following oral administration, with peak plasma concentrations attained within 6–12 hours. Absolute bioavailability is low (about 5%), due to presystemic metabolism in the intestine; presystemic metabolism decreases from proximal to distal parts of intestine. Bioavailability of extended-release preparation is increased since nisoldipine is released in the colon where presystemic metabolism is reduced.

Food

A high-fat meal increases peak plasma concentrations by about 300%, but decreases extent of absorption by 25% (since more of the drug is released proximally).

Special Populations

In geriatric patients, plasma concentrations increased about 2- to 3-fold. In patients with hepatic cirrhosis, plasma concentrations increased by 4–5 times.

Distribution

Extent

Not known whether nisoldipine is distributed into milk.

Plasma Protein Binding: >99%.

Elimination

Metabolism

Thought to be metabolized principally by CYP isoenzymes. Precise enzymes responsible for metabolism are unknown, but other dihydropyridine-derivative calcium-channel blocking agents are metabolized by CYP3A4.

Elimination Route: Excreted principally in urine (60–80%) as metabolites.

Half-life: Approximately 7–12 hours.

Indication:

Nisoldipine, a dihydropyridine calcium-channel blocker, is used to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina.

Contraindications

Nisoldipine is contraindicated in patients with known hypersensitivity to dihydropyridine calcium channel blockers.

Precautions

Hypotension

Because Nisoldipine, like other vasodilators, decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of Nisoldipine is recommended. Close observation is especially important for patients already taking medications that are known to lower blood pressure. Although in most patients the hypotensive effect of Nisoldipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment.

Congestive Heart Failure

Although acute hemodynamic studies of Nisoldipine in patients with NYHA Class II-IV heart failure have no demonstrated negative inotropic effects, safety of Nisoldipine in patients with heart failure has not been established. Caution therefore should be exercised

when using Nisoldipine in patients with heart failure or compromised ventricular function, particularly in combination with a beta-blocker.

Patients with Hepatic Impairment

Because Nisoldipine is extensively metabolized by the liver and, in patients with cirrhosis, it reaches blood concentrations about 5 times those in normal, Nisoldipine should be administered cautiously in patients with severe hepatic dysfunction.

Common Adverse Effects

Peripheral edema, headache, dizziness, pharyngitis, vasodilation, sinusitis, palpitation, chest pain, nausea, rash**.**

Body As A Whole: Cellulitis, chills, facial edema, fever, flu syndrome, malaise

Cardiovascular: Atrial fibrillation, cerebrovascular accident, congestive heart failure, first degree AV block, hypertension, hypotension, jugular venous distension, migraine, myocardial infarction, postural hypotension, ventricular extrasystoles, supraventricular tachycardia, syncope, systolic ejection murmur, T wave abnormalities on ECG (flattening, inversion, nonspecific changes), venous insufficiency

Digestive: abnormal liver function tests, anorexia, colitis, diarrhea, dry mouth, dyspepsia, dysphagia, flatulence, gastritis, gastrointestinal hemorrhage, gingival hyperplasia, glossitis, hepatomegaly, increased appetite, melena, mouth ulceration

Endocrine: diabetes mellitus, thyroiditis

Hemic and Lymphatic: anemia, ecchymoses, leukopenia, petechiae

Metabolic and Nutritional: gout, hypokalemia, increased serum creatine kinase, increased nonprotein nitrogen, weight gain, weight loss.

Musculoskeletal: arthralgia, arthritis, leg cramps, myalgia, myasthenia, myositis, tenosynovitis

Nervous: abnormal dreams, abnormal thinking and confusion, amnesia, anxiety, ataxia, cerebral ischemia, decreased libido, depression, hypesthesia, hypertonia, insomnia, nervousness, paresthesia, somnolence, tremor, vertigo

Respiratory: asthma, dyspnea, end inspiratory wheeze and fine rales, epistaxis, increased cough, laryngitis, pharyngitis, pleural effusion, rhinitis, sinusitis

Skin and Appendages: acne, alopecia, dry skin, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes zoster, maculopapular rash, pruritus, pustular rash, skin discoloration, skin ulcer, sweating, urticaria

Special Senses: abnormal vision, amblyopia, blepharitis, conjunctivitis, ear pain, glaucoma, itchy eyes, keratoconjunctivitis, otitis media, retinal detachment, tinnitus, watery eyes, taste disturbance, temporary unilateral loss of vision, vitreous floater

Urogenital: dysuria, hematuria, impotence, nocturia, urinary frequency, increased BUN and serum creatinine, vaginal hemorrhage, vaginitis

The following post marketing event has been reported very rarely in patients receiving Nisoldipine: systemic hypersensitivity reaction which may include one or more of the angioedema, shortness of breath, tachycardia, chest tightness, hypotension, and rash. A definite causal relationship with Nisoldipine has not been established. An unusual event observed with immediate release Nisoldipine but not observed with Nisoldipine was one case of photosensitivity. Gynecomastia has been associated with the use of calcium channel blockers.

Over dosage

There is no experience with Nisoldipine over dosage. Generally, over dosage with other dihydropyridines leading to pronounced hypotension calls for active cardiovascular support including monitoring of cardiovascular and respiratory function, elevation of extremities, judicious use of calcium infusion, pressure agents and fluids. Clearance of Nisoldipine would be expected to be slowed in patients with impaired liver function.

Since Nisoldipine is highly protein bound, dialysis is not likely to be of any benefit; however, plasmapheresis may be beneficial.

Dosage and administration

The dosage of Nisoldipine must be adjusted to each patient's needs. Therapy usually should be initiated with 17 mg orally once daily, and then increased by 8.5 mg per week or longer intervals, to attain adequate control of blood pressure. Usual maintenance dosage is 17 to 34 mg once daily. Blood pressure response increases over the 8.5 - 34 mg daily dose range but adverse event rates also increase. Doses beyond 34 mg once daily are not recommended. Nisoldipine has been used safely with diuretics, ACE inhibitors, and beta-blocking agents. Patients over age 65 or patients with impaired liver function are expected to develop higher plasma concentrations of Nisoldipine. Their blood pressure should be monitored closely during any dosage adjustment. A starting dose not exceeding 8.5 mg daily is recommended in these patient groups. Nisoldipine tablets should be administered orally once daily. Nisoldipine should be taken on an empty stomach (1 hour before or 2 hours after a meal). Grapefruit products should be avoided before and after dosing. Nisoldipine is an extended release dosage form and tablets should be swallowed whole, not bitten, divided or crushed.

Nisoldipine Dosing Information

Usual Adult Dose for Angina Pectoris Prophylaxis:

Slow release (old formulation):
Initial dose: 20 mg orally once a day
Maintenance dose: 10 to 60 mg orally once a day

Controlled release (new formulation):
Initial dose: 17 mg orally once a day
Maintenance dose: 8.5 to 34 mg orally once a day

Usual Adult Dose for Hypertension:

Slow release (old formulation):
Initial dose: 20 mg orally once a day
Maintenance dose: 10 to 60 mg orally once a day

Controlled release (new formulation):
Initial dose: 17 mg orally once a day
Maintenance dose: 8.5 to 34 mg orally once a day

Usual Geriatric Dose for Angina Pectoris Prophylaxis:

Slow release (old formulation);
Initial dose: 10 mg orally once a day
Maintenance dose: 10 to 60 mg orally once a day

Controlled release (new formulation):
Initial dose: 8.5 mg orally once a day
Maintenance dose: 8.5 to 34 mg orally once a day

Blood pressure should be monitored closely during any dosage adjustment.

Usual Geriatric Dose for Hypertension:

Slow release (old formulation);
Initial dose: 10 mg orally once a day
Maintenance dose: 10 to 60 mg orally once a day

Controlled release (new formulation):
Initial dose: 8.5 mg orally once a day
Maintenance dose: 8.5 to 34 mg orally once a day
Blood pressure should be monitored closely during any dosage adjustment

Interactions for Nisoldipine

Drugs Affecting Hepatic Microsomal Enzymes

Inducers of CYP3A4: Decreased plasma nisoldipine concentrations. Avoid concomitant use.

Specific Drugs and Foods

TABLE 2.3 DRUG FOOD INTERACTION

Drug or Food	Interaction	Comments
β-Adrenergic blocking agents	Increased risk of hypotension and exacerbation of CHF	
Digoxin	Pharmacokinetic interaction unlikely	
Grapefruit juice	Increased nisoldipine bioavailability	Avoid grapefruit-containing foods and beverages for at least 1 hour before and after administration of a dose
Histamine H_2-receptor antagonists	Possible increased nisoldipine concentrations with cimetidine; no significant interaction with ranitidine	
Phenytoin	Decreased plasma concentrations of nisoldipine to undetectable levels	Avoid concomitant use
Quinidine	Possible decreased AUC of nisoldipine	Clinical significance unknown
Warfarin	Pharmacokinetic interaction unlikely	

2.4 INTRODUCTION TO POLYMERS

2.4.1 Cellulose Acetate [5]

Functional category:

Coating agent; extended release agent; tablet and capsule diluent.

Solubility:

The solubility of cellulose acetate is greatly influenced by the level of acetyl groups present.

In general, cellulose acetates are soluble in acetone–water blends of varying ratios, Dichloromethane–ethanol blends, dimethyl formamide, and dioxane.

Viscosity (dynamic):

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

Various grades

TABLE 2.3 COMPARISONS OF DIFFERENT TYPES OF CELLULOSE ACETATE

Type	Acetyl (%)	Viscosity (mPa s)	Hydroxyl (%)	Melting range (°C)	*Tg* (°C)	Density (g/cm3)	MWn
CA-320S	32.0	210.0	8.7	230–250	180	0.4	38 000
CA-398-3	39.8	11.4	3.5	230–250		0.4	30 000
CA-398-6	39.8	22.8	3.5	230–250		0.4	35 000
CA-398-10NF	39.8	38.0	3.5	230–250		0.4	40 000
CA-398-30	39.5	114.0	3.5	230–250		0.4	50 000
CA-394-60S	39.7	228.0	4.0	240–260			60 000
CA-435-75	43.5	-	0.9	280–300		0.7	122 000

Application

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

2.5.1 β -cyclodextrin [22]

Synonyms: β cycloamylose, β -dextrin, Cavamox W7 Pharma, Cyclo-heptamaylose, kleptose

Chemical Formula: $C_{42}H_{70}O_{35}$

Molecular structure: as shown in Figure number 2.7

Melting point: 255-265 $^{\circ}C$

Density (bulk):0.523g/cm^3

Compressibility: 21-44%

Density (tapped):0.754.

Moisture content: 13-15%w/w.

Particle size distribution: 7-45μm.

Solubility: Soluble 1 in 50 of water at 20°C, 1 in 20 at 50°C, practically insoluble in acetone, ethanol(95%) and methylene chloride.

Chapter 3

Literature review

3.1 Review of work done on osmotic controlled drug delivery

Edavalath et al.[6] developed controlled porosity osmotic pump tablets of Diclofenac sodium. Osmotic agent sodium chloride and pore former PEG 400 was considered as independent variables. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through osmosis. The increase in concentration of pore former and osmotic agent after a limit, changes the release from zero order to Higuchi based release. 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 optimized formulation which demonstrates the feasibility of the optimization procedure in successful development of porous osmotic pump tablets containing Diclofenac sodium (100mg) by using sodium chloride (100mg) as osmotic agent and 20%w/w (with 80% w/w cellulose acetate) of PEG 400 as pore former. Stability studies revealed that optimized formulation is stable.

Lin et al.[7] develop a micropore-controlled release tablet for Theophylline. The tablets were composed of a drug core surrounded by a microporous film. The major components of coating film included a biocompatible semipermeable polymer, cellulose acetate, and a water soluble pore-forming agent, poly(ethylene glycol). The effect of the coating film composition and the type of excipient incorporated in the drug core on drug release were demonstrated via an *in vitro* release study. The optimized formulation was further investigated *in vivo* of rabbits. The results showed that micropore-controlled release tablets continuously released drug for 24-36 hours depending on the type of excipient in the drug core and the coating film composition. Incorporation of lactose in the drug core enhanced drug release from micropore controlled release tablets. *In vivo* animal study revealed that the micropore-controlled release tablets reduced the maximum concentration and prolonged the mean residence time of drug.

Hou et al.[8] developed controlled porosity osmotic pump system with biphasic release of theophylline for the nocturnal therapy of asthma. The developed system was composed of a tablet-in-tablet (TNT) core and a controlled porosity coating membrane. Release pattern of the developed system was influenced by amount of pore former (18.2-45.5%, w/w of polymer), weight gain (16-26 mg per tablet) of the coating membrane and osmotic agents used in inner layer of the TNT core. When sodium phosphate and sodium chloride were selected as the osmotic agents in inner and outer layer of the TNT core respectively, target release profile was obtained with coating solution cellulose acetate–polyethylene glycol 400–diethyl phthalate (54.5–36.4–9.1%, w/w) at a weight gain of 16-22 mg per tablet. To examine the mechanism of drug release, release profiles of osmotic agents, micro-environmental osmotic pressure and micro-environmental pH of the formulation during dissolution were studied. Microenvironmental osmotic pressure and microenvironmental pH of the developed formulation were proved to be two dominant factors for the biphasic release. The first slow theophylline release was dominated by the osmotic pressure originated from the dissolution of sodium chloride. By adjusting the components of the TNT core, this osmotic pump system may be applicable for the biphasic delivery of other drugs.

Parth et al.[9] develop controlled porosity osmotic tablets of Propranolol HCl which will deliver the drug at zero order for 12hour. Core tablet of Propranolol hydrochloride was prepared using sodium chloride, PVP K30, MCC, talc & Mg. stearate; and the tablets of selected batch was coated with coating solution containing different proportions of cellulose acetate, sodium chloride, castor oil and PEG400 and evaluated for in vitro drug release studies. The observed result revels that osmotic agent and pore former have significant effect on drug release up to 12h. In successful development of micro porous osmotic pump tablets containing Propranolol Hydrochloride by using sodium chloride and PEG400 as key excipients.

Kapoor D. et al.[10] developed controlled porosity osmotic pump of Valsartan. The drug selected for this study, Valsartan, has low water solubility and hence is unable to create osmotic pressure to cause drug release. To augment the solubility and its osmotic pressure, this study was conducted with a solubility enhancer HPMC (Hydroxy propyl methyl cellulose), PEG-6000 and osmogents KCl. Valsartan has a short plasma half life of 3-5 h. Hence, Valsartan was chosen as a model drug with an aspire to develop a controlled porosity system for periods of 9 hours. This system was found to deliver Valsartan at a zero order rate for 9 hours.

Kumaravelrajan et al.[11] 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.

Kanagale et al.[12] developed controlled porosity osmotic pump for controlled release of Oxybutynin. The porous osmotic pump contains pore-forming water-soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a microporous structure. The dosage regimen of oxybutynin is one 5-mg tablet 2 to 3 times a day. The plasma half-life ranges from ~2 to 3 hours. Hence, oxybutynin was chosen as a model drug with an aim to develop a controlled release system for a period of 24 hours. Linear and reproducible release similar to that of Ditropan XL was achieved for optimized formulation independent of hydrodynamic conditions. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain, and level of pore former on the in vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. It was found that drug release rate increased with the amount of osmogent because of the increased water uptake, and hence increased driving force for drug release. Oxybutynin release was inversely proportional to the membrane weight gain; however, directly related to the level of pore former, sorbitol, in the membrane. This system was found to deliver oxybutynin at a zero-order rate for 20 hours. The effect of pH on drug release was also studied

Mahalaxmi.R et al[13] developed extended release controlled porosity osmotic pump formulations of model drug Glipizide using a wicking agent and a solubilizing agent. Glipizide osmotic tablets were evaluated for their flow properties, weight variation, hardness, friability and content uniformity. The effect of different formulation variables like level of wicking agent, solubilizing agent, level of pore former and membrane weight gain on *in vitro* release were studied. Drug release was found to be affected by the level of wicking agent and solubilizing agent in the core. Glipizide release from controlled porosity osmotic pump was directly proportional to the pore former (sorbitol) and inversely proportional to membrane weight gain. Drug release from the developed formulations was independent of pH and agitational intensity and was dependent on osmotic pressure of the release media. The optimized formulation was
also found to stable upon stability studies.

3.2 Review of work done on calcium channel blocker

Y.-B. Huang et al.[14] optimize the pH-dependent release of Nicardipine hydrochloride extended release formulations by using simultaneously combination two hydrophilic polymers: hydroxypropyl methylcellulose (HPMC) and sodium alginate as retardant and avicel as additive. The drug release percent at 3, 6 and 12 h were the target responses and were restricted to 10–30% (*Y*3 h), 40–65% (*Y*6 h)and not less than 80% (*Y*12 h), respectively. The results showed that the effect of combination of HPMC and sodium alginate was the most influence factor on the drug release from extended-release matrix tablets. The release kinetic of drug from HPMC matrix tablets with alginate was followed the zero-order release pattern.

Deters et al.[15] developed push-pull osmotic pump with immediate release coat comprising a member selected from the group consisting of Nicardipine and its pharmaceutically acceptable salts for administering to a patient in need of cardio-vascular therapy to provide immediate Nicardipine therapy over a prolonged period of time up to 24 hours

Roy et al.[16] develop and characterize an oral sustained release matrix tablet of complexed Nicardipine Hydrochloride by employing hydrophilic and hydrophilic polymers. Due to poor water solubility of the drug its bioavailability is dissolution rate limited. The purpose of the study was to increase the solubility of Nicardipine by Cyclodextrin inclusion complex technique. Complexes of different molar ratio were prepared. Kneading method was employed for preparation of inclusion complexes. Among different complexes, a complex with 1:1 molar ratio of drug and β- Cyclodextrin showed the highest dissolution rate. Matrix tablets were prepared by direct compression technique using different concentration of polymers and selected complex. The *invitro* dissolution study was carried out in acidic medium (pH 1.2) for 2 hrs, followed by phosphate buffer dissolution medium (pH 6.8) for next 12 hrs. The *invitro* release pattern indicated that optimized formulation was good releasing the drug for period of 12 hrs and was best fitted to Higuchi release profile.

J. Webster et al.[4] studied a novel formulation of Nicardipine (25% standard, 75% sustained release-SR) was evaluated in mild hypertension in a double-blind, randomized, placebo controlled comparison with standard Nicardipine (STD), using clinic measurements (Hawksley)augmented by home recorded blood pressures (Copal UA 251). At 2 h after dosing (peak effect) both STD Nicardipine (30 mg three times daily) and SR Nicardipine (60 mg twice daily) for 28 days produced a highly significant reduction in sitting and standing blood pressure. The mean sitting blood pressure was reduced by 20/16 mm Hg (STD) and by 25/18 mm Hg (SR) compared with placebo. Pre dose (8-11 h after last dose of STD, 12-15 h after last dose of SR) the reductions in sitting blood pressure relative to placebo were 11/6 mm Hg (STD) and 14/7 mm Hg (SR). Home recordings confirmed the hypotensive effect of both formulations. Both exhibited a distinct 'peak dose' effect between 1-3 h after dosing. The effect of the SR formulation was sustained throughout the 12 h dosing interval. Of the 60 patier .s entering the study, one died of unexplained staphylococcal septicaema, two -withdrawn for non drug-related reasons and 14 (32%) were withdrawn because of adverse effects on active therapy (headaches, facial flushing, leg oedema, chest pain, dizziness). In the 43 patients who completed the study adverse symptoms were reported more frequently while they were on the two active formulations of Nicardipine compared with placebo. Most of these reactions were again of vasodilator origin. This sustained release formulation of Nicardipine is an effective anithypertensive and may be more convenient for patients than the equivalent dose of the standard formulation. However, at the fixed doses used in this study, both are characterized by a significant incidence of adverse effects.

3.3 Review of work done on cellulose acetate, ethyl cellulose

Vavia et al.[17] developed Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine: I. Cellulose acetate as a semipermeable membrane. Different channelling 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. It 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 channelling agent in order to achieve the desired zero order release profile. Also the lag time seen with tablets coated using diethylphthalate as channelling 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.

Sunada et al.[18] evaluated the release *in vitro* and the absorption *in vivo* for elementary osmotic pump tablet (EOPT) of Captopril In the drug release study *in vitro*, the influences of the tablet formulation variables, the amount of NaCl, Hydroxypropyl methylcellulose K15 (HPMCK15), microcrystalline cellulose (MCC) in the core, the concentration of cellulose acetate (CA), dibutylphthalate (DBP), and polyethylene glycol 400 (PEG-400) in the coating solution have been investigated. It was found that the drug release was mostly affected by the amount of NaCl, HPMCK15, and MCC in the core, and the amount of PEG-400 in the coating solution. To a certain extent, drug release was less affected by the orifice size, concentration of coating solution, and the coating weight.

N. Ramakrishna et al[19]**.** compared the performance of cellulose acetate (CA) and ethylcellulose (EC)–HPMC combination coatings as semipermeable membranes (SPMs) for osmotic pump tablets (OPTs) of naproxen sodium (NPS) so as to deliver a constant, predetermined amount of drug in solution form over a fixed span of time, independent of external environmental conditions. Osmotic pump tablets were designed with different coating variables and optimized in terms of nature of plasticizer, membrane thickness, and orifice diameter. Osmotic pump tablets composed of membranes with water-soluble plasticizer, propyleneglycol (PG), released drug mainly through diffusion, whereas those designed with CA and EC–HPMC (4:1) coats containing water-insoluble plasticizer, castor oil, released their contents by perfect zero-order kinetics over a prolonged period of time, though the average release rate that could be achieved with the EC–HPMC (4:1) membrane was only about half the rate achieved with the CA membrane for the same membrane thickness. Release rates for both the membranes decreased with increasing membrane thickness and were found to be independent of orifice diameter, agitation intensity, and pH of
the dissolution medium.

Bajaj A.N. et al.[20] oral monolithic osmotic system for highly water-soluble pramipexole dihydrochloride monohydrate. Monolithic osmotic system was developed using controlled porosity membrane, this system delivers drug in controlled manner for prolonged period of time. Controlled porosity osmotic membrane consists of cellulose acetate as coating polymer and water-soluble pore formers, which forms an in-situ microporous membrane after imbibing water, hence no laser drilling is required. Pore formation was controlled by varying concentration of pore forming agents to get controlled release of pramipexole for period of 24 hrs. Scanning electron microscopy was carried out to confirm the microporous structure. An optimized system was selected to study the effect of different concentration of coating polymer, osmotic agents, pH of dissolution media and effect of agitation on the release of drug. From in vitro release studies it was evident that drug release was independent of pH and agitation but highly dependent on concentration of pore forming agents used. Increasing concentration of cellulose acetate from 2 % - 5 % w/v drastically retarded drug release.

3.4 Review of inclusion complex with Cyclodextrin

Sharma G.S. et al.[43] Has prepared the inclusion complex of Gliclazide and β-Cyclodextrin by different methods (physical mixture, kneading method and solvent evaporation method) in different molar ratios (1:1, 1:1.5 and 1:2) and Solubility studies for Gliclazide and β-Cyclodextrin were carried out which reveals that it follows B_S type profile. They conclude that complex prepared by solvent evaporation method at 1:2 molar ratio has faster dissolution rates when compared with all the other complexes.

Patel H.M. et al.[45] prepared inclusion complex of Etoricoxib with β-Cyclodextrin by kneading method. A drug β-Cyclodextrin interaction in solution was investigated by the phase solubility analysis. They concluded that the dissolution of Etoricoxib was notably increased as compared to pure drug as well as its physical mixture. They also proved that complex showed more than 75% drug released in 30 min.

Chandrakant D.S. et al.[46] Investigated the effect of β-Cylcodextrin and hydorxypropyl β-Cylcodextrin on the aqueous solubility and dissolution rate of Ramipril in order to develop a new oral dosage form of Ramipril with enhanced dissolution rate and bioavailability following Cyclodextrin complexation. Drug-Cyclodextrin solid systems were prepared by kneading method. The formation of inclusion complexes with β-Cylcodextrin in the solid state were confirmed by (FT-IR) Fourier transform infrared spectroscopy and differential scanning calorimetry and comparative studies and the in vitro dissolution were carried out. They prepared Solid inclusion complexes of Ramipril: β-Cyclodextrin in 1:1, 1:2, and 1:3 ratios. In vitro studies showed that the solubility and dissolution rate of Ramipril were significantly improved by complexation with β-Cyclodextrin with respect to pure drug alone. The phase solubility studies indicated the formation of 1:1 for both β-Cyclodextrin. The apparent stability constant Ks was found to be 308.692 m^{-1}. Solid complexes of Ramipril-β-Cyclodextrin at 1:2 ratio prepared by kneading method exhibited higher dissolution rate and dissolution efficiency values than the pure drug and other complexes. Tablet formulations prepared with Ramipril- β-Cyclodextrin 1:2 molar ratio prepared by kneading method exhibited faster dissolution rate and dissolution efficiency values.

Prameela Rani. A et al[44] Prepared inclusion complex of anti diabetic drugs that is Nateglinide, Repaglinide, and Glimepiride with β-Cyclodextrin and Hydroxy propyl β-Cyclodextrin and then the possibility of improving the solubility of these drugs by complexation were investigated. They performed phase solubility studies which shows the formation of Nateglinide- β-Cyclodextrin , Repaglinide- β-Cyclodextrin , Glimepiride- β-Cyclodextrin , Nateglinide- Hydroxy propyl β-Cyclodextrin , Repaglinide- Hydroxy propyl β-Cyclodextrin and Glimepiride- Hydroxy propyl β-Cyclodextrin inclusion complexes at 1:1 M ratio in solutions with stability constant of 345 M^{-1}, 267 M^{-1},329 M^{-1}, 433 M^{-1}, 319 M^{-1}, and 406 M^{-1} respectively. They conclude that the solubility was markedly enhanced by complexation with β-Cyclodextrin and Hydroxy propyl β-Cyclodextrin.

F. Veiga et al [26] prepared inclusion complexes of Tolbutamide with β-Cyclodextrin and Hydroxy propyl β-Cyclodextrin using different methods: kneading, coprecipitation and freeze-drying. Inclusion complexation in aqueous solution and in solid phase state was studied by the solubility method, X-ray diffractometry, thermal analysis and Raman spectroscopy. The solubility of Tolbutamide increased as a function of Cyclodextrin concentration, showing Bs and A_L type diagrams for with β-cyclodextrin and Hydroxy propyl β-Cyclodextrin, respectively. The dissolution rate of Tolbutamide/Cyclodextrin complexes were investigated and compared with those of the physical mixtures and pure drug. They concluded that, the dissolution rate of Tolbutamide from the inclusion complexes was much more rapid than Tolbutamide alone.

J.R. Moyano et al [27] they prepared inclusion complex of Oxazepam and β-Cyclodextrin. The value of the apparent stability constant, Kc, calculated using these techniques, was 205 and 498 M^{-1} respectively. Solid complexes of Oxazepam and β-Cyclodextrin were prepared using the kneading and spray-drying methods. These complexes led to an improvement in the dissolution rate over free Oxazepam, spray-drying being the most efficient technique.

Chapter 4

Experimental Work

4. EXPERIMENTAL WORK

4.1 MATERIALS AND EQUIPMENT USED

Materials used:

TABLE 4.1: LIST OF MATERIALS USED

Materials	Company name
Nisoldipine	Gifted by Zydus Cadila Health Care, Ahmedabad
Cellulose acetate	Oxford chemicals
PEG 400	Central Drug House Ltd., New Delhi
PVP K 30	S.D. Fine-Chem Ltd.,Baroda
Diethyl phthalate	S.D. Fine-ChemLtd.,Baroda
Dibutyl phthalate	S.D. Fine-ChemLtd.,Baroda
Methanol	Central Drug House Ltd., New Delhi
Isopropyl alchohol	ACS chemicals, Ahmedabad
Sodium dihydrogen phosphate	S.D. Fine-ChemLtd.,Baroda
Potassium dihydrogen phosphate	S.D. Fine-ChemLtd.,Baroda
Sodium chloride	S.D. Fine-ChemLtd.,Baroda
Potassium chloride	S.D. Fine-ChemLtd.,Baroda
Sodium hydroxide	S.D. Fine-ChemLtd.,Baroda
Mannitol	S.D. Fine-ChemLtd.,Baroda
Lactose	S.D. Fine-ChemLtd.,Baroda
Hydrochloric acid AR	S.D. Fine-ChemLtd.,Baroda

Equipment Used:

TABLE 4.2: LIST OF EQUIPMENTS USED

Equipments	Company name
Magnetic stirrer with hot plate	EIE Instrument Pvt Ltd., Ahmedabad
Tablet Coating Machine	Riemek, Karnavati Eng. Pvt. Ltd, Ahmedabad
Rotary tablet machine	Riemek, Karnavati Eng. Pvt. Ltd, Ahmedabad
Sonicator Bath	Trans-o-Sonic D-Compact, Ahmedabad
UV/VIS Double beam spectrophotometer	Shimdzu UV 1800 corporation, Japan
Dissolution test apparatus USP	Electrolab TDT-08L, Mumbai
Hot air oven	EIE Instruments Pvt. Ltd., Ahmedabad
pH meter	Analab scientific instruments, India.
FTIR	Jasco FTIR 6100 Type-A, Japan
Digital Balance	Citiweigh, Tejas exports, Ahmedabad
Thermonik Tablet Tester, DTH - 250	Campbell electronics, Mumbai
Friability tester	Roche friability tester

4.2 IDENTIFICATION OF NISOLDIPINE

4.2.1 Melting Point Determination

Description:

Melting point is the temperature at which the pure liquid and solid exist in the equilibrium. In the practice it is taken as equilibrium mixture at an external pressure of 1 atmosphere; this is sometime known as normal melting point. The thiel's tube method of melting point determination in liquid paraffin was used in the present study. Melting point was found to be 152 °C

TABLE 4.3: MELTING POINT DETERMINATION OF NISOLDIPINE

No	Reported Melting Point	Observed Melting Point
1	150-155 °C	152 °C

Result:

The melting point of Nisoldipine was found to be 152˚C.

Conclusion:

The melting point determined is within the range of standard value, hence, it is concluded that the drug sample having intimate physical property as standard drug.

4.2.2 FTIR Spectra

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

FIGURE 4.1: REFERENCE FTIR SPECTRA OF NISOLDIPINE

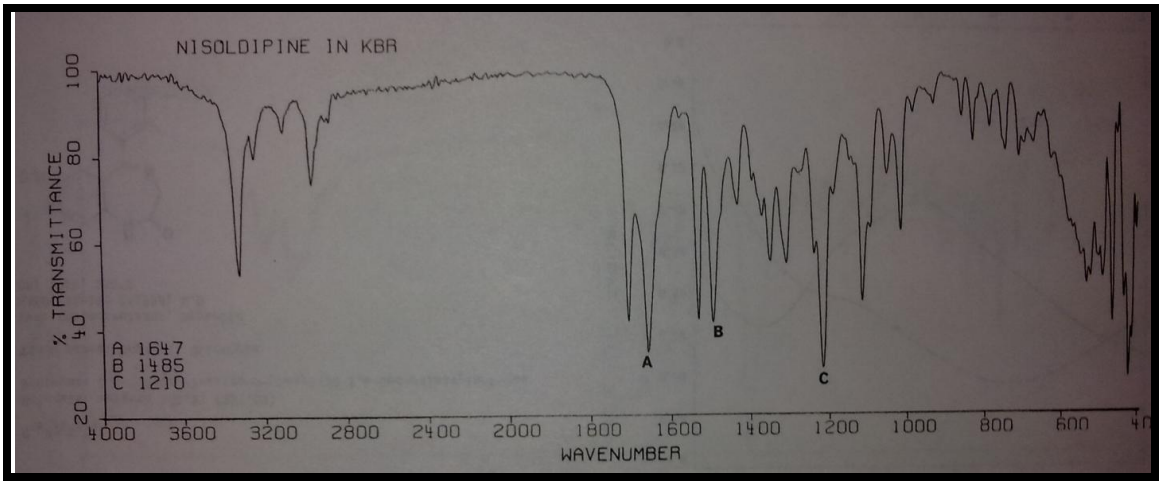


FIGURE 4.2: TEST FTIR SPECTRA OF NISOLDIPINE

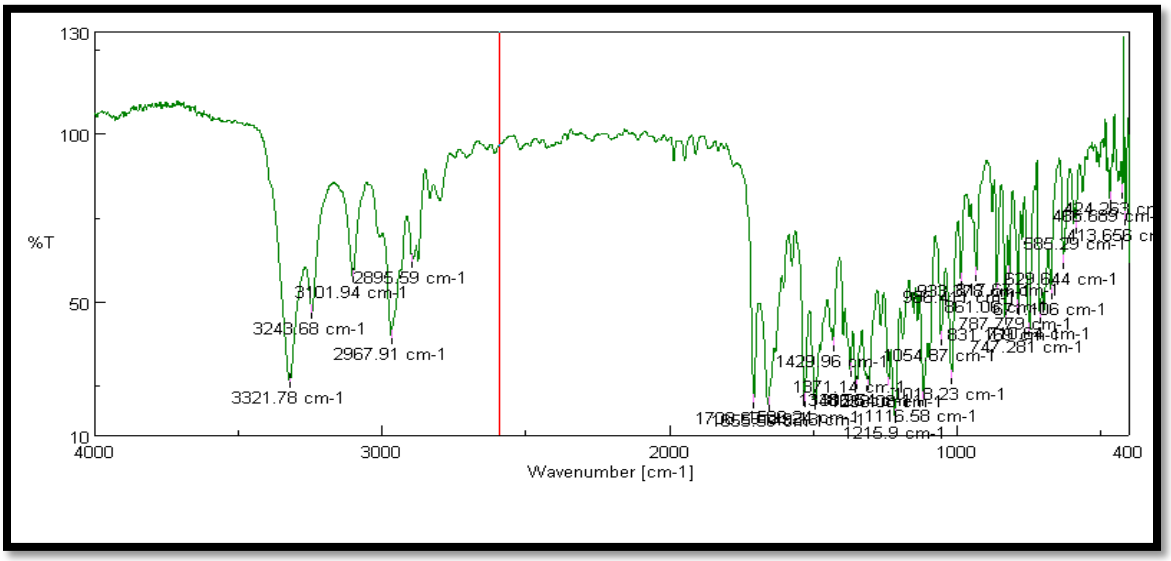


TABLE 4.4: COMPARISON OF REFERENCE AND TEST IR FREQUENCY OF NISOLDIPINE

Functional group	Standard frequency (cm^{-1})[33]	Observed frequency (cm^{-1})
N-H	3500 - 3100	3321.78
Sp^3 C-H	3100 - 3000	2967.68
Sp^2 C-H	3150 - 3050	3101.94
C=O	1750 - 1730	1706.69
N=O	1550 - 1350	1320.12

Discussion:

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

4.2.3 UV Absorbance Spectra

Powder of Nisoldipine equivalent to 5 mg was accurately weighed and transferred into the 100 ml volumetric flask and then volume was made using 0.1 N HCl containing 0.3% w/v SLS which give concentration of 50 µg/ml.

Then 20 ml of above stock solution (50 µg/ml) was taken in 50 ml volumetric flask. To this 50 ml of 0.1 N HCl was added. The resultant solution strength was found to be 20 µg/ml.

From the above (20 µg/ml) solution, 5 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark with 0.1 N HCl, resultant solution (10µg/ml) was scanned in the range of 200 nm to 400 nm using Shimadzu double beam UV/Visible spectrophotometer.

FIGURE 4.3: UV ABSORBANCE SPECTRA

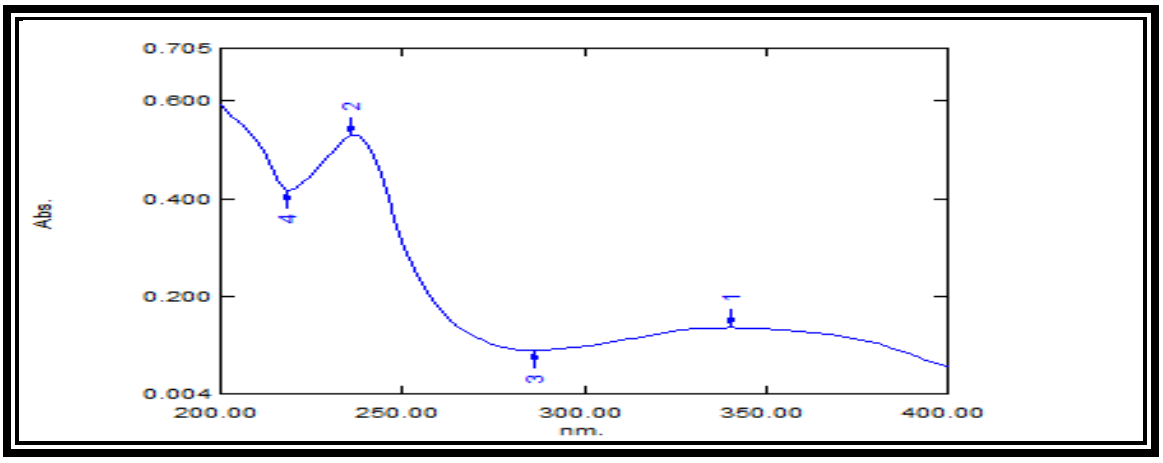


TABLE 4.5: PEAK POINTS OF NISOLDIPINE UV SPECTRA

Number	Wavelength(nm)	Absorbance
1	343	0.183
2	236	0.520
3	283	0.104
4	225	0.409

Discussion: The absorption maximum was found to be 236 nm and the absorbance value was 0.520.

4.3 ESTABLISHMENT OF CALIBRATION CURVE OF NISOLDIPINE IN DIFFRENT BUFFER SOLUTIONS

Preparation of reagents and solutions

a) Preparation of 0.1 N HCl

8.5 ml of concentrated hydrochloric acid was transferred to 1000ml volumetric flask. To this 300mg of SLS was added and diluted to 1000 ml with distilled water.

b) Preparation of pH 7.4 phosphate buffer

50 ml of 0.2 M sodium dihydrogen phosphate was transferred in a 200 ml volumetric flask, add 39.1 ml of 0.2 M sodium hydroxide was added and then volume was made up to the mark with distilled water .

c) Preparation of pH 6.8 phosphate buffer

50 ml of 0.2 M sodium dihydrogen phosphate phosphate was transferred in a 200 ml volumetric flask, add 22.4 ml of 0.2 M hydroxide was added and then volume was made up to the mark with distilled water .

d) Preparation of 0.2 M sodium dihydrogen phosphate solution

31.206 gm of sodium dihydrogen phosphate in distilled water was dissolved and diluted with distilled water to 1000 ml.

e) Preparation of 0.2 M sodium hydroxide solution

8.0 gm of sodium hydroxide in distilled water was dissolved and diluted with distilled water to 1000 ml.

g) Preparation of stock solution of drug

Accurately about 5 mg Nisoldipine drug was weighed and transferred to 100ml amber color volumetric flask, then drug was dissolved in 0.1 N HCl containing 0.3% W/V SLS so to get 50 µg/ml.

4.3.1 Establishment of calibration curve of Nisoldipine in 0.1 N hydrochloric acid

Preparation of stock solution

Accurately about 5 mg Nisoldipine drug was weighed and transferred to 100ml amber color volumetric flask, then drug was dissolved in 0.1 N HCl containing 0.3% W/V SLS so to get 50 µg/ml.

Then 20 ml of above stock solution (50 µg/ml) was taken in 50 ml volumetric flask. To this 50 ml of 0.1 N HCl was added. The resulting solution strength was 20 µg/ml.

Preparation of dilutions

From the stock solution (20 µg/ml) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ml transferred to 10 ml volumetric flask and diluted up to the mark with 0.1 HCl to give 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml concentration respectively. The absorbance of dilutions were measured at λ max 236 nm using Shimadzu double beam UV/Visible spectrophotometer in triplicate and the plot of average absorbance vs. concentration was established.

Figure 4.4 UV ABSORBANCE SPECTRA IN 0.1 N HCl (pH 1.2)

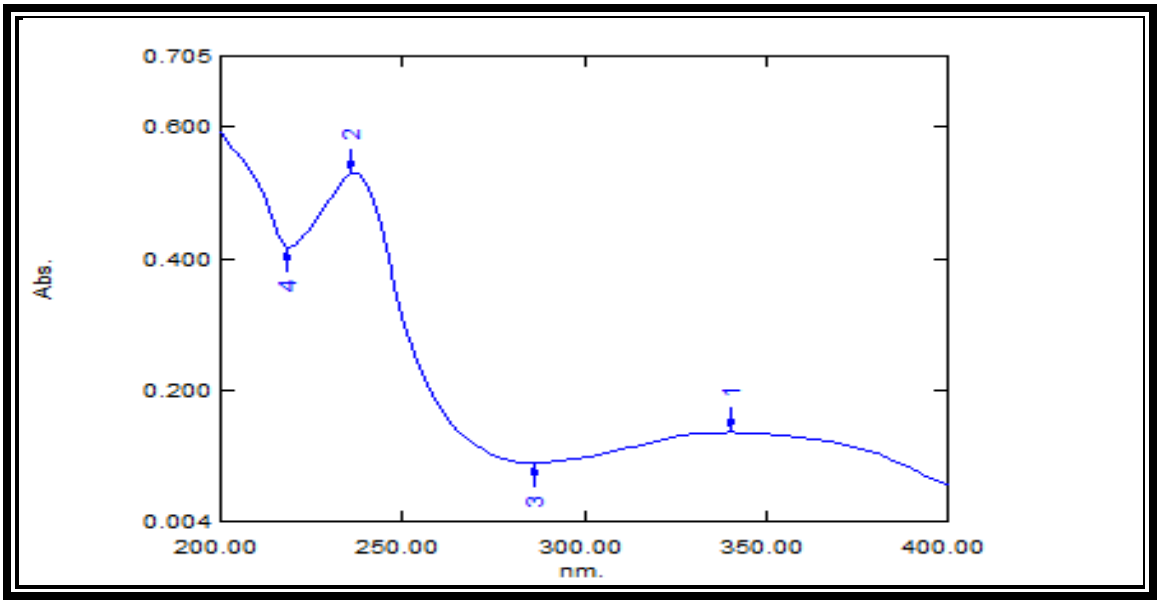
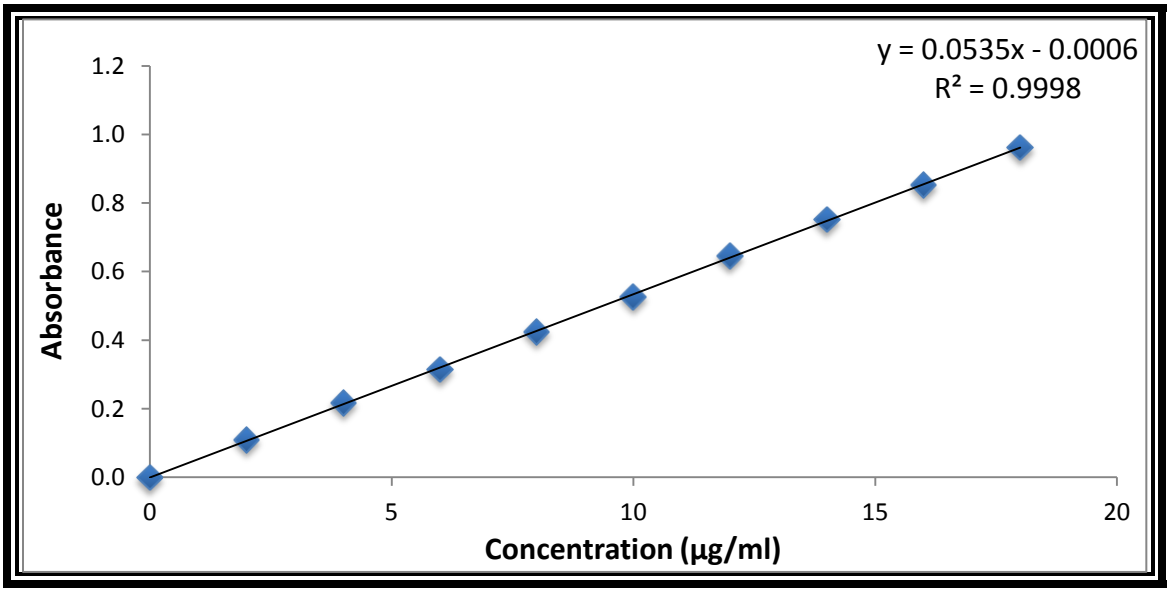


TABLE 4.6: STANDARD CURVE OF NISOLDIPINE IN 0.1 N HCl

Conc. (µg/ml)	Absorbance			Avg. Absorbance	Standard Deviation
	A1	A2	A3		
0	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.1001	0.1157	0.1129	0.1095	0.0083
4	0.2023	0.2250	0.2242	0.2171	0.0129
6	0.3011	0.3207	0.3228	0.3148	0.0120
8	0.4209	0.4353	0.4349	0.4236	0.0082
10	0.5215	0.5350	0.5328	0.5264	0.0072
12	0.6367	0.6524	0.6482	0.6457	0.0081
14	0.7417	0.7587	0.7586	0.7530	0.0098
16	0.8410	0.8593	0.8575	0.8526	0.0101
18	0.9540	0.9673	0.9682	0.9631	0.0080

Figure 4.5 STANDARD CURVE OF NISOLDIPINE IN 0.1 N HCl



Regression Analysis

TABLE 4.7: REGRESSION ANALYSIS FOR STANDARD CURVE OF NISOLDIPINE IN 0.1 N HCl

Regression parameter	Value
Correlation coefficient	0.9998
Slope	0.0535
Intercept	0.0006

4.3.2 Establishment of calibration curve of Nisoldipine in phosphate buffer pH 7.4

Preparation of stock solution

Procedure is same as given in section 4.3.1. Instead of taking 0.1 N HCl the phosphate buffer pH 7.4 was taken.

Preparation of dilutions

Procedure is same as given in section 4.3.1. Instead of taking 0.1 N HCl the phosphate buffer pH 7.4 was taken.

Figure 4.6 UV ABSORBANCE SPECTRA IN PHOSPHATE BUFFER (pH 7.4)

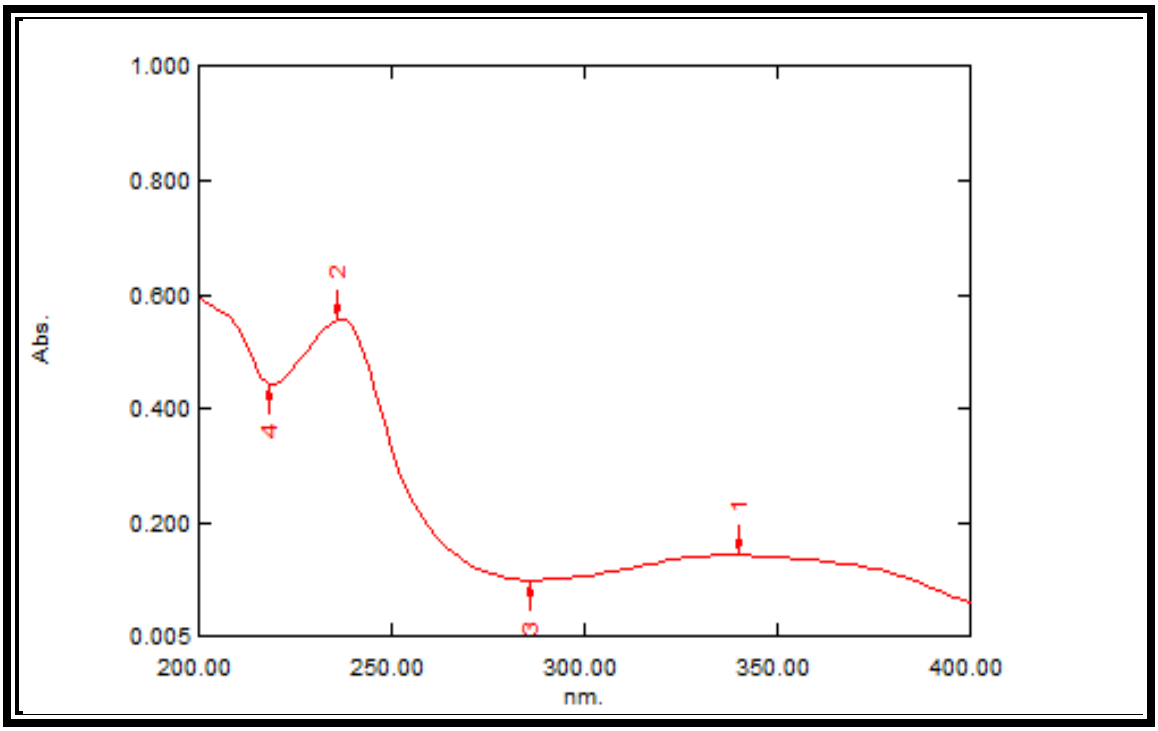
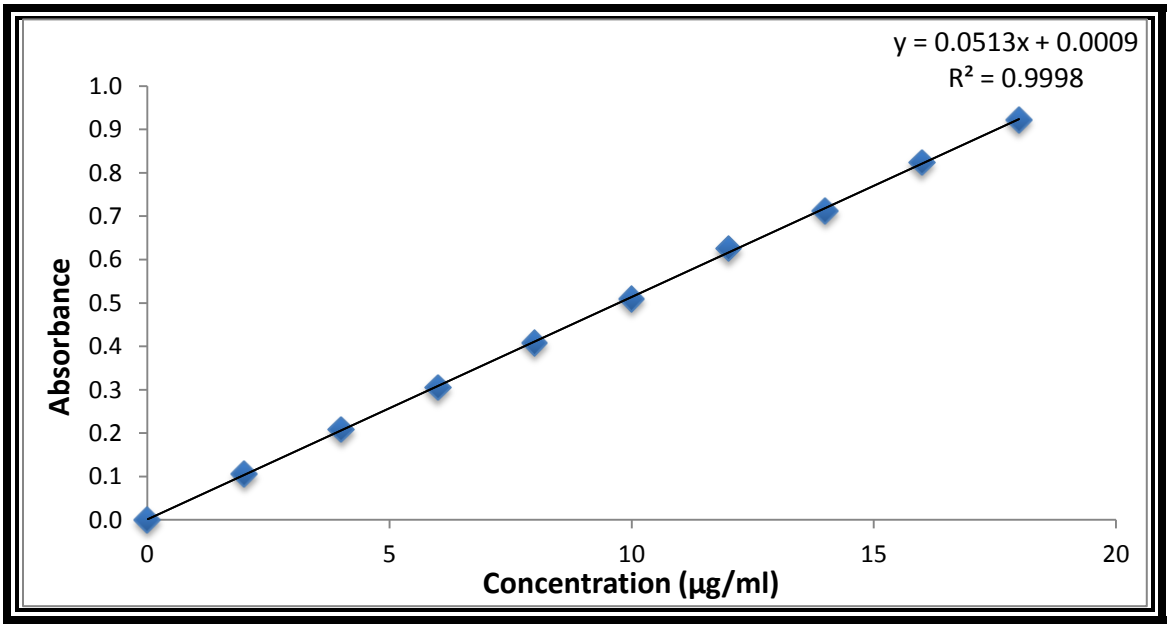


TABLE 4.8: STANDARD CURVE OF NISOLDIPINE IN PHOSPHATE BUFFER (pH 7.4)

Conc. (µg/ml)	Absorbance			Avg. Absorbance	Standard Deviation
	A1	A2	A3		
0	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.1058	0.1049	0.1056	0.1054	0.0005
4	0.2080	0.2086	0.2082	0.2083	0.0003
6	0.3034	0.3081	0.3054	0.3056	0.0024
8	0.4099	0.4033	0.4121	0.4084	0.0046
10	0.5176	0.5058	0.5072	0.5102	0.0064
12	0.6444	0.6104	0.6235	0.6261	0.0171
14	0.7278	0.7056	0.7048	0.7127	0.0131
16	0.8397	0.8082	0.8242	0.8240	0.0158
18	0.9420	0.9031	0.9226	0.9226	0.0195

Figure 4.7 STANDARD CURVE OF NISOLDIPINE IN PHOSPHATE BUFFER (pH 7.4)



Regression Analysis

TABLE 4.9: REGRESSION ANALYSIS FOR STANDARD CURVE OF NISOLDIPINE IN BUFFER pH 7.4

Regression parameter	Value
Correlation coefficient	0.9998
Slope	0.0513
Intercept	0.0009

4.3.3 Establishment of calibration curve of Nisoldipine in phosphate buffer pH 6.8

Preparation of stock solution

Procedure is same as given in section 4.3.1. Instead of taking 0.1 N HCl the phosphate buffer pH 6.8 was taken.

Preparation of dilutions

Procedure is same as given in section 4.3.1. Instead of taking 0.1 N HCl the phosphate buffer pH 6.8 was taken.

Figure 4.8 UV ABSORBANCE SPECTRA IN PHOSPHATE BUFFER (pH 6.8)

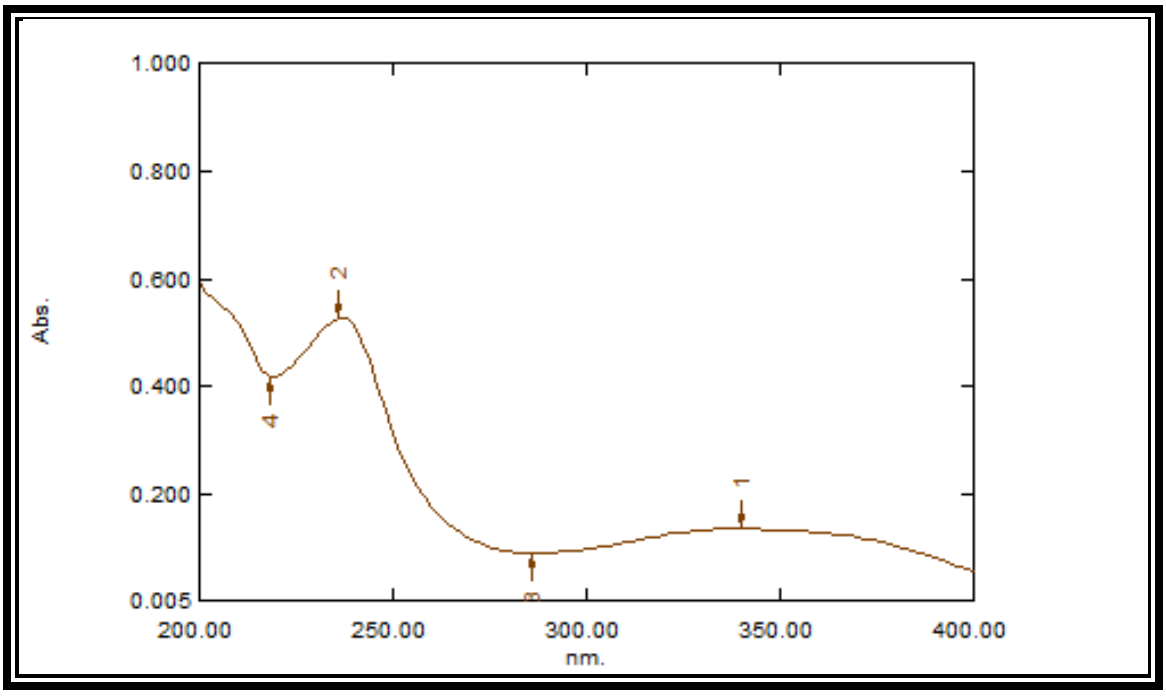
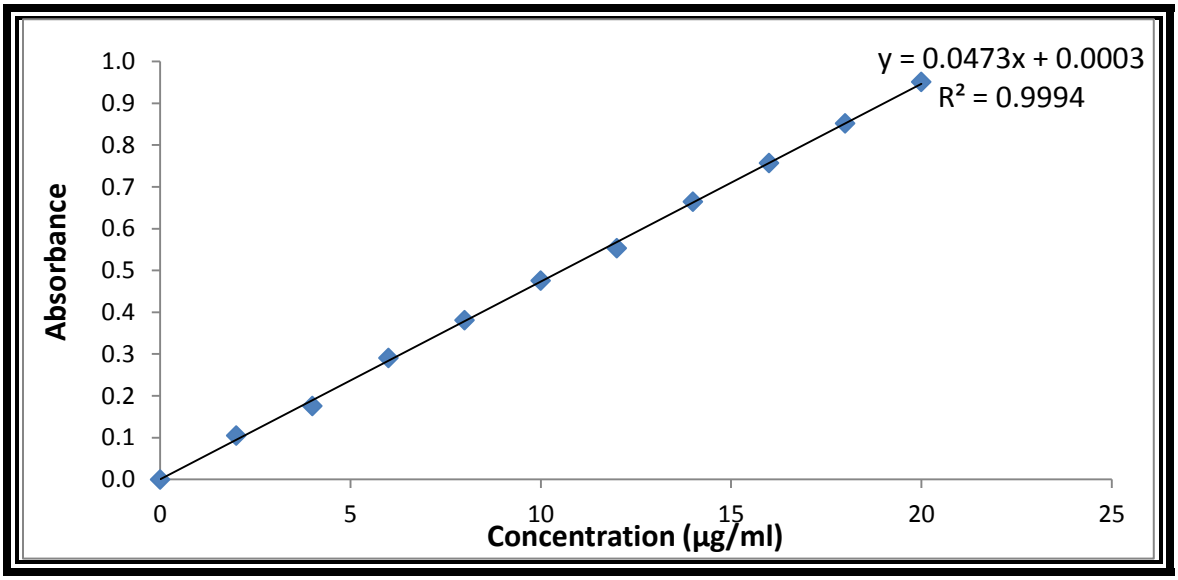


TABLE 4.10: STANDARD CURVE OF NISOLDIPINE IN PHOSPHATE BUFFER (pH 6.8)

Conc. (µg/ml)	Absorbance			Avg. Absorbance	Standard Deviation
	A1	A2	A3		
0	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.1045	0.1039	0.1072	0.1052	0.0018
4	0.1796	0.1689	0.1792	0.1759	0.0061
6	0.2819	0.2924	0.2983	0.2909	0.0083
8	0.3786	0.3892	0.3759	0.3812	0.0070
10	0.4789	0.4796	0.4693	0.4759	0.0058
12	0.5575	0.5489	0.5542	0.5535	0.0043
14	0.6687	0.6544	0.6712	0.6648	0.0091
16	0.7520	0.7533	0.7665	0.7573	0.0080
18	0.8461	0.8482	0.8623	0.8522	0.0088

Figure 4.9 STANDARD CURVE OF NISOLDIPINE IN PHOSPHATE BUFFER pH 6.8



Regression Analysis

TABLE 4.11: REGRESSION ANALYSIS FOR STANDARD CURVE OF NISOLDIPINE IN BUFFER pH 6.8

Regression parameter	Value
Correlation coefficient	0.9994
Slope	0.0473
Intercept	0.0003

4.4 DISSOLUTION ENHANCEMENT OF NISOLDIPINE

Dissolution study of pure drug

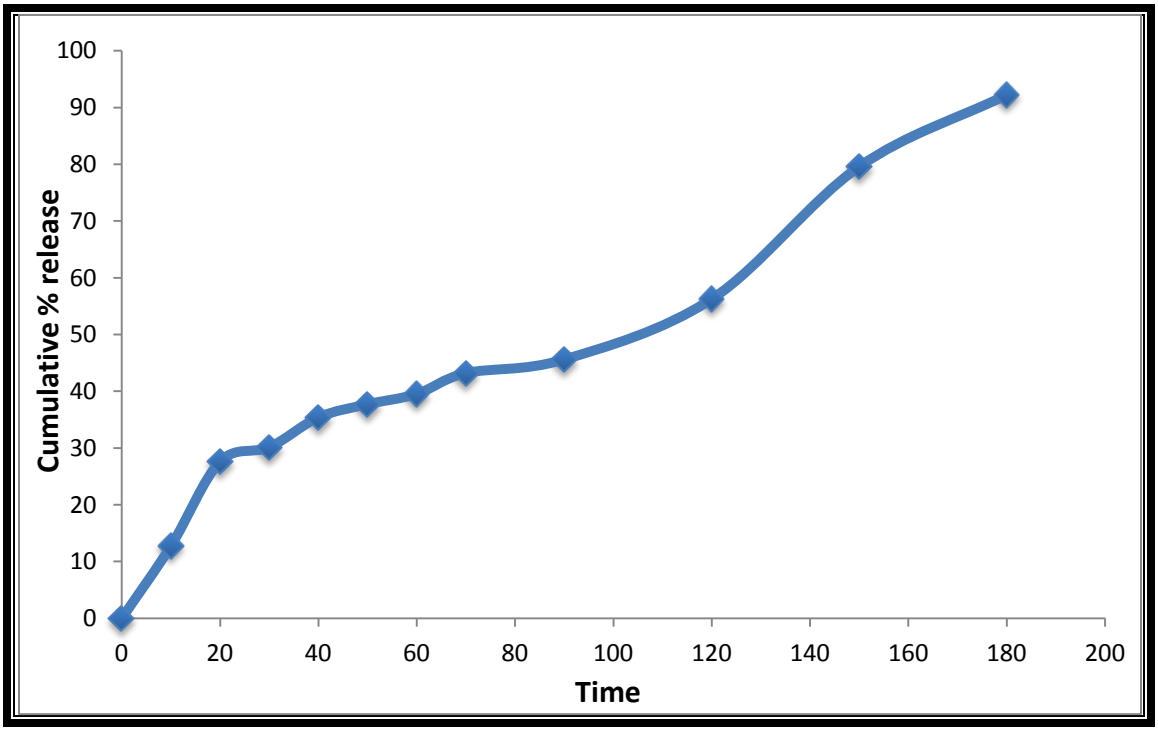
Nisoldipine is a poorly soluble drug, thus, in order to study the release behavior, the dissolution study was carried out in pH 7.4

Phosphate buffer (with 0.3 % w/v SLS) using USP Type I apparatus. The basket was covered with muslin cloth. The stirring speed was kept at 100 RPM and the temperature was maintained at $37 \pm 0.2^{\circ}C$ and volume of dissolution medium taken was 900 ml. The dissolution data are as shown in below table 4.12.

TABLE 4.12: IN VITRO RELEASE PROFILE OF PURE DRUG

Time (min)	Abs.	Con. (µg/ml)	mg/5ml	mg/900ml	Cumulative release	Cumulative % drug release
0	0	0.000	0.000	0.000	0.000	0.000
10	0.1127	2.398	0.012	2.158	2.169	12.759
20	0.2428	5.166	0.026	4.649	4.695	27.617
30	0.2638	5.613	0.028	5.051	5.123	30.134
40	0.3091	6.577	0.033	5.919	6.018	35.402
50	0.328	6.979	0.035	6.281	6.413	37.724
60	0.3422	7.281	0.036	6.553	6.720	39.529
70	0.3729	7.934	0.040	7.141	7.344	43.201
90	0.3922	8.345	0.042	7.510	7.753	45.608
120	0.4822	10.260	0.051	9.234	9.565	56.263
150	0.6834	14.540	0.073	13.08	13.532	79.599
180	0.7875	16.755	0.084	15.08	15.680	92.235

Figure 4.10 IN VITRO RELEASE PROFILE OF PURE DRUG



Result and discussion:

The dissolution profile of pure drug showed that it required about 3 – 4 hours for complete drug release. Thus, the dissolution study of pure drug (without dissolution enhancement) revealed that there is a need to enhance dissolution of nisoldipine in order to achieve better release profiles. Hence, the dissolution enhancement approach was opted in the present investigation before formulating its osmotic tablets.

In present investigation, the dissolution enhancement was carried out using β-cyclodextrin inclusion complex method.

4.4.1Dissolution enhancement of nisoldipine

The enhancement of solubility of Nisoldipine was tried using β-cyclodextrin. The inclusion complexes were prepared by two methods; kneading method and physical mixture.

4.4.2 Preparation of inclusion complexes of nisoldipine with β-cyclodextrine by kneading method:

The required quantity of β-cyclodextrin and Nisoldipine was weighed as per the molar ratio and was transferred in to glass mortar. The sufficient quantity of water was added in to mixture to form thick paste and mixture was kneaded for one hour and it was dried in desiccators till constant weight was obtained. The dried mass was sieved through 100 # sieve. The prepared inclusion complex powder was stored in the dessicator.

Evaluation of inclusion complex:

1) Percentage yield of the complex

The Nisoldipine - β-cyclodextrin complex obtained was weighed accurately and the percentage yield was calculated using the following equations.

$$\%\ \text{yield of complex} = \frac{\text{Final weight of complex obtained } \times 100}{\text{Initial weight of Nisoldipine and } \beta - \text{cyclodextrin}}$$

2) Percentage drug content

The Nisoldipine content of the Nisoldipine:β-cyclodextrin complex was determined by dissolving powder mixture equivalent to 5 mg of Nisoldipine in 100 ml volumetric flask containing 6.8 pH phosphate buffer and sonicated for 25 minutes and then measure the absorbance at 236 nm against respective blank.

$$\%\ \text{Nisoldipine content} = \frac{\text{Practical amount of drug analyzed } \times 100}{\text{Theoretical drug content}}$$

3) In- Vitro drug release:

In- vitro drug release studies were carried out using USP Type I (Basket type) dissolution test apparatus. The drug: β-cyclodextrin inclusion complex /physical mixture equivalent to 17 mg of nisoldipine was taken for the dissolution study and 900 ml of pH 6.8 phosphate buffer containing 0.3% SLS was used as dissolution medium. The stirring speed was kept at 100 RPM and the temperature was maintained at $37 \pm 0.2^{\circ}$C. 5 ml of sample was withdrawn at various time intervals and filtered through Whatman filter paper (0.7 µ size). The volume of dissolution medium was adjusted by replacing 5ml of dissolution medium after each sampling. The absorbance of each sample was measured at 236 nm and concentration of drug was calculated using standard curve equation.

4) FTIR Spectroscopy:

FTIR spectrum of β-cyclodextrin and Nisoldipine: β-cyclodextrin inclusion complex was taken using KBr at moderate scanning speed between 4000 to 400 cm^{-1}. Both the spectra were compared with the FTIR spectra of pure Nisoldipine to check the entrapment of the drug inside the cyclodextrin cavity.

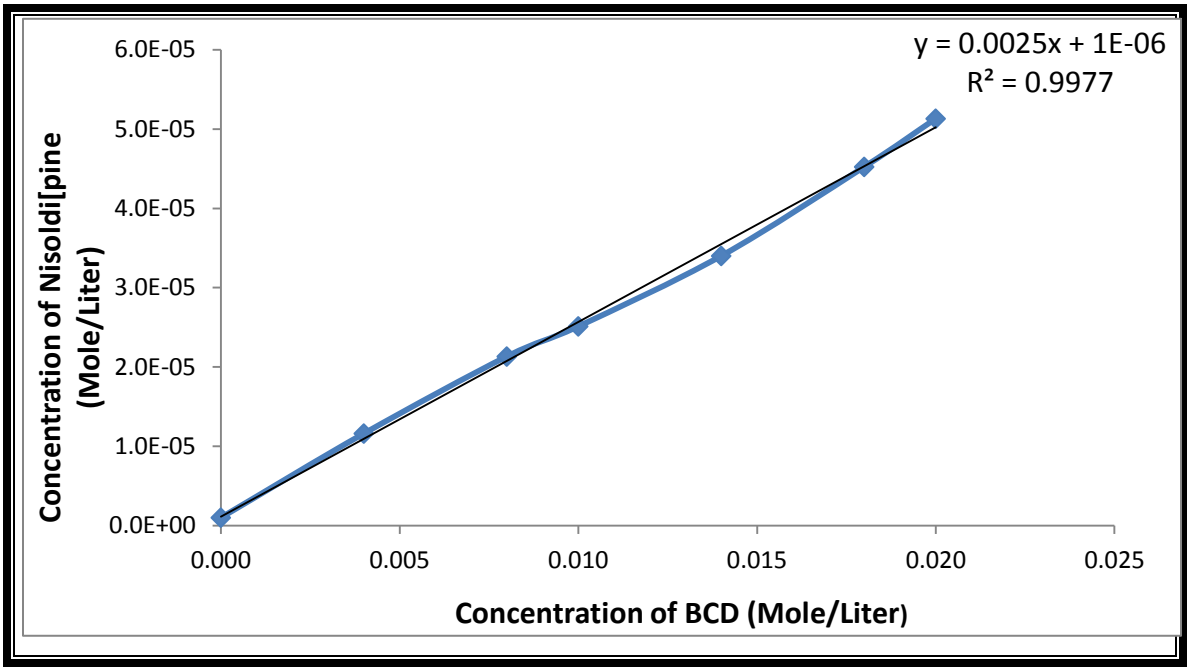
4.4.3 Phase solubility studies

The phase solubility studies were performed according to the method described by Higuchi and Connors. In the 10 ml volumetric flask an excess amount of Nisoldipine (15 mg) was added to 10 ml of pH 6.8 phosphate buffer containing increasing amount of β-cyclodextrin ranging from 0-20 mM and shaken at room temperature until equilibrium (24 hours). Then the solutions were centrifuged and filtered, an aliquot was withdrawn, analyzed for nisoldipine content by spectrophotometry at the wavelength 236 nm and the apparent solubility constant was calculated from the phase solubility diagrams using following equation

$$K_{1:1} = \frac{\text{Slope}}{\{So(1 - \text{Slope})\}}$$

Where; the slope is obtained from the initial straight line portion of the plot and So is the intrinsic solubility of drug in medium (intercept).

Figure 4.11 PHASE SOLUBILITY STUDY GRAPH



Phase solubility study of Nisoldipine

The phase solubility diagram of Nisoldipine/ β-cyclodextrin is shown in above graph; the diagram obtained was classified as A_L type, showing a linear increase in the amount of Nisoldipine solubilized as β-cyclodextrin concentrations increases. From the linear part of the curve, apparent stability constant ($K_{1:1}$) was estimated and it was found to be 2004.008 M^{-1}.

It is reported that the drug/ β-cyclodextrin complexes with stability constant value s in the range of 100-5000 M^{-1} exhibits improved dissolution properties of drug and hence the better bioavailability [31], thus , it can be concluded that the prepared Drug/ β-cyclodextrin, complexes may help in improving dissolution characteristics and thereby the improved bioavailability. Hence the slope is less than 1 which suggests molar inclusion complex of drug: β-cyclodextrin which can enhance the solubility.

4.4.4 Comparison of dissolution profile of kneading mixture (km), physical mixture (pm) and pure drug

Dissolution profile of pure drug was compared with physical mixture and kneading mixture of drug with β-cyclodextrin in 1:1 molar ratio.

Release profile of pure drug was already discussed before.

Result and discussion:

Comparative dissolution profiles of physical mixture and pure drug revealed that, at 40 minute 35 % drug release was occurred in case of API while 59 % drug release was occurred in case of inclusion complex prepared by Physical mixture method so there was improvement in solubility of drug after inclusion complex with β-cyclodextrin.

Comparative dissolution profile of physical mixture and kneading method revealed that, at 40 minute 59 % drug release was occurred in case of inclusion complex prepared by physical mixture method while 78 % drug release was occurred in case of kneading method. So the solubility of Nisoldipine can be enhanced better with kneading method rather than physical mixture.

4.4.5 Optimization of drug: β-cyclodextrin ratio

The solid inclusion complex of Nisoldipine was prepared using β-cyclodextrin by kneading method at various molar ratios as shown in the table 4.15.

TABLE 4.15: FORMULATION OF NISOLDIPINE/ Β-CYCLODEXTRIN INCLUSION COMPLEX

Batch	M_1	M_2	M_3	M_4
Nisolodipine	1	1	1	1
β-cyclodextrin	0.50	0.75	1	2

the amount of Nisoldipine and β-cyclodextrin are shown in terms of molar ratio.

Result and discussion:

All the inclusion complexes prepared with β-cyclodextrin shown faster drug release than the pure drug.

Increment of drug: β-cyclodextrin molar ratio from 1:1 to 1:2 does not resulted significant improvement in drug dissolution.

Thus, from the above discussion, we can conclude that the inclusion complex with 1:1molar ratio is sufficient to enhance the dissolution of Nisoldipine. Hence, it was selected further for formulating the osmotic tablet.

4.4.6 Charecterization of inclsion complex by FTIR spectroscopy

Fourier transform infrared spectroscopy (FTIR) has been used to assess the interaction between β-cyclodextrin and the drug molecule in the solid state. The FTIR spectra of Nisoldipine, β-cyclodextrin, Drug/ β-cyclodextrin inclusion complex nd overlay of above three are shown in figure 4.41

Comparison of FTIR spectra of β-cyclodextrin and Drug- β-cyclodextrin complex:

The analysis of FTIR spectra of the drug, β-cyclodextrin, Drug- β-cyclodextrin complex spectra (as shown in figure) showed that in the spectra of inclusion complex , absence of prominent peaks of the drug was observed, i.e., at 3321.78 cm^{-1} i.e. the characteristic peak of secondary aliphatic amine (-NH-). Also the peak at 2967 cm^{-1}, which was interpreted as the valence bond of C-H in plane vibrations of the aromatic ring, is absent. The differences also appeared in the band correspond to the vibrations of carbonyl group in the ester bonds. In the spectra of drug, the band occurs around the 1706.69 cm^{-1}, while in the spectra corresponding inclusion complex, it is broadened and shifted towards shorter wavelengths. This may be due to hydrogen bonding or vander wal forces. Some differences are also noted in the range of 1500-1600 cm^{-1}. These indicate that the vibrating and banding of the Nisoldipine was restricted due to the formation of an inclusion complex.

Thus, the absence of characteristic peak of Nisoldipine and the presence of characteristic peaks of β-cyclodextrin in the FTIR spectra of complexes indicate that the drug is completely entrapped inside the cavity of β-cyclodextrin to form inclusion complex.

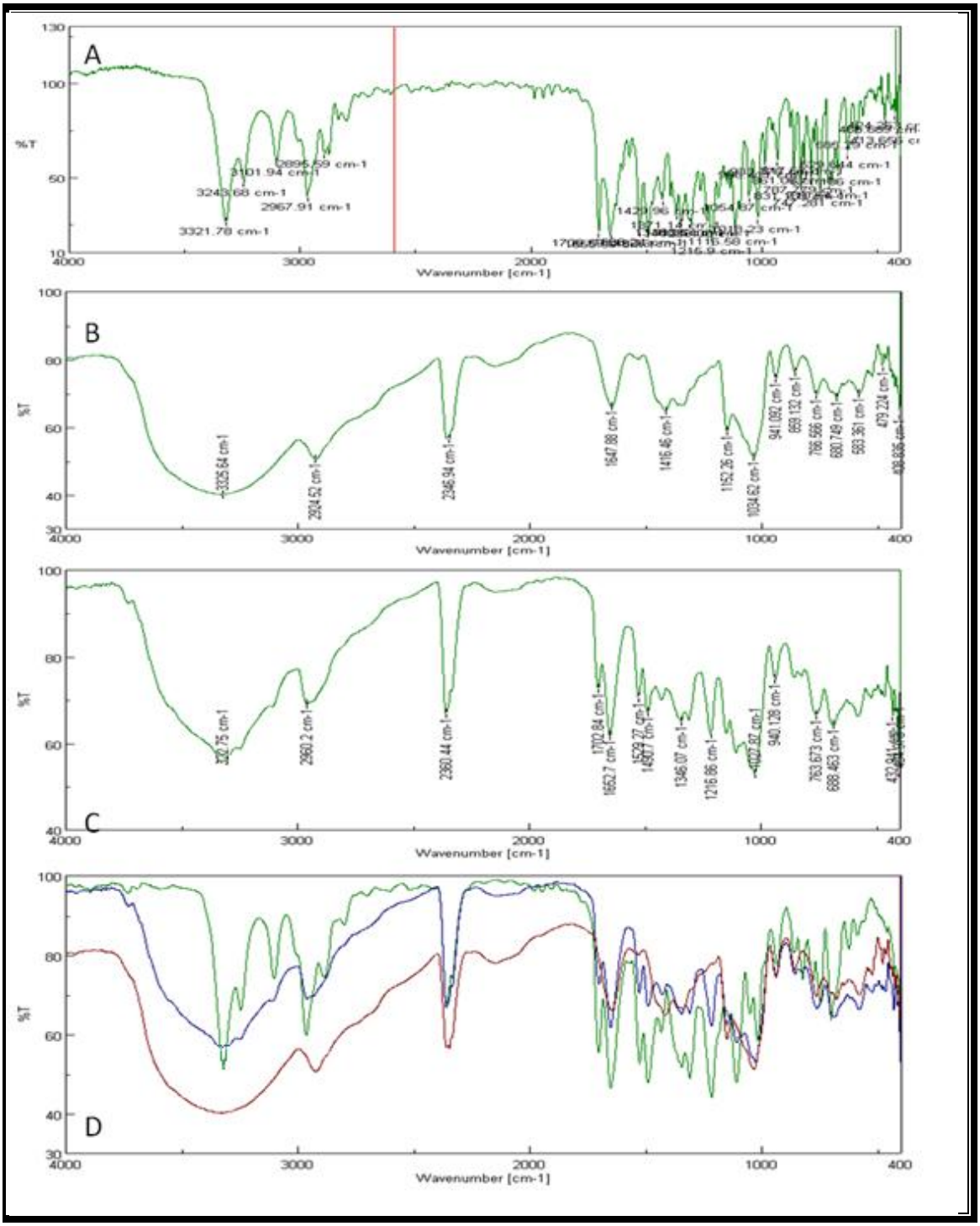


Figure 4.14 FTIR SPECTRAS OF (A) NISOLDIPINE, (B) β-CYCLODEXTRIN, (C) INCLUSION COMPLEX, (D) OVERLAY OF NISOLDIPINE, β-CYCLODEXTRIN AND INCLUSION COMPLEX

4.5 PREPARATION OF CONTROLLED POROSITY OSMOTIC TABLETS

The core tablet was prepared by wet granulation method and then it was coated with semipermeable coating to formulate CPOP tablet. The ingredients used to formulate osmotic tablets are shown in following table 4.20.

TABLE 4.20: GENERAL COMPOSITION OF CPOP

Core tablet composition			
Ingredients	**Category**	**Amount per tablet (mg)**	**Varying range (mg)**
Nisoldipine	Drug	8.5	8.5 - 40
β-cyclodextrin	Solubility enhancer	29.665	10 - 125
Sodium chloride	Osmotic agent	160	0 - 250
Potassium chloride			0 - 123
Mannitol			0 - 250
Lactose			0 - 350
PVP K- 30	Binder	30 (7.5 %)	2.5-15 %
Microcrystalline cellulose	Filler	q.s to 400	q.s
Talc	Glident	8 (2%)	-
Magnessium stearate	Lubricant	4 (4%)	-
Coating composition			
Cellulose acetate	Semipermeable polymer (SP)	3 %	1 - 4 %
Ethyl Cellulose	SP	3 %	1 - 4 %
PEG 400	Pore former	20 %	5 - 50 %
Diethyl pthalate	Plasticizer	20 %	1-20 %
Dibutyl pthalate	Plasticizer		1-20 %
Acetone	Solvent	q.s.	q.s
Isopropyl Alcohol	Solvent	q.s.	q.s
FDC color	Color	q.s.	q.s

4.5.1 Preparation of CPOP tablet

Powders were transferred in geometric ratio in to polybag for obtaining uniform mixing. The mixture was blended for 10 minutes after addition of required quantity of drug.

The PVP K30 in sufficient quantity of Iso propyl alcohol (IPA) was added and damp mass was prepared. The damp mass was passed from sieve number 10 # to obtain granules. The granules were allowed to dry in hot air oven at 40 ^{o}C for 30 minutes.

The granules obtained was passed from sieve number 35 # and retained on sieve number 60 #. 10% fines were added. The granules were mixed with sufficient quantity of talc and magnesium stearate.

Core Tablets was prepared using rotary tablet punching machine. The coating was carried out by spray pan coating machine under IR lamp. The components of coating solution are given in Table 4.11. Pan was made up of stainless steel, having diameter of 22 cm and was rotating at a speed of 30 rpm. The spray rate was fixed at 4-6mL/min. Coated tablets was dried at 50˚C for 12 h and the average weight gain after drying was controlled up to 20±1% (n=20)

Evaluation of film properties:

Semipermeable film was formed on surface of core tablets by the phenomenon of film casting. The coating solution was poured into the petridishes to get thickness similar to that of the coated tablets. The films were left overnight for air drying then removed from petridishes. The film property like film tensile strength; elasticity and physical appearance were evaluated.

In- vitro release studies

Drug release studies were carried out using an USP Type II : paddle apparatus, 50 rpm, 37± 0.5 °C for 24 hr in 0.1 N HCl (900 ml). During each sampling period, 5ml of samples were withdrawn and filtered with whatman filter paper and analyzed for Nisoldipine content by UV spectrophotometry method. Withdrawn volume of dissolution medium was replaced with fresh dissolution medium.

Effect of pH

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of optimized formulations were conducted in media of different pH [SGF (pH 1.2), SIF (pH 7.4) and CSF (pH 6.6)]. Dissolution apparatus used was USP Type II: paddle apparatus, 50 rpm, 37± 0.5 °C. The samples (5ml) were withdrawn at predetermined intervals and analyzed.

Effect of agitation intensity

To study the effect of agitation intensity of release media, release studies of optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP Type II: paddle apparatus at 50, 75, 100 rpm, 37± 0.5 ° C.

4.6 PRELIMINARY TRIALS

4.6.1 Selection of binder concentration

TABLE 4.21: SELECTION OF BINDER CONCENTRATION

Ingredients	**B_1**	**B_2**	**B_3**
Nisoldipine inclusion complex	38.165 mg	38.165 mg	38.165 mg
Sodium chloride	80 mg (20 %)	80 mg (20 %)	80 mg (20 %)
PVP K 30	***20 mg (2.5 %)***	***30 mg (7.5 %)***	***40 mg (10 %)***
Talc	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)
Magnesium stearate	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)
Microcrystalline cellulose	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg
Core tablet evaluation			
Hardness	4.10 Kp	4.12 Kp	4.93 Kp
Friability	0.850	0.534	0.213
Remark	Capping observed	No capping observed	No capping observed

Result and Discussion:

In preliminary batches the core tablet was prepared using wet granulation. In all above batches (B_1 to B_3), tablets with sufficient hardness were produced. However the problem of friability and capping was observed in batch B_1 having lower binder concentration. Hence, to overcome this problem, binder (PVP K 30) concentration was increased gradually. Batch B_2 containing binder concentration (7.5 %) had given desirable tablet properties.

4.6.2 Preparation of coating solution

In the present study, Cellulose acetate polymer was utilized to form semipermeable membrane.

General coating composition:

TABLE 4.22: GENERAL COATING COMPOSITION

Ingredient	Category	Varying range
Cellulose acetate (CA)	Semipermeable membrane	1-5 %
Polyethylene glycol 400	Channeling agent	1-60 %
Acetone	Solvent	q.s. up to 100 ml
Dichloromethane		
Isopropyl Alcohol		
Methanol		
Diethyl phthalate (DEP)	Plasticizer	1-30 %
Dibutyl Phthalate (DBP)		
FDC color	Color	q.s.

Selection of solvent for cellulose acetate

The solvent in which the polymer dissolves completely was selected for preparing coating solution in given solvent system.

TABLE 4.23: SELECTION OF SOLVENT FOR CELLULOSE ACETATE

Solvent	Solubility
Acetone	Soluble
Isopropyl Alcohol	Partial soluble
Dichloro methane	Partial soluble
Ethyl alcohol	Partial soluble

Preparation of coating solution:

The cellulose acetate (CA) powder was accurately weighed and added to required amount of solvent. In case of mixed solvent system, cellulose acetate was first dissolved in solvent having higher solubility for CA. Another solvent having lesser capacity to dissolve CA was added to the above solution. The magnetic stirrer was used for mixing to avoid lump formation. Accurately weighed amount of PEG 400 (as pore former) and plasticizer was added to above clear solution. The required quantity of FDC yellow color was added to coating solution and mixed properly to get uniform blend.

Film casting method:

The coating solution was casted in petry plate to get coating thickness similar to tablet coat thickness. It was dried in hot air oven at 50˚C temperature for 12 Hrs. Film was removed from petry plate and characterized for tensile strength measurement.

TABLE 4.24: EFFECT OF SOLVENT COMPOSITION ON TENSILE STRENGTH OF FILM AND TABLET COAT SURFACE APPEARANCE

Batch	Acetone (ml)	DCM (ml)	Methanol (ml)	IPA (ml)	Tensile Strength (N/cm^2)	Tablet coat surface
S_1	100	-	-	-	279.30	Rough
S_2	80	-	20	-	219.82	Rough
S_3	60	-	40	-	209.63	Rough
S_4	-	100	-	-	262.04	Rough
S_5	-	80	-	20	240.87	Rough
S_6	-	60	-	40	268.93	Rough
S_7	80	-	-	20	569.20	Smooth
S_8	60	-	-	40	598.35	Smooth

Result and discussion:

The optimum solvent composition was determined to be acetone: isopropyl alcohol (80:20). All batches show no significant difference in tensile strength made by solvent casting method. Batches S_1-S_6 does not contain IPA as solvent, when these coating solution sprayed the rough tablet surface was generated. The smooth surface obtained in Batch S_7.

4.6.3 Selection of Plasticizer by film casting method:

The coating solution was prepared with formula as shown in below table and casted in petry plate to get coating thickness similar to tablet coat thickness. It was dried in hot air oven at 50˚C temperature for 12 Hrs. Films were removed from petry plate and subjected to tensile strength measurement.

TABLE 4.25: SELECTION OF PLASTICIZER BY FILM CASTING

Ingredients	**K_1**	**K_2**	**K_3**	**K_4**	**K_5**	**K_6**	**K_7**	**K_8**
CA	3 %	3 %	3 %	3 %	3 %	3 %	3 %	3 %
DEP	5 %	10 %	15 %	20 %	-	-	-	-
DBP	-	-	-	-	5 %	10 %	15 %	20 %
PEG 400	20 %	20 %	20 %	20 %	20 %	20 %	20 %	20 %
Acetone	16 ml	16 ml	16 ml	16 ml	16 ml	16 ml	16 ml	16 ml
IPA	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml	4 ml
Evaluation of film								
Tensile strength (N/cm^2)	46.45	81.46	104.95	168.10	84.97	109.51	155.43	252.22

Result and discussion:

As the concentration of Plasticizer DEP and DBP increased there was increased in tensile strength of the film so here highest tensile strength was observed in Batch K_4 and K_8. So the highest concentration of DEP and DBP was selected for further optimization.

4.6.4 Selection of plasticizer based on release profile of drug:

TABLE 4.26: SELECTION OF TYPE OF PLASTICIZER

Ingredients	**K_9**	**K_{10}**
Nisoldipine inclusion complex	38.165 mg	38.165 mg
Sodium chloride	80 mg (20 %)	80 mg (20 %)
PVP K 30	30 mg (7.5 %)	30 mg (7.5 %)
Talc	8 mg (2 %)	8 mg (2 %)
Magnesium stearate	4 mg (1 %)	4 mg (1 %)
Microcrystalline cellulose	q.s up to 400 mg	q.s up to 400 mg
Core tablet evaluation		
Hardness	4-6 Kp	
Friability	< 0.1 %	
Coating composition		
Cellulose acetate	3 % w/v in Acetone : Isopropyl alcohol (80 : 20)	
Poly ethylene Glycol 400	20 % w/w of dry cellulose acetate powder	
Di ethyl phthalate	***20 % w/w of dry cellulose acetate powder***	**-**
Di butyl phthalate	**-**	***20 % w/w of dry cellulose acetate powder***
FDC COLOR	q.s	q.s

Result and conclusion:

Influence of plasticizer on drug release is shown in above graph. Formulation containing plasticizer di ethyl phthalate (DEP) i.e. in Batch K_9 showed higher drug release compared to di butyl phthalate(DBP) i.e. in Batch K_{10}, this is mainly because of higher molecular weight of DBP (more lipophilic) compared to DEP. So DEP was selected as plasticizer for further optimization.

4.6.5 Optimization Of Coating Thickness:

Coating membrane integrity study:

The tablets were coated for 1%, 2%, 3%, and 4% weight gain. Then the tablets were dried for 50˚C in hot air oven for 12 Hrs. Coated tablets then subjected to 500 ml of distilled water under stirred condition. At different time intervals the coat of tablets was examined manually for any cracks in coating surface. The tablets which remain intact up to 24 Hrs. is observed and relevant coating thickness should be kept constant throughout study.

TABLE 4.29: SELECTION OF COATING THICKNESS

Ingredients	**N_1**	**N_2**	**N_3**	**N_4**
Nisoldipine inclusion complex	38.165 mg	38.165 mg	38.165 mg	38.165 mg
Sodium chloride	80 mg (20 %)	120 mg (30 %)	160 mg (40 %)	200 mg (50 %)
PVP K 30	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5%)	30 mg (7.5 %)
Talc	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)
Magnesium stearate	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)
Microcrystalline cellulose	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg
Core tablet evaluation				
Hardness	4-6 Kp			
Friability	< 1 %			
Coating composition				
Cellulose acetate	3 % w/v in Acetone : Isopropyl alcohol (80:20)			
PEG 400	20 % w/w of dry cellulose acetate powder			
Diethyl phthalate	20 % w/w of dry cellulose acetate powder			
FDC color	q.s	q.s	q.s	q.s
Coating level	**Tablet coat rupture after following time**			
1	4 hrs	3 hrs	2 hrs	1 hrs
2	Remain intact for 24 hrs			
3				
4				

Result and discussion:

In the core composition osmogens are there, due to solubilization of osmogen pressure on walls of coat was generated. The coat thickness should be in such a manner that it can withstand internal pressure and can remain intact throughout dissolution study. As the coating thickness increases the coat integrity also increases. But in case of coating level 1%, as the water penetrates into core solubilization of osmogen was took place and the pressure generated on coat wall and coating had been ruptured. The coating thickness 2% can withstand pressure created by solubilization of Osmogen up to 24 hrs. So, throughout study the coating thickness had been maintained for 2%.

4.6.6 Selection of osmotic agent :

TABLE 4.30: SELECTION OF OSMOTIC AGENT

Ingredients	**A_1**	**A_2**	**A_3**	**A_4**
Nisoldipine inclusion complex	38.165 mg	38.165 mg	38.165 mg	38.165 mg
Sodium chloride	**80 mg (20 %)**	-	-	-
Potassium chloride	-	**80 mg (20 %)**	-	-
Mannitol	-	-	**80 mg (20 %)**	-
Lactose	-	-	-	**80 mg (20 %)**
PVP K 30	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)
Talc	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)
Magnesium stearate	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)
Microcrystalline cellulose	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg
Core tablet evaluation				
Hardness	4-6 kp			
Friability	<0.1 %			
Coating composition				
Cellulose acetate (CA)	3 % w/v in Acetone : Isopropyl alcohol (80 : 20)			
PEG 400	20 % w/w of dry cellulose acetate powder			
Diethyl phthalate	20 % w/w of dry cellulose acetate powder			
FDC color	q.s	q.s	q.s	q.s
Coating level	1.8 %	2.1 %	2.2 %	2.0 %

Result and Discussion:

Batch A_1 containing sodium chloride as osmotic agent showed highest drug release at 9 th hour as compared to Batches A_2, A_3 and A_4.

Osmotic pressure of sodium chloride and potassium chloride are higher compared to mannitol and lactose [32], higher release rate was observed with sodium chloride.

Thus, in further optimization of formulation, sodium chloride was chosen as the osmotic agent.

4.6.7 Optimization of amount of sodium chloride:

TABLE 4.35: SELECTION OF AMOUNT OF SODIUM CHLORIDE

Ingredients	**O_1**	**O_2**	**O_3**	**O_4**
Nisoldipine inclusion complex	38.165 mg	38.165 mg	38.165 mg	38.165 mg
Sodium chloride	40 mg **(10 %)**	80 mg **(20 %)**	120 mg **(30 %)**	160 mg **(40 %)**
PVP K 30	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)
Talc	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)
Magnesium stearate	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)
Microcrystalline cellulose	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg
Core tablet evaluation				
Hardness	4-6 kp			
Friability	<0.1 %			
Coating composition				
Cellulose acetate (CA)	3 % w/v in Acetone : Isopropyl alcohol (80 : 20)			
PEG 400	20 % w/w of dry cellulose acetate powder			
Diethyl phthalate	20 % w/w of dry cellulose acetate powder			
FDC color	q.s	q.s	q.s	q.s
Level of coating	1.9 %	2.0 %	2.1 %	2.1 %

Result and Discussion:

Batch O_4 showed the highest drug release among the Batches O_1, O_2, and O_3.

As the amount of sodium chloride increases, there is increase in the release rate. The more sodium chloride incorporated in to tablet, the more water was imbibed and the more core formulation could be liquefied and, as a consequence, more Nisoldipine was released.

Increasing in the amount Sodium chloride from 0 to 160 mg, there was increase in the drug release. Highest limit of sodium chloride as Osmogen that is 160 mg was chosen for further optimization.

4.6.8 Optimization of concentration of poreformer PEG 400:

TABLE 4.39: SELECTION OF CONCENTRATION OF POREFORMER PEG 400

Ingredients	P_1	P_2	P_3	P_4
Nisoldipine inclusion complex	38.165 mg	38.165 mg	38.165 mg	38.165 mg
Sodium chloride	160mg (40 %)	160mg (40 %)	160mg (40 %)	160mg (40 %)
PVP K 30	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)
Talc	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)
Magnesium stearate	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)
Microcrystalline cellulose	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg
Core tablet evaluation				
Hardness	4-6 kp			
Friability	< 0.1 %			

Coating composition				
Cellulose acetate (CA)	3 % w/v in Acetone : Isopropyl alcohol (80 : 20)			
PEG 400	***10 % w/w***	***15 % w/w***	***20 % w/w***	***25% w/w***
Diethyl phthalate	20 % w/w CA			
FDC color	q.s	q.s	q.s	q.s
Coating level	2.0%	2.1 %	2.1 %	1.8 %

Weight PEG 400 & Diethyl phthalate are with respect to dry weight of CA.

Result and discussion:

Influence of the poreformer (PEG 400) level on drug release is shown in above graph. Formulation containing highest amount of poreformer PEG 400 (Batch P_4) exhibited higher drug release among batches having different level of PEG 400.

Figure indicates that the amount of plasticizer have pronounced influence on the drug release. As increasing the amount of PEG 400 in semipermeable coat, there is linearly increased in the drug release. Since PEG 400 is hydrophilic in nature, it could be leached out easily and left behind porous structure. The more PEG 400 incorporated into cellulose acetate semipermeable membrane, the higher membrane permeability and drug release rate obtained.

4.6.9 Optimization of coating level on drug release:

TABLE 4.44:SELECTION OF COATING LEVEL

Ingredients	**L_1**	**L_2**	**L_3**	**L_4**
Nisoldipine inclusion complex	38.165 mg	38.165 mg	38.165 mg	38.165 mg
Sodium chloride	160mg (40 %)	160mg (40 %)	160mg (40 %)	160mg (40 %)
PVP K 30	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)	30 mg (7.5 %)
Talc	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)	8 mg (2 %)
Magnesium stearate	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)	4 mg (1 %)
Microcrystalline cellulose	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg	q.s up to 400 mg
Core tablet evaluation				
Hardness	4-6 kp			
Friability	<0.1 %			
Coating composition				
Cellulose acetate (CA)	3 % w/v in Acetone : Isopropyl alcohol (80 : 20)			
PEG 400	25% w/w			
Diethyl phthalate	20 % w/w			
FDC color	q.s	q.s	q.s	q.s
Coating level	1.98	2.97 %	4.11 %	5.16 %

Release and discussion:

Above graph shows that release rate decreased as the coating level increased. In Batch L_1 that is 1.98 % weight gain about 99.79 % drug was released in 18 hrs only, while Batch L_2 shows 99.71 % drug release in 24 hrs. Further increased in coating level that is Batch L_3 and L_4 there was decreased in drug release.

As the thickness increased, the resistance of membrane to water diffusion increased and the rate of imbibing water decreased and, in turn, the liquefaction rate of the tablet core decreased, resulting in the decrease in drug release rate.

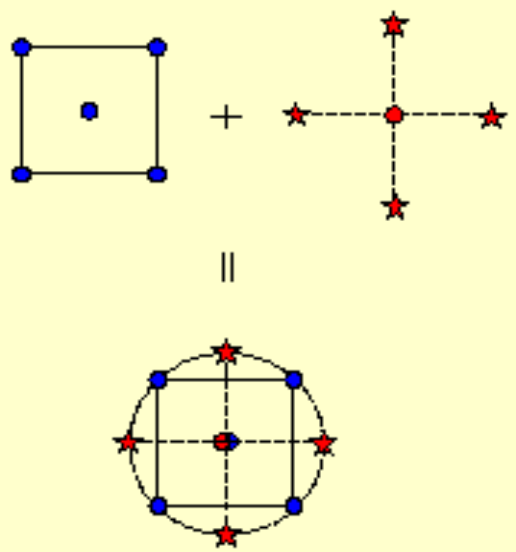
4.7 INTRODUCTION TO OPTIMIZATION DESIGN

Central Composite Designs

A Box-Wilson Central Composite Design, commonly called `a central composite design,' contains an imbedded factorial or fractional factorial design with center points that is augmented with a group of `star points' that allow estimation of curvature. If the distance from the center of the design space to a factorial point is ±1 unit for each factor, the distance from the center of the design space to a star point is $\pm\alpha$ with $|\alpha| > 1$. The precise value of α depends on certain properties desired for the design and on the number of factors involved.

Similarly, the number of center point runs the design is to contain also depends on certain properties required for the design.

Figure 4.20 GENERATION OF A CENTRAL COMPOSITE DESIGN FOR TWO FACTORS



A central composite design always contains twice as many star points as there are factors in the design. The star points represent new extreme values (low and high) for each factor in the design.

Determining α in Central Composite Designs

To maintain rotatability, the value of α depends on the number of experimental runs in the factorial portion of the central composite design:

$$\propto = [\text{number of factorial runs}]^{1/4}$$

If the factorial is a full factorial, then

$$\propto = [2^k]^{1/4}$$

TABLE 4.49: DETERMINATION OF A FOR ROTATIBILITY

Number of factors	Factorial portion	Scale value for α relative to $\pm$ 1
2	2^2	$2^{2/4}$=1.414
3	2^3	$2^{3/4}$ =1.682
4	2^4	$2^{4/4}$ =2.000
5	2^{5-1}	$2^{4/4}$ =2.000
5	2^5	$2^{5/4}$ =2.378
6	2^{6-1}	$2^{5/4}$ =2.378
6	2^6	$2^{6/4}$ =2.828

Central composite design for three factors

It consists of a 2^3 factorial design plus 6 "star" or axial points, plus points at the centre of the domain. The two parts of the experiment may be carried out separately, provided enough experiments are done at the centre of the domain as part of each block. For the star design one can imagine starting at the centre point then moving along each axis (in each direction, positive and negative) a set distance $\alpha = \pm 1.68$. The advantage of this design is that less number of batches are required to formulate compared to 2^3 factorial design.

The aim of the study was to optimize the CPOP formulation on the basis of response parameters: drug release in 1 hr (Y_1), drug release in 6 hr (Y_2), drug release in 12 hr (Y_3); using central composite design. The three factors were selected on the basis of preliminary trials that are % sodium chloride, % poly ethylene glycol, and percentage weight gain. These were studied at different levels as per central composite design.

The formulation of these batches was shown in below table. All batches were evaluated for drug release in 1 hr (Y_1), drug release in 6 hr (Y_2), and drug release in 12 hr (Y_3). The results were shown in table.

Mathematical model

For analyzing the influence of multiple factors, a mathematical polynomial equation model of design was established. A quadratic model expressed as following equation was used to correlate the theoretical responses (Y) to the coded variables. where β_0, β_i, β_{ii}, and β_{ij} are the regression coefficients, for intercept, linear, quadratic, and interaction terms, respectively.

$$Y= \beta+\beta_1A+\beta_2B+\beta_3C+\beta_{12}AB+\beta_{13}AC+\beta_{23}BC+\beta_{11}A^2+\beta_{22}B^2+\beta_{33}C^2+\beta_{123}ABC$$

Where A, B and C sodium chloride, % poly ethylene glycol, and percentage weight gain respectively. The polynomial equation obtained for each response property was analyzed using Response surface methodology. The optimum levels of the selected variables were obtained by solving the regression equation and also by analyzing the response surface contour and surface plots.

Selection of formulation parameters as Factors for DoE

- Batch A_1 to A_4 were formulated using variety of osmogens (i.e. Sodium chloride, Potassium chloride, Mannitol, Lactose) at similar concentration 20 % w/w. The drug release study (Figure 4.16) revealed that sodium chloride acted as best Osmogen among all Osmogen by providing comparatively faster drug release which indicates higher osmotic pressure created by sodium chloride.

  Moreover, Batches O_1 to O_4 formulated by varying the concentration of Osmogen (NaCl) from 10% to 40% shown the significant effect on drug release as shown in Figure 4.17.

  Hence, Sodium chloride concentration was opted as one of the most significant factor.
- Batches P_1 to P_4 formulated by varying the concentration of pore former (PEG 400) from 10%w/w to 25%w/w of coating solution, shown the significant effect on drug release as shown in Figure 4.18.

  Hence, PEG 400 was selected as one of the most significant factor.
- Batches L_1 to L_4 formulated by varying the coating level from 2% to 5% weight gain by coating solution over core tablet, shown the significant effect on drug release as shown in Figure 4.19.

  Hence coating level was also considered as one of the most significant factor.
- The remaining factors varied in preliminary trials like binder amount in core tablet, type and concentration of plasticizer and the solvent system for coating solution shown negligible effect on drug release profile of CPOP tablet. Therefore these parameters have not been considered for experimental design.
- Based on the type of factors and their influence over the drug release profile of at the given concentrations, the central composite design was selected as design of experiment. The selected factors were varied for the following concentration range as shown in design matrix of Table 4.50.

TABLE 4.50: INDEPENDENT VARIABLES AND THEIR CODED LEVELS INVESTIGATED IN CENTRAL COMPOSITE DESIGN

Factor	Limit				
	-1.68	**-1**	**0**	**+1**	**+1.68**
% NaCl (A)	8.2	15	25	35	41.8
% PEG (B)	6.6	10	15	20	23.4
% Weight gain (C)	2.32	3	4	5	5.68

Selection of evaluation parameters as responses for DoE

The selected factors (formulation parameters) which affect the drug release from the formulation so drug release was selected as response.

The response (drug release) was selected based on pharmacokinetic parameters of drug.

I. 10 % drug should release at 1st hour (Provide loading dose)
II. 30 % drug should release at 6 th hour.
III. 50 % drug should release at 12 th hour.
IV. 100 % drug should release at 24 th hour.
V. It should follow zero order kinetic for drug release.

TABLE 4.51: FORMULATION OF CPOP USING CENTRAL COMPOSITE DESIGN FOR OPTIMIZATION

Batch	Coded value			Actual value		
	A	B	C	A	B	C
	% NaCl	% PEG	% Weight gain	% NaCl	% PEG	% Weight gain
T_1	-1	-1	-1	15.00	10.00	3.00
T_2	0	0	0	25.00	15.00	4.00
T_3	0	0	0	25.00	15.00	4.00
T_4	0	-1.68	0	25.00	6.59	4.00
T_5	0	0	0	25.00	15.00	4.00
T_6	0	0	0	25.00	15.00	4.00
T_7	0	0	+1.68	25.00	15.00	5.68
T_8	+1	+1	-1	35.00	20.00	3.00
T_9	0	0	0	25.00	15.00	4.00
T_{10}	+1	-1	-1	35.00	10.00	3.00
T_{11}	-1	+1	-1	15.00	20.00	3.00
T_{12}	0	0	0	25.00	15.00	4.00
T_{13}	-1	-1	+1	15.00	10.00	5.00
T_{14}	-1	+1	+1	15.00	20.00	5.00
T_{15}	- 1.68	0	0	8.18	15.00	4.00
T_{16}	+1.68	0	0	41.82	15.00	4.00
T_{17}	+1	-1	+1	35.00	10.00	5.00
T_{18}	0	+1.68	0	25.00	23.41	4.00
T_{19}	0	0	-1.68	25.00	15.00	2.32
T_{20}	+1	+1	+1	35.00	20.00	5.00

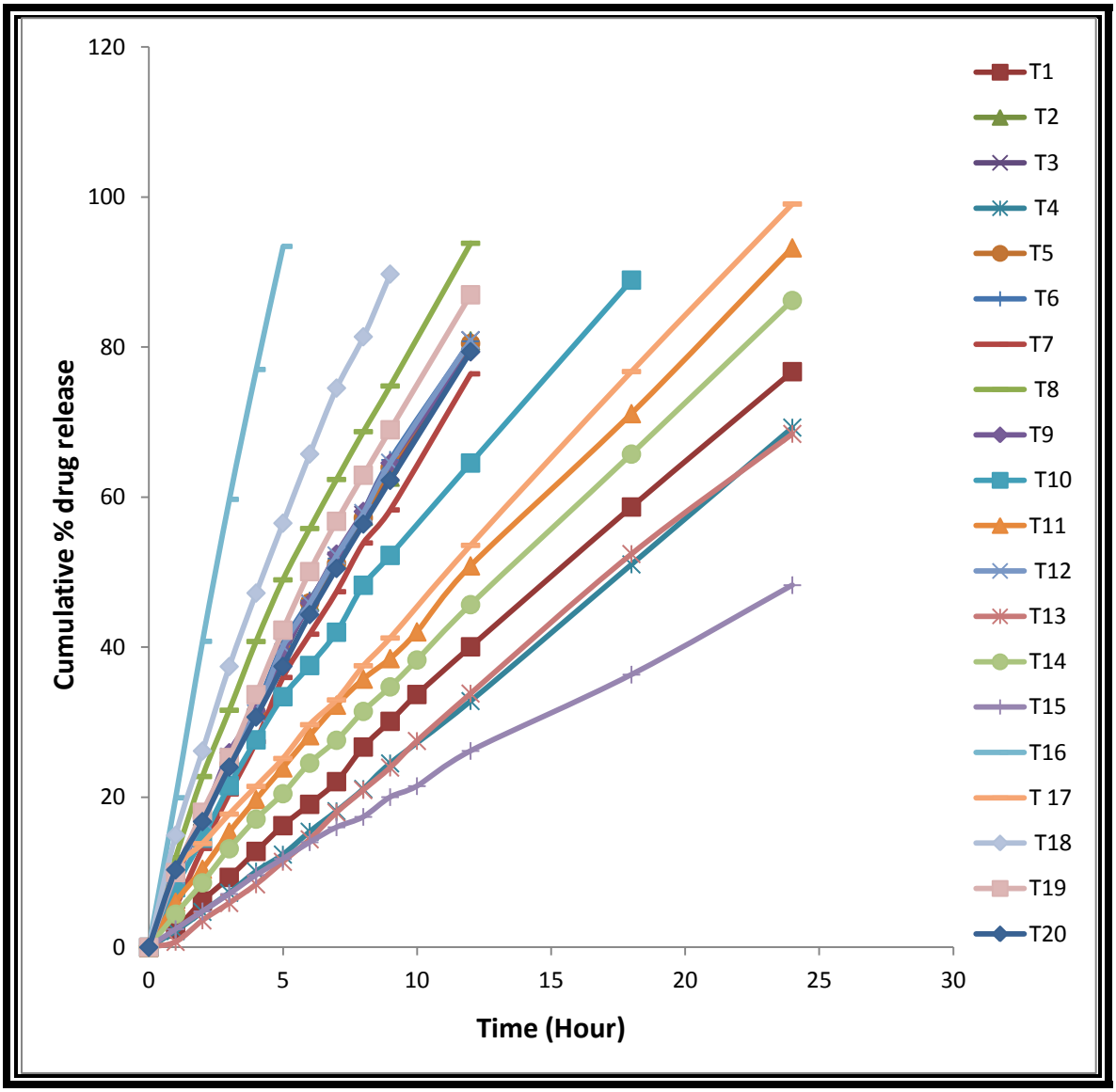

120
100
80
60
40
20
0
Cumulative % drug release
0
5
10
15
20
25
30
Time (Hour)
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
T13
T14
T15
T16
T 17
T18
T19
T20

TABLE 4.72: EXPERIMENTAL RESULTS GENERATED BY CENTRAL COMPOSITE DESIGN

Batch	% NaCl (A)	% PEG (B)	% Weight gain (C)	T_{1hr}	T_{6hr}	T_{12hr}
T_1	15.00	10.00	3.00	2.41	19	40.05
T_2	25.00	15.00	4.00	9.66	46.04	80.83
T_3	25.00	15.00	4.00	9.61	46	80.9
T_4	25.00	6.59	4.00	2.15	15.4	32.81
T_5	25.00	15.00	4.00	9.65	45.9	80.4
T_6	25.00	15.00	4.00	9.87	46.23	80.7
T_7	25.00	15.00	5.68	5.47	41.73	76.43
T_8	35.00	20.00	3.00	11.94	55.81	93.84
T_9	25.00	15.00	4.00	9	45.89	79.97
T_{10}	35.00	10.00	3.00	7.95	37.55	64.54
T_{11}	15.00	20.00	3.00	6.01	28.2	50.84
T_{12}	25.00	15.00	4.00	9.6	45.87	80.9
T_{13}	15.00	10.00	5.00	0.711	14.38	33.82
T_{14}	15.00	20.00	5.00	4.41	24.54	45.61
T_{15}	8.18	15.00	4.00	2.41	14	26.17
T_{16}	41.82	15.00	4.00	19.93	99.49	100.00
T_{17}	***35.00***	***10.00***	***5.00***	***10.2***	***29.67***	***53.45***
T_{18}	25.00	23.41	4.00	14.94	65.75	89.73
T_{19}	25.00	15.00	2.32	9.96	50.07	86.97
T_{20}	35.00	20.00	5.00	10.32	44.34	79.39

Figure 4.22 COMPARISON OF DRUG RELEASE PROPERTY OF CENTRAL COMPOSITE DESIGN BATCHES $T_1 - T_{20}$

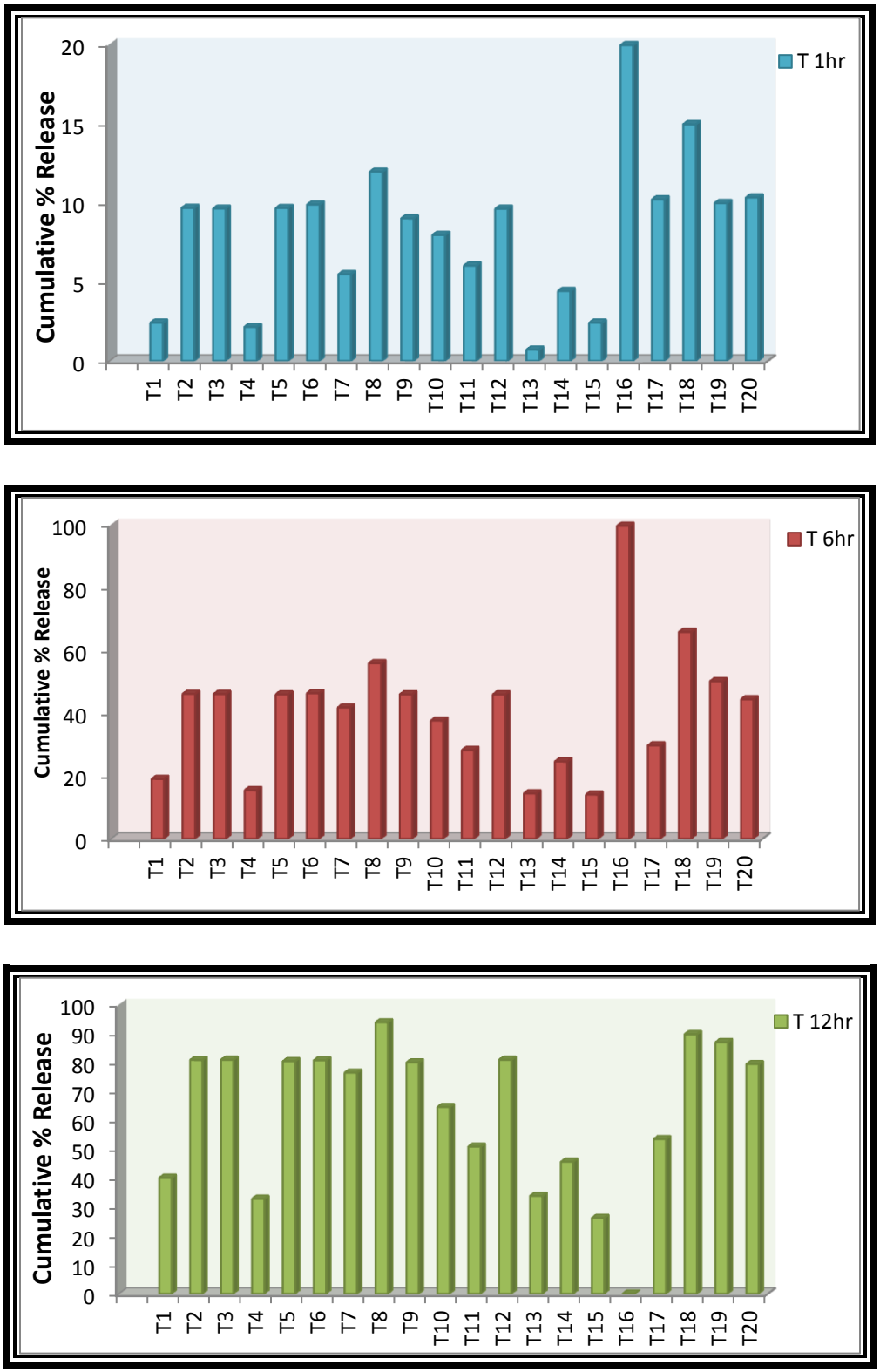


TABLE 4.73: STATISTICAL ANALYSIS OF CENTRAL COMPOSITE DESIGN BATCHES

Y	Coefficients										
	β_0	β_1	β_2	β_3	β_4	β_5	β_6	β_7	β_8	β_9	β_{10}
t_{1hr}	9.64	4.12	2.41	- 0.75	- 0.40	0.49	- 0.47	0.67	- 0.86	- 1.16	- 0.50
t_{6hr}	46.5	16.4	10.0	- 3.05	1.70	-1.38	-0.33	0.39	-5.32	-3.44	-0.57
t_{12hr}	80.7	14.0	12.7	-4.01	4.08	- 1.76	- 0.29	- 12.8	-7.82	- 0.59	- 0.55

TABLE 4.74: EFFECT OF INCREMENT IN FACTOR LEVEL ON RESPONSES

Factor	Responses		
	Y_1	Y_2	Y_3
	t_{1hr}	t_{6hr}	t_{12hr}
% NaCl	↑	↑	↑
% PEG	↑	↑	↑
% Weight gain	NS	NS	↓

NS: No significant changes in response, ↑ : Increase, ↓ : Decrease

In the above table following effect on the responses came to seen due to increment in level of factors

- **t_{1hr}:** As the level of % NaCl and % PEG increase there is increase in drug release so both these factors having positive effect on drug release. While % weight gain shows negligible effect on drug release in first hour.
- **t_{6hr}:** As the level of % NaCl and % PEG increase there is increase in drug release so both these factors having positive effect on drug release. While % weight gain shows negligible effect on drug release at 6 th hour.
- **t_{12hr}:** As the level of % NaCl and % PEG increase there is increase in drug release so both these factors having positive effect on drug release. While % weight gain shows negative effect on drug release at 12 th hour.

4.7.2 INTERPRETATION:

Drug release in 1 hr:

The drug release of individual batches of prepared formulations is presented in table 4.72. The values of t_{1hr} were ranged between 0.711% and 14.94%, which indicate that the response was sensitive toward the studied factors. The selected quadratic model was used to generate the following polynomial equation for the cumulative release:

$T_{1hr} = 9.64 + 4.12A + 2.41B - 0.75C - 0.40AB + 0.49AC - 0.47BC + 0.67A^2 - 0.86B^2 - 1.16C^2 - 0.50ABC$

The above equation was also used to generate three dimensional response surface plot by keeping one factor at optimum level.

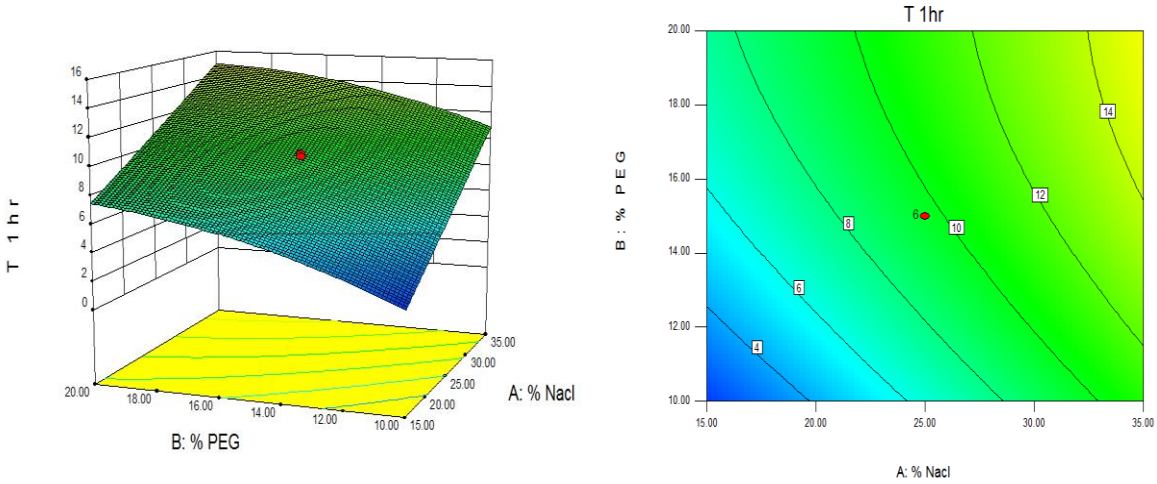


Figure 4.23 RESPONSE SURFACE PLOTS OF DRUG RELEASE AT t_{1HR} VERSUS THREE FACTORS (THIRD FACTOR WAS HELD AT OPTIMUM LEVEL C = % WEIGHT GAIN), B = % PEG, A = % NaCl.

Above figure 4.23 indicates that the relationship between percentage sodium chloride, percentage poly ethylene glycol and drug release property of tablet at t_{1hr}. It observed from the response surface plots that higher amount of sodium chloride and polyethylene glycol will increase the release of drug compared to lower amount. Percentage sodium chloride and percentage poly ethylene glycol have significant effect on drug release.

Drug release in 6 hr:

The drug release of individual batches of prepared formulations is presented in table 4.72. The values of t_{6hr} were ranged between 14.38% and 99.49%, which indicate that the response was sensitive toward the studied factors. The selected quadratic model was used to generate the following polynomial equation for the cumulative release

$T_{6hr} = 46.51 + 16.48A + 10.03B - 3.05C + 1.70AB - 1.38AC - 0.33\ BC + 0.39A^2 - 5.32B^2 - 3.44C^2 - 0.57ABC$

The above equation was also used to generate three dimensional response surface plot by keeping one factor at optimum level.

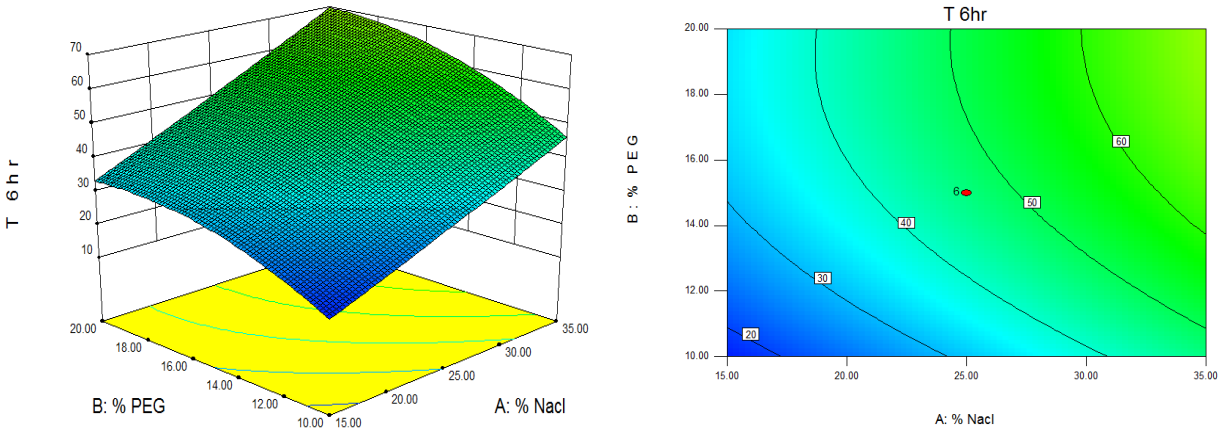


Figure 4.24 RESPONSE SURFACE PLOTS OF DRUG RELEASE AT t_{6hr} VERSUS THREE FACTORS (THIRD FACTOR WAS HELD AT OPTIMUM LEVEL C = % WEIGHT GAIN), B = % PEG, A = % NaCl.

Above figure 4.24 indicates that the relationship between percentage sodium chloride, percentage poly ethylene glycol and drug release property of tablet at t_{6hr}. It observed from the response surface plots that higher amount of sodium chloride and polyethylene glycol will increase the release of drug compared to lower amount. Percentage sodium chloride and percentage poly ethylene glycol have significant effect on drug release.

Drug release in 12 hr:

The drug release of individual batches of prepared formulations is presented in table 4.72. The values of $t_{12\ hr}$ were ranged between 26.17% and 93.84%, which indicate that the response was sensitive toward the studied factors. The selected quadratic model was used to generate the following polynomial equation for the cumulative release:

$T_{12hr} = 80.77 + 14.01A + 12.71B - 4.01C + 4.08AB - 1.76AC - 0.29BC - 12.82A^2 - 7.82B^2 - 0.59C^2 - 0.55ABC$

The above equation was also used to generate three dimensional response surface plot by keeping one factor at optimum level.

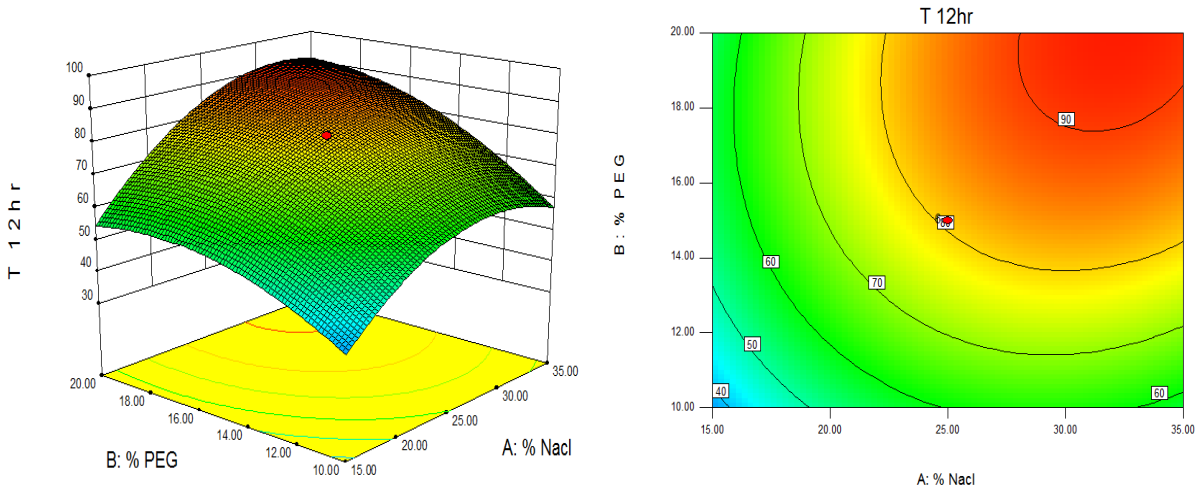


Figure 4.25 RESPONSE SURFACE PLOTS OF DRUG RELEASE AT t_{12hr} VERSUS THREE FACTORS (THIRD FACTOR WAS HELD AT OPTIMUM LEVEL C = % WEIGHT GAIN), B = % PEG, A = % NaCl.

Above figure 4.25 indicates that the relationship between percentage sodium chloride, percentage poly ethylene glycol and drug release property of tablet at t_{12hr}. It observed from the response surface plots that higher amount of sodium chloride and polyethylene glycol will increase the release of drug compared to lower amount. Percentage sodium chloride and percentage poly ethylene glycol have significant effect on drug release.

4.7.3 SELECTION OF OPTIMIZED BATCH

Best batch was selected on following basis

VI. 10 % drug should release at 1st hour.

VII. 30 % drug should release at 6 th hour.

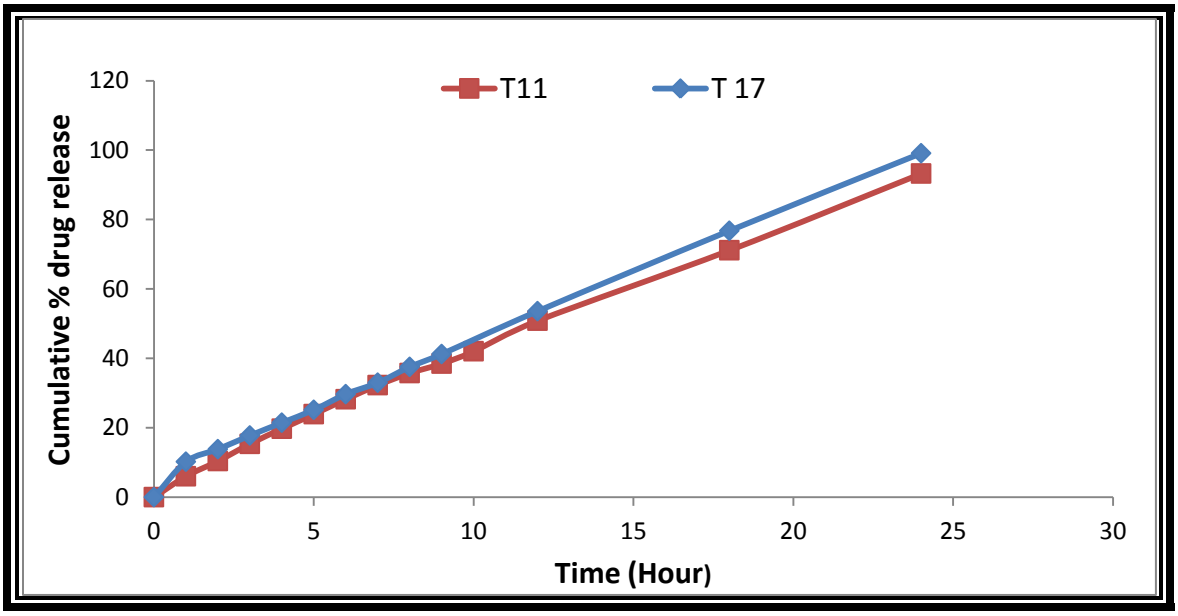
VIII. 50 % drug should release at 12 th hour.

IX. 100 % drug should release at 24 th hour.

X. It should follow zero order kinetic for drug release.

Here from table number 4.72, batches T_{11} & T_{17} were complied with above criteria. The comparison of release profile of both batches was carried out as shown in figure 4.26.

***Figure 4.26* COMPARISON OF RELEASE PROFILE OF BATCH T_{11} AND T_{17}**



Release and discussion:

Among the batches T_{11} and T_{17}, batch T_{17} showed satisfactory result that is it releases the loading dose that is 10% CPR in first hour. So batch T_{17} was selected as optimized batch.

4.7.4 STUDIES OF DRUG RELEASE RATE KINETICS

Release of drug from the insoluble coat is extremely highlighted in the literature. To obtain the dissolution rate constants of drug from semipermeable membrane, various models are reported. Various models were tried to fit the optimized batch to determine the mechanism of drug release.

Zero order model:

In many of the modified release dosage forms particularly controlled or sustained release dosage form is zero-order kinetics.

$$M = k \times t$$

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.

First order model:

Most conventional dosage forms exhibit this dissolution mechanism. Some modified release preparations, particularly prolonged release formulations, adhere to this type of dissolution pattern.

$$M = e^{a} \times e^{-bt}$$

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.

Higuchi model:

A large number of modified released forms contain some sort of matrix system. In such instances, the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion controlled) and thus the following relationship applies.

$$M = (100 - q) \times \sqrt{t}$$

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

In Higuchi model, a plot of % drug unreleased (or released) vs. square root of time ($\sqrt{t}$) is linear.

Korsmeyer-Peppas model:

$$\frac{Mt}{M} = k \times t^n$$

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, N = 0.5, release best explained by Fickian diffusion, 0.5<n<1, release is through anomalous diffusion or case-II diffusion.

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

Hixon-Crowell model:

Some dosage forms contain many particles of the same size and shape or their agglomerates that dissolve evenly. In such instances the cube root law can express the dissolution process.

$$M = \left(100^{1/3} - (k \times t)\right)^3$$

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

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

The result of model fitting of selected batch T_{17} is shown in below table 4.75.

TABLE 4.75: RESULT OF MODEL FITTING

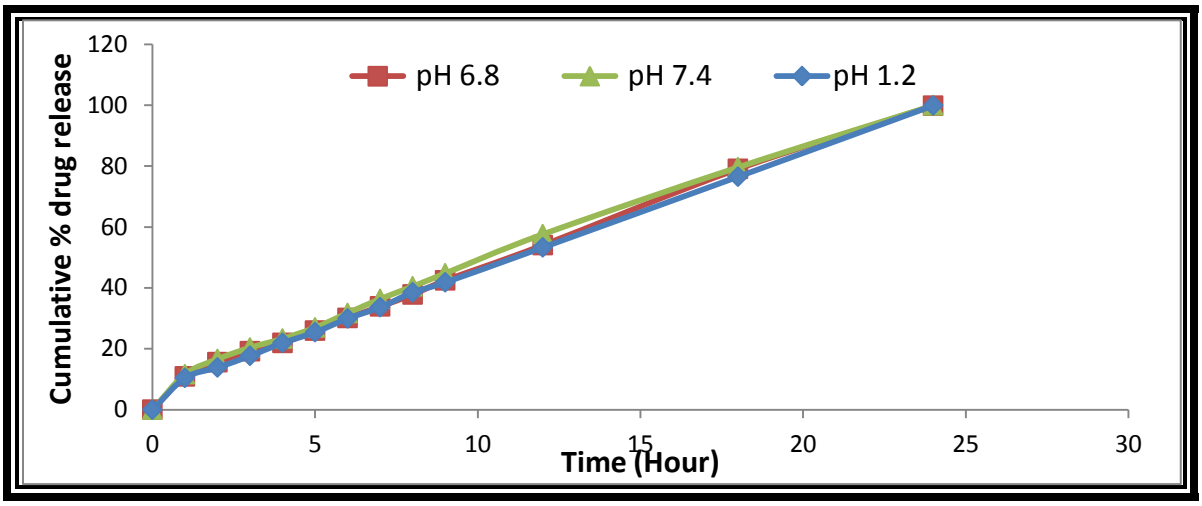
Model	R^2 value	SSR
Zero order	0.9982	32.3
First order	0.7831	8643.52
Higchi model	0.9289	649.02

Result and discussion:

The drug release profile of the Batch T_{17} fitted best to the zero order kinetic models with least residual sum of square (SSR) and showed 100% drug release at 24 hour.

Influence of pH of the dissolution medium on drug release

Figure 4.27 INFLUENCE OF pH ***OF DISSOLUTION MEDIUM ON DRUG RELEASE***

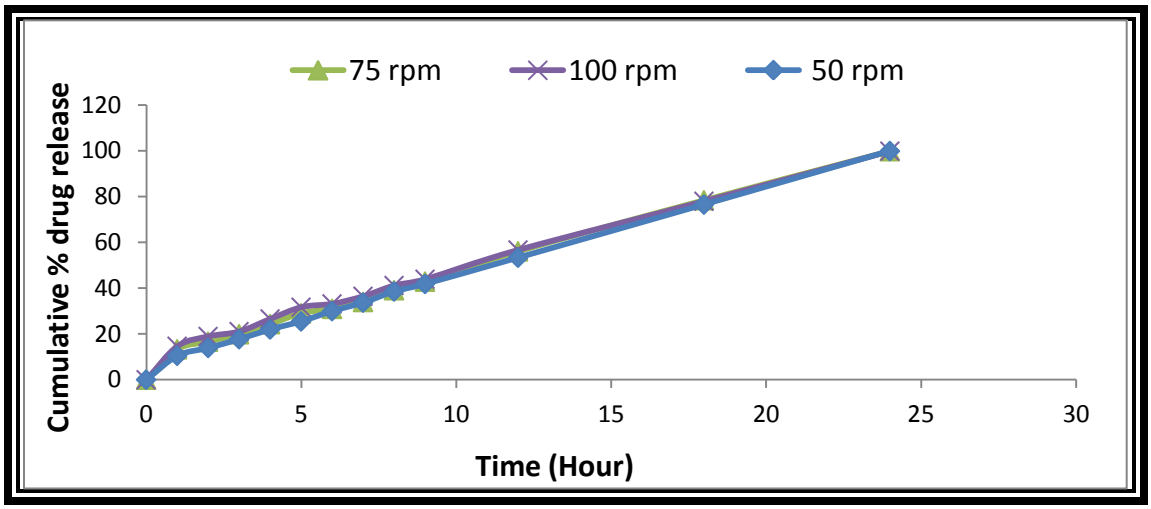


Result and discussion:

Figure 4.27 shows the influence of pH of dissolution medium on drug release. It revealed that there was no significant effect of pH of dissolution medium on the drug release.

Influence of hydrodynamic condition of release media on drug release

Figure 4.28 INFLUENCE OF HYDRODYNAMIC CONDITION OF DISSOLUTION MEDIUM ON DRUG RELEASE



Result and discussion:

Figure 4.28 shows the influence of hydrodynamic condition of dissolution medium on drug release. It revealed that there was no significant effect of hydrodynamic condition of dissolution medium on the drug release.

Chapter 5

Summary

5.1 SUMMARY

Nisoldipine is substituted dihydropyridine that is used in the treatment of mild to moderate hypertension as well as in the treatment of angina. Nisoldipine is BCS class II drug and it is practically in soluble in water. It undergoes extensive hepatic biotransformation. This necessitates a twice daily dosage regimen which is inconvenient for maintenance therapy in asymptomatic patients. An alternative formulation of Nisoldipine that was osmotically controlled oral drug delivery approach was taken to deliver Nisoldipine in controlled manner.

Quantitative estimation of Nisoldipine was carried out using UV- visible spectrophotometry using three different dissolution medium containing 0.3 % Sodium lauryl sulphate and measuring absorbance at 236 nm.

The rate of drug release from osmotic tablet depends on the drug solubility and the osmotic pressure of the core of the tablet. So improvement of the solubility of Nisoldipine was done using β-cyclodextrin for developing the CPOP.

Dissolution enhancement of Nisoldipine was carried out using inclusion complexation. Phase solubility study was conducted as the method described by Higuchi and Connors. The study revealed that preparation of inclusion complexes may help in improving dissolution characteristics. Inclusion compexes of drug were prepared with β-cyclodextrin with different drug: β-cyclodextrin ratio by kneading method and physical mixing method. Inclusion complex prepared by kneading method showed faster dissolution rate and higher solubility compared to other method. The 1:1 ratio of drug: β-cyclodextrin was optimized. FTIR study indicated the complete inclusion of drug inside β-cyclodextrin cavity. Thus the Nisoldipine/ β-cyclodextrin inclusion complexes were used in the formulation of Controlled porosity osmotic (CPOP) tablet.

Here core tablet was prepared by wet granulation using PVP K 30 as binder. Osmotic agent like sodium chloride, potassium chloride, mannitol and lactose were tried. Drug/sodium chloride combination showed higher drug release, thus sodium chloride was chosen as osmogent in the system and its concentration was optimized.

Cellulose acetate was tried as coating polymer to form semipermeable membrane around core tablet. Various plasticizers like diethyl phthalate and dibutyl phthalate were tried out of that diethyl phthalate were chosen because it allows high permeability of membrane compared to dibutyl phthalate. The PEG 400 was chosen as pore former and its concentration was optimized. Than coating thickness was optimized. Final formulation was optimized using central composite Design Using Design of Expert (DOE) software.

Dissolution data of optimized formulation was fitted to various mathematical models to describe kinetic of drug release. Optimized formulation was found to deliver nisoldipine at zero order rates. The effect of pH, hydrodynamic condition on in vitro release of optimized batch was studied. Drug release from optimized batch was found to be independent of pH and hydrodynamic condition of release medium.

Chapter 6

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