FORMULATION AND EVALUATION OF BIOEQUIVALENT PRODUCT FOR VILOXAZINE SUSTAINED RELEASE TABLETS

A Dissertation Submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSTIY, CHENNAI

In partial fulfillment for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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CERTIFICATE

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During the project period, we found he was sincere, dedicated & hardworking. We wish him all the best & good luck in all his future endeavors.

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Acknowledgement

At the outset, I thank the God who brought this opportunity, gave me the abundance of requisite determination and strength to pursue and complete this course and dissertation successfully. It is my immense pleasure privileges to acknowledge the untold contributions, thankfully received, the blessed inspiration and the unreserved support I have had from the individual and institutional sources with whom I have been in association during the course of my last two years of pursuit I hereby take this opportunity to acknowledge all those who have helped me in the completion of this dissertation work.

I am extremely grateful to ***Dr.S.Devaraj, Chairman*** *and* ***Mr. Devanand, secretary Annaiveilankanni's Pharmacy College , Saidapet, Chennai – 600015*** *for providing me the opportunity to do my project at Steril-Gene Life Sciences (P) Ltd., Pondicherry.*

It's a fact that every mission needs a spirit of hard work and dedication but it needs to be put on the right path to meet its destination and in my case this credit goes to my respected teacher and guide, ***Dr.M.Senthil Kumar, principal , Department of pharmaceutics, Annaiveilankanni's Pharmacy College****. I am very much thankful to him for his inspiration, kind co-operation, caring attitude, timely help, valuable guidance and constant encouragement during every phase of this dissertation. His patience way of sharing knowledge, our numerous discussions support always propelled and boosted me to perform better. I would remain grateful to him.*

My sincere and heartful thanks to my teachers, ***Mrs.S.Valarmathi, Ms.Devi, Mrs.Kaniyakumari & Mrs.Kanchana*** *for their help and co-operation.*

I am extremely grateful to ***Mr. Sidharth Baid, Chief executive officer,*** *for providing me the opportunity to do my project at* ***Steril-Gene Life Sciences (P) Ltd., Pondicherry.***

I am indebted to industrial guide ***Mr.S.Selvam, Manager, Formulation R&D, Steril-Gene Life Sciences (P) Ltd.,*** *Pondicherry for allowing me to accomplish the project work in this industry. He was always there with his enthusiastic suggestions and corrections, despite of his extremely busy schedule rendered me the freedom to explore the facilities in the laboratory and utilize them up to my learning capabilities. His innovative ideas helped me to successfully complete my project and my thesis work with spontaneity and enthusiasm.*

I profoundly express my sincere thanks to ***Mr.B.Periyandavar, Manager, Analytical R&D, Steril-Gene Life Sciences (P) Ltd.,*** *Pondicherry for their valuable suggestions and kind encouragement during the dissertation work.*

I would also like to extend my sincere thanks to the entire staff of the Annaiveilankanni's pharmacy college, Saidapet, Chennai, formulation & Analytical department, Steril-Gene Life Sciences (P) Ltd., Pondicherry.

I would like to thank my friends Sasi kumar, Logan, Eswar, Subba rao, Jalachandra reddy and Arul murugan for their co-operation and help in carrying out my project work.

I thank everyone who helped me directly or indirectly in the successful completion of this dissertation.

And at last but not least my heartiest and dearest gratitude to my lovable friends Dinesh, Ashok kumar, Jenish, Marshal Joseph, Suresh babu, Srinivas rao and Anusha for their love, faith, care and support. And to my beloved friends Mohan, Balakrishna, Sujith, Sadhana and Raghunath.

I would like to express my deep sense of love and affection to my family members especially to my dad ***Mr.M.Dayalan*** *and my mom* ***Mrs.D.Syamala****, my beloved brother* ***Mr.D.Maheswaran &*** *my beloved sister* ***Mrs.P.Subha*** *for their strong piety and pantheism enable me to face the world without fear and with pedantic strength.*

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ABBREVIATIONS

nm	Nanometer
µm	Micrometer
mm	Millimeter
cm	Centimeter
µl	Micro liter
ml	Milli liter
UV	Ultra violet
USP	United States Pharmacopeia
IP	Indian Pharmacopeia
mcg	Microgram
mg	Milligram
gm	Gram
cps	Centipoise
DT	Disintegration time
FT-IR	Fourier Transform-Infra Red
rpm	Rotations per minute
ppm	Parts per million
DCP	Dicalcium Phosphate
PVP	Poly vinyl pyrrolidone
MG stearate	Magnesium Stearate
HPMC	Hydroxy Propyl Methyl Cellulose
EC	Ethyl Cellulose
HCO	Hydrogenated Castor Oil
SR	Sustained Release
HCl	Hydrochloric Acid
min	Minute
ºC	Degree Celsius
RMG	Rapid Mixer Granulator
FBP	Fluid Bed Processor
LOD	Loss on drying
RSD	Relative Standard Deviation

INTRODUCTION

INTRODUCTION

The main objective of any drug therapy is to achieve a desired concentration of drug in blood or tissue, which is therapeutically effective and non-toxic for an extended period of time. This goal can be achieved by proper design of a sustained release dosage regimen. To achieve this, new technique may be applied to design novel drug delivery systems.

Novel drug delivery systems[2] can be broadly classified into two groups

- Sustained release drug delivery system (SRDDS)
- Controlled release drug delivery system (CRDDS)

❖ SUSTAINED RELEASE DRUG DELIVERY SYSTEM (SRDDS)

SRDDS include any drug delivery system that achieves slow release of drug over an extended period of time. This leads to increase in duration of effect so that therapeutic effect is sustained.

❖ CONTROLLED RELEASE DRUG DELIVERY SYSTEM (CRDDS)

CRDDS has a meaning that goes beyond the scope of sustained action. It implies when the system is successful at maintaining constant drug levels in target tissue or cells.

The ideal goal in designing a controlled release system is to deliver drug to the desired site at a pre-determined rate according to the needs of the body, i.e. a self regulated system based on feedback control.

In general[3], the dosing interval may be increased by any one of the following:

1. By modifying the drug molecule to decrease the rate of elimination.
2. By modifying the release rate of dosage form to decrease the rate of absorption.

Both approaches seek to decrease fluctuations in plasma levels during multiple dosing allowing the dosing interval to increase without either overdosing or under dosing.

When attempts to extend the dosing interval by decreasing the rate of absorption, the formulation will be confronted with the physiological constraint of a finite residence time at the absorption site. Other factors which limit the designing of once a day dosage form are

1. Plasma half life.
2. Therapeutic index.
3. Presence of absorption window.

Only when the rate limiting step resides in the drug delivery system and not in physiological constraints, can control over drug administration be achieved.

Controlled delivery attempts to:

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.

2. Localize drug action by spatial placement of a controlled release system (usually rate controlled) adjacent to or in the diseased tissue or organ.

3. Target drug action by using carriers or chemical derivatization to deliver drugs to a particular “target” cell type.

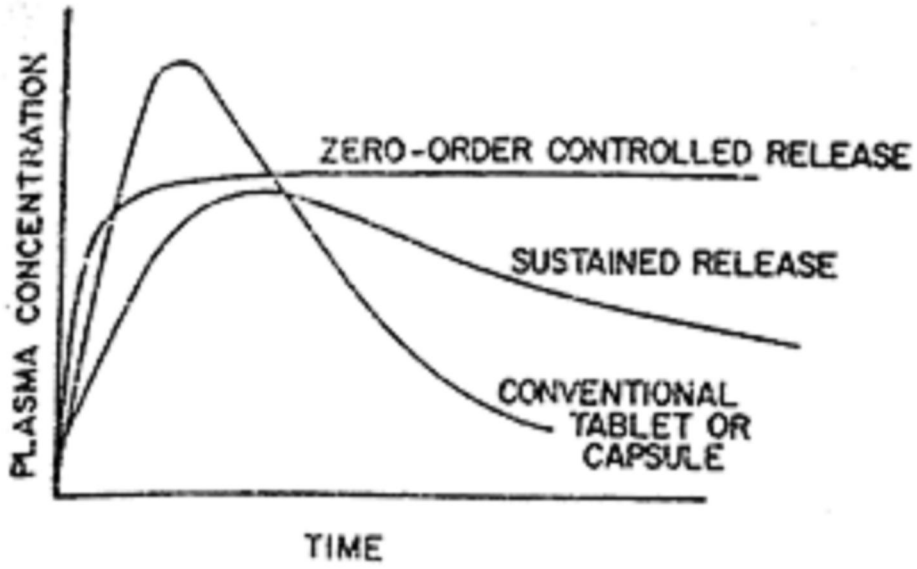
Figure no: 1 shows the comparative release of

i) Conventional tablet
ii) Sustained release tablet
iii) Controlled release tablet

In order to maintain a constant drug level in either plasma or target tissues, release rate from the controlled release system should be equal to the elimination rate from plasma or target tissue. The most conventional method to achieve a constant plasma level is the use of intravenous infusion. However, this would be inconvenient for most therapeutic situations so that other non-invasive routes such as the oral or transdermal route are preferred.

Figure No: 1

Schematic representation of release pattern of Conventional drug delivery systems, SRDDS and CRDDS.



Tablets:

The oral route is the most popular route of drug administration. The duration of a drug after oral administration is mainly a function of drug related properties such as rate of absorption and clearance as well as residence time of the delivery system at the absorption site. Most sustained release drug delivery systems developed thus far, are aimed at slowing the apparent absorption rate by reducing the drug release rate from the dosage form.

Because of limited residence time and possible existence an absorption window for some drug, control of gastrointestinal transit time and site specific release through specific binding of the drug delivery system to the absorption sites are attractive approaches to control and administration. With same expectations targeting of drugs is not the primary concern for most orally administered drugs. Rather, the aim is to increase the amount of drug delivered to, with concomitant prolongation in the general circulation. Hence, most systems employed are of the sustained release type. In cases, where systems are used to target a drug, the site of absorption rather than the site of action in targeted.

The following materials are used as retardants in matrix tablet formulations.

Types of matrix tablets and materials used in matrix tablets:

Matrix characteristics	Materials
❖ Insoluble, inert	Polyethylene, PVC, Methacrylate copolymer, ethyl cellulose.
❖ Insoluble, erodible	Carnuba wax, Stearyl alcohol, Stearic acid, PEG, Castor wax, Triglycerides, PEG monostearate.
❖ Hydrophilic	Methyl cellulose, Hydroxy ethyl cellulose, HPMC, Sodium alginate, Galactomannose.

The first class consists of retardants that form insoluble or skeleton matrices; the second class represents water insoluble materials that are potentially erodible; and the third class consists of polymers that form hydrophilic matrices. Loading doses are best included as the second layer of a two layer tablet or in coatings applied to the matrix core.

Tablets may be directly compressed from mixtures of drug and ground polymer; however if ethyl cellulose is used as matrix former, a wet granulation method using ethanol can be used. The rate limiting step in controlling release from these formulations is liquid penetration into the matrix unless channeling agents are included to promote permeation of the polymer matrix by water, which allows drug dissolution and diffusion from the channels created in the matrix.

Drug bioavailability which is critically dependent on the drug: polymer ratio may be modified by inclusion of other additives.

Design and fabrication of oral CRDDS:

A sustained release oral dosage form usually consists of two parts: An immediately available dose to establish the blood level quickly and a constraining part that contains several times the therapeutic dose for protracted drug levels. Several approaches are available to add the immediately available portion to the sustaining part. Simple addition of non-sustained dose of drug to a capsule or tablet is the most direct method; Placement of the initial dose in the tablet coat with the sustaining the portion in the core represents an alternative approach. The heart of the system, nevertheless resides with the sustaining portion of the dosage form.

Potential physiological methods that can be used to retard drug release are:

- Capsules of polymeric material filled with a solid or liquid drug in which drug release is controlled by diffusion through the capsule wall.
- A heterogeneous disruption of drug particles in a solid matrix which can be either biodegradable or non-biodegradable and which controls drug release by diffusion through the matrix, by erosion of the matrix, or by a combination of both diffusion and erosion.
- A laminate of agent and polymeric material made by coating a film of biodegradable or non-biodegradable material with solid drug and then by forming the film into a sealed "sandwich" or " jelly roll", in which drug release is by diffusion , erosion or both.
- A heterogeneous dispersion or solution of drug in a water swellable hydrogel matrix, which controls drug release by slow surface-to-center swelling of the matrix by water and subsequent diffusion of the drug from the water- swollen part of the matrix.
- Liquid- liquid encapsulation of the drug in a viscous solution of polymer, which controls drug release by slow diffusion through dilution of the medium.
- Pumps that either mechanically or chemically (osmotic pressure) provide drug in a controlled manner.
- Drug coated micro pellets which have an apparent density lower than that of gastric secretions. Thus, the final product floats on gastric secretions for an extended period, while slowly releasing drug.
- Drug contains bioadhesive polymers that adheres to the mucin coating of the gastrointestinal tract and which is retained on the surface epithelium to extend

gastrointestinal transit time of the drug. Drug is released at a constant rate from the bioadhesive polymer for subsequent absorption.

- ❖ Chemical bonding of a drug to polymer back bone by pendent amide or ester linkages, which controls the drug release by hydrolysis.
- ❖ Formation of macromolecular structures of the drug via ionic or covalent linkages, which controls drug release by hydrolysis, thermodynamic dissociation or microbial degradation.

The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug to the gastrointestinal tract.

Factors influencing the design and performance of the sustained release / controlled release products[4]:

1. Drug properties:

The physicochemical properties of a drug includes stability, solubility, partition characteristics, pH, dissociation constant charge and protein binding propensity play a dominant role in the design and performance of controlled release systems.

2. Routes of drug delivery:

The drug delivery systems in certain routes of administration can exert a negative influence on drug efficacy particularly during chronic administration and hence other routes of administration should be considered. Performance of controlled drug release systems may also influenced by physiological constraints imposed by a particular route such as first pass metabolism, gastrointestinal motility, blood supply.

3. Target sites:

In order to minimize the unwanted side effects, it is desirable to maximize the fraction of applied dose reaching the target organ or tissue. This can be partially achieved by local administration or by the use of a carrier.

4. Acute or chronic therapy:

Consideration of whether one expects to achieve cure or control of a condition and the expected length of drug therapy are important factor in designing controlled drug delivery system. Attempts to generate one year contraceptive implant present significantly different programs in design than does an antibiotic for acute infection.

5. Disease:

Pathological changes during the course of a disease can play a significant role in the design of suitable drug delivery systems.

For example, in attempting to design an ocular controlled release product for an external inflammation, the time course of changes in protein content in cellular fluids and in the integrity of the ocular barriers would have to be taken into considerations.

6. Patient:

Whether the patient in ambulatory or bedridden, young or old, obese or gaunt etc, can influence the design of a controlled release product. In implant or intramuscular injection of a drug to a bedridden patient with little muscle movement may perform in a manner significantly different from that of an ambulatory patient.

ADVANTAGES OF SRDDS AND CRDDS:

- Patient compliance.
- Minimize drug accumulations with chronic dosing.
- Minimize or eliminate local and systemic side effect.
- Improve efficiency in treatment by controlling the condition more promptly reduce the fluctuation in plasma drug level.
- Targeting the drug material towards tissues or organs or site of action.
- Prolongation of drug action.
- Precise control of response to ultra short acting drugs.
- Avoidance of first pass metabolism.
- Absorption rate independent of environmental conditions.

DISADVANTAGES OF SRDDS AND CRDDS ARE:

- Over dosing due to dose dumping by drug release.
- Sub-optimum bioavailability.
- Less flexibility in dosage adjustments.
- Prompt termination of therapy is not possible.
- High cost.
- Un predictable and often poor *in vitro-in vivo* correlation.
- Variability in drug levels.

However, in properly designed delivery system these negative aspects can be minimized to an acceptable level.

Drugs that are not suitable for SRDDS / CRDDS are:

- Drug with long biological half-life.
- Drugs with a narrow requirement for absorption.
- Drugs which are not effectively absorbed in the lower intestine.
- Drugs which are insoluble and whose availability is controlled by dissolution.

ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS[5]:

The basic concept underlying the design of oral sustained release the drug delivery system is to maintain a steady therapeutic drug level over a period of 12-24 hrs.

Different types of the oral sustained dosage forms:

Most of the oral sustained release dosage forms can be classified as follows:

- Single units (matrix tablets, coated tablets and spansules).
- Multiple units (granules, beads, micro capsules and micro spheres).
- Inert insoluble matrix.
- Hydrophilic gel matrix.
- Ion exchange resins.

Single and Multiple units:

The choice between the single unit and multiple units would depend upon the drugs and desired release pattern. For example, multiple units will exhibit less. Variable performance, especially for the enteric coated products. However, the small tablets (<2mm) in the presence of food are retained in the stomach for a much shorter time than the large tablets. The gastrointestinal time therefore, would be an important factor to consider in selecting a type of dosage form in relation to the duration of drug release and available performance.

Insoluble matrix tablets:

Inert insoluble matrix tablets are prepared from insoluble waxes such as carnuba wax, bees wax, and polymers like ethyl cellulose, cellulose acetate, stearyl alcohol and stearic acid are widely utilized in the sustained release formulation.

Hydrophilic matrix dosage formulations:

They are usually made up of cellulose, carboxy vinyl polymers, acrylate and methacrylate polymers.

Other dosage forms like coated tablets, spansules, granules, microcapsules and ion exchange resins are prepared by using various microencapsulation techniques.

In matrix devices, the solid drug is dispersed in an insoluble matrix. The rate of drug released is dependent on the rate of drug diffusion but not on the rate of solid dissolution.

The appropriate equation describing drug release from this system is as following.

$$Q = [D\varepsilon/T\,(2A - \varepsilon Cs)\,Cst]^{1/2}$$

Where;

Q – Weight in gm of drug released per unit surface area.

D – Diffusion co-efficient of drug in the release medium.

E – Porosity of matrix.

T – Totuosity of the matrix.

Cs – Solubility of the drug in the release medium.

A – Concentration of drug in tablet (g/ml).

The assumptions to derive the above equation are as follows:

1. A pseudo-steady state is maintained during release.
2. A >> Cs i.e, excess solute is present.
3. C = 0 in solution at all times (perfect sink).
4. Drug particles are much smaller than those in the matrix.
5. The diffusion co-efficient remains constant.
6. No interaction between the drug and the matrix occurs.

For purposes of data treatment, the equation is reduced to

$$Q = Kt^{1/2}$$

Therefore the plot of amount of drug released versus the square root of time should be linear if drug release from the matrix is diffusion controlled.

As in the reservoir device, it is often necessary that a portion of the drug be released quickly for immediate absorption. This is usually accomplished by placing the initial dose in the coat of the tablet. The coat and matrix can be tableted together by press-coating. In non-coated systems, the initial dose is simply tableted with the sustaining dose.

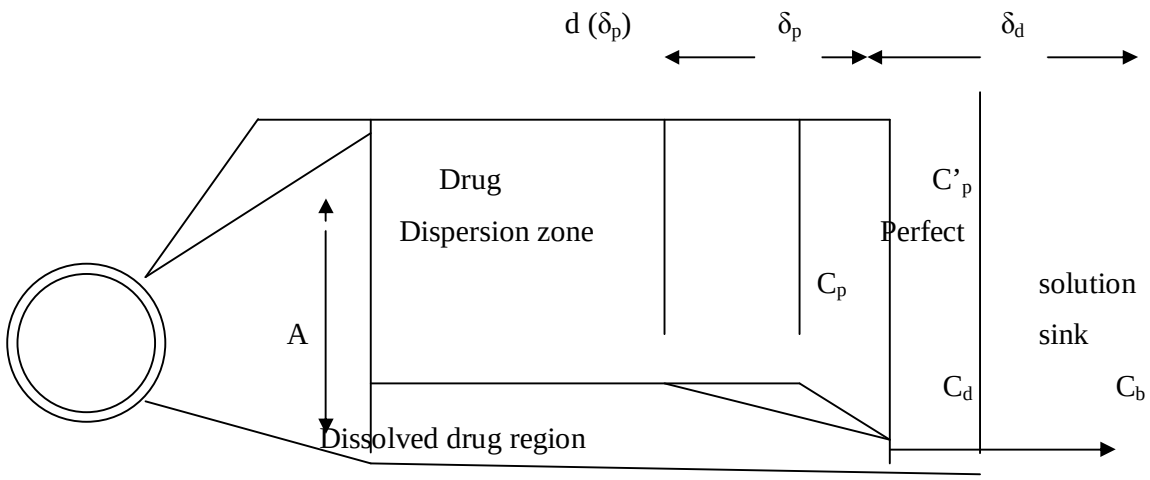
The three major types of matrix diffusion control devices are insoluble plastic, fatty and hydrophilic matrices. However, there are problems that arise from chewing an

insoluble matrix. If the drug was contained within pores and channels of a polymeric matrix following compression, then upon mastication the drug would be released very quickly. This could be dangerous in the case of drugs with a narrow therapeutic index.

In this drug delivery system, the drug is homogenously dispersed as discrete crystals or solid particles in a matrix environment formed by the cross-linking of linear polymer chains. The drug molecules elute out of the matrix only by dissolution in and then by diffusion through the polymer structure. The drug solids in the layer closer to the surface of the device are the first to elute, and when this layer becomes exhausted, the drug solid in the next layer begins to get depleted.

Figure No: 2

Schematic representation of drug dissolution.



Where;

A – Initial amount of drug solids impregnated in a unit volume of polymer matrix.

C_p – solubility of drug in polymer phase.

C'_p – concentration of drug at polymer/solution interface.

C_d - concentration of drug at solution/ polymer interface.

C_b - concentration of drug in the bulk of elution solution.

δ_p& δ_d- thickness of drug depletion zone in the matrix and of the Hydrodynamic layer on the immediate surface of the device.

d (δ_p) - differential thickness of depletion zone formed after more drug solid elute out.

Advantages:

1. A unique dual release mechanism ensures complete release of the active ingredients.
2. A high yield is obtained and tablets have elegant properties.
3. Extended day time and night time activity of the drugs.
4. Potential for reduced incidence of side effects.
5. Reduced dose frequency.
6. Increased patient compliance.

Disadvantages:

1. Not applicable to liquids.
2. Potential gastrointestinal side effects.

LITERATURE REVIEW

LITERATURE REVIEW

- **Pabon *et al* (1992)[6],** has studied the dissolution rates of mixed controlled release matrix tablets containing hydroxy propyl methyl cellulose and polyamide 12 for metaclopromide hydrochloride and a reference tablet using cellulose microcrystalline as excipient and has concluded that dissolution kinetics were markedly different for the different formulations studied depending upon the proportions of excipients.

- **Sheu *et al* (1992)[7],** has studied the effects of the media on the dissolution of diclofenac sodium from voltaren and hydroxy propyl methyl cellulose matrix tablets and has concluded that drug release from hydroxy propyl methyl cellulose matrices was non-Fickian in all media and also concluded that diclofenac release from hydrophilic and hydrophobic tablets is dependent on the dissolution media.

- **Pabon *et al* (1994)[8],** has studied the fracture and dissolution rates of matrix tablets prepared with hydroxy propyl methyl cellulose and polyamide 12 at different proportions using metaclopromide hydrochloride as model drug and has concluded that the dissolution rates was different for each formulation and depended on the specific polymer percentage.

- **Dong *et al* (1996)[9],** has studied the effect of hydroxy propyl methyl cellulose on the mechanism of soluble drug release from hydrophilic matrix tablets prepared with captopril and albuterol sulfate and confirmed that the drugs were released by non-Fickian diffusion mechanism and concluded that the different contents of hydroxy propyl methyl cellulose in the matrices only affected Higuchi release patterns.

- **Sung *et al* (1996)[10],** has studied the effect of hydroxy propyl methyl cellulose and lactose ratio and hydroxy propyl methyl cellulose viscosity grade on the release of a model drug, adinazolam mesylate and hydroxy propyl methyl cellulose from a hydroxy propyl methyl cellulose matrix tablet and concluded that with higher drug and polymer release rates found for formulations with lower polymer lactose ratio and lower polymer viscosity grades.

- **Vazquez *et al* (1996)[11],** has studied the potential value of hydroxy propyl methyl cellulose mixture as gelling agents in matrix tablets for hydro soluble drugs and the relationship between the gelling agent viscosity and the kinetics of drug release from atenolol hydrophilic matrix tablets and has concluded that all drug s release was diffusion limited.

- **Dortunc *et al* (1997)[12],** has studied the effect of polymer grade, influence of the additive magnesium stearate and lactose, particle size and pH of dissolution medium on the release of acetazolamide from a controlled release swellable tablets prepared by direct compression and found that hardness slightly increased with increasing the amount of hydroxy propyl methyl cellulose drug release decreased when the polymer amount was increased.

- **Traconis *et al* (1997)[13],** has prepared the matrix tablets containing metronidazole and 10% of polymer, different proportions of sodium carboxy methyl cellulose plus hydroxy propyl methyl cellulose or ethyl cellulose plus hydroxy propyl methyl cellulose and studied the release of metronidazole from tablet in acidic medium and found that the addition of sodium carboxy methyl cellulose produced biphasic linear kinetics, before and after the transition point, increasing in concentration of sodium carboxy methyl cellulose resulted in decreasing dissolution rates.

- **Relasco *et al* (1999)[14],** has studied the influence of drug : hydroxy propyl methyl cellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from hydroxy propyl methyl cellulose tablets and observed that the rate and mechanism of drug release matrices were mainly controlled by the drug: polymer ratio, the drug and polymer particle size influence on the drug release parameters and found that compressional force influence only on lag time.

- **Heng *et al* (2001)[15],** has studied the influence of mean hydroxy propyl methyl cellulose particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets by preparing the tablets with different concentrations of different size fractions of hydroxy propyl methyl cellulose as well as lactose and magnesium stearate and has concluded that the release of aspirin from matrix tablet formulations increased markedly when hydroxy propyl methyl cellulose particle size

was greater than 113µm and release rate was much less sensitive to changes in hydroxy propyl methyl cellulose particle size below 113µm.

- **Rao *et al* (2001)[16],** has studied the effect of SBE 7M-beta-cyclodextrin as a solubilizing agent on prednisolone, a poorly water soluble drug, release from hydroxy propyl methyl cellulose matrix tablets and found that there is enhanced drug release to a control formulation, prepared using lactose instead of SBE 7M-beta-cyclodextrin.

- **Shiva kumar *et al* (2001)[17],** has studied the effect of hydroxy propyl methyl cellulose and hydroxy ethyl cellulose on release of the cetostearyl alcohol embedded diclofenac sodium from tablets for controlled release and found that hydroxy propyl methyl cellulose and hydroxy ethyl cellulose was showing differences in their behavior in controlling the release of diclofenac sodium.

- **Obadiat AA *et al* (2002)[18],** has studied the release of dextro methorphan hydrobromide DM-HBR) from matrix tablets containing sodium CMC and hydroxy propyl methyl cellulose and found that the results obtained indicated that the nonionic hydroxy propyl methyl cellulose had little retarding effect on drug release from the matrix, anionic sodium CMC significantly reduced the release rate of the drugs. An effect which was attributed to interaction between the drug and sodium CMC due to formation of insoluble complex. The pH affected both the solubility of the drug and die erosion rate of the matrix. Combination of both HPMC and sodium CMC in optimum proportions would result in a near zero order release.

- **Reynolds *et al* (2002)[19],** has studied the effect of tablet surface area and/or volume on drug release from matrix tablets containing hydroxy propyl methyl cellulose using soluble drugs (Promethazine hydrochloride, Diphenhydramine hydrochloride, and proponalol hydrochloride) by comparing the drug release from tablets having similar values of surface area and/or volume within the same tablet shape and among different shapes and has concluded that surface area and/or volume is one of the key factor in controlling the drug release from hydroxy propyl methyl cellulose matrix tablets.

- **Sapna *et al* (2002)[20],** prepared venlafaxine hydrochloride sustained release tablets by using matrix system based on swellable and no swellable polymers such as hydroxy

propyl methyl cellulose, ethyl cellulose, cellulose acetate and eudragit RSPO were selected. Combinations of non swellable polymers were also studied with hydroxy propyl methyl cellulose for sustained release up to 16 hours. The effect of drug to polymer in vitro release was studied.

- **Al taani BM *et al* (2003)[21],** prepared pH dependent swellable and erodible-buffered matrix tablets by using hydrophilic polymers HPMC and pH dependent solubility polymer(eudragit L100-55) with different micro environment pHs. Diclofenac sodium was chosen as choice of drug. The swelling and erosion matrices containing only hydroxy propyl methyl cellulose and eudragit L100-55 were studied in phosphate buffer solution of pH similar to the microenvironment pHs of the matrices and found to be the drug release is linear as a function of time (amount of drug released was found to be higher in the medium of pH 7.4 than that of pH 5.9).

- **Amaral MH *et al* (2003)[22],** has studied the effect of water soluble carriers on naproxen release from hydrophilic matrix tablets and found that the release profile of naproxen from hydroxy propyl methyl cellulose matrices remained unchanged when lactose and PEG-4000 were added to the same drug and polymer concentrations due to the higher water solubility of PEG-4000, the erosion of compressed mixtures of hydroxy propyl methyl cellulose k-100M/ PEG-4000(1:1)was higher than the erosion of tablets containing the same proportion of lactose.

- **Chowdary KP *et al* (2003)[23],** have prepared mucoadhesive matrix tablets employing sodium CMC, hydroxy propyl methyl cellulose and EC using diltiazem as a model drug. Tablets formulated employing sodium CMC with 5% EC gave slow and complete release over a period of 12 hrs. These tablets exhibited good mucoadhesion in the intestine for 10-12 hrs in the X-Ray studies. Non-Fickian release was observed from most of the formulations (A two layer tablet formulation, an immediately releasing layer consisting of diltiazem and croscarmellose sodium (A super disintegrate) and a matrix consisting of diltiazem, sodium CMC and EC as a second maintenance layer, gave release close to the theoretical sustained release (SR) needed for diltiazem.
- **Gohel MC *et al* (2003)[24],** has prepared pH independent sustained release matrix tablets by using rate controlling polymers such as eudragit RSPO/ RlPO, HPMCK_4M.

Verapamil hydrochloride was chosen as model drug. Tablets were prepared by wet granulation method and succinic acid and KH were incorporated in the matrix in order to obtain pH independent drugs release. They found that the required release rate obtained with low level of eudragit RSPO/RLPO (30% w/w), low level of HPMC K4M (- 10% w/w), high level of PEG 4000 (15% w/w) and desired drug release pattern can be obtained by adopting a systemic formulation approach.

- **Samani SM *et al* (2003)[25],** has studied the effect of polymer blends of hydroxy propyl methyl cellulose (viscosity grades 60 and 500mpas), carbopol-940 on release profile of diclofenac sodium from matrices and found that when hydroxy propyl methyl cellulose viscosity grade (60 mpas) at higher polymer drug ratio (more than 0.8:1). The Carbopol can extend the release time appreciably best release profile have fluctuations. When an appreciate blend of hydroxy propyl methyl cellulose and Carbopol was used the drug release became more uniform and it's kinetic approached to zero order and release fluctuations were diminished.

- **Vostalova L *et al* (2003)[26],** has formulated hydrophilic matrix tablets by using hydroxy propyl methyl cellulose and other cellulose derivatives and chosen well soluble diltiazem chloride and badly soluble ibuprofen as model drugs. Evaluated and found that the formulation and manufacture variables can influence the rate of drug release from matrix. Higher solubility of the drugs and lower solubility of compacts resulted in more rapid release of the active ingredient and lower concentrations of hydroxy propyl methyl cellulose accelerates release of both drugs.

- **Bravo SA *et al* (2004)[27],** has formulated the swellable matrices for the controlled release of diclofenac sodium by using hydroxy propyl methyl cellulose and carboxy polymer (carbopol-934) as rate controlling polymers and studied for the influence of polymer content, the polymer ratio, the polymeric swelling behavior and pH changes on the release rate of diclofenac sodium. Combination of these two polymeric matrix formers resulted in near zero order release rate of diclofenac sodium. The diclofenac release from matrix tablets was pH dependent, being markedly reduced at lower pH (could be attributed to the poor solubility of diclofenac sodium at this pH values) in 0.1N HCl solution, HPMC controlled drug release. As the pH increases, both hydroxy propyl methyl cellulose and Carbomer controlled release occurs, as a result of

Carbomer became ionized being able to interact with hydroxy propyl methyl cellulose to control drug release.

- **Martinez Gonzelez *et al* (2004)[28],** has formulated matrix tablets using hydroxy propyl methyl cellulose as rate controlling polymer and 4-amino pyridine was chosen as model drug and studied for the influence of enteric coated lactose on the release profile from hydroxy propyl methyl cellulose matrix tablets were prepared by wet granulation method and found that decreasing release constant values were observed with increasing enteric coated lactose concentrations up to 9%. This is attributing to an increasing obstruction of the diffusion path by isolated enteric coated lactose particles that are insoluble in HCl and/or surrounded by a water filled space. After a critical enteric coated lactose concentrations, the water filled spaces surrounding enteric coated lactose particles percolate, producing opposite effect, increasing release constant as the enteric coated lactose proportion increases from 10-50%.

- **Cao QR *et al* (2005)[29],** have studied the effect of pharmaceutical excipients on the *in vitro* release profiles and the release mechanism of monolithic hydroxy propyl methyl cellulose (4000Cps) matrix tablets (m-HPMC), in terms of mimicking the dual drug release character of bi layered tylenol-SR tablets was studied and acetaminophen was used as the model drug. The m-HPMC tablets were prepared using wet granulation method followed by direct compression. Release profile and swelling rate of m-HPMC tablets were found to be highly influenced by the types and amounts of pharma excipients incorporated. Starch -1500 and sodium lauryl sulphate played a key role in determining the dissolution rate of m-HPMC tablets. Additional excipients i.e. MCC and sodium di hydrogen phosphate used to tune the release profile of m-HPMC tablets. The effect of excipients on the drug release from HPMC based matrix tablets was found to be mainly due to a change in hydrophilic gel expansion and on physical interaction between the drug and HPMC.

- **Genc L *et al* (2005)[30],** has prepared sustained release matrix tablets using different polymers such as hydroxy propyl methyl cellulose, carbopol-934 and eudragit-RL /PO by direct compression technique. Clarithromycin was chosen as model drug and evaluated for influence of polymer type and concentration on drug release from matrix were investigated by 23 factorial designs and found that tablets containing hydroxy

propyl methyl cellulose, carbopol-934 and eudragit-RL/PO were found suitably to sustained drug release.

- **Peng HL *et al* (2005)[31],** has formulated SR matrix tablets using carbopol-71G and m-HPMC and selected hydrochlorthiazide as model drug and studied for factors influencing dissolution rate. Tablets were prepared by wet granulation method. The factors affecting the drug release behaviors from the matrix tablets included the quantity of HPMC and carbopol-71G, tablet hardness, pH environment of the dissolution media paddle rotating speed.

- **Srivathsva AK *et al* (2005)[32],** has formulated floating matrix tablets to prolong gastric residence time and to increase drug bioavailability and tablets prepared by direct compression method by using polymers such as hydroxy propyl methyl cellulose (K-15M and K-4M), guar gum and the sodium CMC- based matrix tablets showed greater swelling indices. The tablets exhibited controlled and prolonged drug release profile while floating over the dissolution medium.

- **Pan WS *et al* (2005)[33],** has formulated acipimox sustained release matrix tablets by using hydroxy propyl methyl cellulose as a drug release retarding material and evaluated for the factors effecting the acipimox release rate from matrix including types and quantity of hydroxy propyl methyl cellulose and additives, and manufacturing procedures were evaluated and found that the types and quantity of hydroxy propyl methyl cellulose used in matrixes and the tablet surface area were closely associated with the acipimox release and the types and quantity of additives and manufacturing procedure(eg: dissolution apparatus rotating speed) showed low significant effect on acipimox release. The diffusion factor place a main role in the entire dissolution slow release of drugs obeys Non-Fickian diffusion mechanism.

- **Vueba ML et al (2005)[34],** has studied the influence of different cellulose ether polymers such as release rate of ibuprofen from hydrophilic matrix tablets [methyl cellulose (MC 25), Hydroxy propyl cellulose (HPC) and HPMC (K 15M and K 100M)]. In addition the influence of diluents- lactose mono hydrate (LAC) and small be cyclodextrin(b-CD) was evaluated, polymers MC-25 and HPC were found to be unsuitable for the preparation of this kind of solid dosage forms, while hydroxy propyl

methyl cellulose K-15M and K-100M showed to be advantageous. The highest MDT (mean dissolution time) obtained with hydroxy propyl methyl cellulose indicating higher drug retarding ability of the polymer. The release process was also found to be slightly influenced by the kind of diluents used.

- **Harish NM *et al* (2006)[35],** has developed sustained matrix tablets by using hydroxy propyl methyl cellulose, eudragit RLPO as rate controlling polymers. Terbutaline sulphate was chosen as model drug. Tablets were prepared by wet granulation method and evaluated for flow properties of granules, compressibility index, swelling index and drug content and *in vitro* studies for drug release and found that granules showed that satisfactory flow properties, compressibility and drug content. The optimized formulation could extend release up to 12 hrs and these optimized formulations showed similar release profile as that of the marketed formulation.

- **Haremath SN *et al* (2007)[36],** has formulated metformin hydrochloride matrix tablets by using different viscosity grades and ratios of hydroxy propyl methyl cellulose and evaluated mainly to assess the effect of drug polymer ratio and hydroxy propyl methyl cellulose viscosity grade and the release of drug from hydrophilic matrices and found that the lower viscosity grade polymer showed a rapid drug release from the matrices than the higher viscosity grades. The higher drug polymer ratio showed a greater drug release than the others.

AIM

&

OBJECTIVE

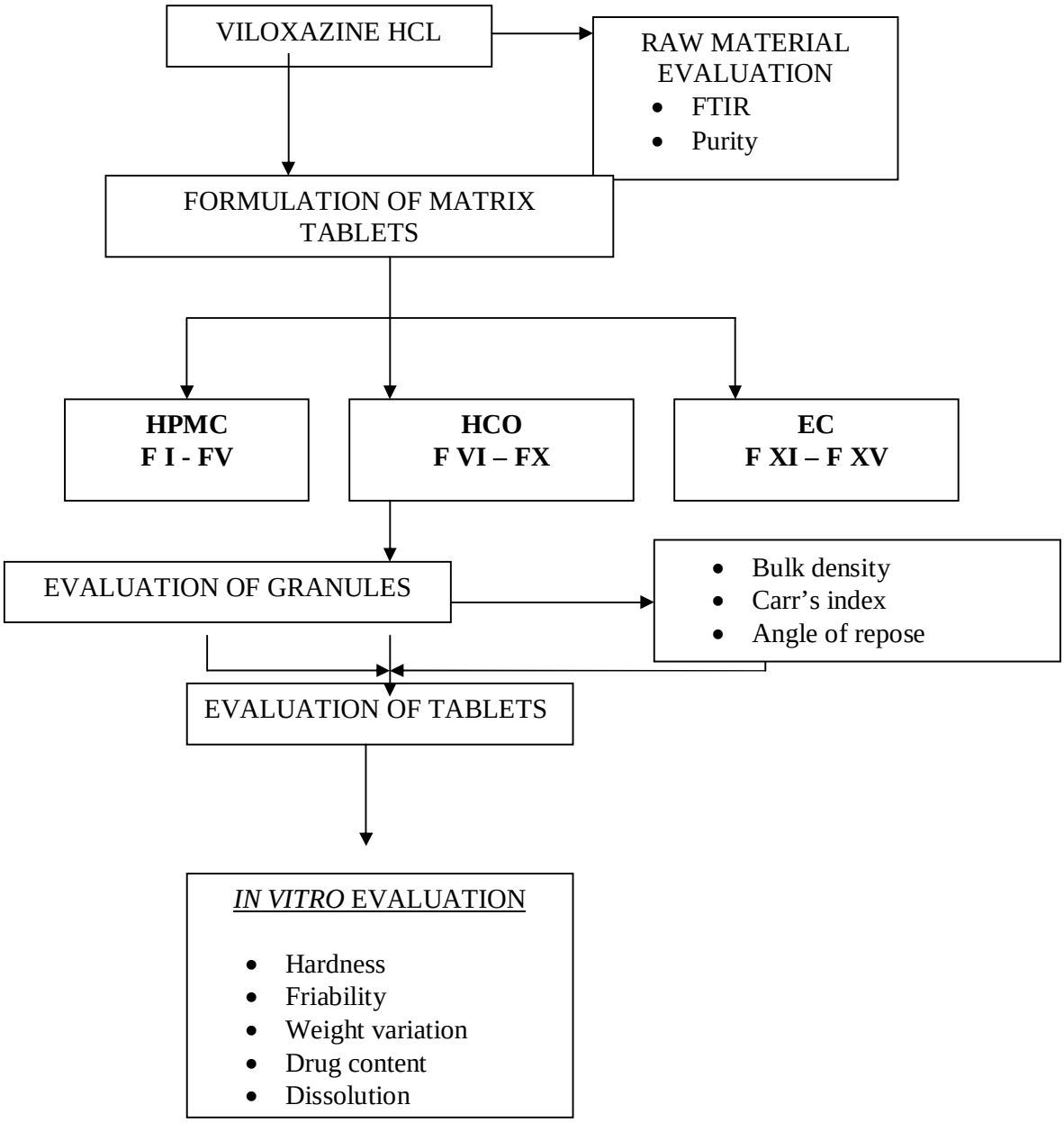
AIM & OBJECTIVE OF THE WORK

Viloxazine is a bicyclic antidepressant morpholine derivative that acts as a selective norepinephrine reuptake inhibitor (NRI). It is a racemic compound with two stereoisomers, the (*S*)-(–)-isomer being five times as pharmacologically active as the (*R*)-(+)-isomer. Recommended daily dose is 100mg in two or three divided doses. If necessary, it may increase up to 150mg. Due to its low biological half life it requires frequent administration, hence extended release dosage forms are formulated to reduce dosing frequency thereby improving patient's compliance.

The main objective of this work is to formulate sustained release matrix tablets by adopting wet granulation method using HPMC, HCO and EC as retarding materials at different concentrations. All the formulations are to be assayed for drug content and *in vitro release* for the best amongst these formulations.

PLAN OF WORK

PLAN OF WORK


VILOXAZINE HCL
RAW MATERIAL EVALUATION
FTIR
Purity
FORMULATION OF MATRIX TABLETS
HPMC
F I - FV
HCO
F VI – FX
EC
F XI – F XV
EVALUATION OF GRANULES
Bulk density
Carr's index
Angle of repose
EVALUATION OF TABLETS
IN VITRO EVALUATION
Hardness
Friability
Weight variation
Drug content
Dissolution

DRUG PROFILE

DRUG PROFILE [37, 38,39,40,41]

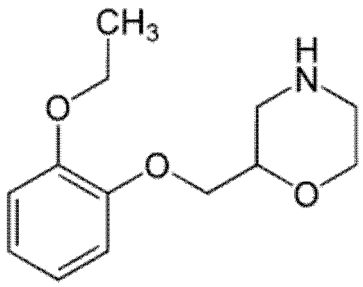
Name:

Viloxazine Hydrochloride

Category:

Anti-depressant

Structure:



.HCL

Chemical name:

(*RS*)-2-[(2-ethoxyphenoxy) methyl] morpholine

Molecular formula:

$C_{13}H_{19}NO_3$ HCL

Molecular weight:

273.8

Characteristics:-

Appearance:

White to off-white crystalline powder.

Solubility:

Soluble in Acetic acid, Methanol and Water.

Standards:

Viloxazine Hydrochloride contains not less than 95.0% w/w and not more than 105%w/w of $C_{13}H_{19}NO_3$ (Calculated with reference to anhydrous substance).

Therapeutic uses:

Viloxazine Hydrochloride is used in the treatment of depression.

Mechanism of action:

- It is a Nor-adrenaline reuptake inhibitor (NRI).
- It also weakly inhibits the dopamine re-uptake.
- It is also reported to have little affinity for Muscarinic, Histaminirgic or α_1-adrenergic receptors.

Pharmacokinetics:-

Absorption:

The drug is readily absorbed from the GIT. Following oral administration, it undergoes extensive first pass metabolism in the liver mainly to the active metabolite O-desmethyl Viloxazine. Peak plasma concentrations of Viloxazine and O-desmethyl Viloxazine appear about 2 and 4 hours after administration respectively.

Distribution:

Protein bindings of Viloxazine and O-desmethyl Viloxazine are low. (Approximately 25%).

Metabolism:

The drug following oral administration, it undergoes extensive first pass metabolism in the liver mainly to the active metabolite O-desmethyl Viloxazine. Formation of O-desmethyl Viloxazine is mediated by the CytochromeP-450 isoenzyme CYP2D6. Other metabolites include N-desmethyl Viloxazine and N, O-di desmethyl Viloxazine.

Elimination:

The mean plasma elimination half life of Viloxazine and O-desmethyl Viloxazine 6 and 8 hrs respectively. Viloxazine is excreted predominantly in the form of its metabolites, either free or in conjugated form, about 2% is excreted in the faecus.

Side effects:

Nausea, Dizziness, dry mouth, Sexual dis-function, may cause sustained rise in BP, needs BP monitoring.

Precautions:

- ❖ It should be used with caution in those with history of myocardial infraction or unstable heart disease.
- ❖ It should also be used with caution in patients with a history of epilepsy and should be discontinued in any patient developing a seizure.

Drug interaction:

Viloxazine is known to increase plasma levels of phenytoin by an average of 37%.It is also known to significantly increase plasma levels of theophylline and decrease its clearance from the body, sometimes resulting in accidental overdose of theophylline.

Availability:

Available in the form of conventional tablets, extended release tablets and capsules.

Packaging and Storage:

Store in air tight container and protected from light.

Marketed Brand Names:

1. **Vivalan** SR tablets.
2. **Emovit** XR capsules.
3. **Vivarint** CR tablets.
4. **Vicilan** XR capsules.

- Austria: Vivarint;
- Belgium: Vivalan;
- Czech Republic: Vivalan;
- France: Vivalan;
- Germany: Vivalan;
- Italy: Vicilan;
- Portugal: Vivalan;
- Spain: Vivarint;
- United Kingdom: Vivalan;

EXICIPIENTS PROFILE

EXICIPIENTS PROFILE

HYDROXY PROPYL METHYL CELLULOSE[42]

Synonyms:

Cellulose, Hydroxy propyl methyl ether, Culminal MHPC, E464, Methocel, HPMC, Methyl cellulose propylene glycol ether, Methyl hydroxy propyl cellulose, Metolose, Pharmacoat.

Chemical name:

Cellulose 2- hydroxy propyl methyl ether.

Empherical formula:

O-methylated and O-(2- hydoxypropylated) cellulose.

Molecular weight:

10000 - 1500000

Description:

It is odorless, tasteless, white or creamy-white colored fibrous or granular powder.

Pharmaceutical specifications:-

pH:

5.5 to 8.0(1 %w/w solution).

Solubility:

Soluble in cold water forming viscous colloidal solution, in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane. Practically insoluble in chloroform, ethanol, ether.

Melting point:

190-200^{0}C

Moisture content:

It absorbs moisture from atmosphere.

Specific gravity:

1-26

Stability:

It is stable, although it is hygroscopic after drying. It is stable between pH 3 – 11. Increasing temperature reduces viscosity. Aqueous solutions are enzyme resistant but prone to microbial spoilage. HPMC powder should be stored in a well closed container, in a cool dry place.

Incompatibility:

It is incompatible with some oxidizing agents. It doesn't complex with any metallic salts and inorganic compounds forming insoluble precipitates.

Safety:

It is non-toxic and non-irritant, but excessive oral consumption has laxative effect.

Applications in pharmaceutical formulations or technology:

- In tabletting technology, 2–5% w/w is used as binder and 2– 10% w/w of polymer is used in film coating. Higher viscosity grades may be used in matrix tablet to retard the water soluble drug release.

- In ophthalmic preparations, it is used as thickening and suspending agent.

- In topical gels and ointments, used as emulsifier, suspending and stabilizing agent.

- Used as film former in tablet dosage form.

HYDROGENATED CASTOR OIL[42]

Non proprietary names:

USPNF: hydrogenated castor oil.

Synonym:

Castor wax, Castor wax MP70, Castor wax MP80, Opal wax, Simulsol.

Chemical name:

Glyceryl-tri-(12- hydroxy stearate)

Empherical formula:

$C_{55}O_9H_{110}$

Molecular weight:

939.50

Functional category:

Extended release agent, stiffening agent, tablet and capsule lubricant.

Description:

It occurred as white color powder or flakes.

Properties:-

Melting point range:

85- 88°C

Specific gravity:

1.023

Moisture content:

≤ 0.1 %

Solubility:

Insoluble in water, soluble in acetone and chloroform.

Incompatibilities:

It is compatible with most natural vegetable and animal waxes. No incompatibilities are reported in the literature.

Stability and Storage:

- It is stable at temperature up to 150^0C. Clear stable chloroform solutions containing up to 15 % w/v of hydrogenated castor oil may be produced.

- It may also be dissolved at temperatures greater than 90^0C.

- Store in a well closed container in a cool dry place.

Application in pharmaceutical field:

- It has hard, high melting point range which is used in oral and topical pharmaceutical formulations.

- In oral formulations, it is used to prepare sustained release tablets and capsule preparations. It is used as a coat or to form a solid matrix. It is additionally used to lubricate the die walls of tablet presses. It is also used in cosmetics.

- In topical formulations, it is used to provide stiffness to creams and emulsions.

ETHYL CELLULOSE[42]

Synonyms:

Aqua coat, E462, Ethocel, Surelease.

Chemical name:

Cellulose ethyl ether.

Functional category:

Coating agent, tablet binder, viscosity increasing agent.

Description:

Ethyl cellulose is a tasteless, free flowing white to light tan coloured powder.

Properties:-

Density:

0. 4 g/cm^3

Glass transition temperature:

130-133^oC

Hygroscopicity:

Absorbs very little water at high relative humidity.

Solubility:

Practically insoluble in glycerin, propylene glycol and water. Freely soluble in chloroform, ethanol, methanol, toluene, methyl acetate, tetrahydrofuran and in mixture of aromatic hydrocarbon with ethanol 95%.

Specific gravity:

1.12-1.15

Incompatibilities:

Incompatible with paraffin wax & microcrystalline wax. No incompatibilities are reported in the literature.

Storage condition:

Ethyl cellulose is a stable, slightly hygroscopic material. It should be stored in a dry place, in a well-closed container at a temperature between 7-32°C.

Applications in pharmaceutical field:

It is used as a coating agent for hygroscopic tablets and granules. It is used to modify the release of a drug to improve the stability of formulation.

POLYVINYL PYRROLIDONE (PVP K-90)[42]:

Polyvinyl pyrrolidone is white creamy white, odorless, hygroscopic powder. It is used as tablet blender, suspending agent or viscosity increasing agent. In tabletting, PVP solutions are used as binders in wet granulation process. PVP is also added to powder blends in the dry form and granulated to situ by the addition of water, alcohol PVP solutions may also be used as coating agent. It is incomplete in solution with a wide range of inorganic salts, natural and synthetic resins and other chemicals. The efficacy of some

preservatives, eg: thiomersol may be adversely affected by the formulation of complexes with PVP.

MAGNESIUM STEARATE[42]:

It is fine white, precipitated or milled, impalpable powder with faint characteristic odor and greasy to touch, it is slightly soluble in warm benzene and warm ethanol but insoluble in water and ether. It is used as lubricant in capsules and tablet granules.

TALC[42]:

Talc is purified, hydrated, magnesium silicate but may contain small amount of aluminium silicate and iron. It is a very fine powder, which is white to grayish white colored, odorless, impalpable and crystalline. It is widely used as a lubricant in oral solid dosage forms.

COLLOIDAL SILICON DIOXIDE[42]:

Colloidal silicon dioxide is submicroscopic fumed silica, with a particle size of about 15 nm. It is a light, loose, bluish-white colored, odorless, tasteless, non gritty amorphous powder. It is used as a glidant to improve the flow properties of dry powder in tabletting.

ISOPROPYL ALCOHOL[42]

Synonym:

Dimethyl carbinol.

Chemical name:

Propan-2-ol.

Empherical formula:

C_3H_8O

Molecular weight:

60.1

Structural formula:

$(CH_3)_2CHOH$

Category:

Disinfectant, solvent.

Description:

Clear, colorless, mobile, volatile flammable liquid with characteristic spirituous odor. Resembling that of a mixture of ethanol and acetone .It has slightly bitter taste.

Solubility:

It is miscible with Benzene, Chloroform, Ethanol, Glycerin and water. It is soluble in salt solutions.

Incompatibility:

It is incompatible with oxidizing agent such as hydrogen peroxide and nitric acid, which cause decomposition. It may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulphide and other salts or the addition of sodium hydroxide.

Stability:

Stored in air tight contains in a cool dry place.

PURIFIED WATER[42]**:** It is a clear, colorless, odorless and tasteless liquid miscible in all polar solvents and widely used solvent vehicle for many formulations.

MATERIALS & METHODS

Table No: 1

LIST OF MATERIALS

S.NO	Name of chemical	Manufacturing company
1	Viloxazine hydrochloride	Gift sample from Lloyd pharma labs, Philippines.
2	Hydroxy propyl methyl cellulose K-100M	S. D fine chem. Ltd., Mumbai
3	Hydrogenated castor oil	S. D fine chem. Ltd., Mumbai
4	Ethyl cellulose 45cps	S. D fine chem. Ltd., Mumbai
5	Di calcium phosphate	S. D fine chem. Ltd., Mumbai
6	Poly vinyl pyrrolidone K-90	S. D fine chem. Ltd., Mumbai
7	Iso propyl alcohol	S. D fine chem. Ltd., Mumbai
8	Magnesium stearate	S. D fine chem. Ltd., Mumbai
9	Aerosil	S. D fine chem. Ltd., Mumbai
10	Purified Talc	S. D fine chem. Ltd., Mumbai
11	Acetone	S. D fine chem. Ltd., Mumbai
12	Hydrochloric acid	S. D fine chem. Ltd., Mumbai
13	Disodium hydrogen phosphate	S. D fine chem. Ltd., Mumbai
14	Potassium dihydrogen phosphate	S. D fine chem. Ltd., Mumbai

Table No: 2

LIST OF EQUIPMENTS

S.No	Name of Equipment	Manufacturing company
1	Electronic balance	Remi Motors Ltd, Mumbai.
2	Sonicator (bath)	Enertech, Chennai.
3	Magnetic stirrer	Remi Motors Ltd, Mumbai.
4	Tabletting machine	Cadmach, Mumbai.
5	Vernier calipers	Digimatic calipers, Japan.
6	Hardness tester	Monsanto Mumbai.
7	Friabilator	Electrolab Mumbai.
8	Dissolution apparatus	Electrolab Mumbai.
9	Hot air oven	Minicon Mumbai.
10	PH meter	EL instruments Chennai.
11	UV spectrometer	Shimadzu, UV- 1601.
12	High Performance Liquid Chromatography	Shimadzu Prominence, LC 10AT (Pump) SPD10A (Detector).
13	Fourier Transform Infrared Spectrometer	AB.Bomem model no. MB 104, Canada.
14	Centrifuge	Remi equipments RM12C, Mumbai.
15	Humidity cabinet	Sigma instruments, Mumbai.
16	Water bath	Indian Scientific, Mumbai.
17	Compression Machine	Cadmach 20 Station, Ahmedabad.

IDENTIFICATION TEST FOR VILOXAZINE HCL[40]

(Raw material evaluation)

Description:

White to off white crystalline powder**.**

Solubility:

Freely soluble in Acetic acid, Methanol, and in water.

Melting point:

Viloxazine HCL melting point was fond to be 185-186°C using melting point apparatus.

Percentage of purity:

Viloxazine HCL contains not less than 98% w/w and not more than 101%w/w calculated with reference to the anhydrous substance.

A. It gives reaction (a) of chlorides.

Tests:-

Alkalinity or acidity:

Dissolve 0.20gm in carbon-di-oxide free water and dilute to 10ml with the same solvent .add 0.05ml of methyl red solution and 0.1ml of 0.01M HCl. The solution is pink, not more than 0.2ml of 0.01M NaOH is required to change the colour of the indicator to yellow.

Assay method by HPLC*:*

pH 3.0 Buffer: Dissolve 3.4 gms of potassium di hydrogen phosphate anhydrous in 700ml of water, add 5ml of triethanolamine, mix well and adjust pH to 3.0 with phosphoric acid.

Mobile phase: Mix pH3.0 buffer and acetonitrile in the ratio 70:30 v/v.

Diluent: Methanol

Standard preparation: Dissolve 58mg of Viloxazine hydrochloride in 50ml of diluent, pipette 5ml and dilute to 50ml with water (100ppm).

Test preparation: Transfer the sample content equivalent 116mg of Viloxazine in 100ml flask, add 70ml of diluent and sonicate for 40mins dilute to volume with the same solvent and centrifuge or filter.

Dilute 5ml of above solution to 50ml with water.

HPLC conditions:

Wavelength: 220nm
Column: Princeton sphere C18, 250 x 4.6mm, 5µm
Flow Rate: 1.0ml/min
Column Temperature: Ambient
Injection volume: 40 µl
Run time: 10min

Identification of VILOXAZINE HCL by Infrared spectroscopy:

Comparison: If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in 2-propanol evaporates to dryness and record new spectra using the residues.

CALIBRATION GRAPH OF VILOXAZINE HYDROCHLORIDE IN 0.1 N HCl.

Preparation of 0.1N HCl

Take 8.5ml of concentrated Hydrochloric acid in 1000 ml volumetric flask and make up the volume up to 1000ml with distilled water.

Procedure for calibration graph

100 mg of Viloxazine hydrochloride was dissolved in 100 ml of 0.1 N HCl and further dilutions were made to obtain concentration ranging from 1 mcg/ml to 10mcg/ml. The absorbance of the solution were measured at 273 nm using SHIMADZU UV-Visible spectrophotometer .The readings obtained were recorded in Table No: 3 and graphically represented in Figure No: 3.

LRA (Linear Regression Analysis) was performed to obtain equation for straight line.

X = Y + 0.0038 / 0.0344

Correlation coefficient was found to be 0.98 which when compared with given standard values is considered as best fit.

CALIBRATION GRAPH OF VILOXAZINE HYDROCHLORIDE IN PHOSPHATE BUFFER pH 6.8

Preparation of Phosphate buffer pH 6.8

Weigh accurately 28.80 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate dissolved in distilled water and make up to 1000 ml with distilled water.

Procedure for calibration graph

100 mg of Viloxazine hydrochloride was dissolved in 100 ml of phosphate buffer pH 6.8 and further dilutions were made to obtain concentration ranging from 1 mcg/ml to 10mcg/ml. the absorbance of the solution were measured at 273 nm using SHIMADZU UV-Visible spectrophotometer. The readings obtained were recorded in Table No: 4 and graphically represented in Figure No: 4.

LRA (Linear Regression Analysis) was performed to obtain equation for straight line.

X = Y - 0.005/.0503

Correlation coefficient was found to be 1 which when compared with given standard values is considered as best fit.

COMPATIBILITY BETWEEN DRUG AND OTHER TABLET COMPONENTS

Viloxazine hydrochloride was mixed uniformly with different components used in formulation of tablet. The drug polymer mixture was kept under conditions of relative temperature 25^0-30^0C and relative humidity 75% for 70 days and the mixture was checked for any visible physical change and IR.

The results are graphically represented in Figure No: 5, 6, 7 & 8.

FORMULATION OF MATRIX TABLETS

All formulations were prepared according to Table no: 6.The tablets are prepared as per the procedure given below and aim is to sustain the release of Viloxazine hydrochloride.

Procedure:

1. Viloxazine hydrochloride, polymers (HPMC K100M, HCO, EC 45cps), Dicalcium phosphate were triturated well and allowed to pass through sieve no.30 and mixed thoroughly.

2. Polyvinyl pyrollidone K-90 dissolved in Isopropyl alcohol was used as binder, the granules were prepared by wet granulation method after passing through sieve no.16.

3. The granules thus obtained were dried at 60 ^{0}C.

4. The dried granules were passed through sieve no.16 and then added with the lubricants like talc, magnesium stearate and aerosil.

5. The granules were compressed to get tablets of average weight 200 mg using double punching machine.

EVALUATION OF GRANULES[43, 44]

The formulated Viloxazine hydrochloride granules were analyzed for its bulk density and flow properties.

Bulk density:

Bulk density is the ratio of weight of the powder to the bulk volume it occupies; expressed in gm/ml. 20 gm of the granules were weighed and poured into a 100ml-measuring cylinder. This is called as bulk density or poured bulk density which is given as,

$$\rho_b = \frac{M}{V_b}$$

Where;

M = mass of granules.

V_b = bulk volume.

Results are reproduced in Table No: 7.

Angle of repose:

The prepared granules were assessed for its flow property by determining the angle of repose. The angle of repose was measured by allowing the granules to fall over a graph paper placed on horizontal surface through a funnel. Kept at a certain convenient height about (6cm). The height of the heap was measured and then circumference of the base of heap was drawn on graph paper with the help of a pencil. The radius of the circle obtained was measured.

The angle of repose was given as,

$$\mathbf{Tan\ \theta = h / r}$$

Where;

θ – Angle of repose.

h – Height of the heap.

r – Radius of the base of the heap.

The results are tabulated in the Table No: 7.

Carr's index:

The percent compressibility of granules was determined by Carr's compressibility index.

Percent of Carr's index =

$$\frac{\text{[Tapped bulk density – poured bulk density]}}{\text{[Tapped bulk density]}} \times 100$$

Tapped bulk density = Mass of granules / tapped volume of packing

Poured density = Mass of granules / volume of packing

The results are tabulated in the Table No: 7.

EVALUATION OF THE TABLETS[43, 44]

The formulated tablets were evaluated for the following physico chemical characteristics.

General appearance:

The formulated tablets were assessed for its general appearance.

Thickness and Diameter:

Thickness and Diameter of the formulated matrix tablets were measured by using Vernier Calipers.
The results were tabulated in Table No: 8.

Weight variation:

The formulated tablets were tested for weight uniformity. 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with the average weight to ascertain whether it is within permissible limits or not.
The results are tabulated in the Table No: 9 to13.

Hardness:

Hardness of the tablets was determined using the Monsanto hardness tester. The lower the plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along the gauge in the barrel to indicate the force.
The results are tabulated in the Table No: 14.

Friability:

The Roche friability test apparatus was used to determine the friability of the prepared tablets. 20 pre-weighed tablets were placed in the apparatus, which was given 100 revolutions. After which the tablets were re-weighed. The percentage friability was calculated.

Percentage of friability =

$$\frac{\text{(Pre-weight) – (post-weight)}}{\text{(Pre-weight)}} \times 100$$

The results are tabulated in the Table No: 14.

Drug content:

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 40mg of Viloxazine was transferred into a 100ml volumetric flask and extracted with distilled water. Then it was filtered and suitable dilutions were made and absorbance was measured by using Shimadzu UV-Visible spectrophotometer (UV-1601) at 273nm.

The results were tabulated in Table No: 15.

In vitro dissolution studies of Viloxazine hydrochloride matrix tablets

In Acid medium:

900ml of 0.1N HCl was placed in a dissolution basket and the USP standard apparatus I was assembled. The medium was allowed to equilibrate to the temperature 37± 0.5°C.

One tablet was placed in the jar and the jar was covered with lid. The apparatus was operated for 2 hours at 100 rpm. At definite time intervals 5ml of the receptor fluid was withdrawn, suitable dilutions were made with 0.1N HCl and analyzed spectrophotometrically at 270 nm using SHIMADZU UV- Visible spectrophotometer.

In buffer medium:

900ml of phosphate buffer pH 6.8 was replaced in a dissolution basket which was prepared as per IP. The medium was allowed to equilibrate to the temperature 37± 0.5°C.

The tablets obtained after dissolution in acid stage were placed in the medium and dissolution was carried out at 100 rpm. At definite time intervals 5ml of the receptor fluid was withdrawn, suitable dilutions were made with phosphate buffer pH 6.8 and analyzed spectrophotometrically at 270nm using SHIMADZU UV- Visible spectrophotometer. The amount of drug released was calculated from the calibration curve.

The results are shown in Table No.16-30 and graphically represented in Figure No: 9-11.

The same procedure is repeated for Viloxazine hydrochloride marketed SR tablet. The results are shown in Table No.31 and graphically represented in Figure No: 12.

Table No: 3

Calibration data of Viloxazine Hydrochloride in 0.1N Hydrochloric acid

S. No	Concentration (mcg/ml)	Absorbance At 270nm
1	1	0.044
2	2	0.071
3	3	0.105
4	4	0.141
5	5	0.174
6	6	0.210
7	7	0.244
8	8	0.280
9	9	0.315
10	10	0.351

Table No: 4

Calibration data of Viloxazine hydrochloride in Phosphate buffer pH 6.8

S. No	Concentration (mcg/ml)	Absorbance At 270nm
1	1	0.051
2	2	0.102
3	3	0.172
4	4	0.200
5	5	0.252
6	6	0.305
7	7	0.357
8	8	0.405
9	9	0.451
10	10	0.515

Table No: 5

Quantity Per Tablet (mg)															
Formulations															
S. No	**Ingredients**	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**	**XII**	**XIII**	**XIV**	**XV**
1	Viloxazine HCl	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
2	Hydroxy propyl methyl cellulose, HPMC(k-100)	12.50	25.00	37.50	50.00	62.50	----	----	----	----	----	----	----	----	----	----
3	Hydrogenated Castor Oil	----	----	----	----	----	12.50	25.00	37.50	50.00	62.50	----	----	----	----	----
4	Ethyl cellulose 45cps	----	----	----	----	----	----	----	----	----	----	12.50	25.00	37.50	50.00	62.50
5	Poly vinyl pyrrolidone(k-90)	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00
6	Dicalcium phosphate	116.50	104.00	91.50	79.00	66.50	116.50	104.00	91.50	79.00	66.50	116.50	104.00	91.50	79.00	66.50
7	Purified talc	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
8	Magnesium stearate	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
9	Aerosil	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
10	Total	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00

Table No: 6

DRUG POLYMER RATIOS

S. No.	Polymer	Formulation	Drug : Polymer
1.	Hydroxy propyl methyl cellulose K-100M	F I	1:0.25
2.		F II	1:0.50
3.		F III	1:0.75
4.		F IV	1:1.00
5.		F V	1:1.25
6.	Hydrogenated castor oil	F VI	1:0.25
7.		F VII	1:0.50
8.		F VIII	1:0.75
9.		F IX	1:1.00
10.		F X	1:1.25
11.	Ethyl cellulose 45cps	F XI	1:0.25
12.		F XII	1:0.50
13.		F XIII	1:0.75
14.		F XIV	1:1.00
15.		F XV	1:1.25

Table No: 7

EVALUATION OF GRANULES

S.NO	Formulation	Angle of Repose	Bulk Density	Carr's index
1	F-I	29.25	0.47	7.57
2	F-II	25.64	0.45	7.87
3	F-III	28.81	0.43	8.24
4	F-IV	27.92	0.46	8.33
5	F-V	27.92	0.44	9.73
6	F-VI	29.25	0.51	7.63
7	F-VII	29.25	0.52	7.81
8	F-VIII	28.37	0.53	8.78
9	F-IX	27.92	0.54	7.59
10	F-X	27.92	0.50	7.21
11	F-XI	26.57	0.51	8.91
12	F-XII	27.92	0.48	9.11
13	F-XIII	29.25	0.49	8.40
14	F-XIV	27.02	0.48	9.03
15	F-XV	27.92	0.52	8.31

Limits: Angle of Repose ≈ 25-30° indicates free flowing material
Carr's index 5-15% indicates free flowing material

Table No: 8

THICKNESS AND DIAMETER MEASUREMENT

S.NO	Formulations	Thickness mm	Diameter mm
1	F-I	3.2	8.0
2	F-II	3.5	8.4
3	F-III	3.4	8.2
4	F-IV	3.2	8.1
5	F-V	3.6	8.3
6	F-VI	3.6	8.5
7	F-VII	3.3	7.8
8	F-VIII	3.4	7.9
9	F-IX	3.3	8.0
10	F-X	3.3	8.5
11	F-XI	3.6	8.6
12	F-XII	3.4	8.5
13	F-XIII	3.2	8.2
14	F-XIV	3.5	7.9
15	F-XV	3.4	8.3

Table No: 9

UNIFORMITY OF WEIGHT

S.NO	Formulation-I		Formulation-II		Formulation-III	
	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation
1	203	1.0956	201	0.2493	202	0.4975
2	200	-0.3984	200	-0.2493	200	-0.4975
3	202	0.5976	200	-0.2493	201	0.0000
4	205	2.9163	199	-0.7481	199	-0.9950
5	199	-0.8964	201	0.2493	200	-0.4975
6	200	-0.3984	202	0.7481	200	-0.4975
7	203	1.0956	200	-0.2493	201	0.0000
8	202	0.5976	202	0.7481	202	0.4975
9	200	-0.3984	201	0.2493	200	-0.4975
10	199	-0.8964	200	-0.2493	204	1.4925
11	200	-0.3984	200	-0.2493	203	0.9950
12	200	-0.3984	199	-0.7481	200	-0.4975
13	201	0.0996	199	-0.7481	200	-0.4975
14	200	-0.3984	203	1.2468	199	-0.9950
15	202	0.5976	198	-1.2468	204	1.4925
16	203	1.0956	201	0.2493	201	0.0000
17	200	-0.3984	200	-0.2493	203	0.9950
18	199	-0.8964	202	0.7481	200	-0.4975
19	200	-0.3984	202	0.7481	200	-0.4975
20	198	-1.3944	200	-0.2493	201	0.0000
Average weight of Tablet	200.8		200.5		201.0	

I.P Limits: Weight variation should not vary beyond ±7.5 % of standard value.

Table No: 10

UNIFORMITY OF WEIGHT

S.NO	Formulation-IV		Formulation-V		Formulation-VI	
	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation
1	200	-0.099	201	0.149	200	-0.199
2	203	1.398	200	-0.348	201	0.299
3	201	0.399	200	-0.348	200	-0.199
4	200	-0.099	199	-0.847	202	0.798
5	199	-0.599	198	-1.345	198	-1.197
6	200	-0.099	201	0.149	202	0.798
7	197	-1.598	202	0.647	201	0.299
8	199	-0.599	203	1.145	200	-0.199
9	200	-0.099	202	0.647	198	-1.197
10	205	2.397	200	-0.348	201	0.299
11	199	-0.599	200	-0.348	200	-0.199
12	200	-0.099	201	0.149	202	0.798
13	201	0.399	198	-1.345	200	-0.199
14	196	-2.097	203	1.145	201	0.299
15	199	-0.599	202	0.647	200	-0.199
16	202	0.899	202	0.647	200	-0.199
17	202	0.899	200	0.348	200	-0.199
18	200	-0.099	201	0.149	202	0.798
19	200	-0.099	200	-0.348	202	0.798
20	198	-1.098	201	0.149	198	-1.197
Average weight of Tablet	200.2		200.7		200.4	

I.P Limits: Weight variation should not vary beyond ±7.5 % of standard value.

Table No: 11

UNIFORMITY OF WEIGHT

S.NO	Formulation-VII		Formulation-VIII		Formulation-IX	
	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation
1	201	0.199	201	0.349	200	-0.049
2	200	-0.299	200	-0.149	202	0.949
3	202	0.697	200	-0.149	201	0.449
4	202	0.697	199	-0.649	199	-0.549
5	199	-0.797	201	0.349	200	-0.049
6	200	-0.299	202	0.848	200	-0.049
7	201	0.199	200	-0.149	201	0.449
8	202	0.697	201	0.349	202	0.949
9	200	-0.299	203	1.347	200	-0.049
10	199	-0.797	200	-0.149	199	-0.549
11	200	-0.299	200	-0.149	198	-1.049
12	200	-0.299	199	-0.649	200	-0.049
13	201	0.199	199	-0.649	200	-0.049
14	200	-0.299	203	1.347	199	-0.549
15	202	0.697	198	-1.148	201	0.449
16	203	1.196	201	0.349	198	-1.049
17	200	-0.299	200	-0.149	201	0.449
18	201	0.199	198	1.148	200	-0.049
19	200	-0.299	201	0.349	200	-0.049
20	199	-0.797	200	-0.149	201	0.449
Average weight of Tablet	200.6		200.3		200.1	

I.P Limits: Weight variation should not vary beyond ±7.5 % of standard value.

Table No: 12

UNIFORMITY OF WEIGHT

S.NO	Formulation-X		Formulation-XI		Formulation-XII	
	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation
1	199	-0.500	200	0.050	199	-0.698
2	201	0.500	201	0.550	200	-0.199
3	200	0.000	200	0.050	200	-0.199
4	200	0.000	200	0.050	199	-0.698
5	199	-0.500	202	1.050	201	0.299
6	200	0.000	201	0.550	199	-0.698
7	201	0.500	203	1.550	203	1.297
8	199	-0.500	200	0.050	201	0.299
9	200	0.000	200	0.050	202	0.798
10	200	0.000	200	0.050	202	0.798
11	200	0.000	200	0.050	200	-0.199
12	201	0.500	198	-0.950	200	-0.199
13	199	-0.500	198	-0.950	200	-0.199
14	202	1.000	201	0.550	199	-0.698
15	198	-1.000	200	0.050	202	0.798
16	202	1.000	199	-0.450	199	-0.698
17	201	0.500	200	0.050	202	0.798
18	200	0.000	195	-2.451	198	-1.197
19	200	0.000	199	-0.450	202	0.798
20	198	-1.000	201	0.550	200	-0.199
Average weight of Tablet	200.0		199.9		200.4	

I.P Limits: Weight variation should not vary beyond ±7.5 % of standard value.

Table No: 13

UNIFORMITY OF WEIGHT

S.NO	Formulation-XIII		Formulation-XIV		Formulation-XV	
	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation	Weight Of Each Tablet(mg)	Percentage Deviation
1	200	-0.149	196	-2.000	201	0.249
2	201	0.349	200	0.000	200	-0.249
3	199	-0.649	201	0.500	202	0.748
4	200	-0.149	201	0.500	201	0.249
5	199	-0.649	200	0.000	201	0.249
6	200	-0.149	199	-0.500	200	-0.249
7	200	-0.149	200	0.000	199	-0.748
8	202	0.848	200	0.000	200	-0.249
9	201	0.349	197	-1.500	201	0.249
10	201	0.349	201	0.500	199	-0.748
11	202	0.848	200	0.000	201	0.249
12	200	-0.149	203	1.500	202	0.748
13	201	0.349	197	-1.500	200	-0.249
14	198	-1.148	202	1.000	199	-0.748
15	199	-0.649	199	-0.500	200	-0.249
16	200	-0.149	203	1.500	201	0.249
17	202	0.848	202	1.000	199	-0.748
18	200	-0.149	199	-0.500	203	1.246
19	200	-0.149	200	0.000	201	0.249
20	201	0.349	200	0.000	200	-0.249
Average weight of Tablet	200.3		200.0		200.5	

I.P Limits: Weight variation should not vary beyond ±7.5 % of standard value.

Table No: 14

HARDNESS AND FRIABILITY

S.NO	Formulation	Percentage Friability	Hardness (N)
1	F-I	0.36	85
2	F-II	0.41	90
3	F-III	0.45	95
4	F-IV	0.38	85
5	F-V	0.42	90
6	F-VI	0.54	90
7	F-VII	0.48	85
8	F-VIII	0.42	90
9	F-IX	0.49	85
10	F-X	0.61	90
11	F-XI	0.31	85
12	F-XII	0.42	90
13	F-XIII	0.48	85
14	F-XIV	0.36	95
15	F-XV	0.45	90

Limits:

- The hardness of about 50N is considered minimum for uncoated tablets.
- Friability weight loss should not more than 1%.

Table No: 15

DRUG CONTENT IN TABLETS

S.NO	Formulation	Amount of drug (mg) in matrix tablets			
		Sample1	Sample2	Sample3	Mean±S.D
1	I	40.6	40.8	40.57	40.99±1.03
2	II	40.5	40.3	39.25	39.35±1.82
3	III	40.3	39.8	40.91	40.67±0.78
4	IV	40.6	40.6	39.49	40.23±1.59
5	V	40.1	40.7	40.53	40.11±0.86
6	VI	40.9	40.6	40.15	40.55±0.83
7	VII	40.9	39.5	40.29	40.23±0.70
8	VIII	40.0	40.6	40.73	40.11±0.77
9	IX	40.5	40.3	40.21	40.67±0.72
10	X	40.5	40.6	39.27	39.79±1.32
11	XI	40.8	40.8	39.41	40.67±1.20
12	XII	39.4	40.6	40.69	40.23±0.72
13	XIII	40.7	39.6	39.75	39.35±1.49
14	XIV	40.1	39.9	39.37	39.79±0.38
15	XV	40.2	40.6	40.53	40.11±0.79

Table No: 16

In vitro drug release of formulation F I

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.115	3.23	14.55	34.64±0.41
2	2	0.149	4.22	19.16	45.62±0.43
3	3	0.046	0.82	23.03	54.85±0.50
4	4	0.078	1.45	25.93	61.76±0.50
5	5	0.113	2.15	29.14	69.39±0.53
6	6	0.146	2.80	32.20	76.68±0.72
7	7	0.178	3.44	35.20	83.83±0.62
8	8	0.191	3.70	36.54	87.01±0.36
9	9	0.193	3.74	36.90	87.88±0.09
10	10	0.203	3.94	37.98	90.45±0.56
11	11	0.206	4.00	38.45	91.56±0.37
12	12	0.209	4.06	38.91	92.68±0.76
13	24	0.209	4.06	39.12	93.16±0.22

Table No: 17

In vitro drug release of formulation F II

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.096	2.68	12.06	30.65±0.4
2	2	0.129	3.64	16.51	41.96±0.68
3	3	0.056	1.01	19.69	50.03±0.20
4	4	0.089	1.67	22.69	57.67±0.34
5	5	0.126	2.41	26.09	66.29±0.60
6	6	0.179	3.46	30.95	78.65±0.75
7	7	0.193	3.74	32.37	82.27±0.44
8	8	0.209	4.06	33.99	86.38±0.58
9	9	0.221	4.29	35.27	89.62±0.73
10	10	0.23	4.47	36.29	92.22±0.28
11	11	0.23	4.47	36.51	92.78±0.41
12	12	0.23	4.47	36.73	93.35±0.60
13	24	0.231	4.49	37.05	94.15±0.45

Table No: 18

In vitro drug release of formulation F III

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.085	2.36	10.62	26.12±0.45
2	2	0.111	3.12	15.70	38.60±0.36
3	3	0.035	0.60	18.84	46.31±0.59
4	4	0.073	1.35	22.53	55.38±0.34
5	5	0.092	1.73	24.33	59.81±0.44
6	6	0.129	2.47	28.06	68.99±0.33
7	7	0.152	2.92	30.40	74.75±0.60
8	8	0.163	3.14	31.56	77.59±0.40
9	9	0.182	3.52	33.48	82.32±0.30
10	10	0.194	3.76	34.70	85.32±0.33
11	11	0.205	3.98	35.82	88.09±0.43
12	12	0.209	4.06	36.25	89.12±0.44
13	24	0.225	4.37	37.85	93.07±0.52

Table No: 19

In vitro drug release of formulation F IV

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.058	1.58	7.09	17.62±0.32
2	2	0.078	2.16	10.86	27.00±0.46
3	3	0.035	0.60	13.95	34.67±0.39
4	4	0.073	1.35	17.76	44.14±0.38
5	5	0.097	1.83	20.21	50.23±0.26
6	6	0.121	2.31	22.69	56.39±0.22
7	7	0.139	2.66	24.31	60.42±0.21
8	8	0.158	3.04	26.50	65.88±0.57
9	9	0.177	3.42	28.62	71.15±0.78
10	10	0.197	3.82	30.74	76.42±0.33
11	11	0.215	4.17	32.70	81.29±0.73
12	12	0.225	4.37	33.88	84.22±0.38
13	24	0.278	5.43	39.48	98.14±0.36

Table No: 20

In vitro drug release of formulation F V

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.033	0.85	3.82	9.29±0.40
2	2	0.056	1.52	6.87	16.71±0.52
3	3	0.039	0.68	9.47	23.04±0.38
4	4	0.075	1.39	12.72	30.95±0.31
5	5	0.111	2.11	16.01	38.96±0.61
6	6	0.139	2.66	18.63	45.31±0.18
7	7	0.185	3.58	22.87	55.64±0.48
8	8	0.209	4.06	25.20	61.30±0.32
9	9	0.239	4.65	28.09	68.32±0.48
10	10	0.268	5.23	30.91	75.20±0.91
11	11	0.279	5.45	32.16	78.23±0.24
12	12	0.293	5.73	33.68	81.94±0.91
13	24	0.352	6.90	39.25	95.47±0.79

Table No: 21

In vitro drug release of formulation F VI

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.115	3.23	14.55	35.01±0.17
2	2	0.135	3.81	17.32	42.14±0.47
3	3	0.035	0.60	20.36	49.52±0.47
4	4	0.075	1.39	23.96	58.29±0.79
5	5	0.098	1.85	26.09	63.47±0.61
6	6	0.129	2.47	28.96	70.44±0.62
7	7	0.175	3.38	33.20	80.75±0.42
8	8	0.205	3.98	36.05	87.69±0.81
9	9	0.209	4.06	36.61	89.04±0.28
10	10	0.211	4.10	36.99	89.97±0.70
11	11	0.211	4.10	37.19	90.47±0.17
12	12	0.211	4.10	37.40	90.97±0.36
13	24	0.213	4.14	37.78	91.90±0.23

Table No: 22

In vitro drug release of formulation F VII

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.095	2.65	11.93	29.66±0.49
2	2	0.118	3.32	15.07	37.46±0.40
3	3	0.041	0.72	18.46	45.88±0.31
4	4	0.075	1.39	21.54	53.53±0.43
5	5	0.103	1.95	24.11	59.93±0.62
6	6	0.126	2.41	26.27	65.29±0.28
7	7	0.171	3.30	30.41	75.60±0.41
8	8	0.192	3.72	32.46	80.68±0.50
9	9	0.211	4.10	34.34	85.36±0.65
10	10	0.213	4.14	34.73	86.32±0.41
11	11	0.215	4.17	35.11	87.28±0.73
12	12	0.215	4.17	35.32	87.80±0.44
13	24	0.225	4.37	36.42	90.54±0.45

Table No: 23

In vitro drug release of formulation F VIII

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.085	2.36	10.62	25.84±0.39
2	2	0.097	2.71	12.31	30.60±0.33
3	3	0.032	0.54	14.86	36.94±0.52
4	4	0.052	0.93	16.68	41.45±0.62
5	5	0.089	1.67	20.03	49.79±0.27
6	6	0.105	1.99	21.55	53.56±0.86
7	7	0.141	2.70	24.87	61.81±0.21
8	8	0.175	3.38	28.04	69.71±0.37
9	9	0.201	3.90	30.54	75.91±0.49
10	10	0.213	4.14	31.81	79.06±0.61
11	11	0.215	4.17	32.19	80.02±0.31
12	12	0.218	4.23	32.67	81.21±0.95
13	24	0.258	5.03	36.46	90.63±0.76

Table No: 24

In vitro drug release of formulation F IX

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.043	1.14	5.13	12.61±0.27
2	2	0.068	1.87	8.46	20.79±0.55
3	3	0.037	0.64	11.47	28.21±0.90
4	4	0.068	1.25	14.28	35.11±0.28
5	5	0.1	1.89	17.20	42.30±0.80
6	6	0.121	2.31	19.18	47.15±0.65
7	7	0.158	3.04	22.60	55.57±0.59
8	8	0.198	3.84	26.33	64.75±0.48
9	9	0.222	4.31	28.67	70.50±0.29
10	10	0.236	4.59	30.14	74.11±0.47
11	11	0.245	4.77	31.17	76.65±0.60
12	12	0.258	5.03	32.58	80.10±0.61
13	24	0.309	6.04	37.39	91.94±0.42

Table No: 25

In vitro drug release of formulation F X

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.032	0.82	3.69	9.27±0.29
2	2	0.052	1.40	6.35	15.95±0.41
3	3	0.032	0.54	8.44	21.20±0.46
4	4	0.068	1.25	11.68	29.36±0.20
5	5	0.1	1.89	14.61	36.72±0.42
6	6	0.121	2.31	16.58	41.68±0.25
7	7	0.142	2.72	18.58	46.69±0.70
8	8	0.198	3.84	23.72	59.62±0.28
9	9	0.222	4.31	26.06	65.50±0.33
10	10	0.245	4.77	28.34	71.21±0.99
11	11	0.258	5.03	29.74	74.73±0.77
12	12	0.271	5.29	31.15	78.29±0.34
13	24	0.332	6.50	36.87	92.67±0.18

Table No: 26

In vitro drug release of formulation F XI

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.096	2.68	12.06	29.66±0.50
2	2	0.125	3.52	15.99	39.31±0.83
3	3	0.037	0.64	19.02	46.77±0.64
4	4	0.095	1.79	24.24	59.61±0.80
5	5	0.132	2.52	27.64	67.97±0.96
6	6	0.178	3.44	31.88	78.40±0.28
7	7	0.211	4.10	35.01	86.08±0.25
8	8	0.228	4.43	36.73	90.32±0.23
9	9	0.231	4.49	37.22	91.53±0.23
10	10	0.233	4.53	37.63	92.52±0.44
11	11	0.234	4.55	37.94	93.30±0.04
12	12	0.234	4.55	38.17	93.86±0.64
13	24	0.235	4.57	38.49	94.64±0.60

Table No: 27

In vitro drug release of formulation F XII

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.087	2.42	10.88	27.05±0.37
2	2	0.105	2.94	13.36	33.21±0.68
3	3	0.037	0.64	16.37	40.69±0.79
4	4	0.067	1.23	19.09	47.44±0.18
5	5	0.121	2.31	23.98	59.61±0.60
6	6	0.142	2.72	25.97	64.56±0.62
7	7	0.195	3.78	30.85	76.69±0.42
8	8	0.231	4.49	34.26	85.16±0.55
9	9	0.238	4.63	35.11	87.28±0.36
10	10	0.241	4.69	35.61	88.52±0.34
11	11	0.243	4.73	36.02	89.55±0.20
12	12	0.244	4.75	36.35	90.36±0.26
13	24	0.251	4.89	37.21	92.51±0.46

Table No: 28

In vitro drug release of formulation F XIII

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.081	2.24	10.10	25.66±0.31
2	2	0.101	2.83	12.83	32.60±0.07
3	3	0.028	0.46	15.03	38.20±0.36
4	4	0.051	0.91	17.11	43.49±0.53
5	5	0.085	1.59	20.20	51.33±0.25
6	6	0.125	2.39	23.86	60.63±0.11
7	7	0.151	2.90	26.30	66.84±0.33
8	8	0.173	3.34	28.42	72.21±0.41
9	9	0.221	4.29	32.88	83.55±0.52
10	10	0.241	4.69	34.88	88.64±0.16
11	11	0.243	4.73	35.29	89.69±0.53
12	12	0.244	4.75	35.62	90.52±0.42
13	24	0.251	4.89	36.48	92.72±0.81

Table No: 29

In vitro drug release of formulation F XIV

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.066	1.81	8.14	20.45±0.42
2	2	0.088	2.45	11.10	27.91±0.65
3	3	0.029	0.50	13.45	33.80±0.95
4	4	0.065	1.19	16.62	41.76±0.79
5	5	0.085	1.59	18.46	46.40±0.34
6	6	0.125	2.39	22.12	55.60±0.56
7	7	0.158	3.04	25.19	63.32±0.25
8	8	0.193	3.74	28.48	71.57±0.53
9	9	0.226	4.39	31.62	79.46±0.33
10	10	0.248	4.83	33.80	84.96±0.53
11	11	0.253	4.93	34.49	86.69±0.61
12	12	0.256	4.99	35.01	87.98±0.46
13	24	0.268	5.23	36.33	91.31±0.45

Table No: 30

In vitro drug release of formulation F XV

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.055	1.49	6.70	16.29±0.07
2	2	0.076	2.10	9.52	23.16±0.99
3	3	0.035	0.60	12.30	29.93±0.99
4	4	0.069	1.27	15.37	37.40±0.32
5	5	0.103	1.95	18.48	44.95±0.76
6	6	0.131	2.50	21.08	51.28±0.06
7	7	0.158	3.04	23.62	57.46±0.37
8	8	0.193	3.74	26.91	65.45±0.27
9	9	0.226	4.39	30.05	73.09±0.20
10	10	0.248	4.83	32.23	78.41±0.46
11	11	0.259	5.05	33.46	81.39±0.23
12	12	0.272	5.31	34.87	84.83±0.54
13	24	0.311	5.92	38.05	95. 62±0.80

Table No: 31

In vitro drug release of Marketed formulation

S.No	Time(hrs)	Absorbance	Concentration (mcg/ml)	Cumulative release(mg)	Cumulative Percentage drug release±SD
1	1	0.051	1.37	6.17	15.35±0.43
2	2	0.074	2.04	9.25	23.00±0.06
3	3	0.042	0.74	12.73	31.64±0.59
4	4	0.081	1.51	16.26	40.41±0.53
5	5	0.105	1.99	18.48	45.93±0.28
6	6	0.142	2.72	21.89	54.41±0.21
7	7	0.169	3.26	24.44	60.75±0.15
8	8	0.194	3.76	26.84	66.72±0.56
9	9	0.219	4.25	29.26	72.74±0.1
10	10	0.241	4.69	31.45	78.16±0.23
11	11	0.265	5.17	33.83	84.08±0.13
12	12	0.273	5.33	34.80	86.51±0.52
13	24	0.314	6.14	38.74	96.29±0.15

Figure No: 3

CALIBRATION OF VILOXAZINE HYDROCHLORIDE

IN 0.1N HCI

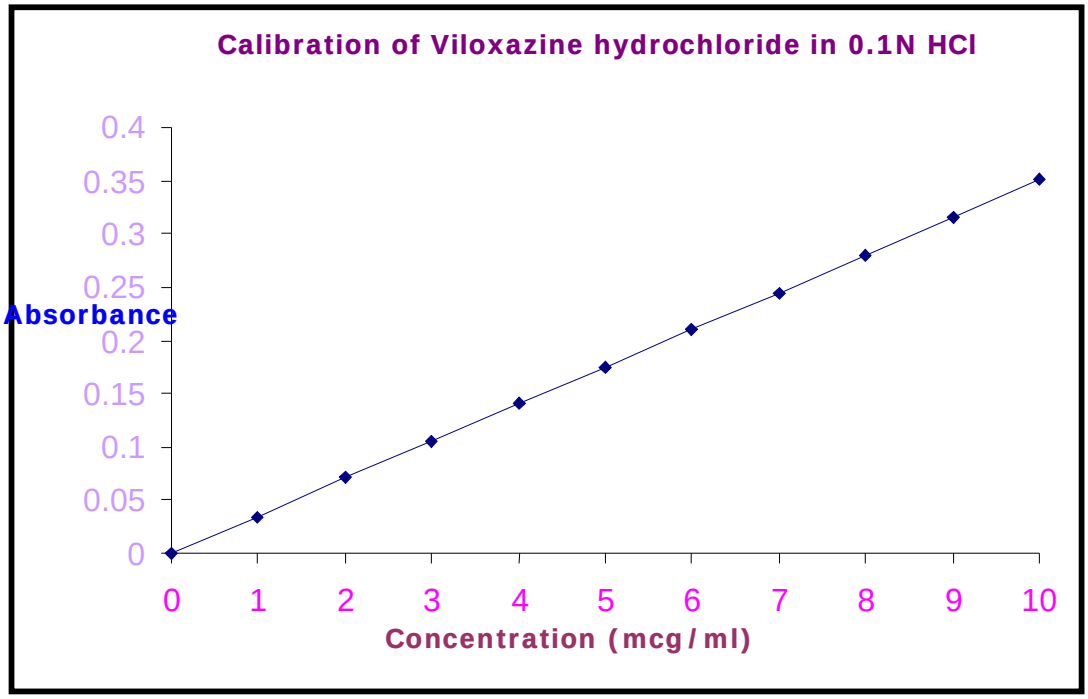


Figure No: 4

CALIBRATION OF VILOXAZINE HYDROCHLORIDE IN PHOSPHATE BUFFER pH 6.8

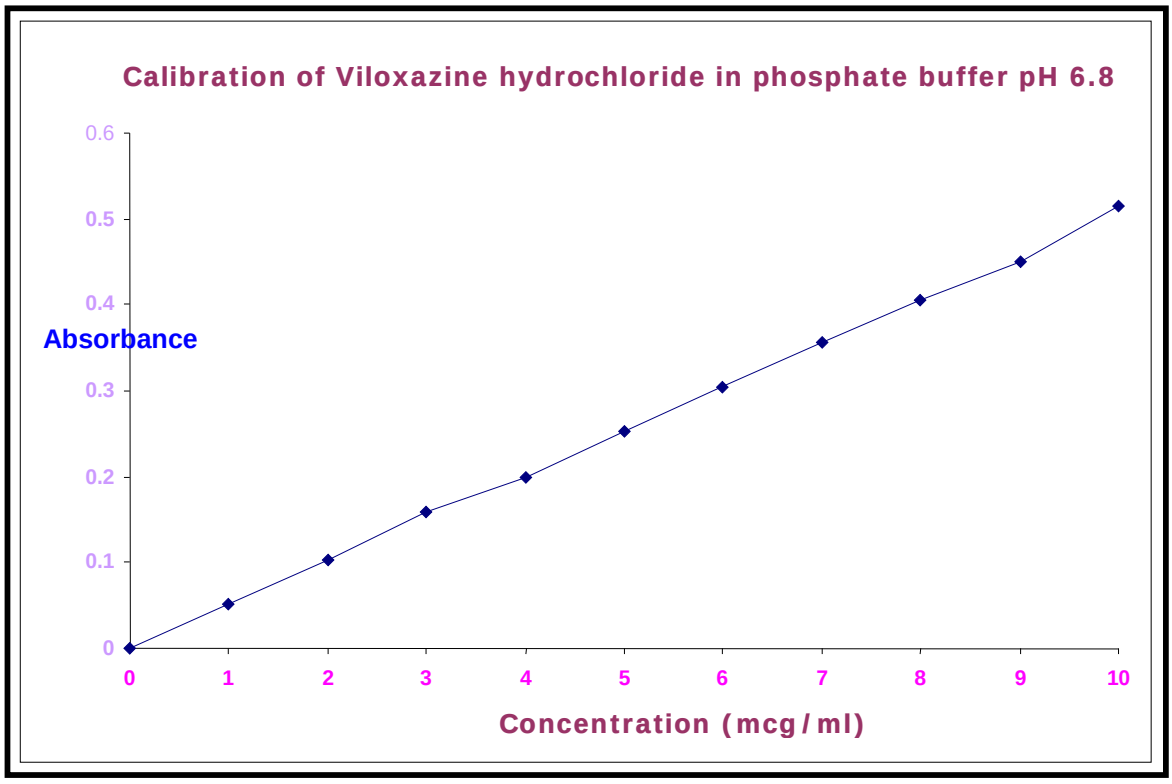


Figure No: 5

FT-IR spectrum of Viloxazine Hydrochloride

DR.CEEAL ANALYTICAL LAB Mode = 2 (Mid-IR)

Sample Description: VILOXAZINE HCL

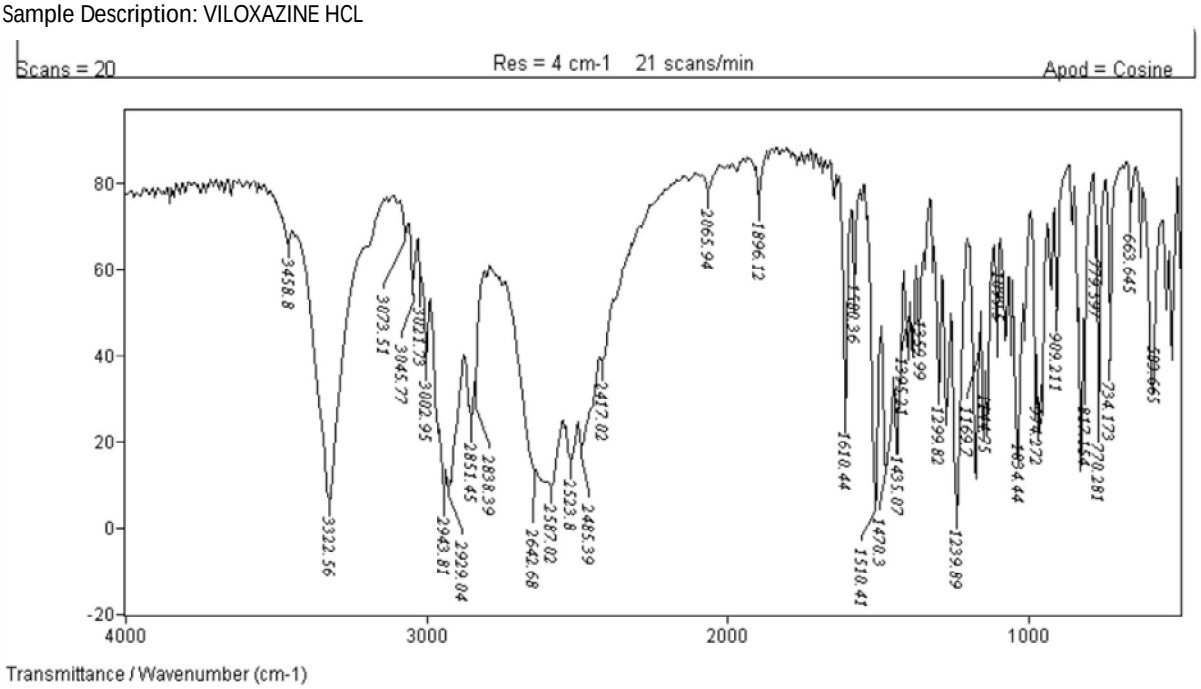


Figure No: 6

FT-IR spectrum of Viloxazine Hydrochloride with HPMC and other excipients

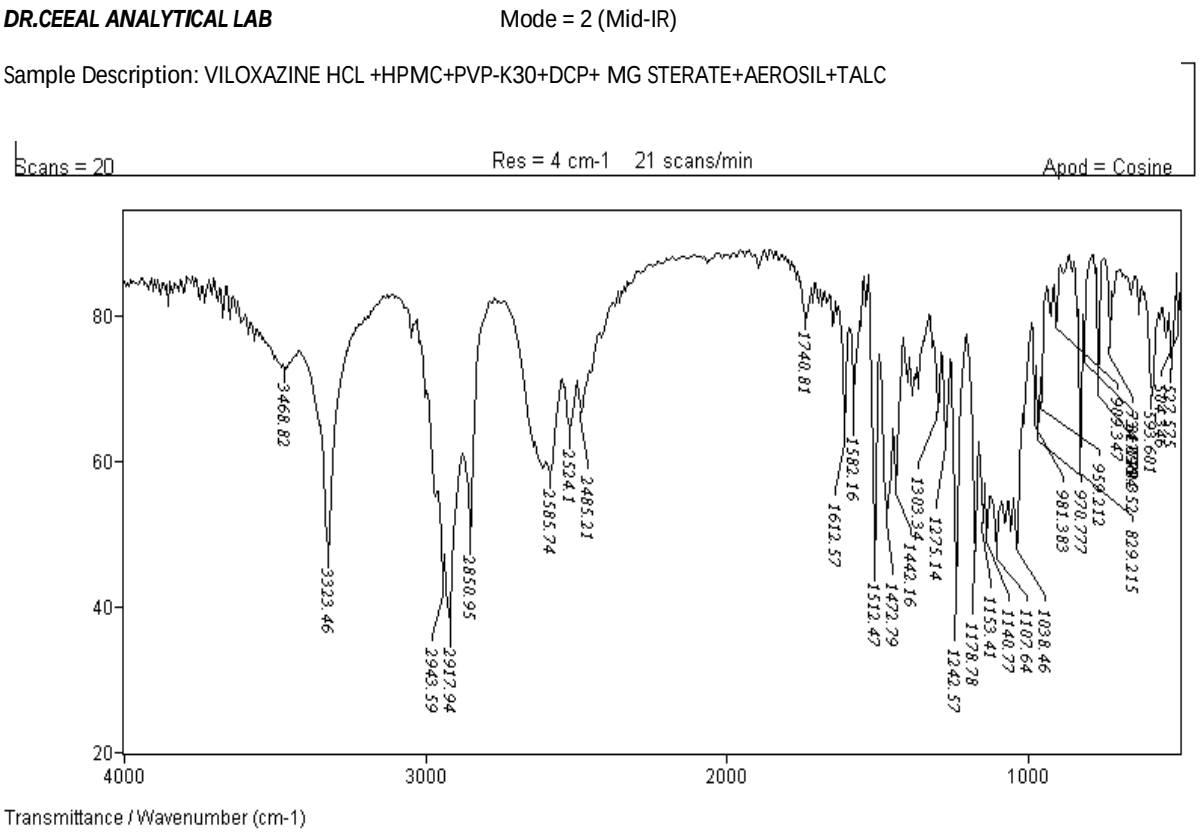
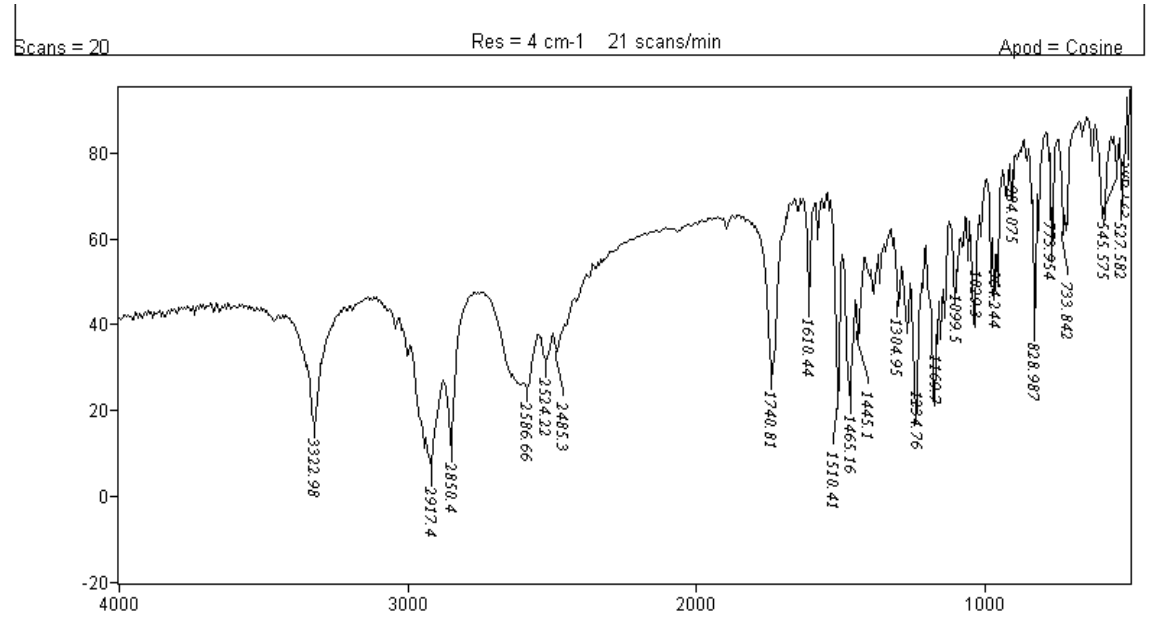


Figure No: 7

FT-IR spectrum of Viloxazine Hydrochloride with HCO and other excipients

DR.CEEAL ANALYTICAL LAB Mode = 2 (Mid-IR)

Sample Description: VILOXAZINE HCL +HCO+PVP-K30+DCP+ MG STERATE+AEROSIL+TALC



Transmittance / Wavenumber (cm-1)

Figure No: 8

FT-IR spectrum of Viloxazine Hydrochloride with EC and other excipients

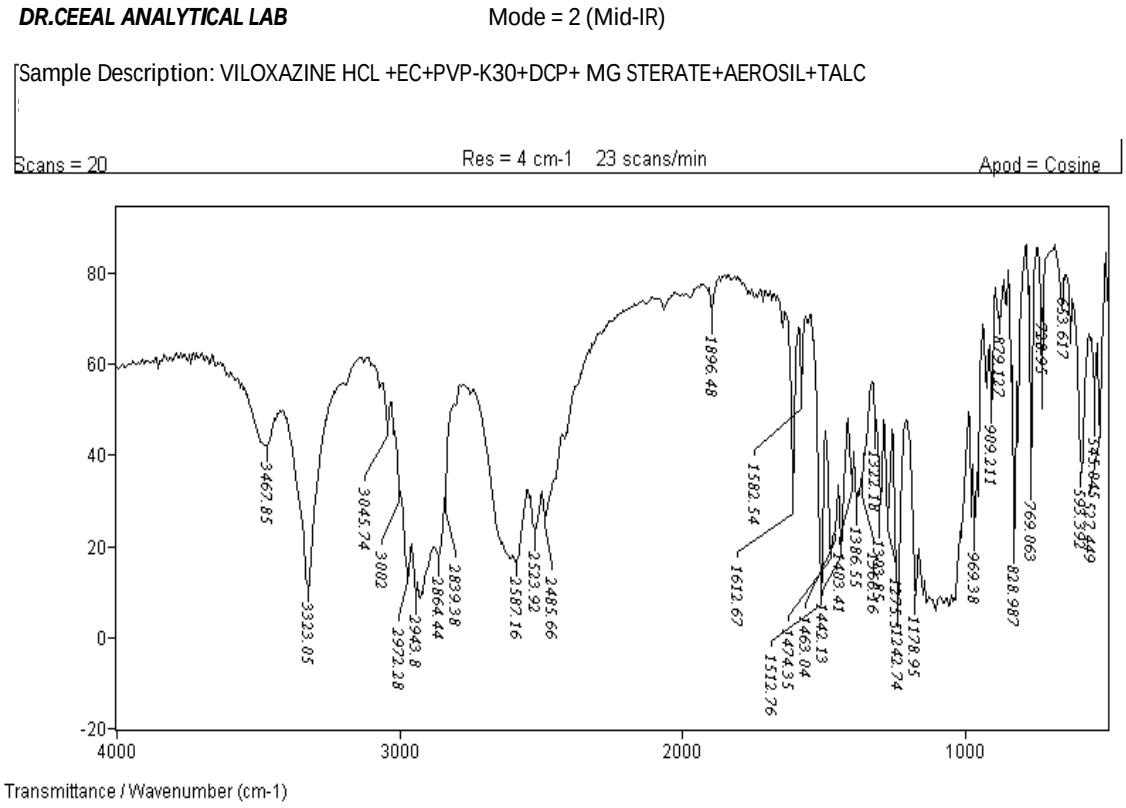


Figure No: 9

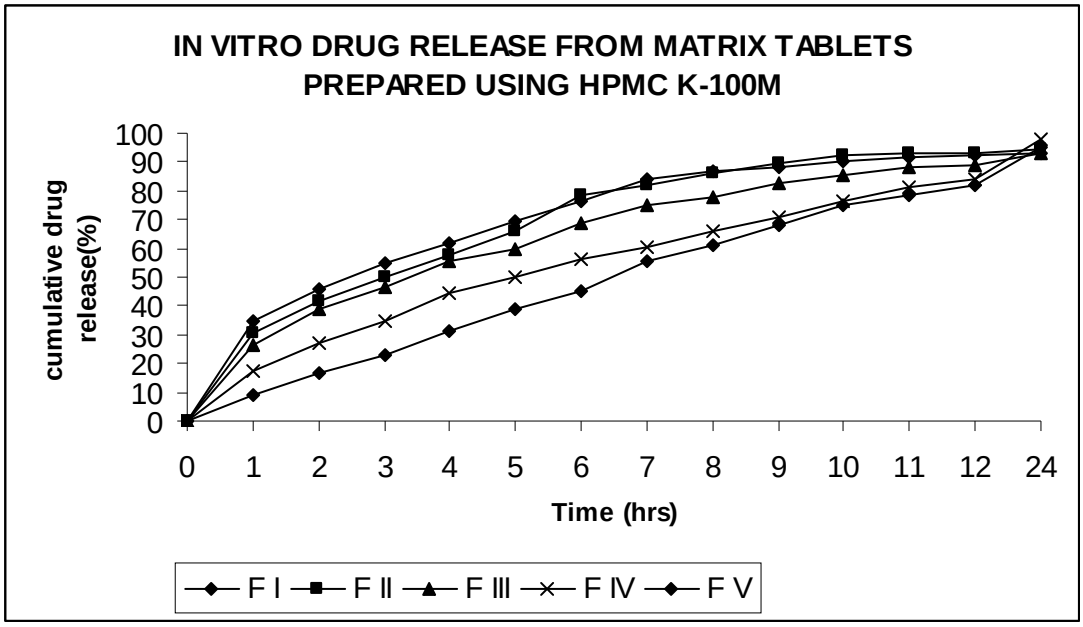

IN VITRO DRUG RELEASE FROM MATRIX TABLETS PREPARED USING HPMC K-100M
cumulative drug release(%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 24
Time (hrs)
F I
F II
F III
F IV
F V

Figure No: 10

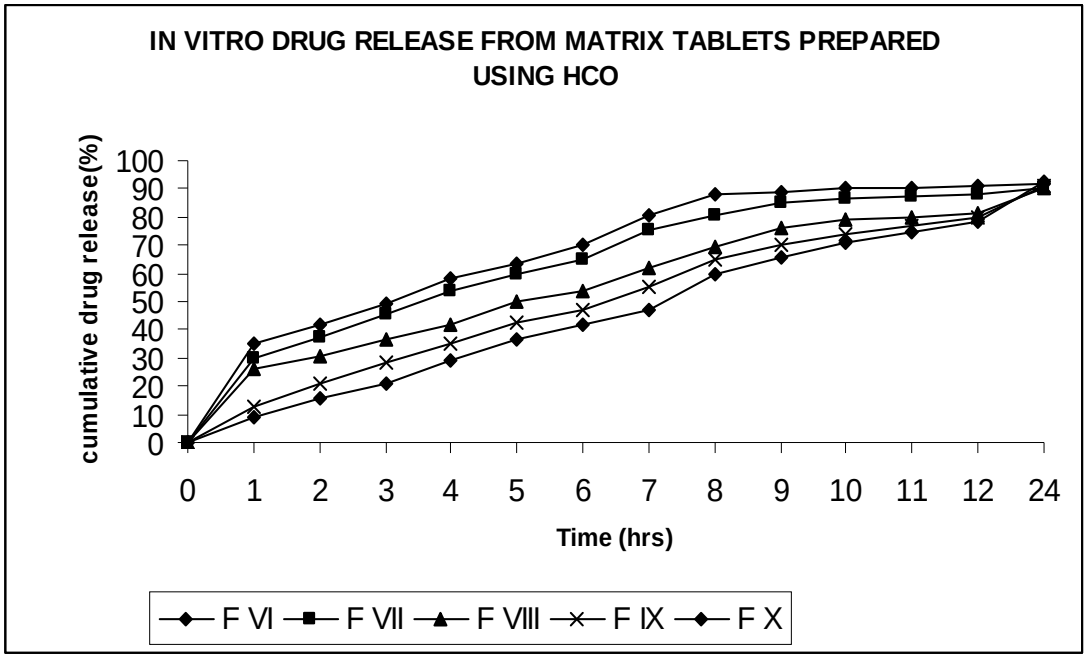

IN VITRO DRUG RELEASE FROM MATRIX TABLETS PREPARED USING HCO
cumulative drug release(%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 24
Time (hrs)
F VI
F VII
F VIII
F IX
F X

Figure No: 11

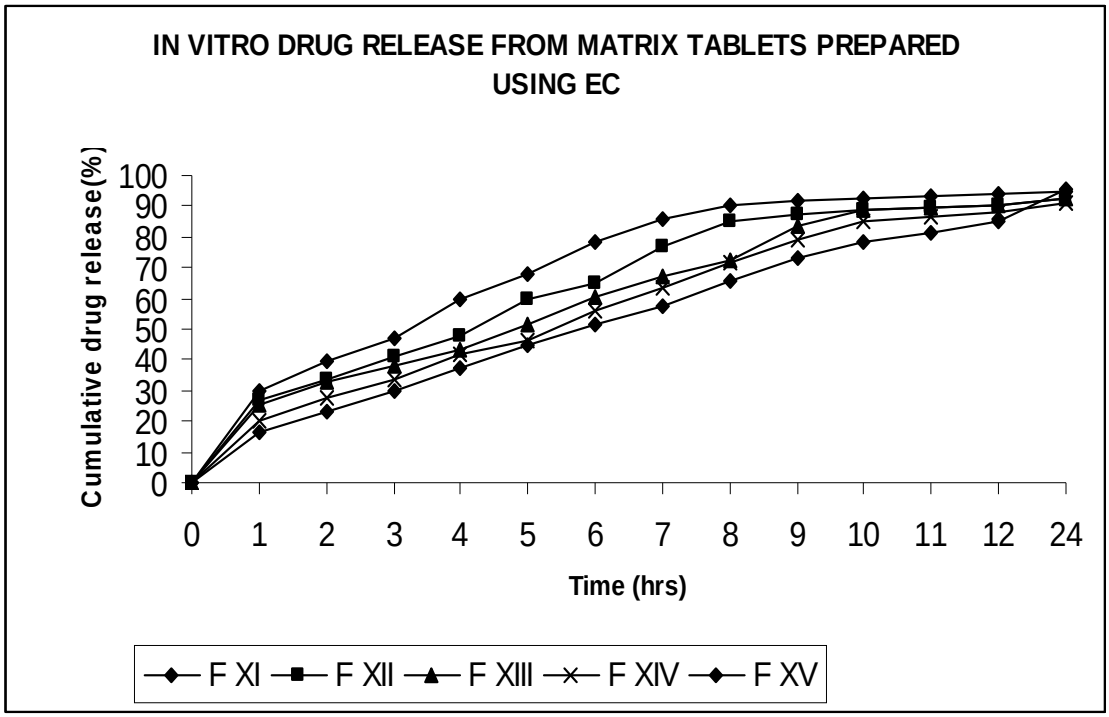
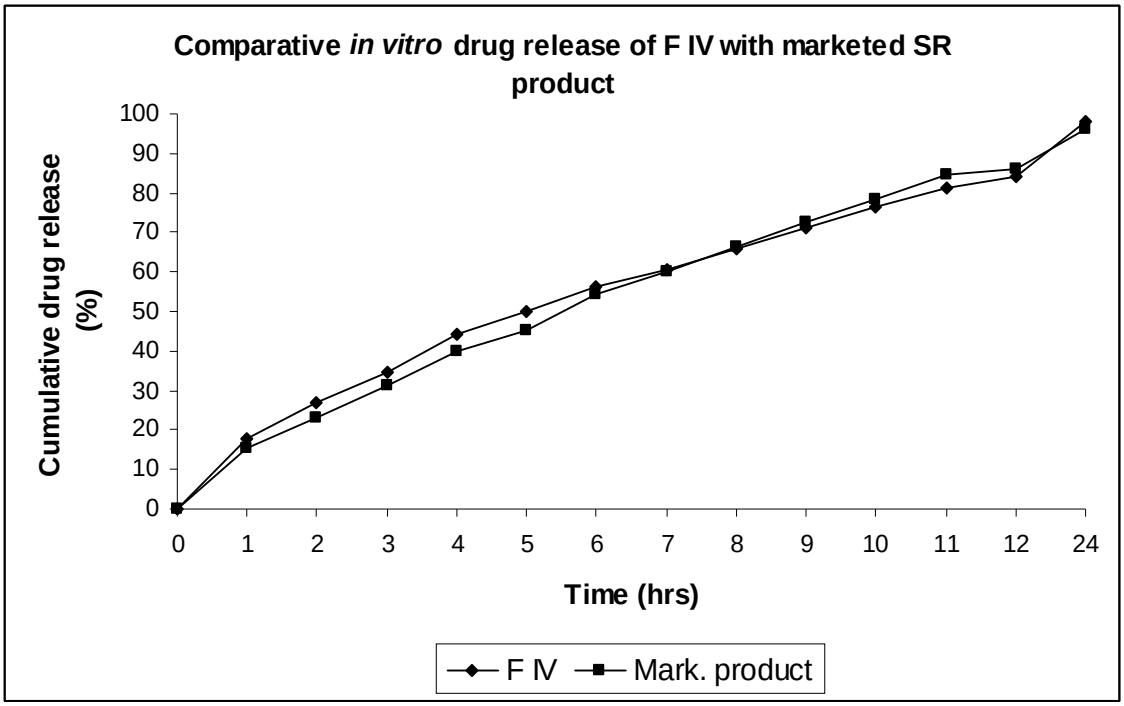

IN VITRO DRUG RELEASE FROM MATRIX TABLETS PREPARED USING EC
Cumulative drug release(%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 24
Time (hrs)
F XI
F XII
F XIII
F XIV
F XV

Figure No: 12


Comparative *in vitro* drug release of F IV with marketed SR product
Cumulative drug release (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 24
Time (hrs)
F IV
Mark. product

RESULTS AND DISCUSSSION

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Identification of Viloxazine Hydrochloride was performed by FT-IR and other identification tests as per B.P. Viloxazine Hydrochloride was mixed with hydroxy propyl methyl cellulose, hydrogenated castor oil and ethyl cellulose separately in 1:1 ratio and stored at different temperatures (25˚C, 35˚C, 40˚C) to study the Viloxazine Hydrochloride, hydroxy propyl methyl cellulose, hydrogenated castor oil and ethyl cellulose interactions. This was performed using FT-IR. Spectra obtained were showed no interactions between Viloxazine and hydroxy propyl methyl cellulose, Viloxazine and hydrogenated castor oil and Viloxazine and ethyl cellulose. No colour change was observed. Hence it was conclude that Viloxazine Hydrochloride is compatible with hydroxy propyl methyl cellulose, hydrogenated castor oil and ethyl cellulose.

Formulations F-I to F-XV were prepared as per Table: 5. Granules were prepared by wet granulation method. The prepared granules were evaluated for bulk density, angle of repose and compressibility.

Bulk density for all the formulations ranged between 0.43 to 0.54. The angle of repose for all formulations ranged between 25˚.64 to 29˚.25 the bulk density indicates good packing characters. The value of angle of repose (between 25˚-30˚) for all the formulation indicates good flow property. The value of Carr's index for all the formulations ranged between 7.212-9.110. The value of Carr's index (between 5-15%) indicates free flowing material.

The granules were then compressed to tablets. The tablets were evaluated for uniformity of weight, hardness, friability, drug content and dissolution.

The tablets prepared were white in color, oval shape. They were smooth, uniform and free from crack and chipping.

Thicknesses of all fabricated formulations are in the range of 3.2-3.6 mm and the values shown in Table no: 8. Weight variation was found with in specifications of I.P limits and the values shown in Table no: 9-13. The hardness of all fabricated formulations were in the range of 80 –95N

Friability for all the formulations was in the range of 0.36-0.61. The value of hardness and percent friability indicates good handling property of prepared tablets. The results for the above parameters were found to be in the recommended range.

The results of drug content for all formulations were found to be between 39.35 mg - 41.99 mg per tablet with ±S.D.

SUMMARY

SUMMARY

Formulations containing different ratios of HPMC showing following drug release profiles

FI and FII released more than 80% of drug at 7^{th} hour, where as FIII, FIV and FV released more than 80% of drug at 9^{th}, 11^{th} and 12^{th} hours respectively.

In case of formulations containing hydrogenated castor oil FVI and FVII releases more than 80% of drug at 7^{th} and 8th hour respectively. FVIII releases more than 80% of drug at 11^{th} hour. Whereas FIX and FX releases more than 80% of drug at 12^{th} hour.

In case of formulations containing ethyl cellulose, FXI and FXII releases more than 80% of drug at 11^{th} and 12^{th} hours. Whereas FXIII, FXIV, FXV are releasing more than 80% of drug at 9^{th}, 10^{th} and 11^{th} hours.

Marketed sustained release formulation (Vivalan) the drug release is 96.29% in 24 hours, where as our selected formulations FIV and FX releases 98.14% and 95.62% of drug in 24 hours respectively. This shows similar drug release profiles with that of marketed formulation. Whereas formulations FX containing hydrophobic polymer Ethyl Cellulose so there are much chances of dose dumping when compared with that of formulation FIV which contains hydrophilic polymer Hydroxy Propyl Methyl Cellulose.

CONCLUSION

CONCLUSION

From the results and discussions, amongst the 15 different formulations designated as FI ,FII ,FIII, FIV, FV ,FVI, FVII, FVIII, FIX, FX, FXI, FXII, FXIII, FIV and FX the formulation FIV was found to be the better formulation in terms of sustained release and maximum percentage drug release and results are comparable with that of the marketed formulation.

To conclude, hydroxy propyl methyl cellulose at a concentration ratio of 1: 1 is suitable for preparing sustained release matrix tablets of Viloxazine hydrochloride.

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