FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF ATORVASTATIN CALCIUM

Dissertation

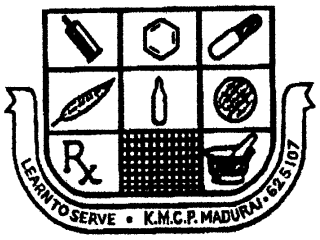
Submitted in partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

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



DEPARTMENT OF PHARMACEUTICS

K.M.COLLEGE OF PHARMACY

UTHANGUDI, MADURAI - 625 107

APRIL – 2012

CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF ATORVASTATIN CALCIUM**" submitted by **Mr**. **M.RAJESH** to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by him under my guidance and supervision during the academic year 2011-2012.

GUIDE

K.KULATHURAN PILLAI, M.Pharm.,(Ph.D)
Asst., Prof., Dept. of Pharmaceutics,
K.M.College of Pharmacy,
Uthangudi, Madurai-625107
Tamilnadu.

PRINCIPAL

Dr.S.JAYAPRAKASH, M.Pharm, Ph.D.,
Prof & HOD Dept. of Pharmaceutics,
K.M.College of Pharmacy,
Uthangudi, Madurai-625107
Tamilnadu.

ACKNOWLEDGEMENT

It affords me immense pleasure to acknowledge with gratitude the help and guidance rendered to me by a host of people, to whom I owe a substantial measure for the successful complements of this project.

I owe my great debt of gratitude and grateful thanks to ***Prof. M.Nagarajan, M.Pharm, M.B.A, DMS (IM) DMS (BM)*** *Correspondent, K. M. College of Pharmacy, Madurai for providing me with all the facilities and encouragement for the successful completion of my thesis work.*

I express my gratification thanks to ***Dr.S.Jayaprakash, Ph.D,*** *Principal and H.O.D., Dept. of pharmaceutics for their invaluable advice, suggestion and encouragement extended throughout the work.*

I express my wholehearted gratitude to my esteemed teacher and guide, ***Mr.K.Kulathuran Pillai, M.Pharm, (Ph.D)*** *Asst., Professor Dept. of Pharmaceutics, for his zealous guidance, indefatigable support and constant encouragement for the entire period of my thesis work.*

I prevail my sense of gratitude to, ***Mr. S.Mohamed Halith, M.Pharm, (Ph.D),*** *Asst.Professor in pharmaceutics, for his invaluable advice, suggestion and encouragement extended through out the work.*

My sincere thanks goes to ***Prof.M.S.Prakash,*** *M.Pharm, HOD of pharmaceutical Analysis and* ***Mr.M.Boopathi,*** *Asst.Professor of Pharmaceutical Analysis, for their valuable help and support during the analytical part of my work.*

A special word of thanks to ***all the professors and Assistant Professors*** *of all departments for their kind holly hortatory constant encouragement and expertise during this course.*

I extend my thanks to ***M.Shanthi,B.A, M.Li.Sc,*** *Librarian,* ***Mrs.Ayyamal*** *Lab Assistants and all other non teaching staff members of our college for their co-operation.*

I cannot forget to express my gratitude to all my friends with heartful thanks to ***N.vignesh, ch.lakshmi, Ram vikas, N.Vinay, Muni Raju, shiv kumar,shailaja*** *and all my classmates who helped me directly and indirectly for the successful completion of my project work.*

The completion of this dissertation is not only fulfillment of my dreams but also the dreams of my ***parents***, ***brother*** *and* ***sister*** *who have taken lots of pain for me in the completion of my higher studies.*

I also take a chance to thank my ***uncle Mr. C. Senthil Pandian I.A.S.*** *for the support he rendered throughout my project work.*

*Finally I thank '****GOD****' to show the path to the ladder of success.*

M.Rajesh

CONTENTS **PAGE NO**

DEDICATED TO MY FAMILY, FRIENDS & TEACHERS

LIST OF ABBREVIATIONS AND SYMBOLS USED

Abs	Absorbance
ARR	Amount remaining to be released
AVG	Average
BP	British Pharmacopoeia
CAR	Cumulative Amount Release
°C	Degree Centigrade
Cm	Centimeter
Conc.	Concentration
CPR	Cumulative Percentage Release
CSF	Cerebro Spinal Fluid
DNA	Deoxyribose Nucleic Acid
FDA	Food and Drug Administration
FDDS	Floating Drug Delivery System
FTIR	Fourier Transform Infrared
GI	Gastro Intestinal
GIT	Gastrointestinal Tract
gm	Gram
GRDDS	Gastro Retentive Drug Delivery System
GRDF	Gastroretentive Dosage Forms
GRT	Gastric Residence Time
HBS	Hydrodynamically Balanced System
HCl	Hydrochloric acid
HPMC	Hydroxy Propyl Methyl Cellulose
ICH	International Conference of Harmonization

IP	Indian Pharmacopoeia
JP	Japanese Pharmacopoeia
K	Dissolution Rate Constant
MCC	Microcrystalline Cellulose
mg	Milligram
ml	Milliliter
MMC	Migrating Myoelectric Complex
µg	Microgram
No.	Number
nm	Nanometer
PEG	Poly Ethylene Glycol
Ph Eur	European Pharmacopoeia
PVP	Poly Vinyl Pyrrolidine
R^2	Regression Coefficient / Correlation Coefficient
RH	Relative Humidity
rpm	Rotations Per Minute
S	Serial
SD	Standard Deviation
Sqrt	Square root
USP	United States Pharmacopoeia
UTI	Urinary Tract Infection
UV	Ultraviolet
λ_{max}	Absorption maxima

1. INTRODUCTION

Oral solid dosage forms are the preferred routes for many drugs and are still the most widely used formulations for new and existing modified release products. The benefits offered by modified release systems include reducing dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects and possible enhanced bio-availability. The rational design of modified release systems where, biological, physicochemical and physico-mechanical considerations have been taken into account during formulations of modified release dosage form, has alleviated the risk of dose dumping *in vivo*.[1]

The success of therapy depends on selection of appropriate delivery systems as much as it depends on drug itself.[2] Hence, in recent years pharmaceutical research considerably focussing on the Controlled release drug delivery systems as these have a number of advantages over conventional preparations. Controlled release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[3]

1.1 MODIFIED RELEASE DELIVERY SYSTEMS[4]

The term modified – release defines preparations that have been designed in such a way that the rate (or) place at which the active ingredients are released has been modified.

Modified release delivery systems may be divided into 4 categories.

A) Delayed release

B) Sustained release

   (a) controlled release

   (b) extended release

C) Site specific targeting

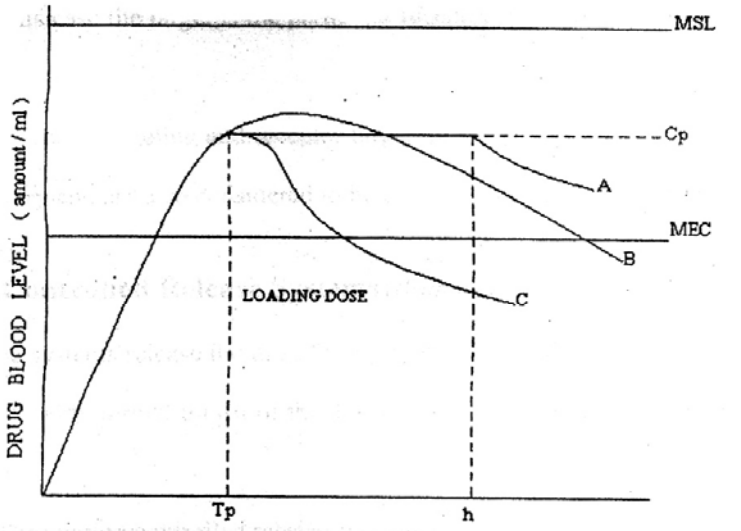
D) Receptor targeting

A) Delayed release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric coated tablets where timed release is achieved by a barrier coating. They do not maintain uniform drug level in therapeutic range.

B) Sustained release:

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.



A - Controlled Release B - Sustained Release C - Conventional Release.

a) Controlled release:

These systems provide continuous release of their active ingredients at a predetermined rate and for predetermined time, or in other words, a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body. This system maintaining constant drug levels in target tissue or cells.

b) Extended release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds.

C) Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue.

Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

1.2 ORAL CONTROLLED RELEASE SYSTEMS [5]

These systems release the drug for a prolonged period of time along the entire length of GIT with normal transit of the dosage form. The various systems under this category are,

1. Dissolution controlled release systems.
2. Diffusion controlled release systems.
3. Dissolution and diffusion controlled release systems.
4. Ion – exchange resin drug complexes.
5. Slow dissolving salts and complexes.
6. pH – dependent formulation.
7. Osmotic pressure controlled systems.
8. Hydrodynamic pressure controlled systems.

1. Dissolution controlled release systems

Such systems are easiest to design. The techniques employed is

1. Embedment is slowly dissolving or erodible matrix.
2. Encapsulation or coating with slowly dissolving or erodible substances.

Matrix (or Monolith) Dissolution Controlled Systems:

Matrix systems are also called as monoliths, since the drug is homogenously dispersed throughout a rate – controlling medium. They are very common and employ waxes such as beeswax, carnauba wax, hydrogenated castor oil, etc which control drug dissolution by controlling the rate of dissolution of fluid penetration into the matrix by altering the porosity of the tablet, increasing its wettability or by itself getting dissolved at a slower rate. The wax embedded drug is generally prepared by dispersing the drug in molten wax and congealing and granulating the same. The drug release is often first order from such matrices.

Encapsulation / coating dissolution controlled system (reservoir devices):

The drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes etc. The resulting pellets may be filled as such in hard gelatin capsules or compressed into tablets. The dissolution rate of coat depends upon the solubility and thickness of the coating which may range from 1-200 microns.

2. Diffusion controlled release systems

The two types of diffusion controlled systems are matrix systems and reservoir devices.

Matrix Diffusion Controlled Systems:

In this system, the drug is dispersed in an insoluble matrix of rigid nonswellable hydrophobic materials or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as PVC and fatty materials like stearic acid, beeswax, etc. With plastic materials, the drug is generally kneaded with the solution of PVC in an organic solvent for granulation and compressed into tablets. Swellable matrix systems are popular for sustaining the release of highly water – soluble drugs. The materials used for such drugs are generally hydrophilic gums and may be of natural origin (guar gum, tragacanth), semi synthetic (HPMC, CMC, xanthan gum) or synthetic (polyacrylamides). The drug and gum are granulated together with a solvent such as alcohol and compressed into tablets. The release of drug from such initially dehydrated hydrogels involves simultaneous absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of drug via

a swelling controlled diffusion mechanism. As the gum swells and the drug diffuses out of it, the swollen mass, devoid of drug appears transparent or glasslike and therefore the system is sometimes called as glassy hydrogel. The drug release follows Fickian first – order diffusion under equilibrium conditions. However during the swelling process, such equilibrium may not exist and the diffusion may be Non – Fickian or anomalous diffusion.

Reservoir devices (or Laminated Matrix Devices):

These systems are hollow containing an inner core of drug surrounded by a water insoluble polymer membrane. The polymer can be applied by coating or microencapsulation techniques. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymer commonly used in such devices are HPC, ethyl cellulose and poly vinyl acetate.

3. Dissolution and diffusion controlled release systems:

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which

a. permit entry of aqueous medium into the core
b. drug dissolution and allow diffusion of dissolved drug out of the system.

An example of obtaining such a coating is using a mixture of ethyl cellulose with PVP or methyl cellulose the latter dissolves in water and create pores in the insoluble ethyl cellulose membrane.

4. Ion – exchange resin drug complexes:

Controlled delivery of the acidic and basic drugs can be obtained by complexing them with the insoluble nontoxic anion exchange and cation exchange resins respectively. The drug is released slowly by diffusion through the resin particle structure. The following equation represents the release of a basic drug, NH_2R, from a cation exchange resin RSO_3H when in contact with GI fluid containing an ionic compound.

$$RSO_3^- \; NH_3^+ \; R^I + A^+B^- \rightarrow RSO_3^-A^+ + NH_3^-R^IB^-$$

A number of basic drugs like phenylpropanolamine and pheniramine have been retarded by such an approach.

5. Slow dissolving salts and complexes:

Salts or complexes of drugs which are slowly soluble in the GI fluids can be used for control release of the active principle. Amine drugs can be reacted with tannic acid to form poorly soluble complexes that can be formulated as long acting tablets. Penicillin G has been complexed with N,N – dibenzyl ethylenediamine to give benzathine penicillin G that can be formulated as oral suspension.

6. pH – Independent formulation:

Such systems are designed to eliminate the influence or changing GI pH on dissolution and absorption of drug by formulating them with sufficient amount of buffering agent that adjust the pH to the desired value as the dosage form passes along the GIT and permit drug dissolution and release at a constant rate independent of GI pH. The dosage form containing drug and buffer is coated with a permeable substance that allows entry of aqueous medium but prevents dispersion of tablet.

7. Osmotic pressure controlled systems:

It works on the principle of osmotic pressure to release the drug at a constant zero order rate. A core comprising of drug and an osmotically active substance such as potassium chloride or mannitol is surrounded by a rigid semipermeable membrane coating such as cellulose ester or cellulose ether having an orifice of 0.4mm diameter produced by laser beam for drug exit. When exposed to GI fluids, water flows through the semi permeable membrane into the tablet due to osmotic pressure difference which dissolves the drug and pumps it out through the orifice by the osmotic force. Such devices can be used to target specific areas of the GIT.

8. Hydrodynamic pressure controlled systems:

The hydrodynamic pressure generating by swelling of a hydrophilic gum can also be used to achieve the delivery of drugs. The device comprises of a rigid, shape retaining housing enclosing a collapsible, impermeable compartment containing liquid drug. The space between the external housing and the drug compartment

contains a layer of swellable, hydrophilic gum such as polyhydroxyalkyl methacrylate. In the GIT, the gum imbibes water through the opening present at the lower side of external housing and swells creating a hydrodynamic pressure. The pressure thus created squeezes the collapsible drug reservoir to release the medicament through the delivery orifice at a zero order rate.

1.3 HYDROPHILIC MATRIX SYSTEMS

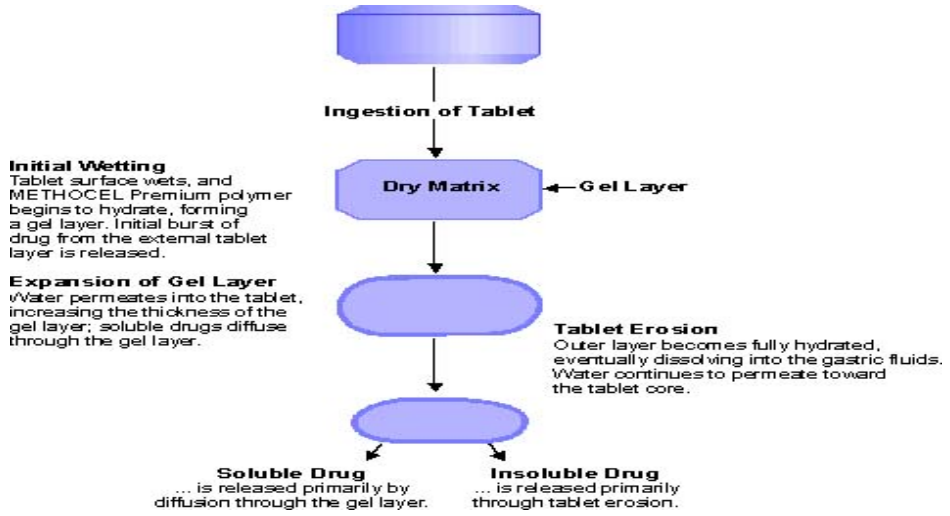
A matrix is a uniform mixture of drug and excipients. For example, polymer that is homogenously mixed in solid dosage form. Oral sustained release dosage forms are commonly prepared by incorporating the drug into a hydrophilic polymer matrix. The hydrophilic matrix consist of a mixture of one more active ingredients with one or more gel forming agents. The mixture is usually compressed into tablets.[6]

The use of hydrophilic matrices has become extremely popular in controlling the release of drugs from solid dosage forms.[7]

Various types of polymers used as hydrophilic matrices. The most commonly used cellulose ethers are hydroxypropyl methyl cellulose (HPMC), hydroxy propyl cellulose, sodium carboxy methyl cellulose (SCMC), and methyl cellulose. This popularity system from their non toxic nature, case of compression, ability to accomodate a large percent of drug and negligible influence of the processing variables on drug release rates.[8]

For matrix devices, drug is often release by diffusion process such that a receding drug boundary will exist within the device.[9]

Mechanism of Release:[10]



The two important parameters for the release of drug from tablet matrices are

- The infiltration rate of medium into the matrix (absorption rate) for which the drugs with aqueous solubility.
- The erosion rate of the matrix system for which the drugs with poor aqueous solubility.

The release rate of poorly soluble drug can be controlled by the rate of tablet erosion. The tablet erosion rate can also be adjusted by the choice of HPMC polymer viscosity or by mixing HPMC of different viscosity grades.

(A) Water penetration, swelling of matrix and Gel layer formation Dynamics:

Swellable matrix tablets are activated by water and drug release control depends on the interaction between water, polymer and drug. Water penetration into the matrix is the first step leading to polymer swelling and drug dissolution. The presence of water decreases the glassy-rubbery temperature (eg, for HPMC from 184^{o}C to lower than 37^{o}C) giving rise to the transformation of glassy polymer in a rubbery phase (gel layer). The enhanced mobility of the polymeric chains favours the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. The later may add a convective contribution to the drug transport mechanism in drug delivery.[11]

Drug release kinetics is strictly associated with the dynamics of the gel layer. It ranges Fickian to anomalous (Non fickian), and subsequently from quasi-constant to constant, becoming first order at the end. Due to the insufficient polymeric mass transfer due to a low chain disentanglement rate, HPMC swellable matrices rarely show all three described regimens during the drug release time.[12]

(B) Boundaries of Gel layer and relevant Fronts:

Gel layer thickness is defined by the front separating the matrix from the dissolution medium, i.e., the erosion front, and by the front separating the glassy from the rubbery polymer (i.e., the swelling front). Therefore, erosion and swelling front movements are the controllers of gel layer behavior. [13]

The presence of a third front inside the gel layer was described by swellable matrices containing Diclofenac, as the consequence of precipitation in gel layer of this poorly soluble drug already molecularly dispersed in the glassy matrix. This front,

named diffusion front, corresponds to the boundary between undissolved and dissolved drug. It was further shown that, depending on the function of drug solubility and loading, its presence is highly probable in swellable matrix tablets.[14] Therefore, in swellable matrix tablets conditions exist under which the following three fronts can be present at the same time.

1.4 CONTROLLED DRUG DELIVERY SYSTEM

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events**.** The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile remaining constant, between the desired maximum and minimum, for an extended period of time. Depending on the formulation and the application, this time may be anywhere from 24 hours (Procardia XL) to 1 month (Lupron Depot) to 5 years (Norplant).[16]

ADVANTAGES OF CONTROLLED DRUG DELIVERY SYSTEM:

- The purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing.
- Using controlled-delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance.[16]
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels**.**
- Oral modified/controlled release delivery systems offer a number of advantages including improvement in patient compliance, greater selectivity of pharmacological activity, therapeutic efficiency and safety, decreased side effects, and reduced dosing frequency.

DISADVANTAGES OF CONTROLLED RELEASE DOSAGE FORMS:

- The possible toxicity or non biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device.
- The higher cost of controlled-release systems compared with traditional pharmaceutical formulations.
- Burst effect: In case of many controlled release formulations, upon placement in the release medium, there is an immediate release of an initial large bolus of drug is released before the release rate reaches a stable profile. This phenomenon is typically referred to as 'burst release'.
- First order release kinetics
- Increase in metabolic rate: This leads to higher initial drug delivery and also reduces the effective lifetime of the device.
- Increase in dosing frequency etc.

1.5 DIFFERENT ROUTES OF THE CONTROLLED RELEASE DRUG DELIVERY SYSTEMS:[17]

The different route of controlled release drug delivery systems as follows,

- Oral
- Transdermal
- Parenteral
- Ophthalmic
- Intravaginal and intrauterine

The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties.

Amongst all of the above controlled drug delivery systems, oral controlled release delivery has received major attention because of its greater popularity, and it provide a uniform concentration/amount of drug at the absorption site and thus after absorption, allow maintaince of plasma concentration with in therapeutic range, which minimizes side effects and also reduces the frequency of administration.[19]

"Oral controlled drug delivery systems are those that provide continuous oral delivery of drugs at predictable and reproducible kinetics, for a predetermined period throughout the course of GI transit.[17]

Advantages of oral route for drug delivery:

- Patient acceptability and compliance.
- Therapeutic advantage
- Reduction in adverse side effects and improvement in tolerability
- Reduction in healthcare cost
- Ideally, oral controlled-release systems are reliant upon the dosage form to control the rate of drug release with little or no effect from the intrinsic properties of the drug or the conditions prevailing within the gastro intestinal (GI) tract.
- Large surface area of small intestine
- High vascular surface of gastrointestinal mucosa.
- Zero order controlled release
- Commercial advantages: The cost of oral therapy is generally much lower in comparison to parenteral and other routes of drug delivery.[17]

Disadvantages:

- Lack of in vitro–in vivo correlation.
- Variability
- Adverse environmental effects: high metabolic activity, extreme of pH, intestinal motility, mucus barrier, P-glycoprotein efflux pump, Impermeable epithelium.

Several terms have been used to describe the various types and modes of action, intended to provide long duration of drug activity. These are

CONTROLLED RELEASE PREPARATIONS

Although this term has been interchanged widely with sustained release preparations in the past, recently it has become customary to restrict the latter term to oral formulations where the mechanism of prolonged action is dependent on one or more of the environmental factors in the gastrointestinal tract such as pH, enzymes, gastric motility etc. On the other hand, the term controlled release dosage form

usually applies to preparations that are designed for all routes of administration and where the mechanism of prolonged action is inherent and determined totally by the delivery system itself. Consequently, this category offers the current state-of-the-art products where the drug release profile is controlled accurately and often can be targeted to a special body site or a particular organ.

1.6 CLASSIFICATION OF ORAL CONTROLLED DRUG DELIVERY SYSTEMS[18]

TYPE OF SYSTEM	RATE-CONTROL MECHANISM
Dissolution controlled	
Monolithic devices	Dissolution of the matrix
Reservoir devices	Dissolution of encapsulation and coating
Diffusion Controlled	
Monolithic devices	Diffusion through membrane
Reservoir devices	Diffusion through bulk polymer
Water Penetration Controlled	
Osmotic systems	Osmotic transport of water through semipermeable membrane, Swelling systems Water penetration into glassy Polymer.
Hydrodynamic pressure systems	Water absorption through the annular openings into hydrophilic polymer
pH controlled gastrointestinal drug	Dissolution of drug at appropriate constant
delivery systems	pH by water permeation into the device.
Chemically Controlled	
Monolithic systems	Either pure polymer erosion (surface erosion) or combination of erosion and diffusion (bulk erosion)
Pendant chain systems	Combination of hydrolysis of pendant group and diffusion from bulk polymer

Ion exchange controlled	Combination of biodegradation of drug bound resin, diffusion through the membrane and exchange of ions.
Gastrointestinal retention controlled	
Mucoadhesives	Prolonging the residence time of dosage form in the GI tract.
Altered density formulations	
High density approach	Increased density of pellets than that of stomach content
Low density approach	Maintaining buoayancy of the device.

1.7 GASTRO INTESTINAL RETENTION CONTROLLED DRUG DELIVERY SYSTEM[20]:

Among the different type of formulation, gastric emptying[8] of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract.

Gastro Retentive drug delivery systems can be retained in the stomach for a long time. Such retention systems are important for drugs that are degraded in intestine or for drugs like antacids or certain antibiotics. The main objective of developing these systems is to increase the safety of a product, to extend its duration of action and decrease the side effects of drugs.

Factors Affecting Gastric Retention [20]

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form. These factors include:

- Density of the dosage form: A dosage form having a density of less than that of the gastric fluids floats.
- Size of the dosage form: Small-sized tablets leave the stomach during the digestive phase while the large-sized tablets are emptied during the

housekeeping waves. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

- Shape of the dosage form: It is reported that tetrahedron and ring-shaped devices have a better gastric residence time as compared with other shapes.
- Gender: Generally females have slower gastric emptying rates than males.
- Posture: When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.
- Temperature of meal: Cold meal increases and hot meal decreases the emptying of gastric contents.
- Composition and Viscosity of meal: Fats, particularly fatty acids inhibit gastric secretion and have a pronounced reductive effect on the rate of emptying. Proteins and starch are shown to have inhibitory effect on gastric emptying, though to a less extent. As the viscosity of the gastric fluids is increased, there is a corresponding decrease in the rate of emptying.
- Volume: As the volume of liquid present in the gastric pouch increases, the rate of gastric emptying decreases.
- Increase in acidity of the duodenal contents slow down gastric emptying time.
- Diseased states: Gastric emptying is affected in diseased conditions like diabetes, Crohn's disease, etc.

Approaches to Design Gastro Retentive Dosage Forms [22]

Over the years, various approaches have been pursued to increase the retention of an oral dosage form in the stomach. Gastro retentive systems remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. These may be:

- *Floating Drug Delivery Systems (FDDS) or Hydrodynamically Balanced Systems (HBS)* : These are systems which have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system.

- *Swelling and Expanding Drug Delivery Systems*: These types of dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as 'plug type systems' since they exhibit a tendency to remain lodged at the pyloric sphincter.
- *Bioadhesive Systems* : These systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approach involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GI tract. The proposed mechanism of bioadhesion is the formation of hydrogen and electrostatic bonding at the mucus-polymer boundary. Rapid hydration in contact with the muco-epithelial surface appears to favor adhesion, particularly if water can be excluded at the reactive surfaces.
- *Modified Shape Systems* : These systems are non disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modulus of the drug delivery device.
- *High Density Systems* : These formulations include coated pellets, which have a density greater than that of the stomach contents (approx. 1.004 g/ cm^3). This is accomplished by coating the drug with a heavy inert material such as barium sulfate, zinc oxide, titanium dioxide, iron powder, etc.
- *Delayed gastric emptying systems* : These approaches of interest include sham feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release.

1.8 Classification of Floating Drug Delivery Systems (FDDS) [21]

Based on the mechanism of buoyancy, FDDS are classified into two distinctly different technologies, i.e., Non-effervescent and Effervescent systems

A) Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like

polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

B) Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Advantages of Floating Drug Delivery Systems [22]

- ✓ Sustained Drug Delivery

  These systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time, encountered with an oral CR formulation can hence be overcome with these systems. These systems have a bulk density of <1, as a result of which they can float on the gastric contents.
- ✓ Site-Specific Drug Delivery

  These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. eg., Riboflavin, Furosemide, Ciprofloxacin, etc.
- ✓ Absorption Enhancement

  Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.
- ✓ Complete eradication of *Helicobacter pylori* in peptic ulcer can be achieved only by floating drug delivery systems.

Limitations of Floating Drug Delivery Systems [22]

- They require a sufficiently high level of fluids in the stomach for the drug delivery system to float therein and to work efficiently. However, this limitation can be overcome by coating the dosage form with bioadhesive polymers, thereby enabling them to adhere to the mucous lining of the stomach wall. Alternatively, the dosage form may be administered with a glass full of water (200–250 ml).
- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids. E.g., Drugs such as nifedipine. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa and those drugs which have multiple absorption sites in the Gastro Intestinal Tract.
- These systems, being matrix formulation, consists of a blend of drug and low density polymers. The release kinetics of drug cannot be changed without changing the floating properties of the dosage form and vice versa.

Evaluation [22]

Gastroretention of the systems can be evaluated by X-ray or γ-scintigraphy. Modern technique of γ-scintigraphy now makes it possible to follow the transit behaviour of dosage form in human volunteers in a non-invasive manner.

Marketed Floating Formulations [23]

- Valrelease® - diazepam (Hoffmann La-Roche,USA)
- Madopar® - benserazide and L-dopa (Roche, USA)
- Liquid gaviscon® - floating liquid alginate preparation(GSK,india)
- Topalkan® -Alginate Al-Mg antacid preparation(pierre fabre drug,france)
- Cytotech® - Misoprostol floating capsule (pharmacia, USA)

The currently available polymer-mediated non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. This is evident from the number of commercial products and a myriad of patents issued in this field.

2. LITERATURE REVIEW

2.1 LITERATURE REVIEW ON GASTRO RETENTIVE FLOATING TABLET:

Shishu[24] et al., (2007) formulated gastro-retentive floating tablets for 5-fluorouracil (5-FU) to prolong the gastric residence time, increase drug bioavailability and target the stomach cancer. This floating tablet consists of gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxypropyl methylcellulose (HPMC) and carbopol 934P. The *in-vitro* release studies showed that the optimized formulation could sustain drug release for 24 h and remain buoyant for 16 h.

Denish Kalaria[25] et al., (2011) formulated the gastro-retentive floating tablets of acyclovir to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug, which results in achieving controlled plasma level as well as improving bioavailability. Compression of tablets by wet granulation with incorporation of gas-generating agent together with polymer HPMC improved drug release and optimal floating (floating lag time ~30 s; total floating time >12 h). The drug release was sufficiently sustained (more than 11h) and non-Fickian as well as zero-order was confirmed.

Gangadharappa H.V[26] et al., (2011) prepared gastric floating tablets of atenolol consists of karaya gum and HPMC as matrix polymers, sodium bicarbonate as a gas-generating agent, which undergoes direct compression technique. The optimized formulation had shown good floating capability, shorter floating lag time, and sustained drug release for 12 h. The *in-vitro* drug release followed different models like korsmeyer-peppas, and huguchi. The diffusion exponent ranges from 0.3771 to 0.6997 indicating the Fickian and anomalous transport.

Lingam Meka[27] et al., (2008) formulated captopril matrix type multiple-unit gastro- retentive floating tablet. The drug containing core units prepared by direct compression process, which are coated with three successive layers of an inner seal coat, effervescent layer (sodium bicarbonate) and an outer gas-entrapped polymeric membrane of an polymethacrylates (Eudragit RL30D, RS30D, and combinations of them). The optimized system completely floated within 3 min and maintained the buoyancy over a period of 12 h.

R. K. Kar[28] et al., (2010) prepared Cefuroxime Axetil gastro retentive floating tablets hydrophilic polymers such as HPMC K15M and HPMC E5LV were used for its release controlling properties and sodium bicarbonate as gas generating agent and Sodium Lauryl Sulfate (SLS) was used as solubility enhancer. It was found that polymer content and amount of floating agent significantly affected 50% drug release (T50%), Mean dissolution time (MDT), release rate constant, and diffusion exponent (n).Kinetic modeling of dissolution profiles revealed that the drug release mechanism could range from diffusion controlled to case II transport, which was co dominated by both diffusion polymer erosion in the release mechanism.

Ajay Bagherwal[29] et al., (2010) developed floating tablet of ciprofloxacin HCl by direct compression techniques using HPMC and carbomer in different proportion (4%, 8% and 12%) polymers, lactose, magnesium stearate, talc with sodium bicarbonate. All the prepared formulation were found to comply with the official tests like precompression parameter like angle of repose and post compression parameters like floating test, content uniformity and *in-vitro* dissolution study. The mechanism of drug release with all the formulations was dominantly diffusion and followed zero order kinetics.

Margret Chandira[30] et al., (2009) studied the formulation of Diltiazem HCl floating tablets by direct compression technique using hydrophilic polymer like HPMC K4M, HPMC K15M and hydrophobic polymer like ethylcellulose as matrix materials in various quantities (%w/w), sodium bicarbonate, citric acid, magnesium stearate, talc and lactose in varying ratio to formulate the floating tablets. It was observed that tablets of optimized formulation showed greater extent of drug release and it was found to be around 99.81 % at the desired time 12 h.

D.Bhowmik[31] et al., (2009) studied poor bioavailability anti-ulcer drugs as Famotidine. Famotidine floating tablets formulated by direct compression technique using polymers like HPMC K4M and HPMC K100M, xanthan gum. The HPMC polymer alone release > 90% drug in 4-6 h itself, while in combination with xanthan gum it release > 90% drug upon 8 h. The result indicates that gas powered gastro-retentive floating tablets of famotidine containing HPMC K100M and Xanthan gum provides a better option for controlled release action and improved bioavailability.

Y.S.Tanwar[32] et al., (2007) prepared Famotidine floating tablets incorporating two different grades of methocel K100 and methocel K15M, sodium bicarbonate. The floating tablets were evaluated for drug content, *in-vitro* buoyancy and dissolution studies. The tablet swelled radially and axially during invitro buoyancy studies. A combination of sodium bicarbonate (130mg) and citric acid (10mg) was found to achieve optimum invitro buoyancy. The tablets with methocel K100 were found to float for longer duration as compared with formulations containing methocel K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Ravi Kumar[33] et al., (2009) developed Floating drug delivery system (FDDS) for famotidine gas-forming agents like sodium bicarbonate, citric acid and hydrocolloids like hydroxypropyl methylcellulose (HPMC) and carbopol 934P to prolong the gastric residence time, increase drug bioavailability and target the gastric ulcer. The formulations were optimized for the different viscosity grades of HPMC, carbopol 934P and its concentrations and combinations. The results of the *in-vitro* release studies showed that the optimized formulation could sustain drug release (98%) for 24 h and remain buoyant for 24 h.

Vishal G. Karkhile[34] et al., (2010) formulated furosemide floating tablet using PEG- 6000 is used as complexing agent for increasing solubility of Furosemide in water, Hydroxy propyl methylcellulose, sodium bicarbonate and carbapol were used as matrixing agent, gas generating agent and floating enhancers respectively. The tablets were evaluated for in-vitro buoyancy and dissolution studies for 8 h. The data of *in-vitro* dissolution study shows that the zero order plots were found to be fairly linear as indicated by their high regression value (R2=0.9772 to 0.9911).

Patel Krunal M[35] et al., (2010) prepared gastro retentive floating tablets of Lansoprazole consists of chitosan, HPMC of different viscosity, sodium bicarbonate; citric acid and stearic acid were used. The formulation containing HPMC K4M show more retardation of drug release from the tablet. Hence to improve the drug release the quantity of HPMC K4M was reduced and chitosan was incorporated in the formulation. After the addition of chitosan the swelling index was increased as well as the drug release

and the floating time was also improved. Finally optimized floating lansoprazole tablet was formulated using two polymer i.e. chitosan and HPMC K4M.

Arunachalam.A[36] et al., (2010) prepared floating tablet of levofloxacin hemihydrates tablets by melt granulation method, using the polymer hydroxypropyl methyl cellulose (HPMC K100M) with different amounts, sodium bicarbonate as gas generating agent and other excipients. Tablets were evaluated by different parameters such as *in-vitro* release studies; Buoyancy determination and kinetic analysis of dissolution data etc., Levofloxacin floating tablet drug delivery system improved the oral bioavailability and extended drug release which may favor the reduced dose frequency and patient compliance**.**

Ganesh Rajput[37] et al., (2009) developed Metformin HCl gastro retentive tablets by directly compressible method using polymers HPMC K100M and HPMC K4M. It was concluded that polymer viscosity had major influence on drug release from hydrophilic matrix tablets as well as on floating lag time. When polymer viscosity increase the similarity factor f2 was increased. Hence, it concluded that the polymer viscosity affected the similarity factor f2. The different ratios of HPMC K4M and HPMC K100M were evaluated to achieve apparent viscosity to 66633 cps. The optimized batch showed the highest f2=82 value, it contained 37.34mg of HPMC K4M and 212.66mg of HPMC K100M.

Laxmi Goswami[38] et al., (2011) studied combined floating bilayer tablet of metformin and pioglitazone used as an oral hypoglycemic agent for control of diabetes. The fabrication of bilayer floating tablet was done by modified direct compression using polymer like HPMC, carbopol, PVP to facilitate immediate release of pioglitazone and sustained release of metformin. The formulated tablets were subjected to various evaluation parameters including buoyancy studies, drug content, *in-vitro* dissolution studies etc,. The formulated tablets remain buoyant over a period of 12-20 h and released more than 80% of drug in study period.

Rajan B Mistry[39] et al., (2011) formulated floating drug delivery system of clarithromycin containing drug, hydroxyl propyl methylcellulose (HPMC), sodium bicarbonate (gas generating agent) and different additives were compressed using wet granulation to prolong the gastric residence time after oral administration. The optimized

formulation was obtained using 150mg of HPMC K4M gave floating lag time less than 30 sec and prolonged 82.56% of drug release up to 6 h.

Krunal Patel[40] et al., (2011) prepared gastro retentive floating tablets of mebendazole consists of chitosan, HPMC of different viscosity, sodium bicarbonate; citric acid and stearic acid were used. The formulation containing HPMC K4M showed more retardation of drug release from the tablet. Hence to improve the drug release the quantity of HPMC K4M was reduced and chitosan was incorporated in the formulation. After the addition of chitosan the swelling index was increased as well as the drug release and the floating time was also improved. Finally optimized formulation was formulated using two polymer i.e. chitosan and HPMC K4M.

Dalavi V.V[41] et al., (2009) developed a gastro-retentive tablet of Zidovudine to enhance its bioavailability and sustained action. In 32 factorial design, amount of HPMC K4M (X1) and gas generating agents (X2) were selected as independent variable. The time required for 50% drug release t50% (Y1) was selected as dependent variable. The derived polynomial equations for t50%were verified by two check point formulations. The results of factorial design showed that factor X1 and X2 significantly affect the studied dependent variables. The formulation with good floating time (24hrs) and the percent drug release (98.05) emerged as optimal.

MD. Selim Reza[42] et al., (2009) formulated floating tablet of theophylline using two hydrophilic cellulose derivatives as Methocel K100M and Methocel K15MCR for their gel forming and release controlling properties, Sodium bicarbonate and citric acid as gas generating agents by direct compression technique. Formulations were evaluated for *in-vitro* buoyancy and drug release study was evaluated for 8 h. The release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 h, release rate constant and diffusion exponent.

Debajyothi Ray[43] et al., (2010) developed floating tablet of tramadol HCl using different grades of HPMC as drug release retarding polymer and sodium bicarbonate as gas generating agent helps tablets to float. From the swelling study of the formulations, optimized formulation was found to be had good swelling properties (220%)**.** The

optimized formulation was found to have better drug release profile than other formulations. From the drug release kinetic study, Higuchi model was found to be best fit. So it could be predicted that release of tramadol HCl from the floating drug delivery formulations were of diffusion type.

N. Damodharan[44] et al., (2009) formulated bi-layered floating tablets of theophylline by wet granulation technique. Bilayer tablets formulated with an immediately releasing layer consisting of theophylline with lactose as diluents and sustained release layer with slow releasing swellable matrix consisting of theophylline with different polymer ratios. The optimized formulation has a combination of hydroxy propyl methyl cellulose and methyl cellulose provide slow release of theophylline over a period of 9 h and were found suitable for maintenance portion of bilayered floating tablets. Theophylline release from these tablets was diffusion controlled and followed first order kinetics.

Kannan C[45] et al., (2010) studied gastro-retentive rosiglitazone maleate floating tablets with various materials like hydroxy propyl methyl cellulose (HPMC) K4, K15, K100 were used for its gel forming and release controlling properties, sodium bicarbonate act as a effervescent agent and hydrophobic meltable material like bees wax formulated by melt granulation technique. The formulation F7 containing HPMC K15M and K100M shows sustained release profile and releases upto 12 h and it shows good buoyancy and total floating time. Floating tablets with sustained release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy.

Girish S. Sonar[46] et al., (2007) developed a bilayer and floating-bioadhesive drug delivery system to prolong residence in the stomach. The sustained layer was compressed and granules of the floating layer were added to it, then both layers were compressed using a single station rotary press. Hydroxy propyl methylcellulose (HPMC) and sodium bicarbonate were added to the floating layer. The *in-vitro* drug release from the tablet was controlled by the amount of HPMC in the sustained release layer and it also affects the buoyancy lag-time, detachment force and swelling characteristics of the tablets. The release of rosiglitazone maleate from the tablets followed the matrix first-order release model.

Puneeth K P[47] et al., (2010) formulated rosigliazone maleate floating tablets using gas forming agents like sodium bicarbonate, tartaric acid and polymers like HPMC K15M and Xanthan gum. The prepared tablets were evaluated in terms of their precompression parameters, physical characteristics, *in-vitro* release, buoyancy and buoyancy lag time. The results of *in-vitro* release studies showed that optimized formulation could sustain drug release (98%) for 12h and remain buoyant for 12h. The optimized formulation was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation.

Chander Shekar B[48] et al., (2010) prepared floating tablets by direct compression technology consists of HPMC K100LV, HPMC K15M, ethyl Cellulose and effervescent sodium bicarbonate. The tablet swelled radically and axially during in vitro buoyancy studies. Final formulation released approximately 89.21% drug in 24 h *in-vitro*, while the floating lag time was not more than 35 Sec and the tablet remained floatable throughout all studies. The release of Ketoconazole was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Prashant Khemariya[49] et al., (2010) prepared ofloxacin floating tablets by dry granulation technique which containing HPMC K100M, xanthan gum, carbopol 934P, PVP K30, MCC, lactose, aerosil, and gas generating agent such as sodium bicarbonate were taken as independent variables. The *in-vitro* studies of optimized formulation released more than 80% drug in 10 h and remained buoyant for more than 24 h. The optimized formulation showed zero order release kinetics with a floating lag time of only 2.9 mins.

D. Saravanan[50] et al., (2010) formulated ofloxacin floating tablet by wet granulation technique using HPMC K4M, HPMC K15M and HPMC K100M as polymers along with sodium bicarbonate as gas generating agent. All the formulations had undergone pre-compression and post-compression parameters. The *in-vitro* cumulative % drug release of the formulations F1A, F1B, F2A, F2B, F3A and F3B were 102.85%,

101.32%, 100.2%, 99.98%, 99.28% and 97.25% for 12 h and remained buoyant throughout the study.

A. Kotwal[51] et al., (2011) developed intra-gastric buoyant tablets of amoxicillin trihydrate using HPMC K15M and HPMC K100 as gelling agents, sodium bicarbonate as gas-generating agent and other excipients had undergone wet granulation technique and compressed into tablets. The *in-vitro* release studies indicated that the floating dosage form containing higher concentration of HPMC K100M showed slower release as 85.2% for 10 h. The *in-vitro* release data was treated with mathematical equations, and it was concluded that Amoxicillin released from the tablet followed Peppas model with non-Fickian diffusion.

V.Narayan[52] et al., (2010) formulated floating gastro-retentive tablets of salbutamol sulphate (a short acting bronchodilators which have short biological half life about 2 - 4 h) by using swelling polymer like Methylcellulose, Hydroxy propyl methyl cellulose (K100M, K4M) in different concentration as 25, 50, 75 % w/w. The optimized formula consists of HPMC K100M at 50% and stearic acid 25%. The formulations, which have stearic acid retards the drug release by controlling the water penetrations in to the floating matrix tablets, sustained their drug release above 12 h.

S.Ramkanth[53] et al., (2010) formulated Diltiazem floating tablets with different concentrations of two grades of HPMC polymers (HPMC K4M and HPMC K100M) by using wet granulation technique and evaluated for the different evaluation parameters such as drug content uniformity, floating lag time, *in-vitro* buoyancy, *in-vitro* drug release studies were performed. The optimized formulation containing 25% HPMC K4M was found to release a maximum of 99.6% at the 12th hour. The drug release from optimized formulaiton was found to follow zero order kinetics. It was also found linear in Higuchi's plot, which confirms that diffusion is one of the mechanisms of drug release.

Anuradha K. Salunkhe[54] et al., (2011) prepared floating pulsatile delivery system consisted of three different parts: a core tablet, containing the active ingredient, an erodible outer shell and a top cover buoyant layer. The rapid release core tablet (RRCT) was prepared by using super-disintegrants along with active ingredient. Dry coating of optimized RRCT was done by using different grades of hydroxy propyl methyl cellulose (HPMC) E5, E15, and E50 and upper most buoyant layer was prepared with HPMC

K15M and sodium bicarbonate. Developed formulations were evaluated for their drug content, *in-vitro* drug release profile (lag time), buoyancy studies and *in-vivo* X-ray study. The optimized formulation showed floating lag time of 4 min, floating time of 12 h and release lag time of 6 h.

Balkrushna K. Patel[55] et al., (2010) prepared Clarithromycin Hydrophilic floating matrix tablets by using different grades of polymer (HPMC) of varying concentrations, sodium bicarbonate and MCC by direct compression technique. Tablets of optimized formulation had good floating property as BLT in 50secs and remain buoyant for more than 12 h along with good swelling behaviors. Hydrophilic matrix floating tablets of Clarithromycin were developed to increase the gastric residence time which leads to increased bioavailability by giving sufficient time to release the drug in GI tract.

D. M. Sakarkar[56] et al., (2010) developed carbamazepine floating tablet containing Hydroxypropyl methylcellulose (HPMC) of different viscosity grades and ethyl cellulose. It was found that both HPMC viscosity, the presence of ethyl cellulose and their interaction had significant impact on the release and floating properties of the delivery system. The observed difference in the drug release and the floating properties of GFDDS could be attributed to the difference in the basic properties of three polymers (HPMC K4M, K15M and ethyl cellulose) due to their water uptake potential and functional group substitution.

Sharad N. Shinde[57] et al., (2010) developed floating tablet of salbutamol sulphate by wet granulation method using hydroxypropyl methylcellulose as a release retardant material, sodium bicarbonate and Citric acid was incorporated as a gas-generating agent. Addition of Citric acid caused the enhancement in drug release and disintegration of tablet that was retarded by incorporation of stearic acid in the formulation. The *in-vitro* drug release followed Korsemeyer-Peppas kinetics and the drug release mechanism was found to be of anomalous type. The similarity factor f2 was found to be 78.19 for the developed formulation indicating the release was almost similar to that of the marketed formulation.

Sameer Singh[58] et al., (2011) studied the floating tablet of Captopril using different viscosity grades of hydroxypropyl methylecellulose K100M, K15M and K4M were used as a floating polymer. Lactose and citric acid were used in different concentration as a channeling and chelating agent had significant effect on the release of the drug from hydrophilic matrix tablet. The *in-vitro* release profiles of drug from all the plots shows high linearity (r2= 0.9813 to 0.9954). Results revealed that the floating formulation of the Captopril is the best formulation to obtain better therapeutic effect and hydroxypropyl methylcellulose at a concentration of 35% up to some extent it increases the bioavailability of the drug to retain the dosage form on the desired site for effective period of the time.

P. N. Kendre[59] et al., (2010) prepared floating matrix theophylline tablet by direct compression method using gas generating agent (sodium bicarbonate) and various viscosity grades of hydrophilic polymers (HPMC K15M, K4M; HPC and Carbapol 934P). The release rate could efficiently be modified by varying the matrix forming polymer, the use of polymer blends and the addition of water soluble or water insoluble fillers (such as dicalcium phosphate, lactose or mannitol). Fitting the in-vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Vishnu M Patel[60] et al., (2009) developed gastro-retentive tablets for verapamil hydrochloride using different hydrocolloid polymers including Carbopol (CP 934P; CP 940P), Hydroxypropyl methylcellulose (HPMC K4M; HPMC K15M; HPMC E15) and Xanthan gum by direct compression technology. All tablet formulations shown good *in-vitro* buoyancy by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The optimized formulation containing Xanthan gum released approximately 97.89% drug in 24 h *in-vitro* dissolution study, while the buoyancy lag time was 24.6 ± 3.2 sec and the tablet remained buoyant for > 24h. Zero order and non-Fickian release transport was confirmed as the drug release mechanism for the selected tablets.

Satish Singh Kadian[61] et al., (2010) formulated floating celecoxib matrix tablet by directly compression technique using Hydroxypropyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC) alone and in combination and effervescent sodium bicarbonate (NaHCO3). The final optimized formulation released approximately 92.5% drug in 24 h

in-vitro, while the floating lag time was not more than 0.35 min and the tablet remained floatable throughout all studies. Final formulation followed the physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45°C/75% RH for three months.

R. S. Thakur[62] et al., (2006) formulated floating Clarithromycin matrix tablets containing hydroxypropylmethylcellulose (HPMC), drug and different additives were compressed using wet granulation and D-optimal design technique. The optimized formulation was obtained using 62.5% clarithromycin, 4.95% HPMC K15M, 18.09% HPMC K4M, 12.96% sodium bicarbonate which gave floating lag time < 30 s with a total floating time > 10 h, *in-vitro* release profile very near to the target *in-vitro* release profile and follows anomalous diffusion as well as zero order pattern of release.

Ziyaur Rahman[63] et al., (2006) developed bilayer-floating captopril tablet by direct compression technology using HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. Final formulation released approximately 95% drug in 24 h in vitro, while the floating lag time was 10 min and the tablet remained floatable throughout all studies. Final formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content and *in-vitro* dissolution pattern after storage at 45°C/75% RH for 3 months.

2.2. LITERATURE REVIEW ON ATORVASTATIN CALCIUM:

Jayabalan nirmal[64] et al., (2008) formulated and evaluated bilayer tablets consisting of atorvastatin calcium (AT) as an immediate release layer using super disintegrant croscarmellose sodium and nicotinic acid (NA) as an extended release layer using hydroxypropylmethyl cellulose (HPMC K100M). Both the matrix and bilayer tablets were evaluated for post compression parameters as drug content uniformity and subjected to *in-vitro* drug release studies. The amount of AT and NA released at different time intervals were estimated by HPLC method and drug release form polymer content by thermogravimetry/ differential thermal analysis (TG/DTA). The results indicated that the bilayer tablets could be a potential dosage form for delivering AT and NA.

Subhadeep Chowdjury[65] et al., (2010) studied glimepride and atorvastatin calcium in immediate release tablet formulation and evaluated, the effects of two independent variables were taken carboxymethylcellulose sodium (CMC-Na) (10mg, 12.5mg and 15 mg) and sodium starch glycolate (SSG) (2.5 mg, 5mg and 7.5mg) on drug release from the tablet in order to optimize the formulation by 2 factor 3 level factorial design. It shows that SSG has more effect than CMC-Na on the tablet formulation and formulation with 14.78 mg of CMC-Na and 7.5 mg of SSG is the optimized formulation. The optimized formulation had showed dissolution profiles that were closed to predicted values.

Patel Geeta M[66] et al., (2010) prepared once a day regioselective dual component tablet of Atorvastatin Calcium (ATC) and Metoprolol Succinate (MP) by direct compression technique. The amount of polymer blends was optimized using 32 full factorial design. All formulations floated for more than 18-20 h. More than 90% of ATC was released within 1 h. HPMC K100M and polyox WSR N-60K sustained the release of MP from the controlled release layer for more than 20 h. Diffusion exponents (n) were determined for all the formulations (0.45-0.89), so predominant drug release mechanism is non-Fickian (anomalous) transport. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets.

Chapalamadugu Ugandhar[67] et al., (2011) formulated immediate release drug combination as Atorvastatin (antihyperlipidemic) and Gliclazide (antidiabetic). Since Atorvastatin has t1/2 is near about 5 h so its release was retarded. HPMC was used as a retardant material. Two grades of Hydroxy Propyl MethylCellulose-4000cps and 100cps were used. The tablets were prepared by wet granulation method had undergone *in-vitro* dissoilution study. For Atorvastatin only 2 h of dissolution study was performed and its release was found to be 97.6%. For Gliclazide dissolution study was performed up to complete 8 h and its release was found to be 89.314% and release rate was found to be nearly similar to marketed product.

Kirti Rode[68] et al., (2011) developed Atorvastatin calcium flim coated tablet by wet granulation technique. All the physical parameters of all batches were determined, from which optimized batch was found to comply with the standard due to its maximum amount of drug was released. The optimized formulation of film coated tablets was formulated by using PEG 6000 as a Plasticizer and HPMC as a Polymer, which showed dissolution profile similar to market product.

N.Arunkumar[69] et al., (2009) formulated Atorvastatin calcium (AT-Ca) nanosuspensions to improve the solubility and dissolution characteristics of a poorly soluble drug (AT-Ca) using nanosuspension technology. The drug AT-Ca nanoparticles were successfully prepared by high pressure homogenization and were evaluated for its various solid state characteristics. Crystallinity of the drug was also evaluated by performing thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to denote eventual transformation to amorphous state during the homogenization process. Finally, crystalline AT-Ca was converted to amorphous form and exhibit improved dissolution and higher solubility leads to a significant impact in the oral bioavailability of the drug.

Sachin V. Wankhede[70] et al., (2010) developed Atorvastatin calcium amorphous into immediate release tablets. Atorvastatin calcium (amorphous) is highly susceptible to hydrolysis and oxidation, so wet granulation method was avoided. All the batches were done by dry granulation method by roller compaction and it under goes pre-compression

and post-compression parameters. *In-vitro* dissolutions were performed and the dissolution profile of optimized formulation was matched perfectly with marketed (innovator) formulation and f2 value was found to be excellent. It can be concluded that the immediate release tablet was beneficial for delivering the drug which needs faster release to achieve the immediate action.

S.Mohideen[71] et al., (2011) formulated bilayered tablets consisting of Atorvastatin calcium (AC) as an immediate release layer and Metformin Hydrochloride (MH) as a sustained release layer. The *in-vitro* release profile showed the desired biphasic behavior. The MH released for more than 12 h, where as Atorvastatin calcium dissolved within 45 min. Bilayer tablet prepared from optimized formula was found to be best suited method for fixed dose combination of sustained release MH and immediate release AC.

Asha S. John[72] et al., (2010) formulated and evaluated buccoadhesive drug delivery system for Atorvastatin calcium using the bioadhesive polymers Carbopol 934P (CP), Sodium CMC, Hydroxy ethyl cellulose (HEC) and Sodium alginate (Na-alginate) along with ethyl cellulose as an impermeable backing layer. All the formulations gave the satisfactory results in terms of bioadhesive performance, physical and mechanical properties and surface pH. The swelling index was proportional to CP content and inversely proportional to sodium CMC content. The formulation containing CP and Na-CMC in the ratio of 3:2 (F2) was optimized based on good bioadhesive strength (19.0 ± 0.30 g) and sustained *in-vitro* drug permeation (85.68 % for 6 h). The chosen tablet containing 8 mg of Atorvastatin calcium performed 6 h sustained drug release with desired therapeutic concentration.

N Arunkumar[73] et al., (2008) prepared formulations of atorvastatin calcium floating tablets containing varying proportions of polymers like HPMC K4M and Ethyl cellulose and fixed amount of gas generating agent as Sodium bicarbonate and hydrophobic meltable material like bees wax by melt granulation technique. The prepared tablets remained buoyant for more than 8 h in the release medium. The data obtained from *in-vitro* dissolution studies of all the four formulations were F1, F2, F3 and F4 released 36.88%, 34.77%, 42.17% and 48.51% respectively at the end of 8 h.

3. AIM OF THE WORK

Oral drug delivery system is the most popular delivery system due to its ease of administration. In the past, oral route has been explored for the systemic delivery of drugs through different types of dosage forms. However the drug or the active moiety must be absorbed well throughout the Gastrointestinal Tract (GIT) in order to produce an optimized therapeutic effect. Absorption may be hindered, if there is a narrow absorption window for drug absorption in the GIT or if the drug is unstable in the GI fluids. Thus the real challenge is to develop an oral controlled release dosage form not only to prolong the delivery but also to prolong the retention of the dosage form in the stomach or small intestine until the entire drug is released.

One of the most important approaches to control the retention of drug delivery system in GIT is by adopting Gastro Retentive Drug Delivery Systems (GRDDS). Such retention systems are important for drugs that are degraded in the intestine or drugs undergo rapid clearance in intestine like Atorvastatin calcium.

- Atorvastatin calcium, an anti-hyperlipidemic drug used in the treatment of dyslipidemia and the prevention of cardiovascular disease was used as a model drug to develop a controlled release formulation.

- Atorvastatin calcium has more absorption in acidic medium and Tmax is very rapid as within 1-2 h. Once the drug reaches the intestine it was rapidly undergo elimination. Hence the present study was aimed to develop a controlled release formulation of Atorvastatin calcium.

- Atorvastatin calcium is taken by the people as a long term therapy; the major side effect experienced by the patients was myopathy, rhabdomyolysis due to more concentration of drug in the blood. Hence the present study is to release the drug in a required quantity to the body for that we planned to develop a controlled release formulation of Atorvastatin calcium.

- The best formulation is to be selected on the basis of evaluation characteristics.

4. PLAN OF WORK

1. Preparation of standard calibration curve for Atorvastatin Calcium.
2. Optimizing the quantity of gas generating agent for the total tablet weight
3. Selection of polymers and polymer concentrations.
4. Compatibility study between drug and selected polymers.
    - By Fourier Transform Infrared Spectroscopy
5. Formulation of granules.
6. Pre-compressional evaluation studies.
    - Angle of Repose
    - Bulk Density
    - Tapped Density
    - % Compressibility
    - Hausner's Ratio
7. Formulation of tablets.
8. Post-compressional evaluation studies.
    - Weight variation
    - Thickness
    - Hardness
    - Friability
    - Drug content
    - Buoyancy lag time
    - Buoyancy time
9. Selection of best formulation.
10. *In-vitro* dissolution studies.
11. Stability studies.
12. Data analysis.(drug release kinetics)

5.1 MATERIALS AND METHODS

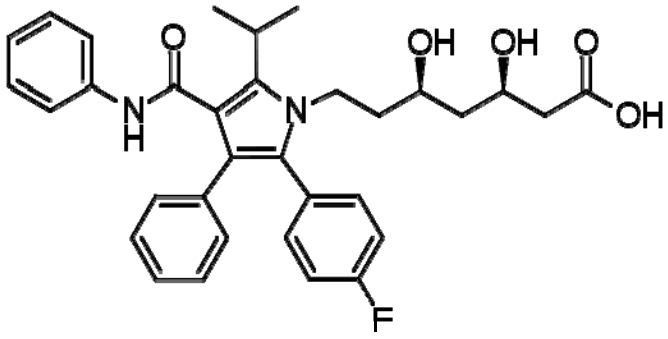
S.No.	MATERIALS	NAME OF THE MANUFACTURER
1	Atorvastatin calcium	MOREPEN Laboratories Ltd., Solan (Himachal Pradesh)
2	HPMC-Methocel (HPMC K4M,K15M,K100M)	Colorcon Asia Pvt., Ltd., Goa.
3	Croscarmellose sodium	Ozone International, Mumbai.
4	Crospovidone	C.Chem, pharma Ltd., Bangalore.
5	Avicel PH-102	Medreich, Bangalore.
6	Polyethylene Oxide WSR 303	Medreich, Bangalore.
7	Sodium bicarbonate	Ranbaxy Laboratories Ltd., Guragan, India.
8	Talc	Loba Chemie Pvt Ltd., Mumbai.
9	Magnesium stearate	Loba Chemie Pvt Ltd., Mumbai.
10	Lactose DC	Juggat Pharmaceuticals Ltd., Bangalore.

5.1.1 INSTRUMENTS AND EQUIPMENTS

S.No.	INSTRUMENTS	NAME OF THE MANUFACTURER
1.	Digital balance	Santorious BT 323S, Germany.
2.	Moisture analyzer	Santorious YCS 01-522-00, Germany.
3.	Hot air oven	C.S. Medical Pvt Ltd. 175-10, Chennai.
4.	16 station Tablet compression Machine	Elit Jemkay Engineers Pvt Ltd., Ahmedabad.
5.	Monsanto Hardness Tester	Scientific Engineering Corp, Delhi.
6.	Friability Testing Apparatus	Roche Friabilitor, EF-2, Bombay.
7.	Dissolution Test Apparatus	Electrolab TDT-08l, Bombay.
8.	U.V.Spectrophotometer	Shimadzu-uv-1601, Japan.
9.	FTIR	Shimadzu 8300, Japan.
10.	Digital pH meter	Eutech cyber scan 500, Singapore.
11.	Sonnicator	Santorious Flexit Lab, Geramany.
12.	Sieves	Campbell Electronics, Bombay.
13.	Bulk Density Apparatus	Campbell Electronics, Bombay.
14.	Digital Vernier Calipers	Mitutoyo Measuring Instruments (Suzhou) Co., Ltd. China.
15.	Thermogravimetry/Differential Thermal Analyzer	SDT Q 600, India.
16.	Stability Chamber	Osworld, Mumbai.

5.1.2. DRUG PROFILE[74,75]

MOLECULAR STRUCTURE OF ATORVASTATIN:



IUPAC NAME:

(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoate

ATORVASTATIN IDENTIFIERS:

CAS number: 134523-00-5

Category: Anti-Hyperlipidemic

Bio Pharmaceutical Classification System: Class-II

CHEMICAL DATA:

Formula: $\mathbf{C_{33}H_{35}FN_2O_5}$

Mol. Mass: 558.64 g/mol

Solubility: soluble in methanol

DESCRIPTION:

Atorvastatin was first synthesized in 1985 by Bruce Roth while working at Parke-Davis Warner-Lambert Company (now Pfizer).**Atorvastatin** is a member of the drug class known as statins, used for lowering blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body.

With 2008 sales of US$12.4 billion, Lipitor was the top-selling branded pharmaceutical in the world. U.S. patent protection was scheduled to expire in June 2011. However, Pfizer made an agreement with Ranbaxy Laboratories that delayed the generic launch in the U.S. until November 30, 2011.

The primary use of atorvastatin is for the treatment of dyslipidemia and the prevention of cardiovascular disease. It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels.

PHARMACOKINETIC DATA[74]:

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 h. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In-vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In-vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 h, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 h due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

MECHANISM OF ACTION:

As with other statins, atorvastatin is a competitive inhibitor of HMG-CoA reductase. Unlike most others, however, it is a completely synthetic compound. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases de-novo cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol.

In clinical trials, drugs that block cholesterol uptake like ezetimibe combine with and complement those that block biosynthesis like atorvastatin or simvastatin in lowering cholesterol or targeting levels of LDL.

SIDE EFFECTS:

Minor effects like: Headache; nausea. Severe allergic reactions in over dosage condition like (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); calf pain; chest pain; confusion; dark urine; fast, slow, or irregular heartbeat; fever, chills, or persistent sore throat; increased coughing or coughing up blood; muscle pain, tenderness, or weakness (with or without fever and fatigue); pale stools; red, swollen, blistered, or peeling skin; severe or persistent dizziness or light headedness; severe or persistent nausea, stomach pain, or vomiting; severe pain or swelling in the ankles, feet, or legs; shortness of breath; unusual bruising or bleeding; yellowing of the skin or eyes.

CONTRAINDICATION:

- Acute liver disease: cholestasis, hepatic encephalopathy, hepatitis, and jaundice
- Unexplained elevations in AST or ALT levels
- Pregnancy
- Breastfeeding

Precaution must be taken when treating with atorvastatin, because rarely it may lead to rhabdomyolysis, it may be very serious leading to acute renal failure due to myoglobinuria. If rhabdomyolysis is suspected or diagnosed, atorvastatin therapy should be discontinued immediately. The likelihood of developing a myopathy is increased by the co-administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, and azole antifungals.

PREGNANCY AND LACTATION:

Atorvastatin is absolutely contraindicated in pregnancy, it is likely to cause harm to fetal development because of the importance of cholesterol and various products in the cholesterol biosynthesis pathway for fetal development, including steroid synthesis and cell membrane production. It is not recommended for nursing mothers to take atorvastatin due to the possibility of adverse reactions in nursing infants, since experiments with rats indicate that atorvastatin is likely to be secreted into human breast milk.

FORMULATIONS:

All atorvastatin formulations are available as solid dosage form. It is under the brand name of Lipitor by Pfizer labs, a-vin by besthochem , atorva by zydus cadila, Atocor by Dr.Reddy's labs, Ateven vy apotex, atorbest by cadila labs, Atorec by Emcure, Atorfit by Ajanta, atoril bu auroindo, Atorlip by Cipla pharmaceuticals.

COMBINATION WITH OTHER DRUGS:

Co-administration of Atorvastatin with one of CYP3A4 inhibitors like itraconazole, telithromycin and voriconazole, may increase serum concentrations of atorvastatin, which may lead to adverse reactions. bosentan, fosphenytoin, and phenytoin, which are CYP3A4 inducers, can decrease the plasma concentrations of atorvastatin. Antacids can rarely decrease the plasma concentrations of atorvastatin but do not affect the LDL-C-lowering efficacy. Niacin is also proved to increase the risk of myopathy or rhabdomyolysis. Statins may also alter the concentrations of other drugs, such as warfarin or digoxin, leading to alterations in effect or a requirement for clinical monitoring.

5.1.3 EXCIPIENTS[76]

1. HYDROXY PROPYL METHYL CELLULOSE[88]

Nonproprietary Names:

USP, BP : Hypromellose

JP : Hydroxypropylmethylcellulose

Ph Eur : Hypromellosum

Functional Category:

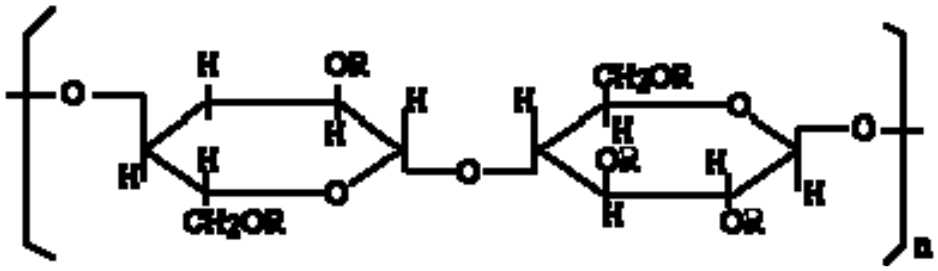
USP : Suspending agent and / or viscosity increasing agent, tablet binder, coating agent.

B.P. : Viscosity increasing agent, adhesive anhydrous ointment ingredient

Others : Film former, emulsion stabilizer.

Synonyms: Methyl Hydroxy Propyl Cellulose (MHPC), Methyl cellulose Propylene glycol ether, Methocel, Metolose, Tylopur, Propylene glycol ether of methylcellulose.

Chemical Name: Cellulose, 2-Hydroxypropylmethyl ether.



n: degree of polymerizetion; R:-H,-CH_3 or $CH_2CH(OH)CH_3$

Empirical Formula : $C_8H_{15}O_6$- $(C_{10}H_{18}O_6)_n$ – $C_8H_{15}O_5$

Molecular Weight: 86,000 (Approximately)

Description: Odorless, tasteless, white or off-white fibrous or granular powder.

Typical Properties:

Browning temperature : 190-200°C

Bulk Density : 0.25-0.70g/cm^2

Specific Gravity : 1.26-1.31

Surface tension : 42-56dynes/cm (2% aqueous solution)

Solubility: HPMC is soluble in water and some organic solvents. Its aqueous solution is of high transparency and stable property. The solubility varies with the viscosity. The lower the viscosity, the higher is the solubility. The different grades of HPMCs vary in some properties and its solubility in water is not affected by pH. It is practically insoluble in ethanol, ether and chloroform.

Moisture Content: HPMC absorbs moisture from the atmosphere. The amount of water absorbed depends upon the initial moisture content and the temperature and the relative humidity of the surrounding air.

Stability: Very stable in dry conditions. Solutions are stable at pH 3 to 11.0.

Storage Condition: It should be stored in well closed containers in a cool and dry place.

Incompatibilities: Oxidizing agents.

Safety: It is a non-toxic and non-irritant polymer.

Regulatory Status: HPMC is accepted for use as a food additive in Europe, included in the FDA Inactive Ingredients Guide, non-parenteral medicines licensed in the UK and in the Canadian List of Acceptable Non-medicinal Ingredients.

Role of HPMC in Controlled Release Systems: In a hydrophilic matrix system, HPMC is uniformly incorporated throughout the tablet. Upon contact with water, it hydrates the outer tablet surface to form a gel layer. The rate of diffusion of drug out of the gel layer and the rate of tablet erosion control the overall dissolution rate and drug delivery.

2. SODIUM BICARBONATE

Nonproprietary Names:

BP: Sodium bicarbonate

JP: Sodium bicarbonate

PhEur: Natrii hydrogenocarbonas

USP: Sodium bicarbonate

Synonyms:

Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

Chemical Name:

Carbonic acid monosodium salt

Empirical Formula and Molecular Weight: NaHCO3; 84.01

Structural Formula: NaHCO3

Functional Category: Alkalizing agent; therapeutic agent.

Applications in Pharmaceutical Formulation or Technology:

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

Tablets may also be prepared with sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation.

Sodium bicarbonate has been used as a gas forming agent in alginate raft systems and in floating, controlled-release oral dosage forms of furosemide, cisapride and atorvastatin. Tablet formulations containing sodium bicarbonate have been shown to increase the absorption of paracetamol, and improve the stability of levothyroxine.

Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis. Sodium bicarbonate may

also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids.

Table:1 Uses of Sodium bi carbonate

Use	Concentration (%)
Buffer in tablet	10-40
Effervescent tablet	25-50
Isotonic injection/infusion	1.39

Description and Solubility:

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particlesizes, from a fine powder to free-flowing uniform granules, are commercially available. Sodium bicarbonate slightly soluble in water but practically insoluble in ether and ethanol (95%).

Typical Properties

Acidity/alkalinity: pH = 8.3 for a freshly prepared 0.1M aqueous solution at 258°C; alkalinity increases on standing, agitation, or heating.

Density (bulk): 0.869 g/cm^3

Density (tapped): 1.369 g/cm^3

Density(true): 2.173 g/cm^3

Freezing point depression: 0.3818°C (1% w/v solution)

Melting point: 2708°C (with decomposition)

Moisture content: Below 80% relative humidity, the moisture content is less than 1% w/w. Above 85% relative humidity, sodium bicarbonate rapidly absorbs excessive amounts of water and may start to decompose with loss of carbon dioxide.

Stability and Storage Conditions:

When heated to about 508°C, sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–308°C, for a short time, sodium bicarbonateis completely converted into anhydrous sodium carbonate.

Sodium bicarbonate powder is stable below 76% relative humidity at 258°C and below 48% relative humidity at 408°C. At 54% relative humidity, the degree of pyrolytic decarboxylation of sodium bicarbonate should not exceed 4.5% in order to avoid detrimental effects on stability.

Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates.

In *powder mixtures*, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid oralum.

In *liquid mixtures containing bismuth subnitrate*, sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt.

In *solution*, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin, amiodarone, nicardipine, and levofloxacin.

Method of Manufacture:

Sodium bicarbonate is manufactured either by passing carbon dioxide into a cold saturated solution of sodium carbonate, or by the ammonia–soda (Solvay) process, in which first ammonia and then carbon dioxide is passed into a sodium chloride solution to precipitate sodium bicarbonate while the more soluble ammonium chloride remains in solution.

Safety:

Sodium bicarbonate is used in a number of pharmaceutical formulations including injections and ophthalmic, otic, topical,and oral preparations.

Sodium bicarbonate is metabolized to the sodium cation, which is eliminated from the body by renal excretion, and the bicarbonate anion, which becomes part of the body's bicarbonate store. Any carbon dioxide formed is eliminated via the lungs. When used as an excipient, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Related Substances: Potassium bicarbonate.

Description: Odorless, white, crystalline powder with a saline, slightly alkaline taste.

3. MICRO CRYSTALLINE CELLULOSE:

Non proprietary names

BP: Micro crystalline cellulose

JP: Micro crystalline cellulose

PhEur: Cellulosum microcrystalanium

USPNF: Micro crystalline cellulose

Synonyms:

Avicel PH, Celex, Cellulose gel, Celphere, Ceolus KG, crystalline Cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

Chemical name: Cellulose

Empirical Formula: $(C_6H_{10}O_5)$ n Where n=220 Molecular weight 36000

Functional category: Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrants

Application in Pharmaceutical formulation or technology:

Micro crystalline cellulose pH 101 is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a binder/diluent, micro crystalline cellulose pH 101 also has some lubricant and disintegrant properties that make it useful in tableting.

Table:2 Uses of Microcrystalline cellulose

Use	Concentration (% w/w)
Adsorbent	20-90
Anti-adherent	5-20
Capsule binder/diluents	20-90
Tablet disintegrant	5-15

Description:

Micro crystalline cellulose pH 101 is purified, partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Solubility: Slightly soluble in 5 % w/v sodium hydroxide solution, practically insoluble in water, dilute acids, and most organic solvents.

4. PURIFIED TALC:

Synonyms:

Hydrous magnesium calcium silicate.

Chemical Name: Talc.

Empirical Formula:

Approximate $Mg_6(Si_2O_5)_4(OH)_4$

Functional Category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Application in Pharmaceutical Formulation:

Table:3 Uses of Purified Talc

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

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

Description:

Talc is very fine, white to grayish white, odorless, impalpable, crystalline powder. It adheres readily to skin and soft to touch and free from grittiness.

pH: 7-9.

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

Stability and Storage:

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 h. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibility: It is incompatible with quaternary ammonium compounds.

5. MAGNESIUM STEARATE:

Synonyms:

Magnesium octadecanoate, Octadecanoic acid, Stearic acid.

Empirical Formula: $C_{36}H_{7O}MgO_4$;

Molecular Weight: 591.34.

Application in Pharmaceutical Formulation:

Primarily used as lubricant in capsule and tablet at a concentration between 0.25% - 5.0% w/w.

Description:

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

Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations. Capsule dissolution is also sensitive to both the amount of magnesium stearate in the formulation and the mixing time; higher levels of magnesium stearate and long mixing times can result in the formation of hydrophobic powder beds that do not disperse after the capsule shell dissolves.

An increase in the coefficient of variation of mixing and a decrease in the dissolution rate have been observed following blending of magnesium stearate with a tablet granulation. Tablet dissolution rate and crushing strength decreased as the time of blending increased; and magnesium stearate may also increase tablet friability. Blending times with magnesium stearate should therefore be carefully controlled.

Loss on Drying:≤6.0%.

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

Incompatibility:

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in product containing aspirin, some vitamins and most alkaloidal salts.

6. LACTOSE ANHYDROUS

Nonproprietary Names:

BP: Anhydrous lactose

JP: Anhydrous lactose

PhEur: Lactosum anhydricum

USPNF: Anhydrous lactose

Synonyms:

Anhydrous Lactose NF 60M; Anhydrous Lactose NF Direct Tableting; Lactopress Anhydrous; lactosum; lattioso; milk sugar; Pharmatose DCL 21; Pharmatose DCL 22; saccharum lactis; Super-Tab Anhydrous

Chemical name:

O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose

Empirical formula and Molecular weight:

$C_{12}H_{22}O_{11;}$ 342.30.

Functional category:

Binding agent; directly compressible tableting excipient; lyophilization aid; tablet and capsule filler

Description:

Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α-lactose. Anhydrous lactose typically contains 70–80% anhydrous β-lactose and 20–30% anhydrous α-lactose.

Applications in Pharmaceutical Formulation or Technology:

Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.

Melting Point:

- 223.0°C for anhydrous α-lactose;
- 252.2°C for anhydrous β-lactose;
- 232.0°C (typical) for commercial anhydrous lactose

Water Content:

Loss on drying ≤0.5% and ≤1.0% water content for Anhydrous Lactose NF Direct Tableting and Anhydrous Lactose NF 60M; 0.2% loss on drying and 0.5% water content for Pharmatose DCL 21 (typical); 0.2% loss on drying.

Solubility: Soluble in water; sparingly soluble in ethanol (95%) and ether

Stability and storage condition:

Mould growth may occur under humid conditions (80% RH and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; At 80°C and 80% RH, tablets containing anhydrous lactose have been shown to expand 1.2 times after one day. Lactose anhydrous should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Lactose anhydrous is incompatible with strong oxidizers. When mixtures containing a hydrophobic leukotriene antagonist and anhydrous lactose or lactose monohydrate were stored for six weeks at 40°C and 75% RH, the mixture containing anhydrous lactose showed greater moisture uptake and drug degradation.

Method of Manufacture:

There are two anhydrous forms of lactose: α-lactose and β-lactose. The anhydrous forms that are commercially available may exhibit hygroscopicity at high relative humidities. Anhydrous lactose is produced by roller, drying a solution of lactose above 93.5°C. The resulting product is then milled and sieved. Two anhydrous α-lactoses can be prepared using special drying techniques: one is unstable and hygroscopic, the other exhibits good compaction properties. However, these materials are not commercially available.

Safety:

Lactose is widely used in pharmaceutical formulations as a diluent and filler-binder in oral capsule and tablet formulations. It may also be used in intravenous injections. Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase, and is associated with oral ingestion of amounts well over those in solid dosage forms**.**

5.2 METHODS:

5.2.1 CONSTRUCTION OF STANDARD CURVE OF ATORVASTATIN CALCIUM[79]:

By UV spectroscopy method:

Atorvastatin calcium estimated spectrophotometrically at 246nm and it obeys beer - lamberts law in the range of 2 – 20 mcg/ml.

PREPARATION OF BUFFER:

0.1N Hydrochloric Acid:

Concentrated hydrochloric acid of 8.5 ml was taken in a 1000 ml standard flask containing distilled water and volume made up to 1000 ml with distilled water.

PROCEDURE:

1) Standard curve of Atorvastatin in 0.1N HCL:

a) preparation of primary stock solution:

Accurately weighed 100 mg of atorvastatin was taken in 100 ml standard flask. Then 25ml of methanol added slowly to dissolve the drug completely. Then it was made up to volume 100 ml with 0.1 N HCL to a concentration of 1000 mcg / ml.

b) preparation of secondary stock solution:

From primary solution flask 2 ml was taken in 100 ml standard flask and made up to 100 ml with 0.1N HCL to a concentration of 20 mcg / ml.

c) sample solution :

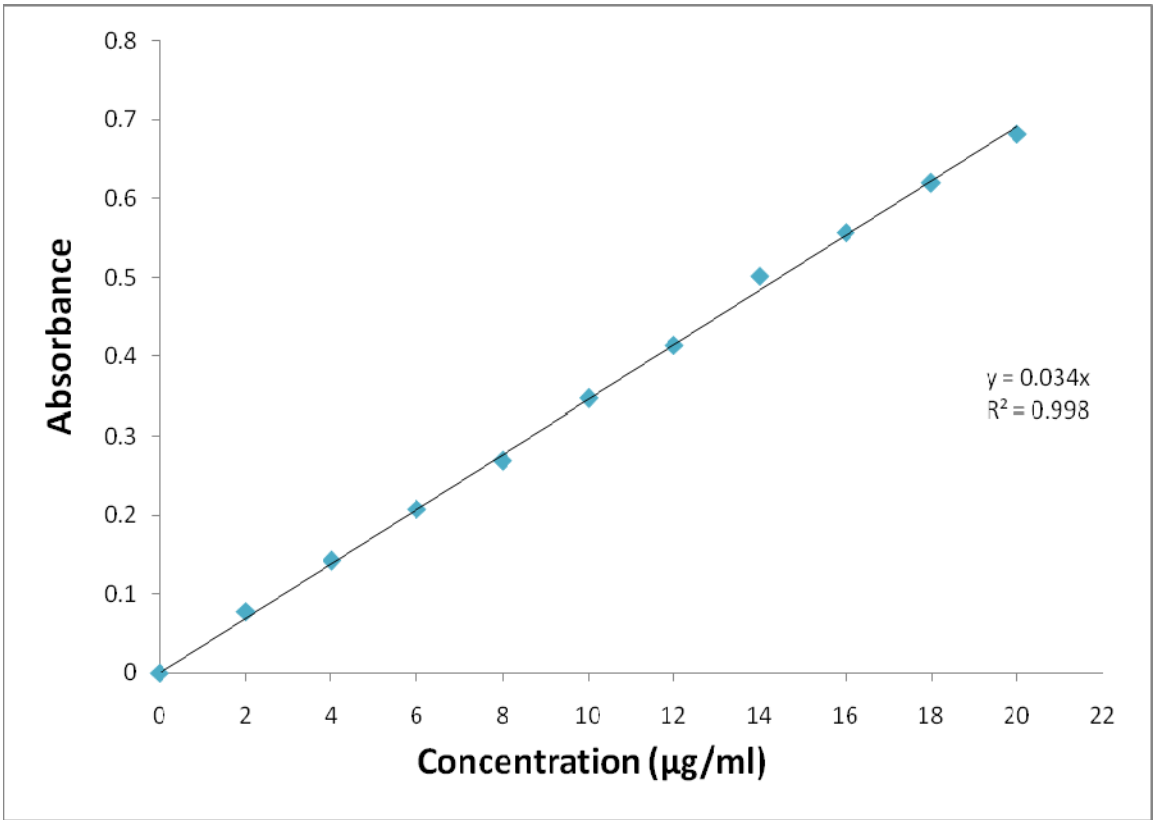
From the secondary stock solution aliquots ranging from 1 to 10 ml were pipetted out and diluted to 10 ml with 0.1N HCL to get the concentration of 2 to 20 mcg / ml then absorbance was measured at 246nm.

A standard graph was plotted by keeping the known concentration on X axis and obtained absorbance on Y axis.

Table:4 Data for standard curve of Atorvastatin calcium in 0.1N HCL:

Concentration (mcg / ml)	Absorbance
2	0.078
4	0.142
6	0.208
8	0.269
10	0.347
12	0.414
14	0.501
16	0.557
18	0.620
20	0.682

Figure:1 Standard curve of Atorvastatin calcium



6. EXPERIMENTAL INVESTIGATIONS

6.1 PREFORMULATION STUDIES:

- Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms.
- The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.
- The use of preformulation parameters maximizes the changes in formulating an acceptable, safe, efficacious and stable product.
- The drug (Atorvastatin Calcium) in powder form and granules were subjected to the following physical test for 3 times and average values were noted.

6.2 Characterization of Drug

6.2.1 UV- Spectrum Analysis of Drug[77]

Atorvastatin drug solution in pH 1.2 was scanned using UV-Spectrophotometer between the range 200-400nm using pH 1.2 as blank.

6.2.2 I.R SPECTRUM FOR ATORVASTATIN CALCIUM:

Instrument used was Shimadzu FTIR-8300 spectrophotometer. In this study, potassium bromide disc method was employed. Both pure drug and its mixture with various grades of HPMC were subjected to IR studies (Table: 12-17). The powdered samples were intimately mixed with dry powdered potassium bromide and were compressed under 15 tones pressure in a hydraulic press to form a transparent disc. The disc was placed in IR spectrophotometer using sample holder and scanned from 4000 to 400cm^{-1} in IR spectrometer. The IR spectrum of substances compared with that obtained concomitantly for the corresponding IP reference standard provides perhaps the most conclusive evidence of the identity of the substance.

6.2.3 DRUG – EXCIPIENTS COMPATIBILITY STUDIES:

About 100 mg of Atorvastatin calcium alone and mixtures, consisting of Atorvastatin calcium with various excipients in 1:1 and 1: 10 ratios were taken in glass vials and kept at various accelerated condition [25^{o}C / 60% RH, 30^{o}C / 65% RH, 40^{o}C / 75% RH] in stability chamber. It is carried out for one month in open and closed glass vials. At the interval days of 1, 2, 3, 4, 5, 6,14, 21 and 30 days samples were withdrawn and physical characteristics like color change, if any were recorded. Finally the mixtures with no color change were selected for formulations.

6.3 Evaluation

Tablets were subjected to 2 types of evaluation, which are as follows

- Pre-compressional evaluation
- Post-compressional evaluation

6.3.1. Pre-compressional Evaluation[86]

Angle of Repose

It is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h) above a flat horizontal surface to which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. It was then calculated using the formula

$$\tan \theta = h/r$$

Where, θ = Angle of Repose

h = Height of Pile

r = Radius of the base of the pile

Table:5 Angle of Repose

S. No.	Angle of Repose (^{0})	Flow
1.	< 25	Excellent
2.	25 – 30	Good
3.	30 – 40	Fair
4.	> 40	Poor

Bulk Density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantities of granules were carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. It was expressed in gm/ ml and given by

$$BD = \frac{Wg}{Bg}$$

Where, BD = Bulk Density

Wg = Weight of granules

Bg = Bulk volume of granules

Tapped Density:

It is the ratio of total mass of the powder to the tapped volume of powder. The weight of sample equivalent to 10 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted. The tapped density was calculated in gm/ cm^3 by the formula,

$$(\rho_t) = M/Vf$$

Where ρ_t - Tapped Density

M = weight of sample powder taken

Vf = tapped volume

Carr's Consolidation Index (% Compressibility)

Carr's Index explains flow properties of the granules. It is expressed in percentage and given by

$$\text{Consolidation Index} = \frac{\text{Tapped Density - Untapped Density}}{\text{Tapped Density}} X 100$$

Table:6 Consolidation Index

S. No.	Consolidation Index %	Flow
1.	5 – 12	Excellent
2.	13 – 16	Good
3.	17 – 21	Fair
4.	≥ 40	Poor

Hausner's ratio:

Tapped density and untapped density were measured and the Hausner's ratio was calculated using the formula,

$$\text{Hausner's ratio} = \rho t/\rho o$$

Where, ρt = tapped density ;

ρo = untapped density

Table:7 Hausner's Ratio

S.NO	Hausner's Ratio	Property
1	0 - 1.2	Free flowing
2	1.2 – 1.6	Cohesive powder

The results of physical properties of drug Atorvastatin calcium and powder blend are given in the Table No.18 and Table No.19 respectively.

7.Formulation of floating tablet:

FORMULATION DEVELOPMENT[83,87]

Design of formula and composition: The design of tablets involved various compositions on the part of the formulator, to produce desired product properties. It involves the correct selection and balance of excipients, materials for active ingredients to achieve the desired response.

Justification for the design of the composition: In addition to the active ingredient, Atorvastatin calcium 20mg SR tablets contained a number of inert materials as diluents, binder, glidant and lubricants, gas generating agent and polymers to impart

satisfactory processing, compression and release characteristics to the formulation. The justification for the inclusion of these functional additives is briefly described below:

a. Diluents: They are inert materials added to increase the bulk in order to make the tablet with a desired particle size for compression. Calcium phosphate anhydrous, mannitol, sucrose and anhydrous lactose were used as diluents.

b. Binders: Materials used to impart cohesive quality to the powdered materials are referred to as binders. They impart cohesiveness to the tablet formulation which ensures the tablet remaining intact after compression as well as improving the free flowing qualities by the formulation of granules of desired hardness and size. AVICEL PH102 was selected as binder in present study.

c. Glidant: It is an inert material used to increase the flow property of the tablet blend. Here talc is used as a glidant.

d.Lubricants: They prevent the adhesion of the tablet material to the surface of the dies and punches reducing inter-particle friction, facilitating the ejection of the tablet from the die cavity and improve the rate of flow of the tablet granulation. In the present study magnesium stearate was used as lubricant.

e.Gas generating agent: It is the major ingredient, which play an important role in floating of the tablet in the gastric medium. Here sodium bicarbonate is used as a gas generating agent.

f**.polymer:** It is used to control the release of drug from the tablet formulation. Different types of polymers are available as HPMC, PEO, HPC, etc,.

7.1. FORMULATION OF SUSTAINED RELEASE TABLET OF ATORVASTATIN CALCIUM:

Composition of Atorvastatin Calcium 20mg Sustained Release Tablet

I) DIRECT COMPRESSION METHOD[81]:

To formulate Atorvastatin Calcium 20mg SR tablet by direct compression method.

Table No: 8 FORMULA COMPOSITION

S.No	Ingredients (mg)	Category	Range
1	Atorvastatin Calcium	Active ingredient	20mg
2	HPMC K15M	Polymer	10%, 20%
3	HPMC K100M	Polymer	10%, 15%, 20%
4	AVICEL PH102	Binder	5%, 10%, 15%
5	Sodium Bicarbonate	Gas generating agent	15%
6	Lactose	Diluent	q.s.
7	Magnesium stearate	Lubricant	0.5%
8	Talc	Glidant	1%
Average weight of tablet			150mg
Dissolution Profile		Dissolution profile for 24th hour	

General Manufacturing procedure for all formulae in table no:8:

Step 1: DISPENSING: All the materials are collected according to the above formula composition.

Step 2: SIFTING:

a. Atorvastatin calcium, HPMC, avicel PH102, sodium bicarbonate, lactose were sifted and passed through # 40 mesh and collected in a double lined poly bag.

b. Magnesium stearate, talc was passed through # 60 mesh and collected it in double lined poly bag separately.

Step 3: MIXING: Then the major raw materials were mixed with the lubricant.

Step 4: COMPRESSION:

Lubricated blend was compressed using 7mm flat round shaped punches plain on both sides in 16 station compression machine with average weight of 150mg. All the parameters of the compressed tablets are given in the Table:19.

6.3.2 Post-Compressional Evaluation[90]

Weight Variation Test

Twenty tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.

$$PD = \frac{W_{avg} - W_{ind}}{W_{avg}} X100$$

where,

PD = Percentage Deviation

W_{avg} = Average weight of tablet

W_{ind} = Individual weight of tablet

Table:10 Weight Variation

S. No.	Average Weight	% Deviation
1.	0.12g or less	± 10
2.	More than 0.12g but less than 0.3g	± 7.5
3.	0.3g or more	± 5

Thickness and Diameter:

The thickness and diameter of the tablets were carried out using vernier caliper (Mitutoyo corps, Japan). Five tablets were used for the above test from each batch and results were expressed in millimeter.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gave a measure of the hardness of tablet. Hardness was expressed in Kg/ cm^2.

Friability

Friability was determined using Roche Friabilator. Twenty tablets were weighed and placed in the friabilator and then operated at 25 rpm for four minutes. The tablets were then dedusted and weighed. It was expressed in percentage. Friability should be < 1%.

The difference in the two weights is used to calculate the friability.

$$Friability = 100X(1 - \frac{W}{W_0})$$

where,

W_0 = Initial weight

W = Final weight

Drug Content

Drug content was determined to check dose uniformity in the formulations. The procedure adopted for determination of drug content as initially 10 tablets were weighed and powdered. A quantity equivalent to 100 mg of Atorvastatin calcium was taken in a 100 ml volumetric flask and dissolved in small volume of methanol and made up the volume with 0.1N HCL and filtered. An aliquot of 10 ml was pipetted out into 100 ml volumetric flask and made up the volume with distilled water. Absorbance was read at 246 nm using 0.1N HCL as a blank.

Buoyancy Studies

The time taken by the tablet to emerge on to the surface is called the floating lag time or Buoyancy lag Time (BLT) and the total time for which the tablet floats on the media surface is the Buoyancy Time (BT). Buoyancy studies were carried out in glass beakers at pH 1.2. Lag time and floating time were noted. (Table: 36)

***In-vitro* Release studies**[82]

In-vitro release studies were carried out using pH 1.2 buffer as dissolution medium at 37^0 ± s0.5^0C and rotational speed of 75 rpm for 24 h. 5ml of dissolution medium was withdrawn at every 1h time intervals and then estimated spectrophotometrically. Dissolution mechanism of the formulations was analyzed by plotting drug release versus time plot (Table: 20-31)

6.4 STABILITY STUDIES:[78,89]

Stability is defined as the extent to which a product retains the contents within specified limit and throughout its period of storage and use i.e. shelf life, the same properties that it possesses at the time of manufacture. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Stability studies are important to prevent the economic repercussions of marketing of an unstable product, since subsequent withdrawal and reformulation may lead to considerable financial loss. From the point of view of safety to patient, it is important that the patient receives a uniform dose of the drug throughout the shelf life of the product.

The International Conference on Harmonization (ICH) guidelines titled "Stability testing of new drug substances and products- Q1A (R2)" describes the stability test requirements for drug registration applications in the United States, European Union and Japan.

As per *in-vitro* release formulation F_{11} was found to be desirable than other formulations. Hence it was chosen for stability studies. The tablets were packed and kept for 3 months at different temperature 25^{o}C / 60%RH, 30^{o}C / 65%RH, 40^{o}C / 75% RH in a stability chamber (Osworld, Mumbai). At the interval of 1 month tablets were withdrawn and evaluated for physical properties like thickness, hardness, diameter, friability, weight variation, buoyancy studies and content uniformity. *In-vitro* drug release is also carried out.

6.5 Kinetic Analysis of *In–Vitro* Release Rates of Controlled Release Tablets of Atorvastatin[80,82]

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative % drug remaining versus time.
3. Higuchi's model – Cumulative % drug released versus square root of time.

4. Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time.

1. Zero order kinetics:

Zero order release would be predicted by the following equation:-

$$A_t = A0 – K_0t$$

Where,

A_t = Drug release at time 't'.

A_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K^0.

2. First Order Kinetics:

First – order release would be predicted by the following equation:-

$$\text{Log } C = \log C_0 – K_t / 2.303$$

Where,

C = Amount of drug remained at time't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

3. Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

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

Where,

Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

τ = Porosity of the matrix.

ε = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes:

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

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' .

4. Korsmeyer equation / Peppa's model:[84]

To study the mechanism of drug release from the sustained – release matrix tablets of Zidovudine, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_a = Kt^n$$

Where,

M_t / M_a = the fraction of drug released at time 't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get:

$$\text{Log } M_t / M_a = \text{Log } K + n \text{ Log } t$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0. The result of *in-vitro* drug release study of all the formulation as shown below.

Table:11 Mechanism of Drug Release as per Korsmeyer Equation/Peppa's Model

S. No.	n Value	Drug release
1.	0.45	Fickian release
2.	0.45 <n <0.89	Non – Fickian release
3.	n> 0.89	Class II transport

TABLE:8 COMPOSITION OF SUSTAINED RELEASE TABLET OF ATORVASTATIN CALCIUM (in mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Atorvastatin Calcium	21.64	21.64	21.64	21.64	21.64	21.64	21.64	21.64	21.64	21.64	21.64	21.64
HPMC 15,000cps	15	15	15	30	30	30	--	--	--	--	--	--
HPMC 100,000 cps	--	--	--	--	--	--	15	15	22.5	22.5	30	30
Sodium bicarbonate	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Avicel PH102	7.5	15	22.5	7.5	15	22.5	7.5	15	15	22.5	15	22.5
Lactose DC	81.11	73.61	66.11	66.11	58.61	51.11	81.11	73.61	66.11	58.61	58.61	51.11
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	150	150	150	150	150	150	150	150	150	150	150	150

***20mg of Atorvastatin is equivalent to 21.64mg of Atorvastatin calcium**

8. RESULTS AND DISCUSSION

The present study was undertaken to formulate Atorvastatin calcium floating tablets. Controlled release dosage forms deliver the drug at a slow release rate over an extended period of time. The drug Atorvastatin calcium is formulated as a floating tablet due to its rapid absorption in acidic pH, high intestinal clearance and maintains required drug concentration in blood.

The tablets prepared in the present study by direct compression technique have advantages over those prepared by wet granulation in terms of time and energy consumption, thus making it possible to formulate tablets at a lower cost because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery.

The study involved pre-formulation of drugs and granules, formulation and processing development along with evaluation of the tablets.

8.1 PRE-FORMULATION STUDY OF DRUG:

- The Atorvastatin calcium was subjected to drug-excipients compatibility study with excipients like hydroxyl propyl methyl cellulose, avicel PH102, sodium bicarbonate, anhydrous lactose, talc and magnesium stearate. The mixtures shown to have no colour change.

- Good flow of powders / granules is essential in tableting, because the compressibility & flow properties of the drugs likely to influence the compression process in the preparation of tablets. In view of this the formulation were prepared by direct compression technique to improve the flow as well as compressability.

8.2 Characterization of Drug

8.2.1 UV- Spectrum Analysis of Drug

Atorvastatin drug solution in pH 1.2 was scanned using UV-Spectrophotometer between the range 200-400nm. which showed the maximum absorbance at 246nm.

Figure 2: UV spectrum of Atorvastatin calcium

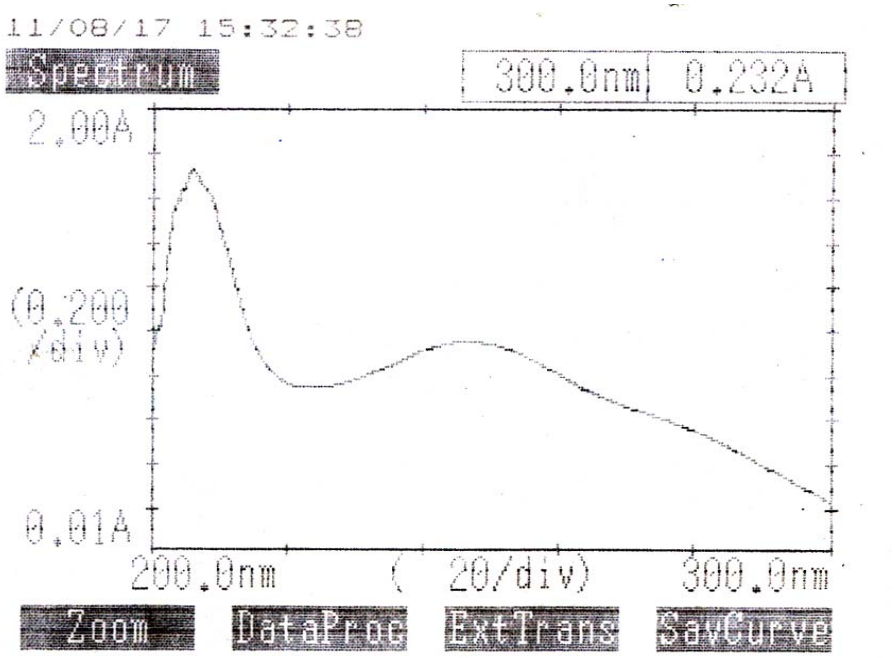
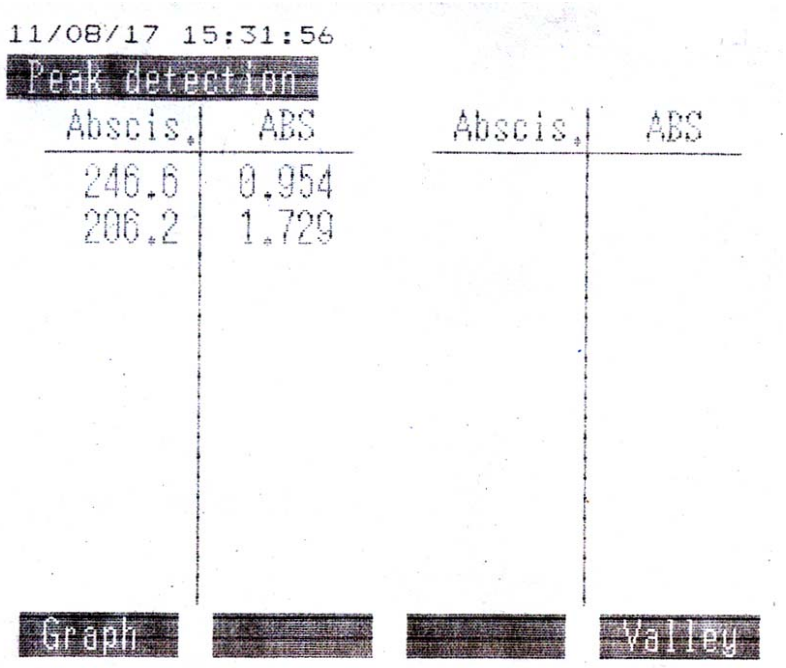


Figure 3: UV spectrum peak value of Atorvastatin calcium



8.2.2 INFRA RED SPECTROSCOPIC STUDIES:

By using FT IR technique, Atorvastatin calcium and polymers like hydroxyl propyl methyl cellulose, Avicel PH102, were identified by the frequency of the obtained peaks.

The interpretation of the infra red spectrum of the drug and polymers are as follows.

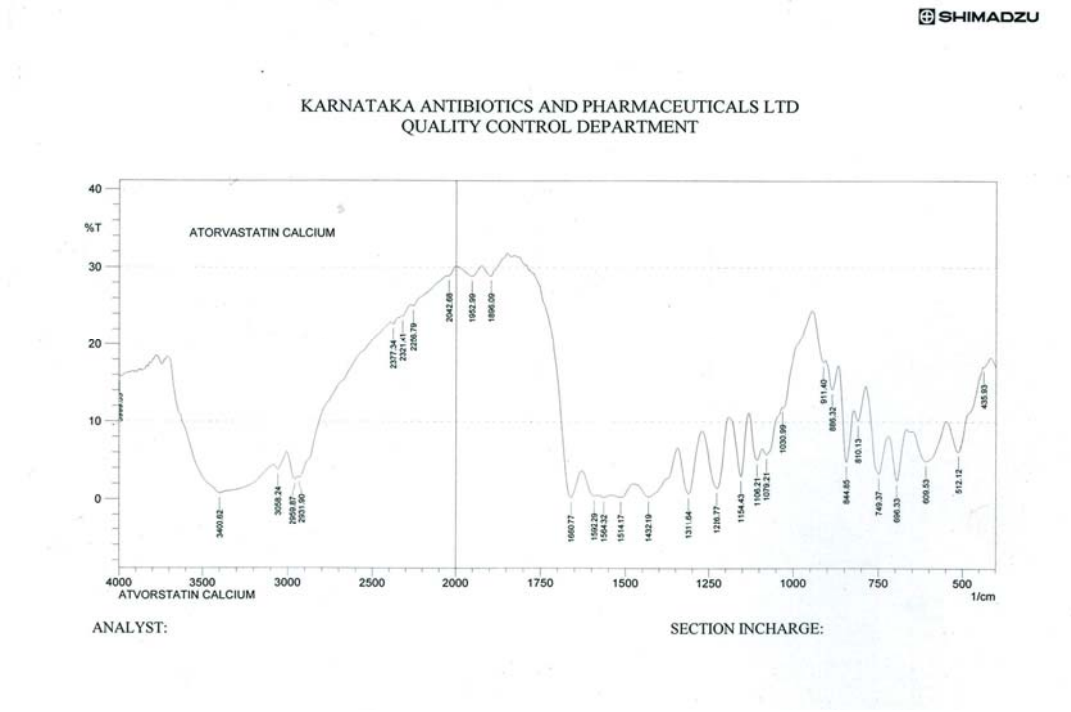


Table:12 IR spectra of pure Atorvastatin calcium:

Frequency (cm^{-1})	Groups assigned
3400.62	O - H stretching (carboxyl)
3058.24	Aromatic C - H stretching
2959.87	Aliphatic C - H stretching
1660.77	C = O stretching (carboxyl)
1432.19	C - H bending
1311.64	C – O stretching
749.37	C – H out of plane bending

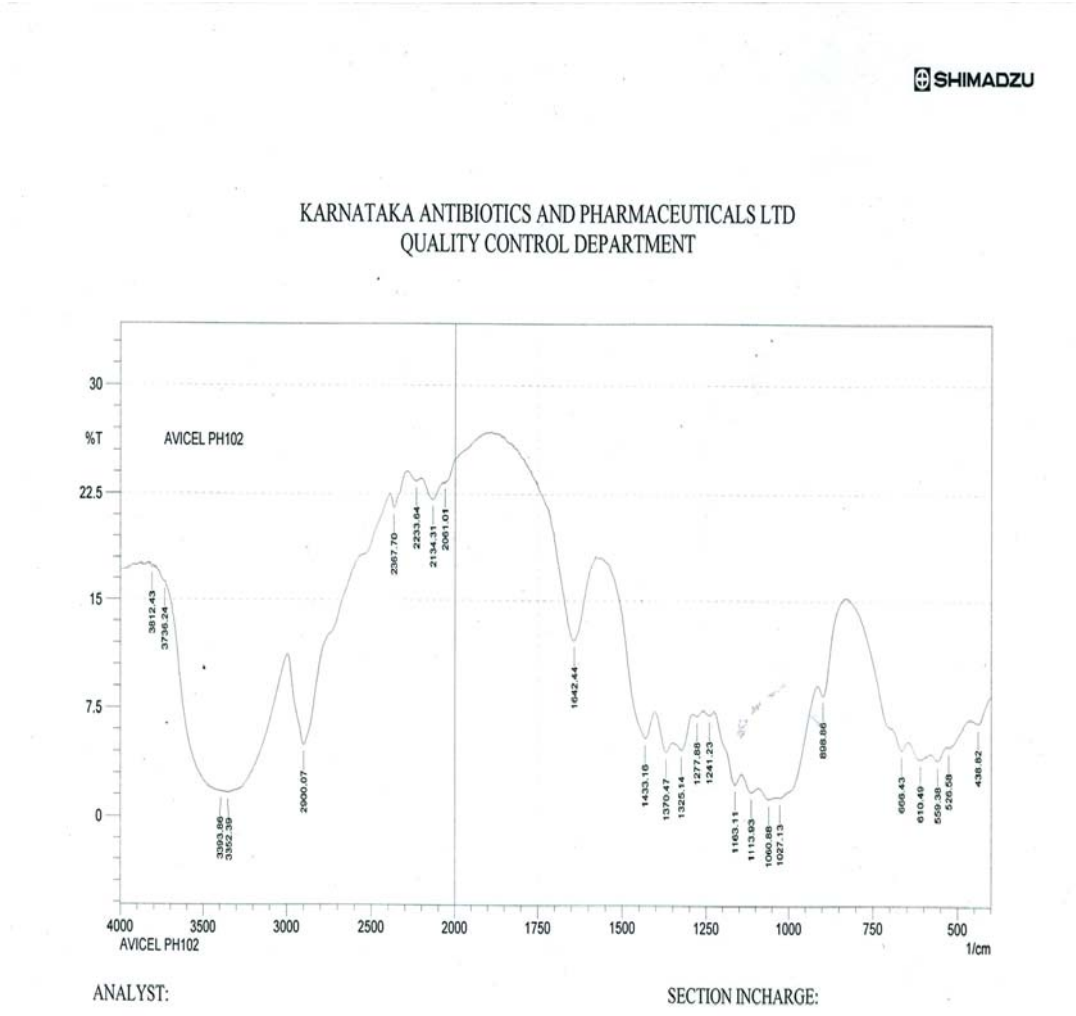


Table:13 IR spectra of HPMC K100M:

Frequency (cm^{-1})	Groups assigned
3469.09	O-H stretching (alcohol)
2930.93	C-H stretching (alkane)
1462.09	C-H bending (alkane)
1121.64	C-O stretching (alcohol)

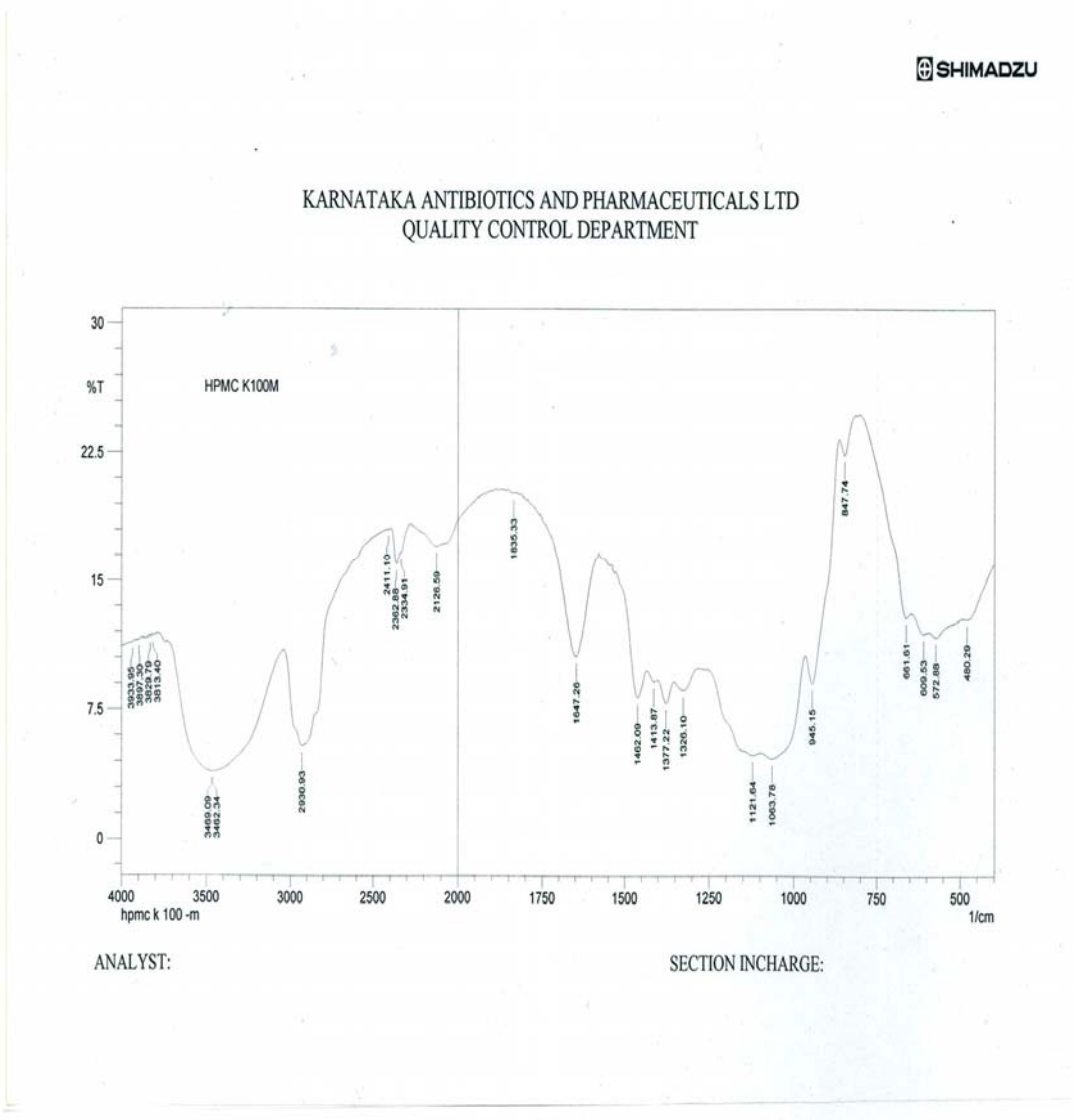


Table:14 IR spectra of Avicel PH102:

Frequency (cm^{-1})	**Groups assigned**
3393.86	O-H stretching
2900.07	Aliphatic C-H stretching
1370.47	Aldehydic C-H bending
1113.93	C-O stretching (2^0 alcohol)
1060.88	C-O stretching (1^0 alcohol)

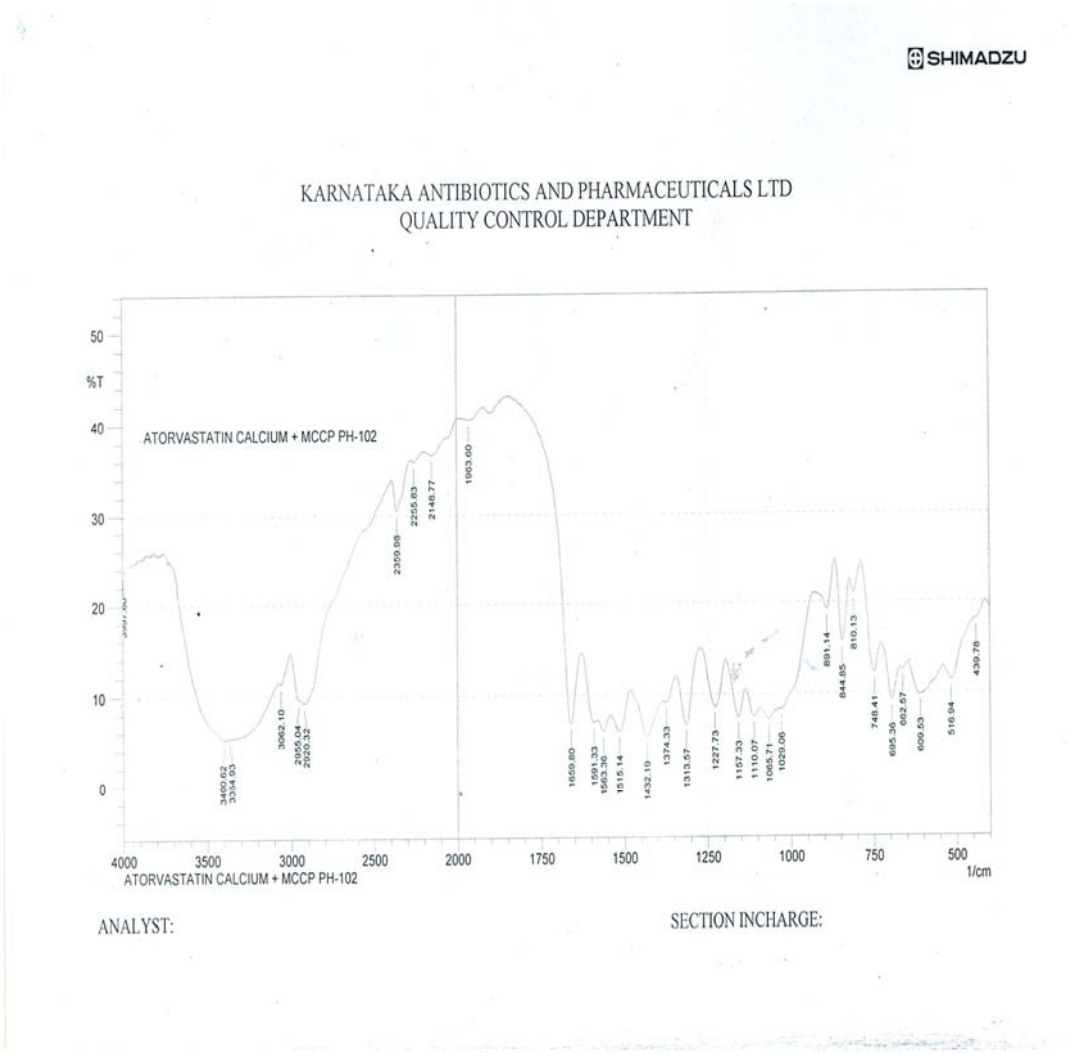


Table:15 IR spectra of Atorvastatin calcium + Avicel PH102:

Frequency (cm^{-1})	**Groups assigned**
3400.62	O-H stretching (alcohol)
3062.10	Aromatic C-H stretching
2955.04	Aliphatic C-H stretching
1659.80	C = O stretching
1227.73	C-O stretching
748.81	C- H out of plane bending

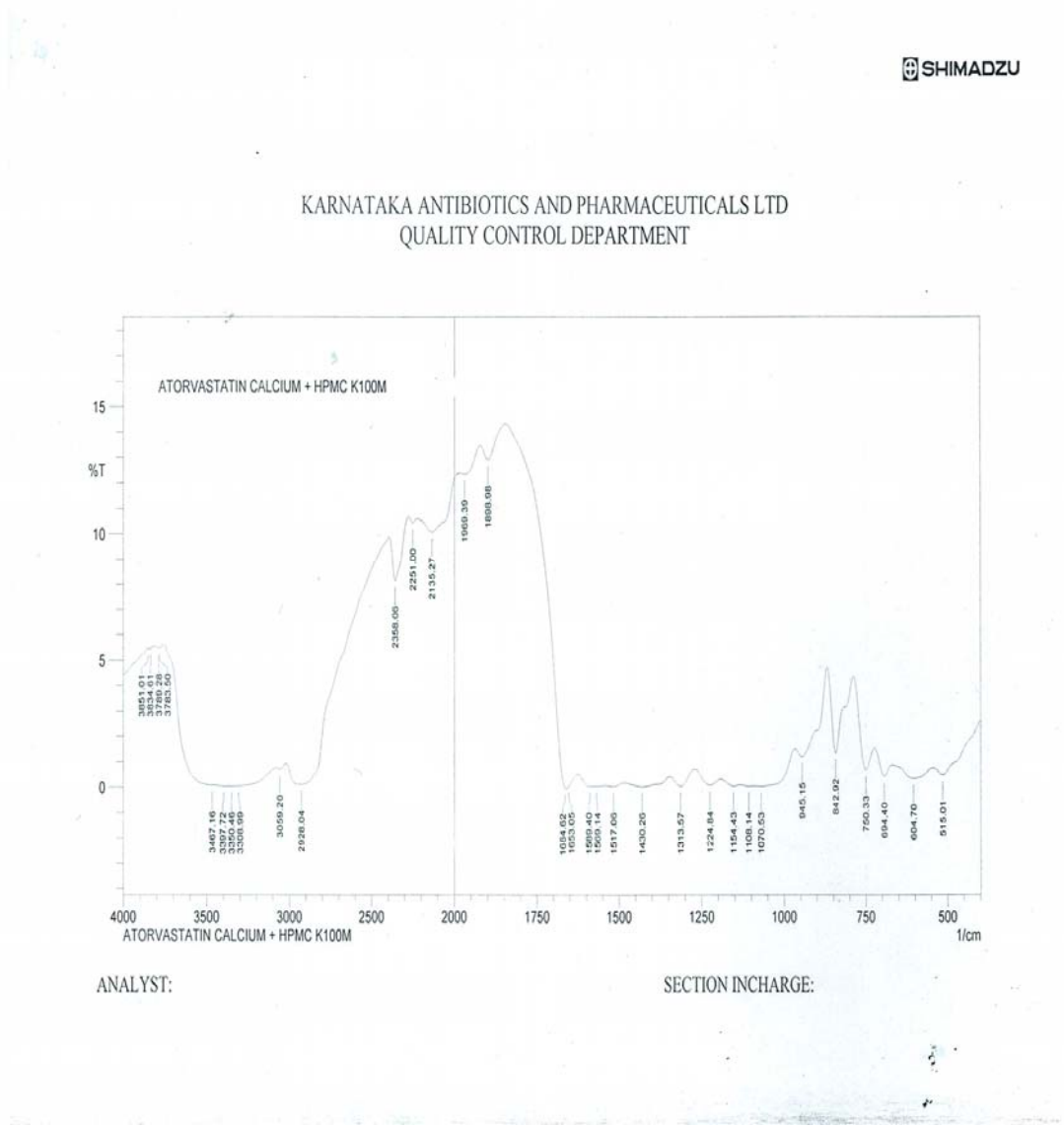


Table:16 IR spectra of Atorvastatin calcium + HPMC K100M:

Frequency (cm^{-1})	**Groups assigned**
3467.16	O-H stretching (alcohol)
3059.20	Aromatic C-H stretching
1664.62	C = O stretching
1224.84	C-O stretching
750.33	C- H out of plane bending

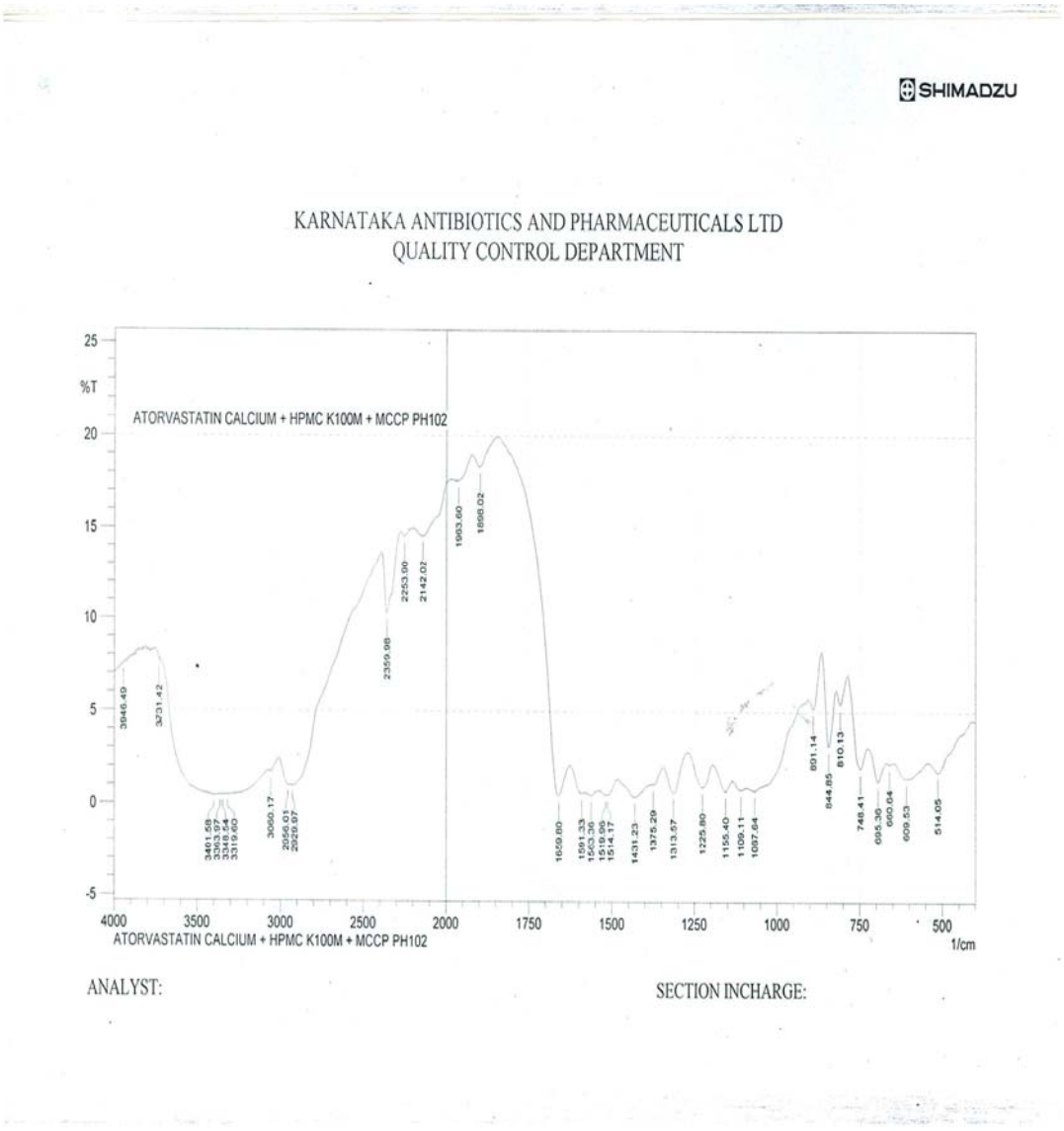


Table:17 IR spectra of Atorvastatin calcium + HPMC + Avicel PH102:

Frequency (cm^{-1})	Groups assigned
3401.58	O-H stretching (alcohol)
3060.17	Aromatic C-H stretching
2956.01	Aliphatic C-H stretching
1659.80	C = O stretching
1225.80	C-O stretching
748.41	C- H out of plane bending

IR Report:

When FT IR Spectrum of Atorvastatin calcium (pure drug), excipients as polymer and disintegrant, there were no major changes in the position of the spectrum. It indicates the absence of physical and chemical interaction among the active components of Atorvastatin calcium and excipients. So the floating tablet of Atorvastatin calcium has no interaction with added excipients.

8.2.3 DRUG – EXCIPIENTS COMPATIBILITY STUDIES:

In this drug-excipient compatability study, by placing drug-excipient composition in different temperature were investigated. There was no change in physical appearance, color change and spectrum taken showing similar results. From this we concluded that there is no interaction between drug-excipients complex.

8.3 EVALUATION OF POWDER BLEND:

The prepared blend of the formulations was evaluated for the parameters like angle of repose, bulk density, tap density, compressibility index and hausner's ratio.

- After granulation, angle of repose was improved.
- Hausner ratio was found to be 1.2 (or) less than 1.2.
- Carr's index was found to be in the range of 12 – 16.
- All these values indicated that the granules have **good flow property** and hence the granulation process has improved the flow property.
- For uniform tablet compression, good flow property is the major criteria.

Table:18 Preformulation study data of the pure drug

S.No	Parameters	Values obtained
1.	Angle of repose (θ)	22º57' 0.1332
2.	Bulk density (gm/ml)	0.3463 ± 0.007
4.	Tap density (gm/ml)	0.4544 ± 0.009
5.	Hausner's ratio	1.312 ± 0.002
6.	Carr's index	23.55 ± 0.212

***Values mentioned are average of 3 determinations**

Table:19 Physical Characteristics of controlled release powder blend

Formulation code	Angle of Repose (^{o})	Bulk density	Tap density	Hausner ratio	Carr's Index
F_1	20º14' ± 0.4649	0.350 ± 0.011	0.410 ± 0.006	1.17 ± 0.003	14.63 ± 0.680
F_2	21º32' ± 0.6133	0.351 ± 0.010	0.412 ± 0.003	1.17 ± 0.004	14.80 ± 0.521
F_3	21º17' ± 0.6158	0.361 ± 0.010	0.430 ± 0.005	1.19 ± 0.002	16.20 ± 0.180
F_4	21º08' ± 0.4255	0.371 ± 0.020	0.442 ± 0.003	1.19 ± 0.003	16.07 ± 0.101
F_5	22º15' ± 0.7862	0.356 ± 0.011	0.421 ± 0.005	1.18 ± 0.002	15.43 ± 0.651
F_6	23º11' ± 0.2606	0.370 ± 0.012	0.440 ± 0.004	1.18 ± 0.001	15.93 ± 0.181
F_7	21º08' ± 0.6799	0.354 ± 0.012	0.425 ± 0.006	1.20 ± 0.002	16.76 ± 0.181
F_8	21º47' ± 0.5718	0.350 ± 0.011	0.420 ± 0.002	1.20 ± 0.004	16.60 ± 0.701
F_9	22º18' ± 0.2554	0.380 ± 0.012	0.450 ± 0.004	1.20 ± 0.002	15.52 ± 0.711
F_{10}	20º24' ± 0.9529	0.361 ± 0.021	0.432 ± 0.002	1.19 ± 0.003	16.43 ± 0.621
F_{11}	20º08' ± 0.4255	0.352 ± 0.011	0.423 ± 0.003	1.17 ± 0.001	14.23 ± 0.651
F_{12}	21º14' ± 0.4649	0.360 ± 0.012	0.440 ± 0.004	1.18 ± 0.001	15.43 ± 0.521

***Values mentioned are average of 3 determinations**

8.4 INVITRO RELEASE OF SUSTAINED RELEASE TABLET:

Table:20 Dissolution data of F_1 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.85	9.25	9.25
1	3.43	17.15	17.20
2	5.04	25.20	25.29
3	7.17	35.85	35.99
4	9.17	45.85	46.04
5	11.47	57.35	57.60
6	13.11	65.55	65.86
7	15.03	75.15	75.51
8	16.42	82.10	82.51
9	17.83	89.15	89.61
10	19.24	96.20	96.69
11	19.87	99.35	99.88

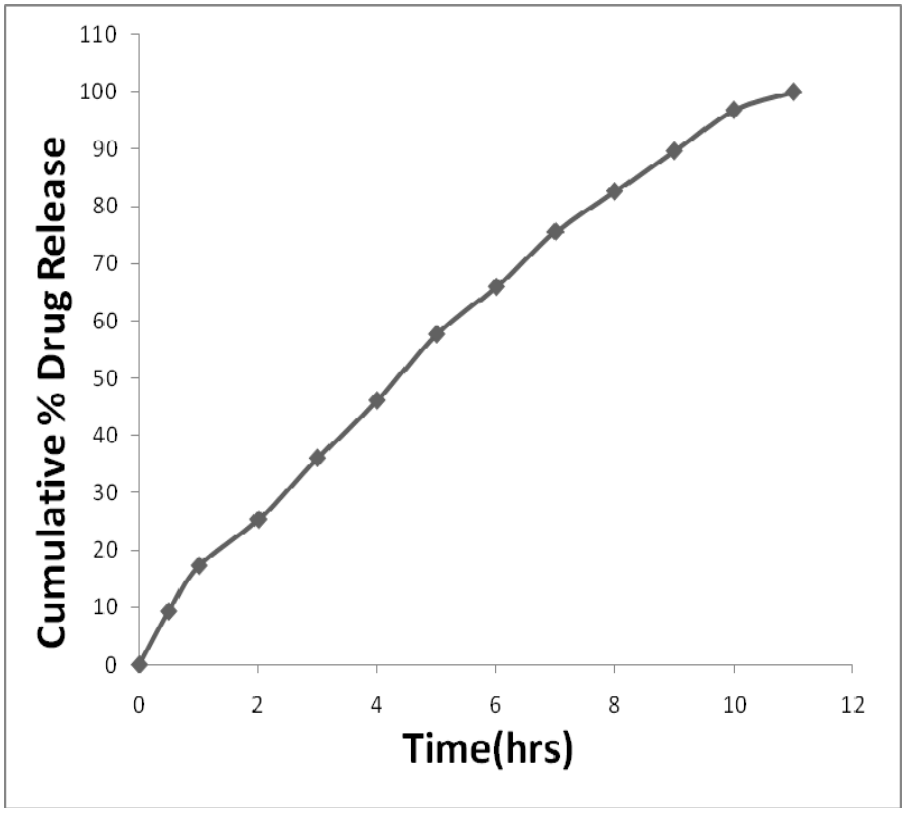


Fig:4 Dissolution profile of F_1 Formulation

Table:21 Dissolution data of F_2 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.58	7.90	7.90
1	3.17	15.85	15.89
2	5.30	26.50	26.58
3	6.64	33.20	33.35
4	9.31	46.55	46.73
5	11.47	57.35	57.60
6	13.11	65.55	65.86
7	14.49	72.45	72.81
8	15.89	79.45	79.85
9	17.56	87.80	88.24
10	18.44	92.20	92.68
11	19.06	95.30	95.81
12	19.43	97.15	97.67
13	19.79	98.95	99.48

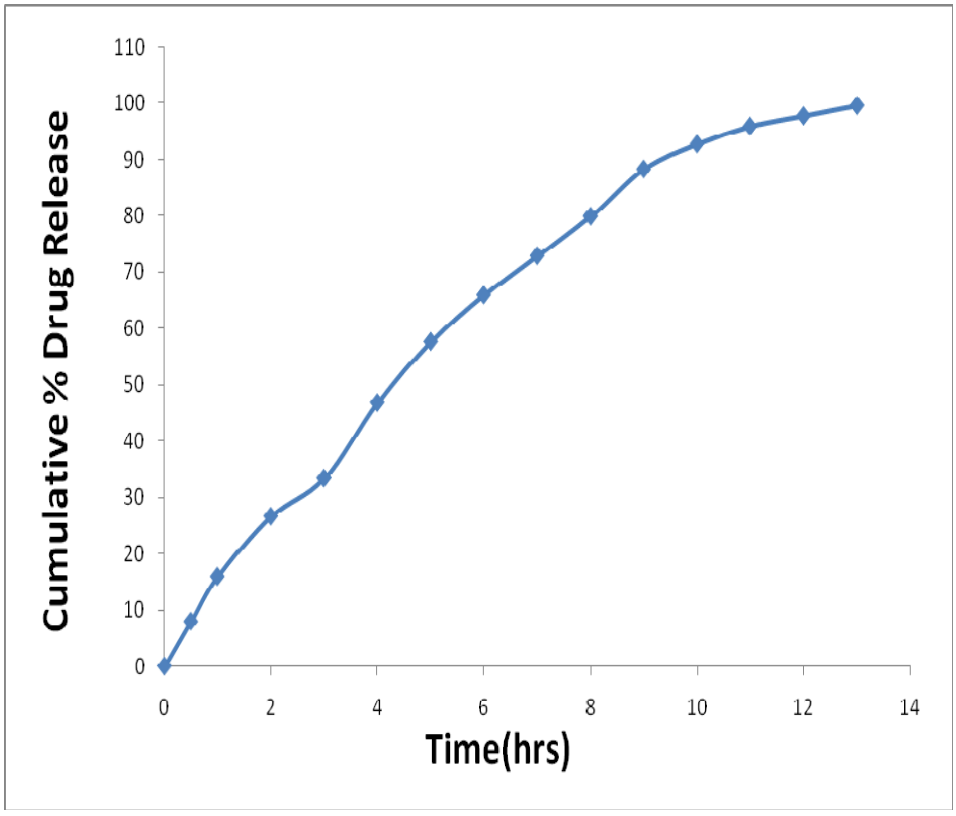


Fig:5 Dissolution profile of F_2 Formulation

Table:22 Dissolution data of F_3 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.32	6.60	6.60
1	2.91	14.55	14.58
2	4.24	21.20	21.28
3	6.11	30.55	30.66
4	7.72	38.60	38.76
5	9.34	46.70	46.91
6	10.97	54.85	55.10
7	12.87	64.35	64.65
8	14.26	71.30	71.65
9	15.92	79.60	79.99
10	17.05	85.25	85.69
11	18.20	91.00	91.47
12	19.08	95.40	95.90
13	19.45	97.25	97.78
14	19.81	99.05	99.59
15	19.90	99.50	100.05

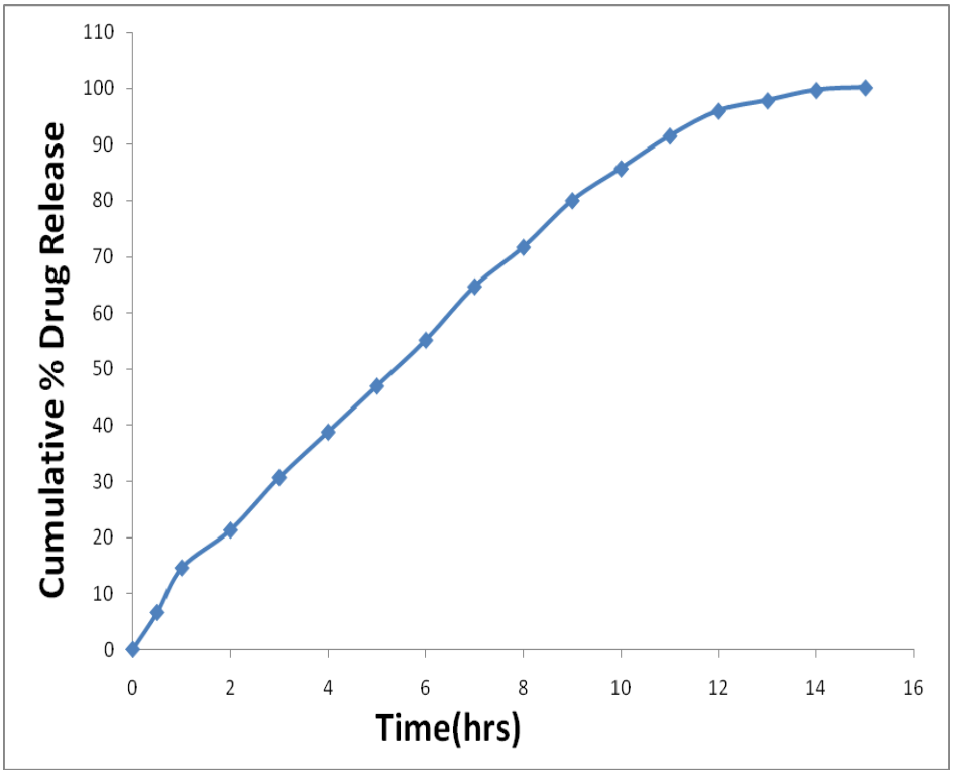


Fig:6 Dissolution profile of F_3 Formulation

Table:23 Dissolution data of F_4 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.05	5.25	5.25
1	2.91	14.55	14.57
2	4.23	21.15	21.23
3	6.11	30.55	30.66
4	7.72	38.60	38.76
5	9.34	46.70	46.91
6	10.97	54.85	55.10
7	12.87	64.35	64.65
8	14.52	72.60	72.95
9	15.91	79.55	79.95
10	17.05	85.25	85.69
11	18.20	91.00	91.47
12	19.08	95.40	95.90
13	19.45	97.25	97.78
14	19.81	99.05	99.59

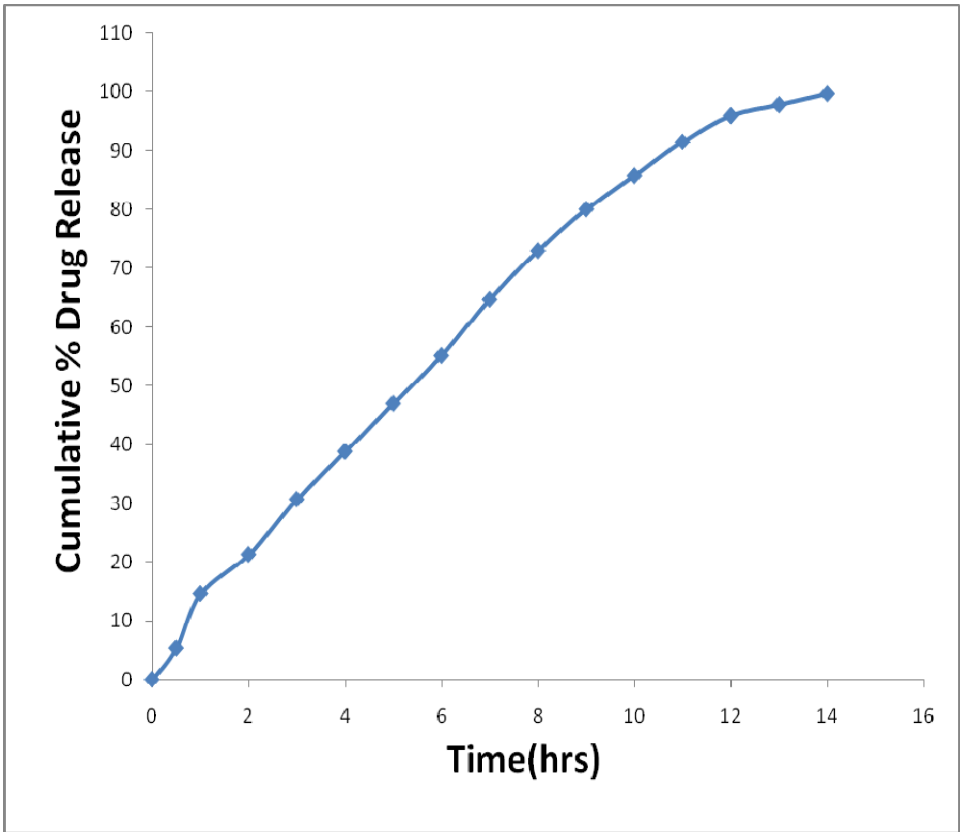


Fig:7 Dissolution profile of F_4 Formulation

Table:24 Dissolution data of F_5 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.58	7.90	7.90
1	2.91	14.55	14.59
2	4.51	22.55	22.63
3	5.84	29.20	29.32
4	7.19	35.95	36.11
5	8.81	44.05	44.24
6	10.17	50.85	51.09
7	11.28	56.40	56.68
8	12.93	64.65	64.96
9	14.31	71.55	71.90
10	15.97	79.85	80.24
11	17.11	85.55	85.99
12	17.99	89.95	90.42
13	18.61	93.05	93.54
14	19.23	96.15	96.66
15	19.60	98.00	98.53
16	19.71	98.55	99.09

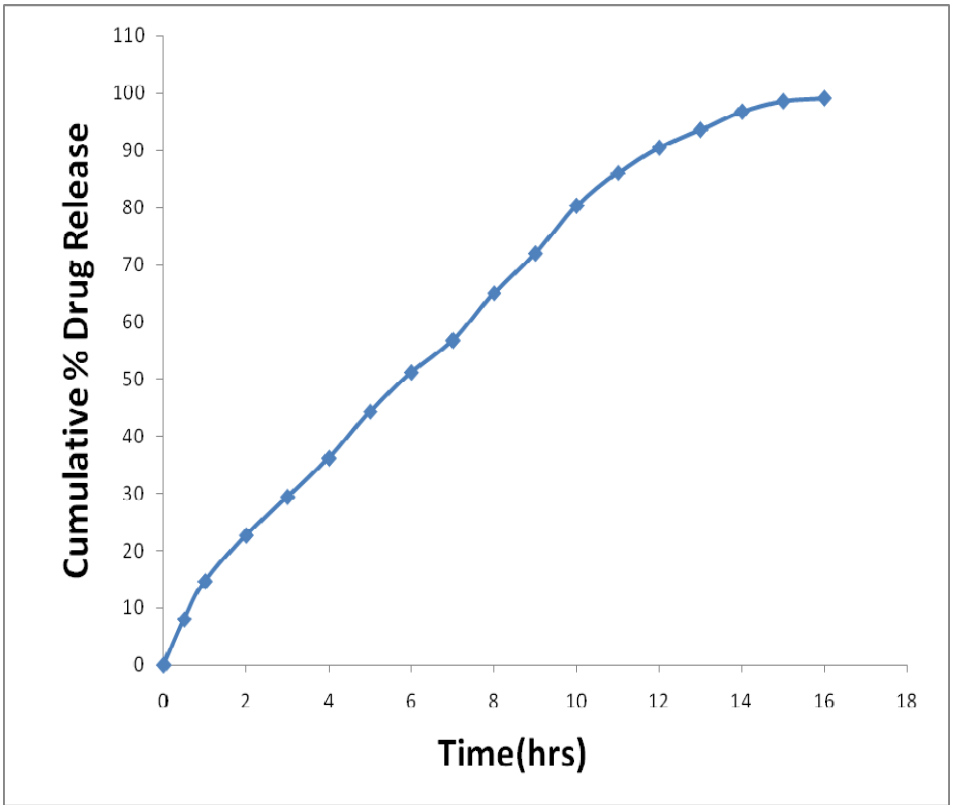


Fig:8 Dissolution profile of F_5 Formulation

Table:25 Dissolution data of F_6 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.32	6.60	6.60
1	2.11	10.55	10.58
2	3.44	17.20	17.25
3	4.78	23.90	13.99
4	6.65	33.25	33.38
5	7.73	38.65	38.83
6	8.83	44.15	44.36
7	10.20	51.00	51.24
8	11.57	57.85	58.13
9	13.21	66.05	66.37
10	14.86	74.30	74.66
11	16.26	81.30	81.71
12	17.40	87.00	87.45
13	18.28	91.40	91.88
14	18.90	94.50	95.01
15	19.27	96.35	96.87
16	19.63	98.15	98.68
17	19.73	98.65	99.19

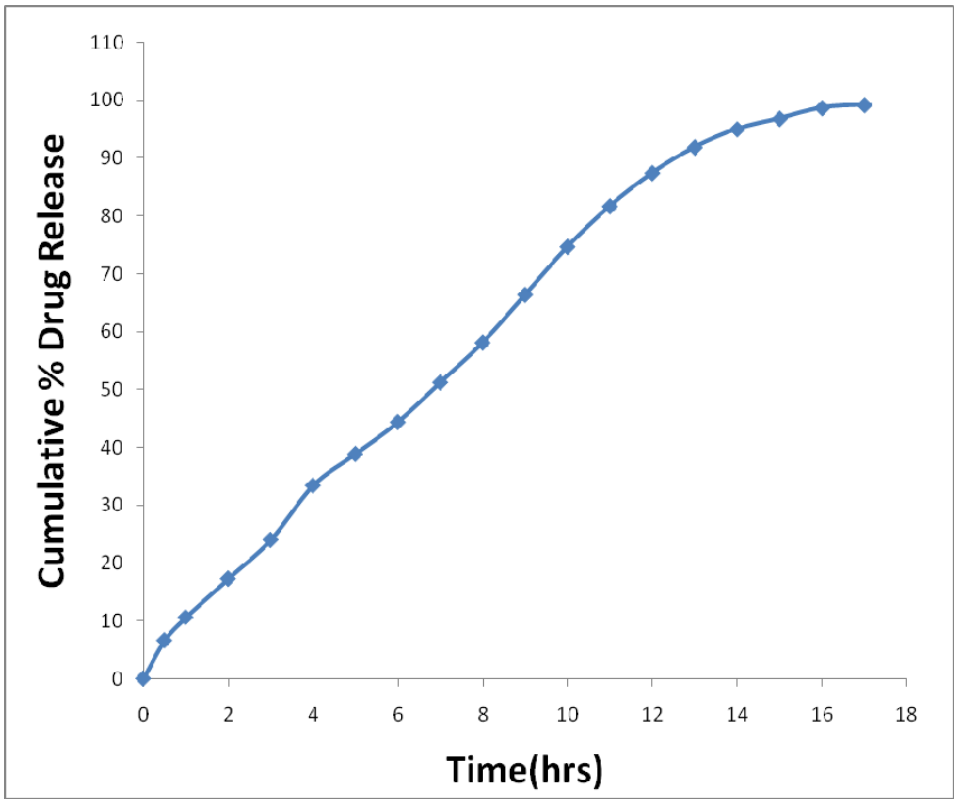


Fig:9 Dissolution profile of F_6 Formulation

Table:26 Dissolution data of F_7 Formulation:

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.05	5.25	5.25
1	2.11	10.55	10.57
2	3.44	17.20	17.25
3	4.78	23.90	23.99
4	6.38	31.90	32.03
5	7.73	38.65	38.82
6	9.09	45.45	45.66
7	9.93	49.65	49.90
8	11.30	56.50	56.77
9	12.68	63.40	63.71
10	14.06	70.30	70.65
11	15.19	75.95	76.34
12	15.80	79.00	79.42
13	16.67	83.35	83.78
14	18.35	91.75	92.21
15	18.97	94.85	95.35
16	19.59	97.95	98.47
17	19.69	98.45	98.99

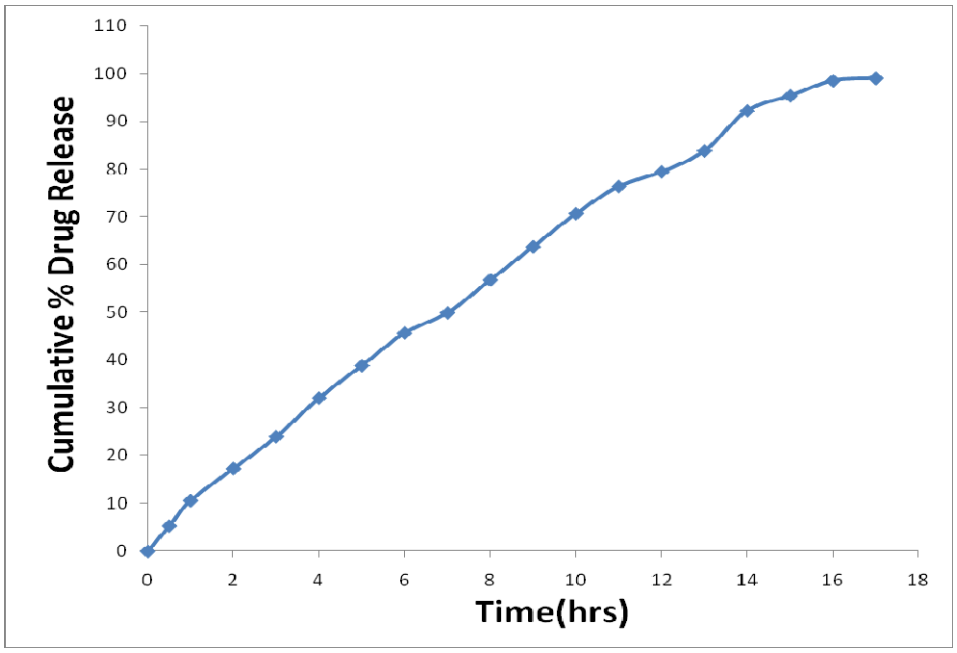


Fig:10 Dissolution profile of F_7 Formulation

Table:27 Dissolution data of F_8 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.32	6.60	6.60
1	2.11	10.55	10.58
2	4.24	21.20	21.25
3	5.31	26.55	26.66
4	6.39	31.95	32.09
5	7.74	38.70	38.87
6	8.84	44.20	44.41
7	9.94	49.70	49.94
8	11.05	55.25	55.52
9	12.42	62.10	62.40
10	13.28	66.40	66.74
11	13.87	69.35	69.71
12	14.74	73.70	74.08
13	15.87	79.35	79.75
14	17.01	85.05	85.49
15	17.89	89.45	89.92
16	18.77	93.85	94.34
17	19.13	95.65	96.17
18	19.50	97.50	98.03
19	19.86	99.30	99.84

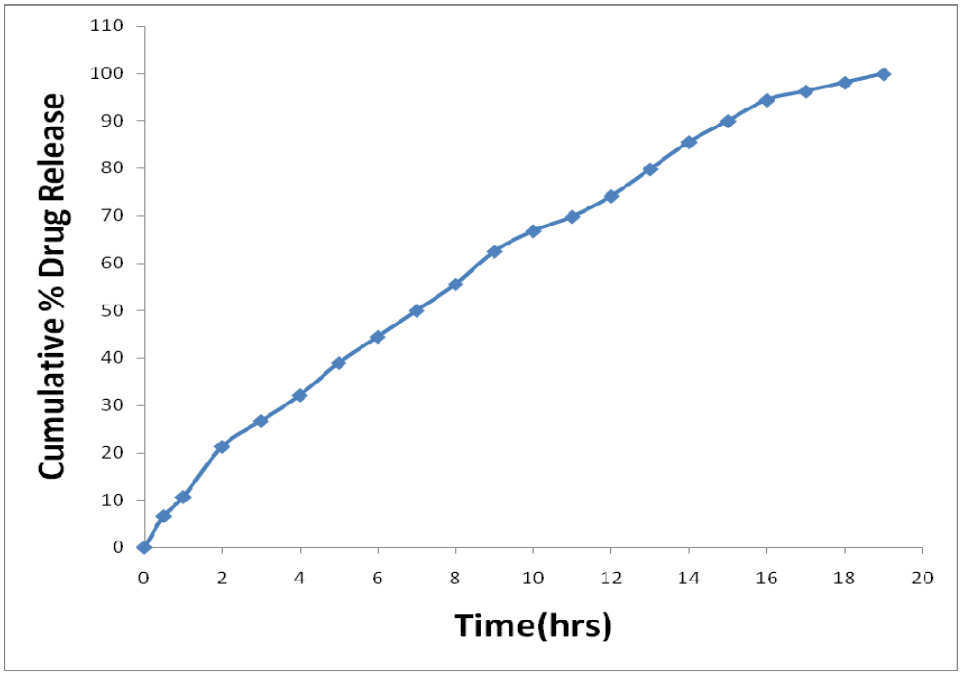


Fig:11 Dissolution profile of F_8 Formulation

Table:28 Dissolution data of F_9 Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	1.05	5.25	5.25
1	1.85	9.25	9.27
2	3.44	17.20	17.25
3	4.78	23.90	23.99
4	6.12	30.60	30.73
5	7.47	37.35	37.52
6	8.56	42.80	43.00
7	9.66	48.30	48.53
8	10.50	52.50	52.76
9	11.35	56.75	57.04
10	12.20	61.00	61.31
11	13.32	66.60	66.90
12	14.18	70.90	71.27
13	15.31	76.55	76.94
14	16.44	82.20	82.62
15	17.59	87.95	88.41
16	17.94	89.70	90.18
17	18.56	92.80	93.29
18	19.19	95.95	96.47
19	19.55	97.75	98.28
20	19.91	99.55	100.09

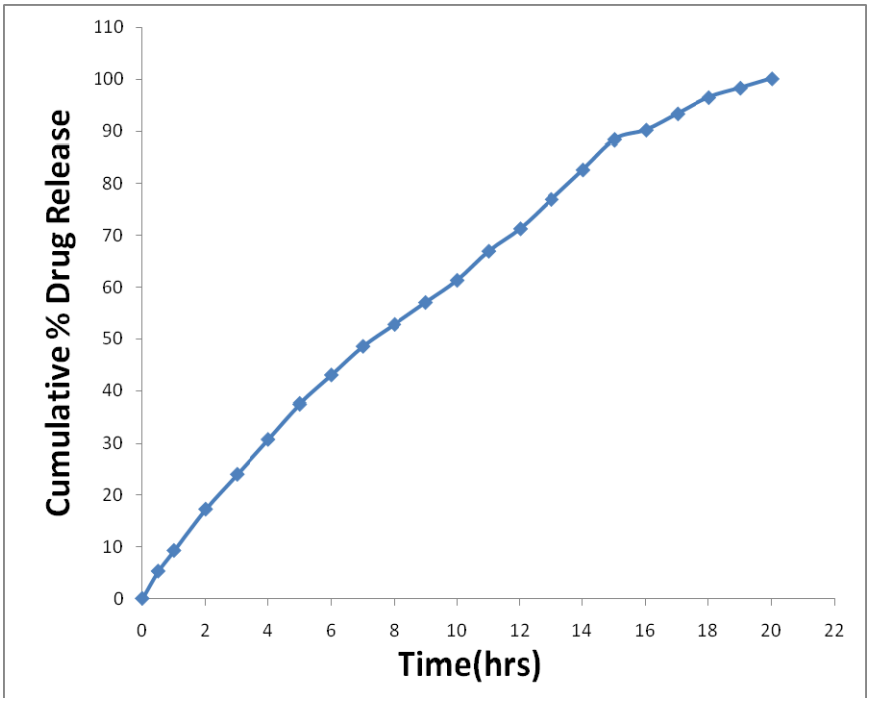


Fig:12 Dissolution profile of F_9 Formulation

Table:29 Dissolution data of F_{10} Formulation:

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	0.79	3.95	3.95
1	1.58	7.90	7.92
2	2.91	14.55	14.59
3	4.24	21.20	21.28
4	5.58	27.90	28.01
5	6.93	34.65	34.80
6	8.02	40.10	40.29
7	8.85	44.25	44.47
8	9.96	49.80	50.04
9	11.06	55.30	55.07
10	12.17	60.85	61.15
11	13.03	65.15	65.48
12	14.15	70.75	71.11
13	15.02	75.10	75.49
14	15.89	79.45	79.86
15	17.03	85.15	85.59
16	18.17	90.85	91.32
17	18.53	92.65	93.15
18	18.89	94.45	94.96
19	19.25	96.25	96.77
20	19.61	98.05	98.58
21	19.71	98.55	99.09

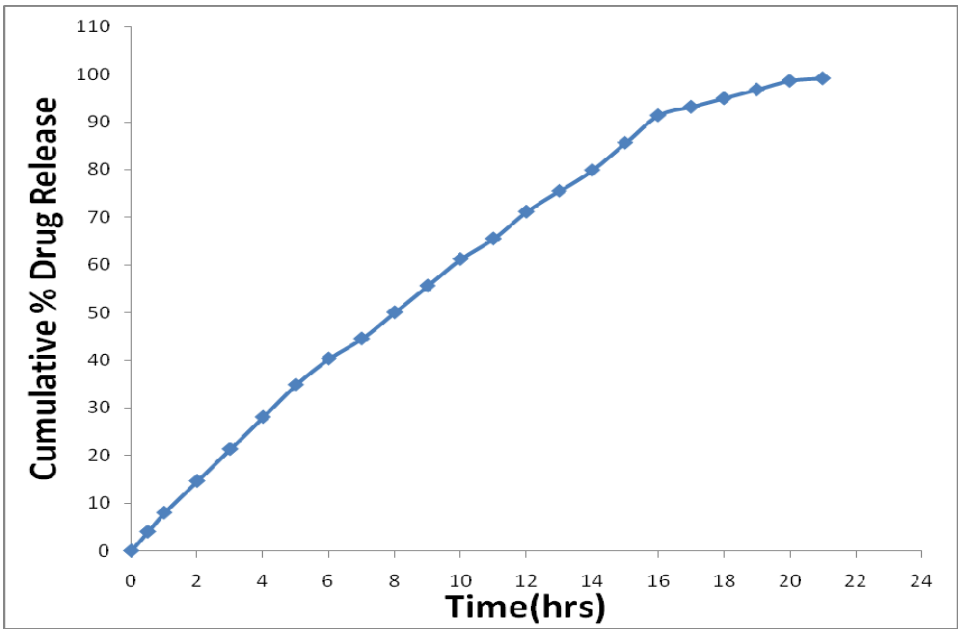


Fig:13 Dissolution profile of F_{10} Formulation

Table:30 Dissolution data of F_{11} Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	0.79	3.95	3.95
1	1.58	7.90	7.92
2	2.91	14.55	14.59
3	3.98	19.90	19.98
4	5.05	25.25	25.30
5	6.13	30.65	30.79
6	7.22	36.10	36.27
7	7.78	38.90	39.10
8	8.62	43.10	43.30
9	9.19	45.95	48.18
10	10.29	51.45	51.70
11	10.87	54.35	54.63
12	11.72	58.60	58.90
13	12.38	61.90	62.22
14	13.43	67.15	67.49
15	14.03	70.15	70.52
16	14.63	73.15	73.53
17	15.50	77.50	77.90
18	16.63	83.15	83.58
19	17.25	86.25	86.71
20	18.13	90.65	91.12
21	18.75	93.75	94.25
22	19.11	95.55	96.07
23	19.47	97.35	97.88
24	19.84	99.20	99.74

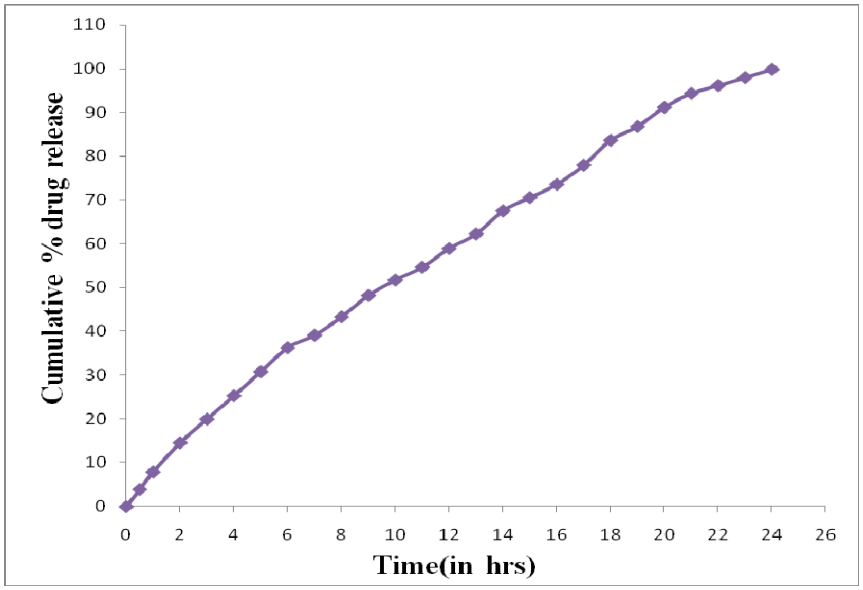


Fig:14 Dissolution profile of F_{11} Formulation

Table:31 Dissolution data of F_{12} Formulation

Time(hrs)	Amount of drug release	% Drug release	Cumulative % drug release
0.5	0.79	3.95	3.97
1	1.32	6.60	6.62
2	2.38	11.90	11.93
3	3.18	15.90	15.96
4	4.25	21.25	21.33
5	5.33	26.65	26.76
6	6.15	30.75	30.89
7	7.24	36.20	36.37
8	8.07	40.35	40.55
9	9.16	45.80	46.02
10	10.00	50.00	50.25
11	10.84	54.20	54.47
12	11.96	59.80	60.11
13	13.07	65.35	65.68
14	13.93	69.65	70.01
15	14.80	74.00	74.38
16	15.40	77.00	77.41
17	15.75	78.75	79.18
18	15.83	79.15	79.60
19	16.18	80.90	81.34
20	16.79	83.95	84.41
21	17.40	87.00	87.50
22	17.75	88.75	89.28
23	18.11	90.55	91.07
24	18.47	92.35	92.86

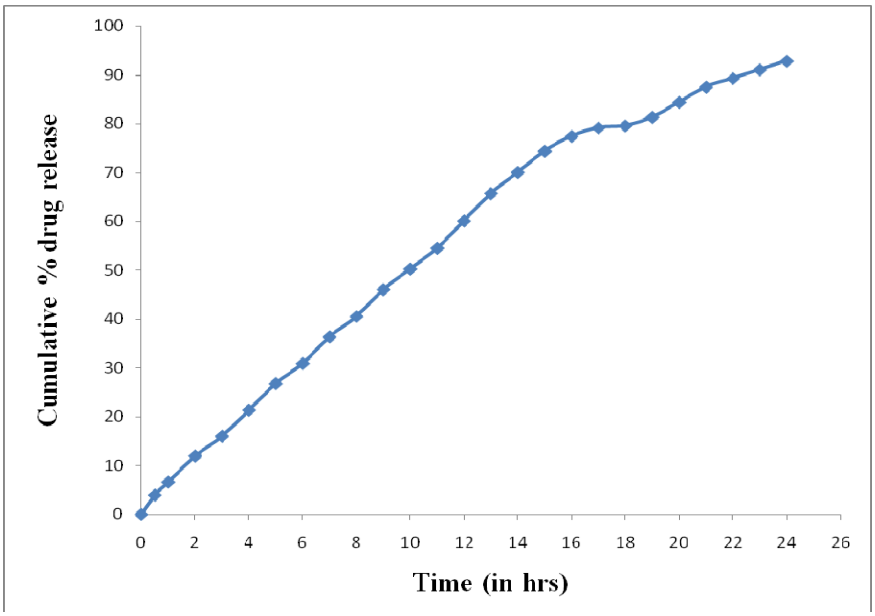


Fig:15 Dissolution profile of F_{12} Formulation

Table:32 COMPARATIVE DISSOLUTION STUDY OF ALL THE BATCHES

S.No	Formulations	Time (hrs) of drug release	%Drug release	Cumulative % drug release
1	F_1	11	99.35	99.88
2	F_2	13	98.95	99.48
3	F_3	15	99.5	100.05
4	F_4	14	99.05	99.59
5	F_5	16	98.55	99.09
6	F_6	17	98.65	99.19
7	F_7	17	98.45	98.99
8	F_8	19	99.3	99.84
9	F_9	20	99.55	100.09
10	F_{10}	21	98.55	99.09
11	F_{11}	24	99.20	99.74
12	F_{12}	24	92.35	92.86

Dissolution profile for all formulations F1-F12:

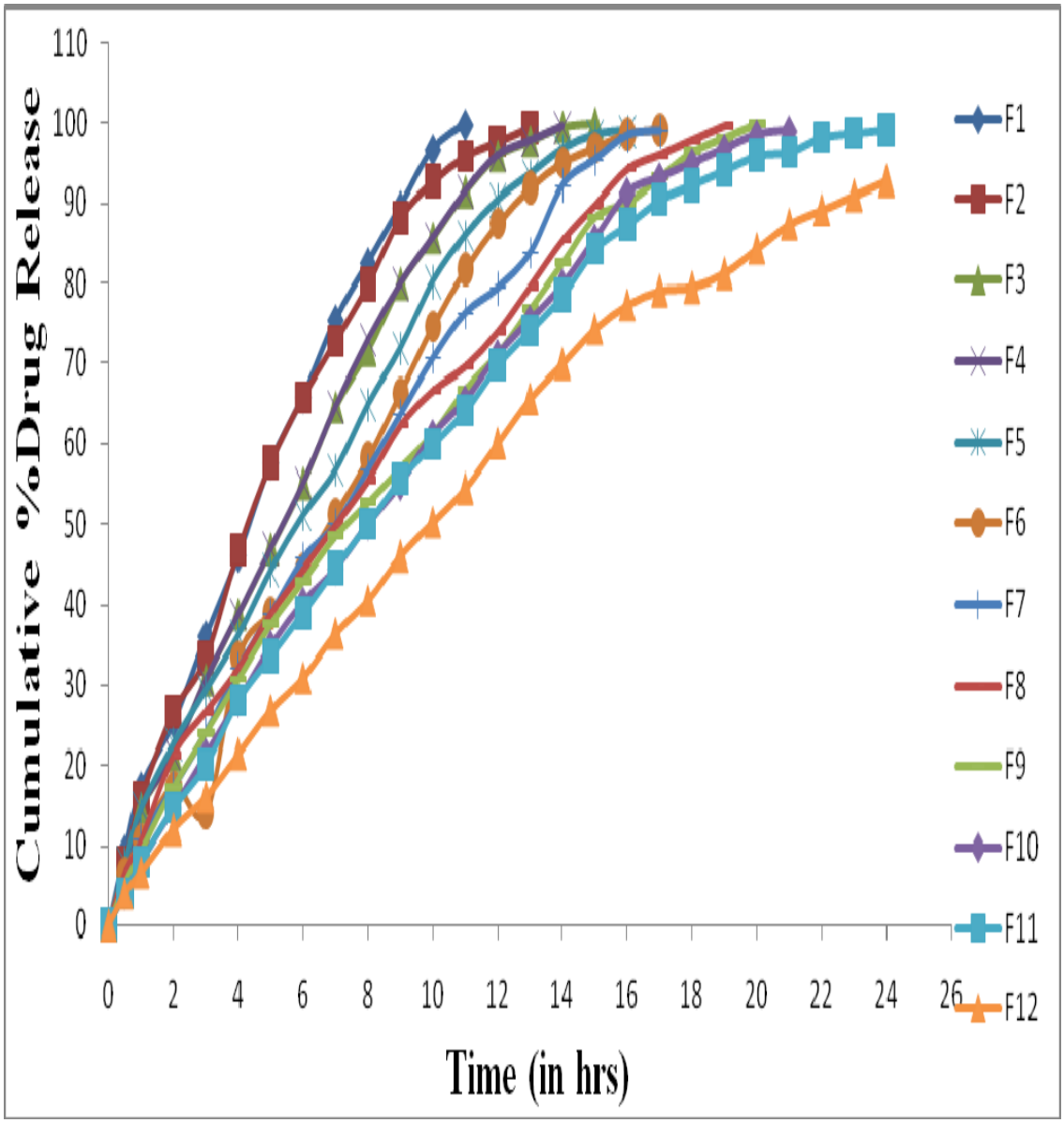


Fig:16 Comparative dissolution profile of all formulations F1-F12

DISCUSSION ON DISSOLUTION PROFILE OF SUSTAINED RELEASE TABLET:

In this formulation, initially we tried with poly ethylene oxide, which had good buoyancy property but no proper invitro drug release due to more viscosity in the gastric fluid, leads to a poor drug release. Then we used HPMC K4M instead of poly ethylene oxide, the tablet was completely disintegrated in gastric medium. So we aimed to use the higher grades of HPMC (HPMC K15M) to improve the stability of tablet.

In F_1, F_2, F_3 formulations, HPMC K15M was used in concentration of 10% and binder Avicel PH102 used in respective formulations as 5%, 10%, 15%. The releases of above formulations were found to be in higher side. So, we planned to increase the concentration of HPMC K15M to improve the sustain release property.

In F_4,F_5,F_6 formulations, HPMC K15M was used in concentration of 30% and binder Avicel PH102 used in respective formulations as 5%, 10%, 15%. The releases of above formulations were sustained but it is not upto 24 h what we expected. So, we planned to increase the viscosity of HPMC K15M to improve the sustain release property further.

Again we tried the formulation with higher grade of HPMC(HPMC K100M) having higher viscosity in different concentration as 10%, 15%, 20% and Avicel PH102 used in concentration of 5%, 10%, 15% to sustain the drug release.

In F_7, F_8 formulations, HPMC K100M of 10% and Avicel PH102 of 5%, 10% were included and the release was extended upto 17 h and 19 h respectively. In F_9,F_{10} formulations, HPMC K100M of 15% and Avicel PH102 of 10 and 15% were included, among that formulation F_{10} showed a dissolution profile upto 21h.

Finally F_{11}, F_{12} formulations consisted of HPMC K100M 20% and avicel PH102 of 10%, 15% in respective formulation. The formulations F_{11}, F_{12} was achieved 24 h dissolution profile due to increase in polymer concentration, but in F_{12} 100% of drug was not released in 24 h. Hence, the formulation F_{11} is the optimized one, which had showed the *invitro* release pattern of sustained release of Atorvastatin calcium was found to be satisfactory as per USP limit.

8.5 EVALUATION OF TABLETS

(a) Thickness and Diameter:

The thickness and diameter were found in the range of 2.78 ±0.04 to 2.84 ±0.03 and 7.2 ± 0.018 to 7.9 ± 0.028 respectively.

Table:33 Thickness and Diameter data of the tablets

Formulation Code	Thickness (mm) ± S.D	Diameter (mm) ± S.D
F_1	2.83 ±0.013	7.1 ± 0.114
F_2	2.79±0.016	7.0 ± 0.89
F_3	2.87± 0.016	7.2 ± 0.018
F_4	2.86 ± 0.018	7.1 ± 0.010
F_5	2.73 ± 0.013	7.2 ± 0.018
F_6	2.81 ± 0.013	7.0 ± 0.014
F_7	2.88 ± 0.011	7.2 ± 0.032
F_8	2.87 ± 0.016	7.2 ± 0.017
F_9	2.9 ± 0.019	7.1 ± 0.016
F_{10}	2.87 ± 0.013	7.0 ± 0.028
F_{11}	2.83 ± 0.015	7.1 ± 0.01
F_{12}	2.84 ± 0.016	7.0 ± 0.028

b) Weight Variation, Hardness and Friability:

Depending upon the ingredients of different formulations, the weight of tablet was fixed. In each formulation, weight variation was within the I.P limit. Mostly, the variation was within ± 5%. The hardness of the different formulations ranged from 5-7 kg / cm^2. All the formulations exhibited less than 1% friability.

Table:34 Hardness, weight variation and Friability data of the tablets

Formulation Code	weight variation (mg) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%) ± S.D
F_1	152 ± 1.09	5.8 ± 0.244	0.31 ± 0.002
F_2	151 ± 1.14	6.4 ± 0.251	0.26 ± 0.004
F_3	150 ± 1.14	6.3 ± 0.244	0.34 ± 0.003
F_4	152 ± 0.41	6.7 ± 0.244	0.36 ± 0.003
F_5	151 ± 1.30	6.5 ± 0.048	0.34 ± 0.014
F_6	151 ± 1.51	6.5 ± 0.447	0.32 ± 0.009
F_7	152 ± 1.48	6.3 ± 0.244	0.33 ± 0.014
F_8	151 ± 0.83	6.2 ± 0.244	0.30 ± 0.009
F_9	150 ± 1.22	6 ± 0.316	0.33 ± 0.007
F_{10}	152 ± 1.30	6.2 ± 0.244	0.39 ± 0.011
F_{11}	150 ± 1.14	6.5 ± 0.447	0.33 ± 0.010
F_{12}	151 ± 1.51	6.8 ± 0.244	0.32 ± 0.006

c) Content uniformity :

The results for content uniformity are presented in table 35. The results were found to be within the limits (98 to 99.5%). It shows that the drug was uniformly distributed throughout the tablets.

Table:35 Content uniformity data of the tablets

Formulation Code	Content uniformity in percentage ± S.D
F_1	99.18 ± 0.11
F_2	99.28 ± 0.43
F_3	98.12 ± 1.00
F_4	99.19 ± 1.00
F_5	98.06 ± 0.03
F_6	99.18 ± 0.43
F_7	99.16 ± 0.10
F_8	98.23 ± 0.20
F_9	98.95 ± 0.20
F_{10}	99.20 ± 0.11
F_{11}	98.26 ± 0.17
F_{12}	99.08 ± 0.43

d) Buoyancy Studies:

The result of buoyancy studies of the formulations were shown in the table:36. It is one of the major property of the floating tablet. In this study, the result had showed all the formulations buoyant for more than 24 h. It shows that all the formulations float for a day and release the drug.

Table:36 Buoyancy Studies of tablets

Formulation Code	Buoyancy Lag Time(in secs)	Buoyancy Time(in hrs)
F_1	32	25
F_2	33	25
F_3	35	26
F_4	30	26
F_5	28	26
F_6	22	26
F_7	35	28
F_8	22	28
F_9	20	28
F_{10}	21	28
F_{11}	25	28
F_{12}	23	30

8.6 STABILITY STUDIES:

The optimized F_{11} formulation was subjected to accelerated stability conditions for 3 months at 25°C/60% RH, 30°C / 75% RH, 40°C / 75% RH in a stability chamber (Osworld, Mumbai), at the interval of 1 month tablets were taken and evaluated for various parameters like thickness, diameter, weight variation, hardness, content uniformity and dissolution. The tablets had showed slight variation in the tested parameters and the results were within the limits.

Table:37 Comparison of physical parameters for optimized formulation F_{11}

S.No.	Parameters	F_{11}	25°C/60%RH		
			At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1.	Thickness (mm)	2.82 ± 0.013	2.82 ± 0.016	2.83 ± 0.014	2.84 ± 0.019
2.	Diameter (mm)	7.9 ± 0.018	7.7± 0.012	7.9 ± 0.015	7.8 ± 0.017
3.	Hardness (kg/cm^2)	6.8 ± 0.244	6.3± 0.316	6.3 ± 0.221	6.2 ± 0.115
4.	Friability (%)	0.36 ± 0.009	0.38 ± 0.007	0.40 ± 0.009	0.41 ± 0.008
5.	Weight Variation (mg)	151 ± 0.815	150 ± 0.525	150 ± 0.265	150 ± 0.151
6.	Content Uniformity	99.25 ± 0.20	99.12 ± 0.110	99.16 ± 0.112	99.16 ± 0.110

- ✓ F_{11}: Optimized formulation
- ✓ Formulation batch F_{11} kept for stability study at temperature (25°C/60%RH).

Table:38 Dissolution data of F_{11} batch at 25°C / 60% RH

Time(hrs)	Cumulative % Drug Release		
	At the end of 1st month	At the end of 2nd month	At the end of 3rd month
0.5	5.25	5.25	5.25
1	9.28	9.27	10.57
2	15.95	14.6	17.25
3	21.34	21.28	21.34
4	28.26	28.06	28.06
5	33.5	34.8	34.85
6	38.98	38.99	41.64
7	45.81	44.56	47.18
8	51.35	51.34	51.41
9	56.93	55.58	55.63
10	60.71	61.21	61.27
11	65.48	65.48	65.53
12	70.66	69.81	69.86
13	75.49	74.18	72.88
14	79.86	79.86	77.25
15	82.94	82.89	82.97
16	86.05	86	87.35
17	89.12	89.12	89.13
18	90.94	90.89	90.94
19	92.75	92.7	92.75
20	94.56	94.51	94.56
21	96.37	96.32	96.37
22	98.18	96.83	96.88
23	98.69	98.63	98.68
24	99.24	99.19	99.17

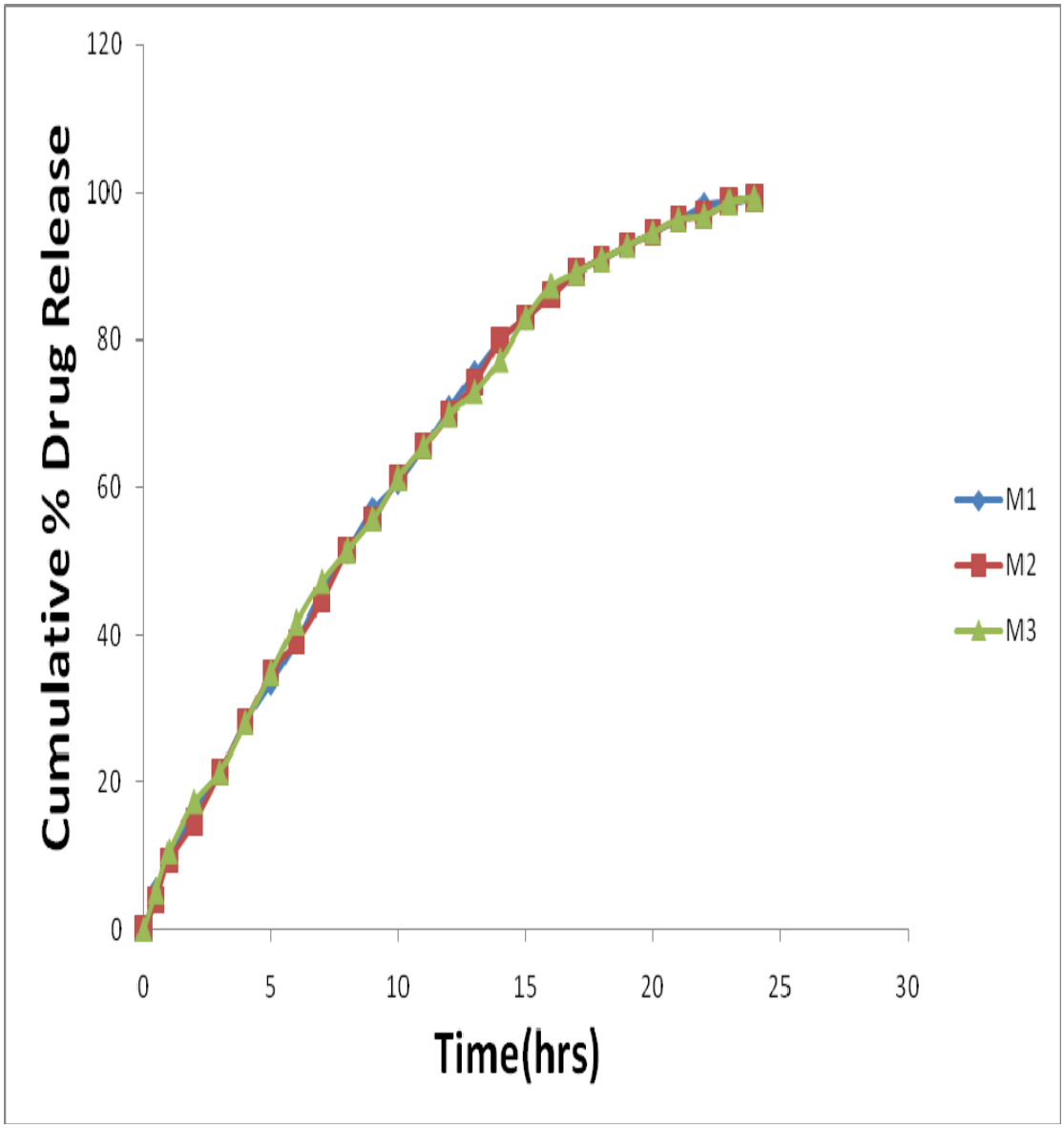


Fig:17 Dissolution profile of F_{11} batch at 25°C/60%RH

Table:39 Comparison of physical parameters for optimized formulation F_{11}

S.No.	Parameters	F_{11}	30°C/65%RH		
			At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1.	Thickness (mm)	2.81 ± 0.018	2.81 ± 0.014	2.80 ± 0.012	2.82 ± 0.014
2.	Diameter (mm)	7.8 ± 0.016	7.6± 0.012	7.5 ± 0.015	7.6 ± 0.017
3.	Hardness (kg/cm^2)	6.6 ± 0.244	6.5± 0.048	6.5 ± 0.251	6.4 ± 0.316
4.	Friability (%)	0.35 ± 0.017	0.37 ± 0.027	0.39 ± 0.007	0.40 ± 0.026
5.	Weight Variation (mg)	150 ± 0.742	150 ± 0.453	150 ± 0.342	149 ± 0.251
6.	Content Uniformity	99.27 ± 0.037	99.22 ± 0.084	99.12 ± 0.114	99.16 0.078

- ✓ F_{11}: Optimized formulation
- ✓ Formulation batch F_{11} kept for stability study at temperature (30°C/65%RH).

Table:40 Dissolution data of F_{11} batch at 30°C / 65% RH

Time(hrs)	Cumulative % Drug Release		
	At the end of 1st month	At the end of 2nd month	At the end of 3rd month
0.5	5.29	5.25	3.95
1	9.27	9.27	7.92
2	14.6	15.95	14.59
3	19.98	22.63	21.28
4	26.71	28.08	26.73
5	32.14	34.86	32.14
6	38.92	41.64	38.92
7	44.46	48.48	45.76
8	49.99	52.71	50.02
9	55.57	58.29	55.57
10	59.85	63.92	61.15
11	64.13	68.2	65.43
12	68.45	72.57	69.76
13	72.77	75.6	72.78
14	75.08	79.96	77.15
15	80.16	84.39	80.22
16	84.59	87.46	84.59
17	87.66	89.23	87.71
18	90.78	92.39	89.48
19	92.6	94.16	91.29
20	94.41	95.97	93.12
21	96.22	96.48	94.91
22	98.03	98.33	95.34
23	98.59	98.84	97.22
24	99.09	99.04	97.73

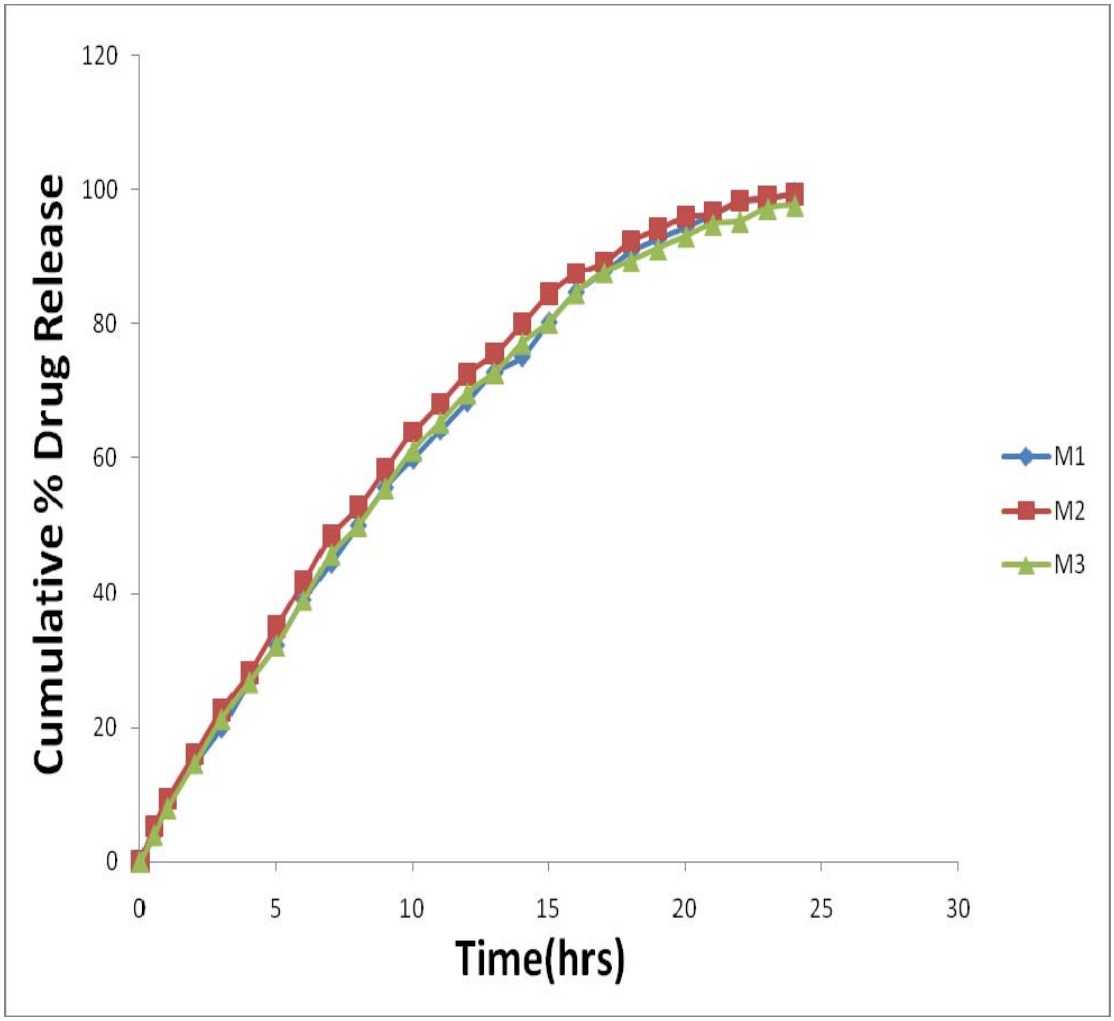


Fig:18 Dissolution profile of F_{11} batch at 30°C/65%RH

Table:41 Comparison of physical parameters for optimized formulation F_{11}

S.No.	Parameters	F_{11}	40°C/75%RH		
			At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1.	Thickness (mm)	2.81 ± 0.016	2.80 ± 0.012	2.81 ± 0.012	2.80 ± 0.014
2.	Diameter (mm)	7.7 ± 0.019	7.8± 0.014	7.7 ± 0.01	7.5 ± 0.018
3.	Hardness (kg/cm^2)	6.7 ± 0.226	6.6± 0.146	6.5 ± 0.251	6.5 ± 0.244
4.	Friability (%)	0.39 ± 0.028	0.40 ± 0.017	0.40 ± 0.009	0.42 ± 0.012
5.	Weight Variation (mg)	151 ± 0.125	150 ± 0.254	150 ± 0.162	149 ± 0.156
6.	Content Uniformity	99.28 ± 0.036	99.15 ± 0.087	99.09 ± 0.112	99.03 ± 0.110

- ✓ F_{11}: Optimized formulation
- ✓ Formulation batch F_{10} kept for stability study at temperature (40°C/75%RH).

Table:42 Dissolution data of F_{11} batch at 40°C / 75% RH

Time(hrs)	Cumulative % Drug Release		
	At the end of 1st month	At the end of 2nd month	At the end of 3rd month
0.5	5.29	5.25	5.25
1	7.92	10.57	10.58
2	14.59	17.25	17.25
3	19.98	23.99	22.64
4	26.06	29.38	29.42
5	33.5	34.86	36.16
6	38.93	40.34	41.65
7	44.56	45.87	47.18
8	49.99	52.7	52.76
9	55.57	56.99	56.99
10	59.85	62.56	61.26
11	64.13	68.24	65.58
12	69.75	72.57	69.91
13	72.78	75.6	75.58
14	77.15	79.96	79.96
15	80.22	84.39	83.04
16	84.59	87.46	84.55
17	87.71	89.23	86.56
18	90.78	91.04	86.67
19	92.6	92.85	90.12
20	93.11	93.31	91.94
21	94.91	95.11	93.75
22	96.72	96.97	95.56
23	98.53	97.43	96.07
24	99.09	97.98	97.83

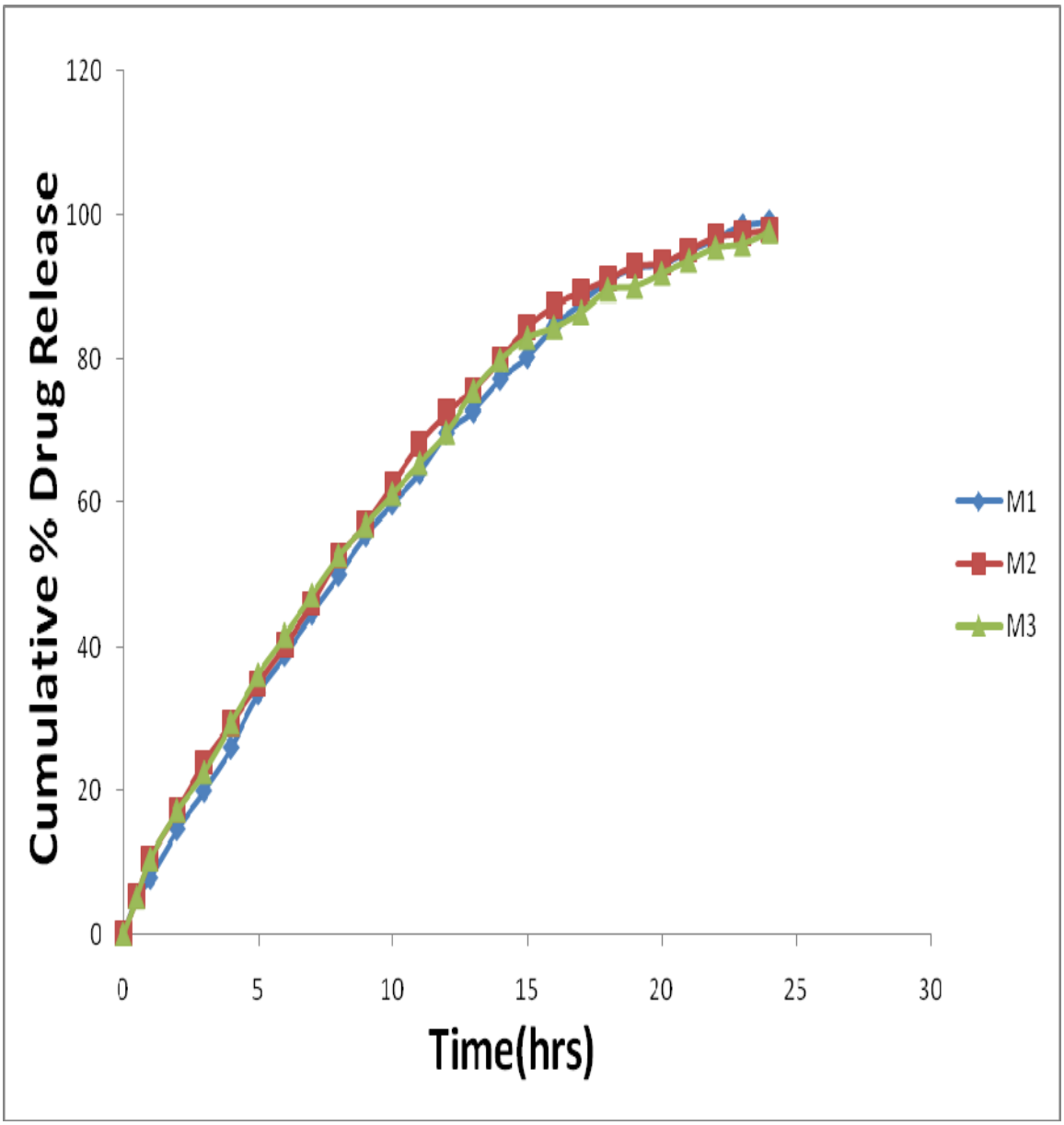


Fig:19 Dissolution profile of F_{11} batch at 40°C/75%RH

8.6 PHENOMENON OF DRUG RELEASE

The formulations was subjected to graphical treatments to assess the kinetics of drug release.

Release was approaching Zero order.

Zero order Equation:

The results data was fitted into the Zero order equation.

$Q = K_0 t$

Q = The amount of drug released at time t

K_0 = Release rate

First order Equation:

The results data was fitted into the first order equation.

$\text{Log } C = \text{Log } C_0 - k\,t / 2.303$

C_0 – is the initial concentration of drug

K – is the first order constant

t - is the time.

Higuchi Plot:

The graph was plotted between cumulative % release and square root of time. The regression value of F_{11} was 0.971. This indicates, that **diffusion** is one of the mechanism of drug release.

Peppas Plot:

The graph was plotted between log cumulative % of release and log time. The slope (n) value of F_{11} was 0.789. This indicates, **swelling mediated diffusion** is the mechanism of drug release.

ANALYSIS OF RELEASE DATA:

In kinectis data, Figure 20, 21, 22, 23 had showed the correlation coefficient of different kinetic models for Atorvastatin calcium optimized (F_{11}) formulation. Higuchi plots were found to be of highest linearity with correlation coefficient greater than that of the zero order kinetics and corresponded to that of the first order kinetics indicating that the drug release mechanism from the tablets by diffusion method. Studies revealed that the release of Atorvastatin calcium was found to be very close to zero-order kinetics in simulated gastric fluid, indicating that the concentration was nearly independent of drug release. Moreover, *in-vitro* release of Atorvastatin calcium was best explained by Korsmeyer-Peppas equation also indicated a good linearity. The release exponent 'n' was 0.789, which indicates anomalous diffusion.

A) Zero-Order Kinetics Plot:

ZERO ORDER PLOT

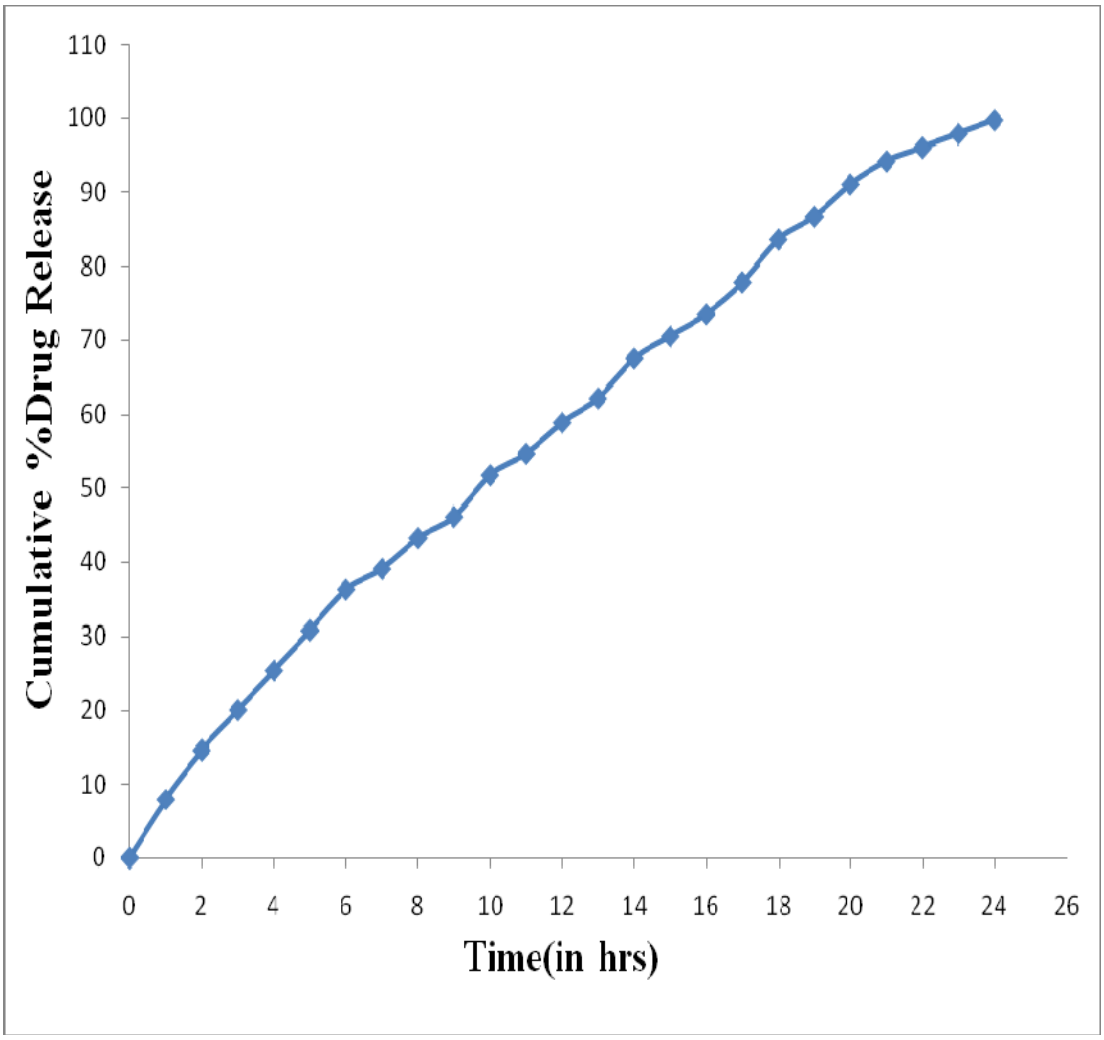


Fig:20 Zero-order release profile of optimized (F_{11}) Formulation

Zero order release kinetics
R^2
0.990

B) First-Order Kinetics Plot:

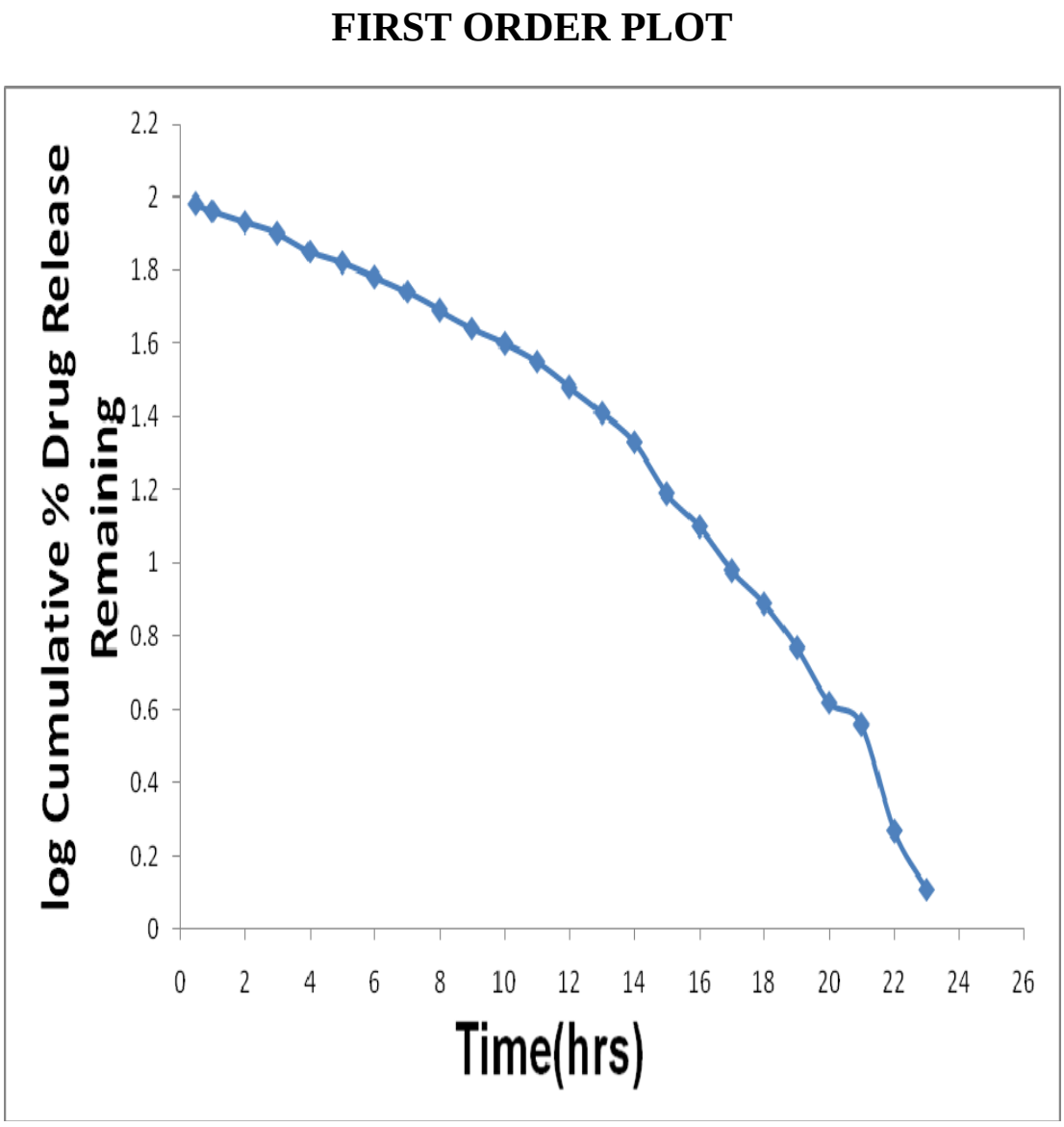


Fig:21 First-order release profile of optimized (F_{11}) Formulation

First order release kinetics
R^2
0.929

C) Higuchi Plot:

HIGUCHI PLOT

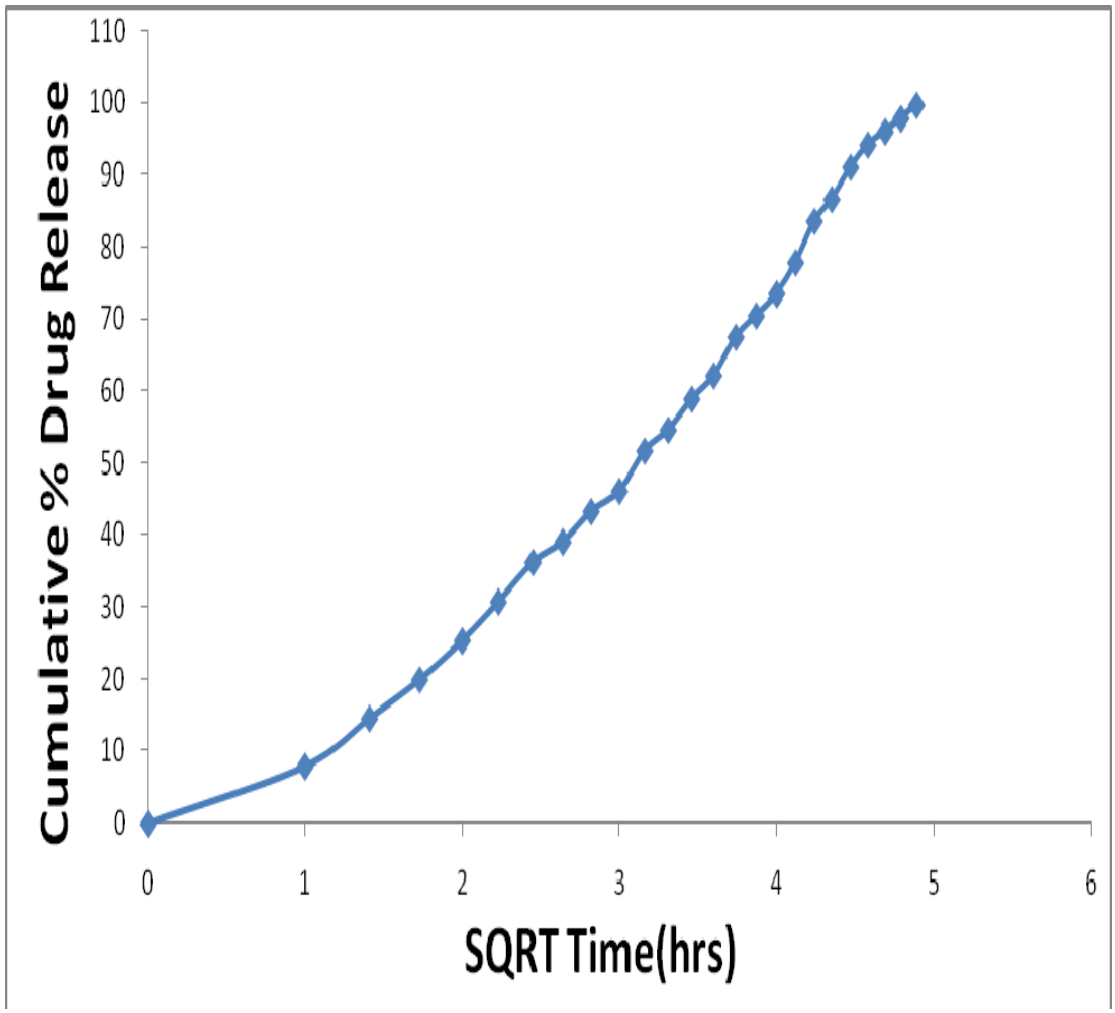


Fig:22 Higuchi release profile of optimized (F_{11}) Formulation

Higuchi release kinetics
R^2
0.971

D)Korsemeyer – Peppas model Kinetics Plot:

PEPPAS PLOT

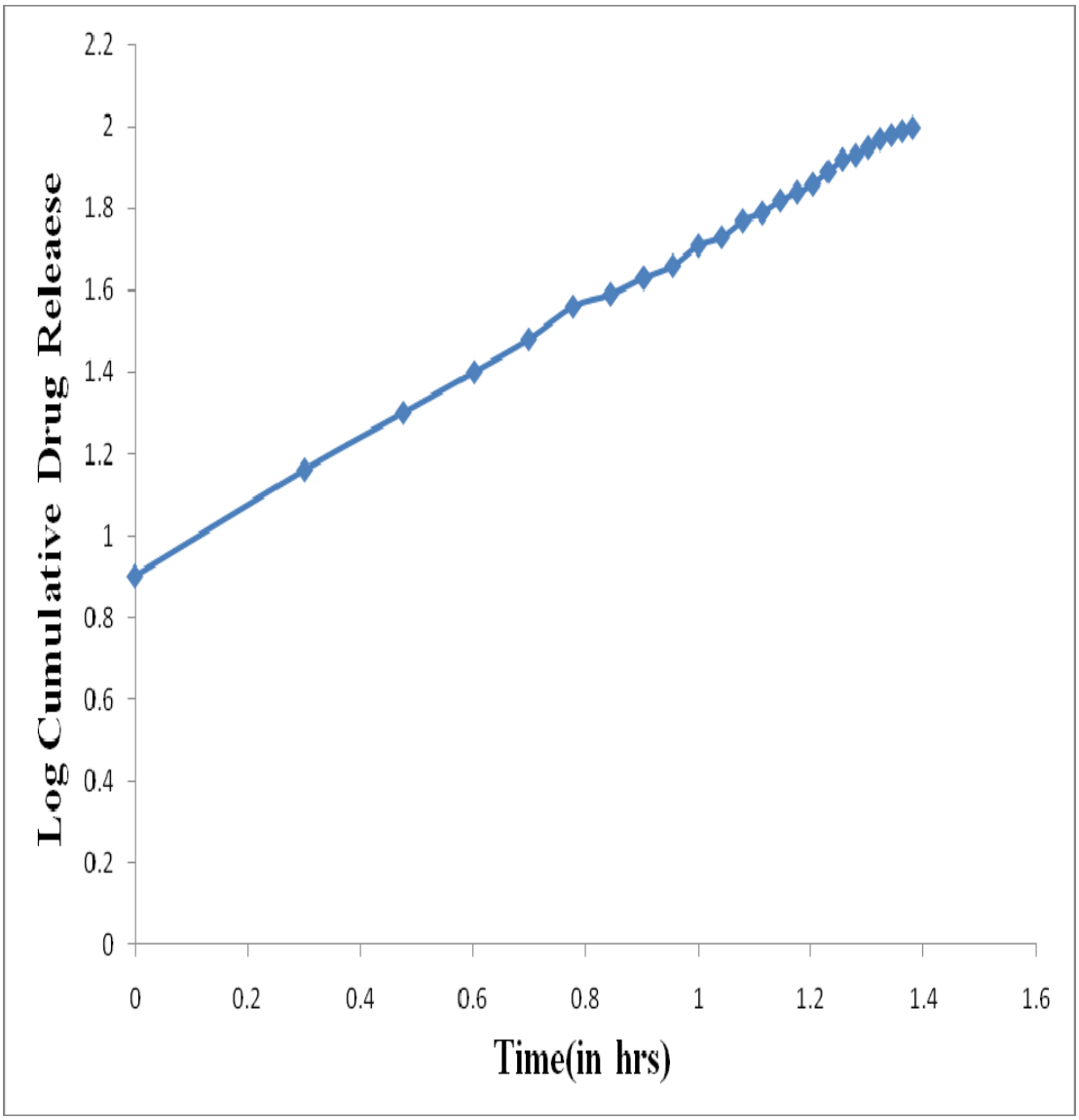


Fig:23 Korsemeyer – Peppas release profile of optimized (F_{11}) Formulation

Korsemeyer – Peppas model release kinetics
n
0.789

9. CONCLUSION

Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzymeA (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Gastro Retentive Drug Delivery System of Atorvastatin calcium could be successfully formulated by direct compression technique, using different viscosity grades of Hydroxy Propyl Methyl Cellulose, Avicel PH102 was used as binder, sodium bicarbonate as gas generating agent, talc as glidant, magnesium stearate as lubricant and lactose as diluent. The optimized tablet formulation had showed 99.74% of drug release in 24 h. Therefore the optimized formulation containing HPMC K100M with Avicel PH102 sustained the drug release for a period of 24 h and remains buoyant throughout the studies. Among the different grades of HPMC, HPMC K100M showed the maximum retardation in drug release.

The invitro dissolution profile of drug release from the tablets followed zero order kinetics. From the higuchi plot of dissolution profile, we found that the drug was released by diffusion mechanism and from the peppas plot we concluded that the release mechanism was found to be non Fickian release. The optimized formulation undergoes stability study at 25°C / 60%RH, 30°C / 65%RH, 40°C / 75%RH. There was a slight change in physical characteristics, buoyancy study and dissolution study.

Finally, it was concluded that Gastro Retentive Drug Delivery System of Atorvastatin calcium prepared with higher viscosity grade HPMC K100M, which sustain the release of the drug in the GIT.

It is a promising approach as it can able to release the required quantity of drug to the body, which results in minimizing the major side effect as rhabdomyolysis by minimizing the drug concentration in blood and also the entire dose was released in acidic medium, where atorvastatin having more absorption and ultimately leads to better patient therapy.

BIBLIOGRAPHY

1. Ali R Rajabi – Siaboomi., An overview of current oral modified released technologies. Business Briefing : Pharmatech., 2003,(1),181 - 184.
2. Gupta, K.P., Joseph R Robinson.,: Kydonieus, A., Treatise on controlled Drug Delivery, Marcel Dekker, Inc., New York, 1992, 2nd ed, 282.
3. Abraham, M.A., Shirwaikar, A., Formulation of multilayered sustained release tablets using insoluble matrix systems. Ind J Pharm. Sci; 1997;59 (6);312 - 315.
4. Mark A Longer., Joseph R Robinson., Sustained release drug delivery systems. Joseph P Remington., The science and practice of pharmacy, The Philadelphia College of Pharmacy and Science, Philadelphia; 18th ed; 1990;1677.
5. Brahmankar.D.M , Sunil B Jaiswal, Biopharmaceutics and pharmacokinetics; Vallabh Prakashan Delhi, 1st ed; 1995; 347 - 354.
6. Hogan, J.E., Hydroxypropyl methyl cellulose sustained release technology. D D Ind Pharm.; 1995; 15; 975 - 999.
7. Manisha Rane, Jayesh Parmar, Ali Rajabi-Siahboomi; Hydrophilic matrices for oral extended release: Influence of fillers on drug release from HPMC matrices; pharma times; Apr 2010; 42(04); 41 – 45.
8. Kamel.S ,Ali.N, Jahangir.K, Ahah.S.M, El-Gendy.A.A; Pharmaceutical significance of cellulose: A Review; express polymer letter; 2008; 2(11); 758 - 778.
9. Sas Baumgartner, Julijana Kristl, Franc Vrec, Polona Vodopivec, Bojan Zorko; Optimisation of floating matrix tablets and evaluation of their gastric residence time; Int J Pharma; 2000; 195; 125 - 135.
10. Tahara, K., Yamamoto, K., Nishirata, T., Overall mechanism behind matrix sustained release tablets prepared with hydroxyl propylmethyl cellulose. Int J Pharma; 1995; 35 (1); 59 - 66.
11. Caramella, C., Ferrari F., Boniferoni M.C., Ronchi M., Colombo P., Rheological properties and diffusion dissolution behaviour of hydrophilic polymers. Boll. chim. Farmaceutico., 1989, 128; 298 - 301.
12. Bettini, R., Peppas, N.A., Colombo, P., Polymer relaxation in swellable matrices contributes to drug release. Int J Pharm.,1996; 25; 26 - 37.

13. Lee, P.I., Diffusional release of a solute from a polymeric matrix approximate analytical solution. J. Membrane. Science., 1980; 255 - 275.
14. Lee, P.I and Kim, C., Probing the mechanisms of drug release from hydrogels. J Controlled. Rel., 1991; 16; 229 - 236.
15. Xiao Huang, Christopher S. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J Cont Release 2001;73(2-3):121 - 36.
16. Gwen M.Jantzen and Joseph Robinson; Modern Pharmaceutics; Gilbert S.Banker, Christopher T.Rhodes; 4th ed,; vol-121; 501 - 512.
17. Chein.Y.W. Novel drug delivery system. 2nd ed. New York: Marcel Dekker. 1992; 140.
18. Hui Ho-lwah, Robinson JR, Lee HL. Controlled drug delivery: fundamentals and applications. 2nd ed., New York: Marcel Dekker, 2005; 419.
19. Khan MA, Savstry SV, Vaithiyalingam SR, Agarwal V, Nazzal S. Captopril gastrointestinal therapeutic system coated with cellulose acetate psedolatex: evaluation of main effects of several formulations variables. Int.J.Pharm 2000; 193; 147 - 56.
20. Hiremath SRR. Absorption of drugs. In: Text book of Biopharmaceutics and Pharmacokinetics, Prism books; 2000; 11 - 2.
21. Arora S, Ali J, Ahuja A, Khar RK, Babota S. Floating Drug Delivery Systems: A Review. AAPS PharmaSciTech. 2005; 6(3): 372 - 388.
22. Mayavanshi AV, Gajjar SS; Floating drug delivery system to increase the gastric retention of drugs: a review; Research J Pharm & Tech; Dec 2008; 345 – 348.
23. http://knol.google.com/k/floating-tablets-a-comprehensive-review#
24. Shishu, N. Gupta, N. Aggarwal.; preparation and evaluation of gastro-retentive floating delivery system for 5-fluorouracil, Asian J Ph.ceutical Scis. 2(4): 143-149, 2007.
25. Denish Kalaria, Natarajan R, Mohan Kumar K, Rajendran N N,; effects of polymers and gas forming agents on gastro-retentive floating tablets of acyclovir, Int J Pharm & Ind. Res.,; Jun 2011 01(02).88 - 94.

26. Gangadharappa H.V., Balamuralidhara V., Pramod Kumar T.M.,; Formulation and in vitro Evaluation of Gastric Floating Tablets of Atenolol, J of Pharm. Res.,; 2010; 3(6):1450 - 1455.
27. Lingam Meka, Bhaskar Kesavan, Krishna Mohan Chinnala, Venkateswarlu Vobalaboina, and Madhusudan Rao Yamsani,; preparation and evaluation of a Matrix Type Multiple-Unit Gastro Retentive Floating Drug Delivery System for Captopril Based on Gas Formation Technique, AAPS Pharm Sci Tech, Jun 2008; 9(2); 612 - 619.
28. R. K. Kar1, S. Mohapatra, D. Mohapatra, R. K. Dash, B. B. Barik,; Preparation and in vitro Characterization of Cefuroxime Axetil Loaded Gastro retentive Floating Tablets, Drug Invention Today, 2(10),.457-459, 2010.
29. Ajay Bagherwal, Dinesh Kumar Patidar and Pradeep Sharma,; studies on formulation and evaluation of floating tablets of ciprofloxacin HCl, Pharmacie Globale Int J Comprehensive Pharm, 2010; 5 (02); 1 - 4.
30. Margret Chandira, Chandramohan, Debjit, Chiranjib, Jayakar.B, Sampath Kumar.K.P,; design and characterisation of sustain release gastro retentive floating tablets of Diltiazem HCl, Scholars Research Library Der Pharmacia Lettre, 2009; 1(2); 25 - 38.
31. Margret Chandira, Bhavesh, B.S.Venkateshwarlu, B.Jayakar, D.Bhowmik, Chiranjib, K.P.Sampath Kumar,; Studies on formulation and evaluation of floating tablets containing anti-ulcer drugs, Scholars Research Library Der Pharmacia Lettre, 2009; 1(2); 102 - 114.
32. M. Jaimini, A.C. Rana and Y.S. Tanwar,; Formulation and Evaluation of Famotidine Floating Tablets, Current Drug Delivery; 2007; 4; 51 - 55.
33. Ravi Kumar, M. B. Patil, Sachin R. Patil, Mahesh S. Paschapur,; Formulation and Evaluation of Effervescent Floating Tablet of Famotidine, Int J Pharm Tech Res,; Sep 2009; 1(3); 754 - 763.
34. Vishal G. Karkhile, Dr. Ritesh R. Karmarkar, Manish A. Sontakke, Shyam D. Badgujar, Lalita S. Nemade,; formulation and evaluation of floating tablets of furosemide, Int J Pharma. Res. Devp., Feb 2010; 1(12); 1 - 9.

35. Patel Krunal M. , Biswajit Biswal., Nabin Karna, Janki Patel,; Preparation and Evaluation of Gastro retentive Floating Tablets of Lansoprazole, J Pharm Res, 2010; 3(12); 2934 - 2936.
36. Arunachalam.A, Stephen Rathinaraj.B, Rajveer.Ch, Kumaraswamy.D, Umarunnisha.A.M,; design and evaluation of levofloxacin hemihydrates floating tablets, Int J Applied Biology and Pharma Tech, Oct 2010; 1(2); 260 – 268.
37. Ganesh Rajput , Dr. Jayvadan Patel, Kalpesh Patel, Bipin Patel, Rashmin Thakor, Ravi Patel,; Development and Optimization of Metformin HCl Gastro retentive Tablets: An Application of Optimized Viscosity Approach, J Pharm Res.; Mar 2009; 2(3), 378 - 384.
38. Laxmi Goswami, Sayantan Mukhopadhyay, Sumit Durgapal,; Formulation and evaluation of combined floating bilayer tablet of metformin and pioglitazone, J Pharm Res., 2011; 4(3); 645 - 646.
39. Nirav S Sheth, Rajan B Mistry,; formulation and evaluation of floating drug delivery system, Int J Pharma and Bio Sciences; Mar 2011; 2(1), 571-580.
40. Krunal Patel M., Biswajit Biswal., Nabin Karna, Janki Patel,; preparation and evaluation of gastro retentive floating tablets of mebendazole, Int J Current Pharma Res., 2011; 3(1); 63 - 65.
41. Dalavi V.V., Patil J. S.,; gastro retentive drug delivery system of an anti-retro viral agent, Int J Pharm. Tech Res., Dec 2009; 1(4); 1678 - 1684.
42. Ferdous khan, MD. Shaikhul millat ibn razzak, MD. Ziaurrahman khan, Mohammad abdul kalam azad, Jakir ahmed chowdhury and MD. Selim reza,; preparation and evaluation theophylline loaded gastro-retentive floating tablets based on hydrophilic polymers: Pak J Pharm. Sci., Apr 2009; 22(2); 155 - 161.
43. Debajyothi ray, Amresh K Prusty,; designing and invitro studies of gastric floating tablets of tramadol HCl, Int J Appl Pharm, Jul 2010; 2(4); 12 - 16.
44. N. Damodharan, M. Mothilal, m.madhavi, P. Thejomayananthan,; Formulation and evaluation of bi-layered floating tablets of Theophylline, Scholars Research Library Der Pharmacia Lettre, 2009; 1 (2); 227 - 233.

45. Kannan C, Karunanithi V, Janarthanan S and Dheivasigamani V; Formulation and in vitro Evaluation of Gastroretentive Rosiglitazone maleate Floating Tablets, Int J Chemical and Pharma Scis., Aug 2010; 1(1); 26 - 32.
46. Girish S. Sonara, Devendra K. Jaina, Dhananjay M. More,; Preparation and in vitro evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate, Asian J Pharma Sciences, 2007; 2 (4): 161 - 169.
47. Kavitha K, Puneeth K P, Tamizhmani T,; Development and evaluation of Rosiglitazone Maleate floating tablets, Int J Appl Pharma, Feb 2010; 2(2); 1 - 10.
48. Chander Shekar B, Shireesh Kiran R, Nagendra Babu B; preparation and evaluation of gastro retentive floating tablets of ketoconazole, Int J Pharma Res Devp,Nov 2010; 2(9); 174 - 184.
49. Prashant Khemariya, Sanjay J. Ingale, Akhilesh K. Singhai, Mohit Bhargava, Gaurav Saraogi, Sanjay K. Singhai and Mayank Nagar,; Formulation and evaluation of sustained release gastro-retentive drug delivery system of ofloxacin, Int J Biopharmaceutics; 2010; 1(2): 85 - 91.
50. J. Padmavathy, Saravanan.D, Rajesh.D; formulation and evaluation of ofloxacin floating tablets using HPMC, Int J Pharm and Pharma Sci., 2011; 3(1);170 - 173.
51. A. Kotwal and A.K. Pathak,; Formulation and evaluation of intragastric buoyant tablets of amoxicillin trihydrate , Int J Pharm. & Life Sci., Feb 2011; 2(2); 546 - 550.
52. I.Sarath Chandiran, B. Pavan Kumar, V. Narayan,; Formulation and *in-vitro* evaluation of floating drug delivery system for salbutamol sulphate, Int J Pharm Biomed Sci, Jun 2010; 1(1); 12 - 15.
53. S.Ramkanth, M.Alagusundaram, K. Gnanaprakash, C.Madhusudhana Chetty, K. Mallikarjuna Rao, Y. Sudhakar, Annie Baby,; Formulation and Characterization of Floating Tablets of Diltiazem Hydrochloride, J Pharm Res., Jun 2010; 3(6); 1263 - 1267.
54. Anuradha K Salunkhe, Remeth J. Dias, Kailas K. Mali, Niranjan S. Mahajan and Vishwajeet S. Ghorpade; Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate, Scholars Research Library Der Pharmacia Lettre, 2011; 3(3); 147 - 160.

55. Balkrushna K. Patel1, Sridhar Bhople, Paresh A. Prajapati1 and Paresh U. Patel,; Characterization and evaluation of Clarithromycin Hydrophilic floating matrix tablets, Pelagia Research Library Der Pharmacia Sinica, 2010; 1(2); 5 - 16.
56. D. M. Sakarkar, R. V. Kshirsagar, R. M. Deshbhratar,; Studies on formulation and invitro evaluation of gastro retentive drug delivery system of carbamazepine, Int J ChemTech Res., Mar 2010; 2(1); 108 - 113.
57. Sharad N. Shinde1, Satej S. Magdum, Shekhar B. Waikar, Maesh R. Mishra, Kamla K. Chandak,; Development and evaluation of floating tablets of salbutamol sulphate, In J Pharma Res. Devp., Jul 2010; 2(5); 1 - 7.
58. Sameer Singh, Kalpana Prajapati,A K Pathak,A Mishra,; Formulation and Evaluation of Floating Tablet of Captopril, Int J Pharm Tech Res , Mar 2011; 3(1); 333 - 341.
59. P. N. Kendre, S.N. Lateef, R.K.Godge, P.D. Chaudhari, S.L. Fernandes, S.K.Vibhute,; Oral Sustained Delivery of Theophylline Floating Matrix Tablets-Formulation and In-vitro Evaluation, Int J Pharm Tech Res, Mar 2010; 2(1); 130 - 139.
60. Vishnu M Patel, Bhupendra G Prajapati, Anand K Patel,; Controlled Release Gastroretentive dosage form of Verapamil Hydrochloride, Int J Pharm Tech Res , Jun 2009; 1(2); 215 - 221.
61. Satish Singh Kadian, Ashwani Kumar, Dennis DM, Anupama diwan,; Formulation design and evaluation of floating matrix tablet of celecoxib by direct compression, Int J Pharma Scis,; Aug 2010; 2(2); 556 - 560.
62. Sanjay s. patel, S. Ray and R. S. Thakur,; Formulaion and evaluation of floating drug delivery system containing claruthromycin for helicobacter pylori, Acta Poloniae Pharmaceutica ñ Drug Research, 2006; 3(1); 53 - 61.
63. Ziyaur rahman, Mushir Ali, RK Khar,; Design and evaluation of bilayer floating tablets of captopril, Acta Pharm. 2006; 56; 49 - 57.
64. Jayabalan nirmal, Srinivasan saisivam, Chintalapati peddanna, Selvadurai muralidharan, Sundaram godwinkumar, and Muthuraja nagarajan,; Bilayer tablets of Atorvastatin calcium and Nicotinic acid: Formulation and Evaluation, Chem. Pharm. Bull. Oct 2008; 56(10); 1455 - 1458.

65. Subhadeep chowdhury , Subhabrota majumdar,; Statistical optimization of fixed dose combination of glimepiride and atorvastatin calcium in immediate release tablet formulation, Int J Pharm and pharma Scis, Sep 2010; 2(4); 194 – 200.
66. Patel Geeta M. and Patel Dinesh H.,; Formulation and Evaluation of Once a Day Regioselective Dual Component Tablet of Atorvastatin Calcium and Metoprolol succinate, Int J Pharm Tech Res, Sep 2010; 2(3); 1870 - 1882.
67. Chapalamadugu ugandhar.; Design, development and evaluation of immediate release drug combination, Asian J Pharm Clin Res, 2011, 4(3); 77 - 79.
68. Kirti Rode1, N .Thirumoorthy, B.Parthsarthi, Ajish john, Pankaj Gawate,; Study on formulation development and evaluation of atorvastatin calcium flim coated tablets , Int J Pharma World Research; Jun 2011; 2(2); 1 - 19.
69. N.Arunkumar, M.Deecaraman, C.Rani, K.P.Mohanraj, K.Venkates Kumar,; Preparation and solid state characterization of atorvastatin nanosuspensions for enchanced solubility and dissolution, Int J Pharm Tech Research; Dec 2009; 1(4); 1725 - 1730.
70. Sachin V. Wankhede, M. Krishnaprasad, SY Manjunath, Subal Debnath,; Formulation and stabilization of Atorvastatin tablets, J Chem. Pharm. Res., 2010; 2(5); 548 - 554.
71. S. Mohideen, B. Jyothi, S. Pavani, T.Satyanarayana, P. Suresh Kumar, S. Navaneetha Krishnan,; Formulation and evaluation of bilayered tablets of metformin hydrochloride and atorvastatin calcium, Int J Pharma Scis Review and Research; Oct 2011; 10(2); 130 - 134.
72. Asha S. John, Sathesh B. P. R, Goli Divakar, Manoj K. Jangid and Kapil K. Purohit,; Development and evaluation of buccoadhesive drug delivery system for Atorvastatin calcium, J Current Pharma Research; Mar 2010; 01; 31 - 38.
73. Arunkumar.N, Rani.C and Mohanraj.K.P,; Formulation and *In-vitro* evaluation of oral floating tablets of atorvastatin calcium, Res. J Pharm. and Tech. Mar 2010; 1(4); 492 - 495..
74. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=11081
75. http://en.wikipedia.org/wiki/Atorvastatin

76. Raymond C Rowe, Paul J Sheskeyand Siân C Owen; Handbook ofpharmaceutical excipients 5th ed, 2006; 1)346 - 349, 2)665 - 668, 3)132 - 135, 4)385 - 388, 5)430 - 433, 6)767 - 769.
77. V. Juyal1, M. Chaudhary, P. Kumar, G. Gnanarajan, P. K. Yadav: Method development and its validation for simultaneous estimation of atorvastatin and amlodipine in combination in tablet dosage form by UV spectroscopy, using multi-component mode of analysis, J Pharma Res.,; Dec 2008; 1(2); 182 - 187.
78. ICH Q1A (R2) stability testing guidelines: stability testing of new drug substances and products. [Online]. 2003 [cited 2008 Nov10]; Available from: URL:http://www.tga.health.gov.au/docs/pdf/euguide/inch/273699r2en.pdf
79. Indian Pharmacopoeia, The Indian Pharmacopoeial commission, Ghaziabad, 2010: vol-2; Atorvastatin tablets; 851.
80. Ansel's, Loyd V Allen, Nicholas.jr, popovich.G; Ansel's pharmaceutical dosage forms and drug delivery systems; Lippincott Williams 2007; 8th ed,; 107 - 109.
81. Ansel's, Loyd V Allen, Nicholas.jr, popovich.G; Ansel's pharmaceutical dosage forms and drug delivery systems; Lippincott Williams 2007; 8th ed,; 233-245.
82. Martin's physical pharmacy and pharmaceutical sciences; Patrick J.Sinko, Lippincott Williams and Wilkins; 2005; 5th ed,; 340 - 344; 348 - 349.
83. Herbert A.Liberman, Leon Lachman, Joseph B.Schwartz, Marcel Dekker; Pharmaceutical dosage forms; 1990; 2nd ed,; vol-1; 88 - 113.
84. Hamed M.Abdou; Dissolution, Bioavailability and Bioequivalence; Mack publishing company; 1989; 1st ed,; 11 - 14.
85. Gilbert S.Banker, Christopher T.Rhodes, Marcel Dekker; Modern Pharmaceutics; 2nd ed; 224.
86. Michael E.Aulton; Pharmaceutics, the science of dosage form design; 2007; 2nd ed;133 - 136.
87. N.K.Jain, Controlled and novel drug delivery; 2008; 1st ed,; 1 - 21.
88. Donald L.Wise, Marcel Dekker; Handbook of pharmaceutical controlled release technology; 3 - 14.
89. Jens T.Carstensen, C.T.Rodes; Drug stability principles and practices; 3rd ed,; 146.

90. Loyd V Allen, Nicholas.jr, popovich.G, Howard C.Ansel; Ansel's pharmaceutical dosage forms and drug delivery systems; 2007; 8th ed,; 234-235.
91. http://www.lipitor.com/aboutlipitor/sideeffects.aspx
92. http://www.emedicinehealth.com/drug-atorvastatin/article_em.htmm
93. http://www.rxlist.com/lipitor-drug.htm
94. http://www.medicinenet.com/rhabdomyolysis/article.htm
95. http://www.drugs.com/sfx/atorvastatin-side-effects.html