FORMULATION AND EVALUATION OF FLOATING MICROPARTICLES OF AMLODIPINE BESYLATE

A Dissertation submitted to
THE TAMIL NADU Dr.M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

In partial fulfillment of the requirements for the award of the Degree of
MASTER OF PHARMACY
IN
Branch -I:**PHARMACEUTICS**

Submitted by

REGISTRATION No.261611004

Under the guidance of
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OCTOBER 2018

CHERRAAN'S COLLEGE OF PHARMACY

(Affiliated to the Tamilnadu Dr.M.G.R medical university, Chennai)

Approved by The Govt. of Tamilnadu, Chennai
All India Council for Technical Education, New Delhi
Recognized by pharmacy council of India, New Delhi

CERTIFICATE

This is to certify that the Dissertation entitled **"FORMULATION AND EVALUATION OF FLOATING MICROPARTICLES OF AMLODIPINE BESYLATE"** submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, is a bonafide project work of **Reg No: 261611004** carried out in the department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore for the partial fulfillment for the degree of Master of Pharmacy under my guidance during the academic year 2017-2018.

This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

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EVALUATION CERTIFICATE

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INTERNALEXAMINER **EXTERNAL EXAMINER**

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DECLARATION

The research work emboided in this work **"FORMULATION AND EVALUATION OF FLOATING MICROPARTICLES OF AMLODIPINE BESYLATE"** was carried out by me in the Department of Pharmaceutics, Cherraan'scollege of Pharmacy, Coimbatore, under the direct supervision of **Mr. J. Karthikeyan.M.Pharm.,(Ph.D.),** Professor Department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore-39.

The dissertation submitted to The Tamilnadu Dr.M.G.R Medical University, Chennai, for the award of degree of Master of Pharmacy in Pharmaceutics during the academic year of 2017-2018.

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Date: **Reg. No: 261611004**

ACKNOWLEDGEMENT

First and foremost, I wish to express our heartful sense of gratitude and faithfulness to god's grace.

I submit my sincere thanks to our Chairman **Mr.K.C.Palanisamy, BE (Agri)** chairman of Cherraan's foundation trust, for providing all the facilities to carry out this thesis work.

My sincere gratitude to my beloved Principal, **Dr.P.Selvam, M.Pharm, Ph.D., FNABS, FISNS,** Department of Pharmaceutical Chemistry Cherraan's College of pharmacy for his kindly support for my project work and for his encouragement and also providing all facilities in this institute to the fullest possible extent enabling me to complete this work.

With the immense pleasure and pride, I would to take opportunity in expressing my deep sense of gratitude to my beloved guide, **Mr.J.Karthikeyan, M.Pharm., (Ph.D.),** Professor & Department of Pharmaceutics Cherraan's college of pharmacy under whose active guidance, innovate ideas, constant inspiration and encouragement of the work entitle **"FORMULATION AND EVALUATION OF FLOATING MICROPARTICLE OF AMLODIPINE FLOATING MICROSPEHRE** has been carried out.

I express my sincere thanks to **Dr.B.Geetha, M.Pharm, Ph.D.,** Vice Principal, Department of Pharmaceutical Chemistry for her support for my project work.

I convey my gratitude to **Mrs.C.RubinaReichal, M.Pharm., (Ph.D.),** Associate Professor Department of Pharmaceutics for her support for my project work.

It is my pleasure to express my honourable thanks to **Mrs. M.Sangeetha, M.Pharm., Asst.Professor,** Department of Pharmaceutical Chemistry for sharing her valuable knowledge.

I convey my gratitude to, **Karunya University, Coimbatore.**

I duly bound to all our **teaching** and **non-teaching staffs, librarians, lab assistants** of Cherraan's college of pharmacy for their valuable advice and co-operation.

I am giving greatful thanks to all my **friends** for their help during my project.

I express my heartful gratitude to the **Almighty,** for giving me the right way to achieve the good for my project.

Last but not least, a great thank's from the heart to my beloved **Mother and Father.** They are **my living God,** as who guided me in the rightful way to achieve all my activities. They gave me the incredible effort to become a successful person for bright future in this world. Thank's a lot to my **Parents.**

USHADEVI.C

DEDICATED TO THE

ALMIGHTY, BELOVED

FATHER, MOTHER AND

TEACHERS

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ABBREVIATIONS

CR	:	Controlled release
SR	:	Sustained release
°C	:	Degree Celsius
DSC	:	Differential scanning Calorimetry
E.g.	:	Example
Fig	:	Figure
Gms	:	Grams
Hrs	:	Hours
IR	:	Infrared Spectroscopy
m	:	Meter
mg	:	Milligram
min	:	Minutes
ml	:	Mililiter
µg	:	Microgram
µg/ml	:	Microgram per ml
%	:	Percentage
RES	:	Reticuloendothelial system
GIT	:	Gastrointestinal tract
Rpm	:	Revolution per minute
S.D	:	Standard Deviation
SEM	:	Scanning Electron Microscope
USP	:	United States Pharmacopoeia
UV	:	Ultraviolet
w/v	:	weight by volume
v/v	:	volume by volume

1. INTRODUCTION

For many decades treatment of acute disease or chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, pills, suppositories, creams, ointments, liquids, aerosols, and injectables. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the effective range needed for treatment, it is necessary to take this type of delivery system several times a day. In order to overcome this criteria the specialized drug delivery system, by which a pharmacologically active moiety may be continuously delivered or monitored either systematically or to target site in an effective, reliable, repeatable and safe manner has been introduced. These system are also capable of delivering the desired concentration of drug in a fixed, predetermined pattern for a definite time period. Thus necessary side effects are avoided and a delivery of a desired concentration of drug in a fixed, predetermined pattern at a precise time is made possible.

"The active ingredient in a medicine is only a part of the arsenal against a disease. The drug must somehow get to the right place at the right time. That is where the drug comes in"

Oral controlled release (CR) dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation.

1.1. Floating drug delivery system[1]

Floating drug Delivery System:

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 the desired rate from the system. After release of drug, the residual

system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

Classification of Floating Drug Delivery System:

A. Effervescent system

- Gas generating system
- Volatile liquid containing system

B. Non-effervescent System:

- Colloidal gel barrier system.
- Alginate beds.
- Hollow microspheres / Microballons.
- Intragastric Floating Drug Delivery Device / Microporous compartment system

A. Effervescent Systems:

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

a. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid(like ether, cyclopentane), that gasifies at body temperature cause the inflatation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

b. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonatesalts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. How the dosage form float is shown in the figure 1.

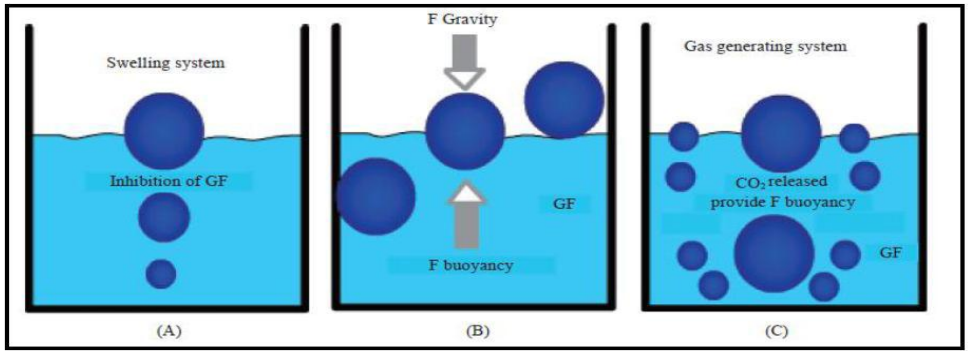

Figure 1: Gas-generating Systems

B. Non-effervescent systems:

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type 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 < 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 allow sustained release of drug through the gelatinous mass.

a. Colloidal gel barrier systems:

Hydro dymamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975.Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage form.

b. Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

c. Hollow microspheres:

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated

continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.

d. Intragastric / Microporous compartment system:

The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the un dissolved drug with walls of the stomach. Novel levodopa gastro retentive dosage form based on unfolding polymeric membranes which combines extended dimensions with high rigidity. It was folded into a large size gelatin capsules. In vitro studies showed that unfolded form reached within 15 minutes after administration and it was confirmed in vivo in beagle dogs. The unfolded form was maintained for at least 2 hours. It was concluded that this dosage form could improve therapy of different narrow absorption window drugs. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction.

Advantages:

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery.

These advantages include:

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.

2. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.

3. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.

4. The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site .

5. Controlled delivery of drugs. It minimizes the mucosal irritation by releasing drug slowly.

6. Treatment of gastrointestinal disorders such as gastro esophageal reflux.

Disadvantages of floating drug delivery system:

1. Floating system is not feasible for those drugs that have solubility or stability problem in GI tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.

3. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, may not be desirable candidate. E.g. Nifedipine.

4. The ability of drug to remain in the stomach depends upon the subject being positioned upright.

5. The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.

6. Not suitable for drugs that cause gastric lesions e.g. Non steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms.

1.2. MODES OF DRUG DELIVERY

1.2.1 Sustained/Controlled drug delivery

1.2.2 Targeted drug delivery

1.2.3 Modulated drug delivery

1.2.1. SUSTAINED/CONTROLLED DRUG DELIVERY[2]

Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist.

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action reducing the dose required, or providing uniform drug delivery. Sustained release constitutes any dosage form that provides medication over an extended time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature or both.

This correctly suggests that there are sustain release system that cannot be considered controlled release system. In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period: this is usually accomplished by attempting to obtain zero order release from the dosage form. Sustained release systems generally do not attain this type of release and provides drug in a slow first order fashion. In recent year sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology is reliably cow field and as a

consequence, research in the field has been extremely fertile and has produced many discoveries. New and more sophisticated controlled release, sustained release delivery system are constantly being developed and tested.

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms terms used to identify drug delivery system that are designed to achieve or prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

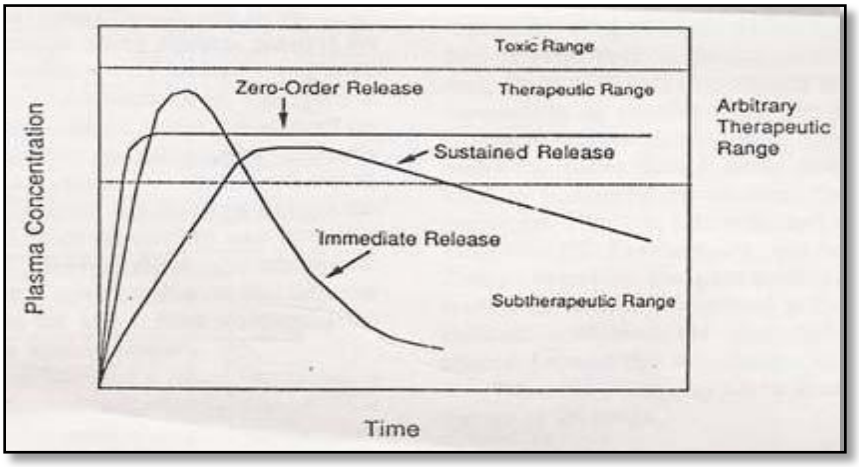

Figure 2: Drug level verses time profile showing differences between zero order controlled release, slow first order sustained release and release from conventional tablet.

Systems that are designed as prolonged release can also be considered as attempts at achieving sustained release delivery. Repeat action tablets are alternative method of sustained release in which multiple doses of drugs are contained within a dosage form, and each dosage is related to periodic interval. Delayed release systems, in contrast may not be sustaining, since often function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly the release rate of drug is no altered and does not result in sustained delivery once drug release has begun.

Successful fabrication of sustained release products is usually difficult and involves consideration of physicochemical properties of drug, pharmacokinetic behavior

of drug, route of administration, disease state to be treated and most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug.

The slow first order obtained by a sustained release pre parathion is generally achieved by the release of the drug from a dosage form. In some cases, this achieved by making slow release of drug from a dosage form. In some cases, this is accomplished by a continuous release process.

ADVANTAGES AND DISADVANTGES OF ORAL SUSTAINED RELEASE SYSTEMS

ADVANTAGES

- Avoid patient compliance problems.
- Employ less total drug.
  - Minimize or eliminate local or systemic side effects.
  - Obtain less potentiation or reduction in activity with chronic use.
  - Minimize drug accumulation with chronic dosing.
- Improve efficiency in treatment
  - Cure or control condition more promptly.
  - Improve control of condition (reduce fluctuation in drug level)
  - Make use of special effects.(e.g. SR Aspirin for morning relief of arthritis by dosing before bed time)
- Improved treatment of chronic illness (e.g. Asthma)
- Maintenance of therapeutic action overnight. (e.g. Overnight management of pain)
- Reduction in amount of drug taken over a period of drug administration.

DISADVANTAGES

- High cost.
- Poor in-vitro/in-vivo correleation.

- Reduced potential for dose change or withdrawal in the event of allergy or poisoning.
- Over dose or dose dumping.
- Loss of flexibility in dosage.

Rationale of Sustained Drug Delivery

The basic rationale for sustained drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and / or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more important to design properly.

As mentioned earlier, primary objectives of controlled/sustained drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This achieved by better control of plasma drug levels and frequent dosing. For conventional dosage forms, only the dose (D) and dosing interval (C) can vary and, for each drug there exists a therapeutic window of plasma concentration, below which therapeutic effect is insufficient, and above which toxic side effects are elicited. This is often defined as the ration of median lethal dose (LD 50) median effective dose (ED 50)

Factors Affecting Sustained Release Dosage Forms:

Physicochemical properties of drug.

- **Dose size**

If an oral product has a dose size greater that 0.5 gm it is a poor candidate for sustained release system. Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptable large.

- **Aqueous solubility**

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes. Aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low mechanism. The lower limit on solubility for such product has been reported .1mg/ml drugs with great water solubility are equally difficult to incorporate into sustained release system. Ph dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate.

- **Partition coefficient**

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very low aqueous solubility. Compounds with very low partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability

- **Pka**

The relationship between Pka of compound and absorptive environment, presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

- **Drug stability**

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach: system that prolong delivery ever the entire course of transiting tried are beneficial. Compounds that are unstable in the small intestine any demonstrate decreased bioavailability when administered from a sustaining dosage from. This is because more dug is delivered in small intestine and hence subject to degradation.

❖ **Molecular size and diffusivity**

The ability of drug diffuse through membranes is so called diffusivity and diffusion coefficient is function of molecular size (or molecular weight)

Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm^2 /sec. thus high molecular weight drugs and/ or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

❖ **Protein binding**

It is well know that many drugs bind to plasma protein with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re-circulate and not eliminated, drug. Protein binding can serve as a depot for drug production a prolonged release profile, especially if a high degree of drug binding occurs.

Extensive binding to plasma proteins will be evidence by a long half life of elimination for drugs and such drugs generally most require a sustained release dosage form. However, drugs that exhibit height degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on drug molecule also increases the binding potential.

Biological factors

- **Biological half life**

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). Therapeutic compounds with short half lives

are excellent candidates for sustained release preparations, since this can reduce dosing frequency. In general drugs with half-lives shorter than 3 hours are poor candidates for sustained release dosage forms because dose size will increase. Compounds with long half lives, more than 8 hours are also not used in sustained release forms because their effect is already sustained.

- **Absorption**

The rate, extent and uniformity of absorption of a drug are important factors when consider its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is essential if the system is to be successful. If we assume that transit time of drug must in the absorptive areas of the GI tract is about 8- 12 hours. The maximum half life for absorption should be approximately 3-4 hours; otherwise device will pass out of potential absorption regions before drug release is complete.

- **Distribution**

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/controlled release products. One must have information of disposition of drug.

- **Metabolism**

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability form slower-releasing dosage forms. Most intestinal wall enzymes systems are saturable. As drug is released at a slower rate to these regions, less total drug is presented to the enzymatic. Process device a specific period, allowing more complete conversion of the drug to its metabolite.

Strategies and Design of oral controlled release systems[5]

The Design and fabrication of oral controlled release systems is reviewed under the following classification

I. Continuous Release Systems

- Dissolution Controlled release systems
  Matrix Type
  Reservoir Type
- Diffusion Controlled release systems
  Matrix Type
  Reservoir Type
- Dissolution and diffusion controlled release systems.
- Ion-Exchange Systems.
- Slow dissolving salts and complexes.
- pH dependent formulations.
- Osmotic pressure controlled release systems.
- Hydrodynamic pressure controlled release systems.

II. Delayed Transit and Continuous release systems

Altered density systems.
Mucoadhesive systems.
Size-based systems.

III. Delayed release systems

Intestinal release systems
Colonic release systems.

CRITERIA FOR EVALUTING ORAL CONTROLLED RELEASE SYTEMS

The ultimate criteria for evaluating such dosage forms are the amount of drug intended to be absorbed is indeed absorbed in a predictable and consistent manner

The steady state ratio of maximum to minimum drug concentration is optimally less than that produced by a more frequently administered conventional dosage form.

In a simplest model, the fate of drug may be characterized by a single compartment which is described by figure given below:

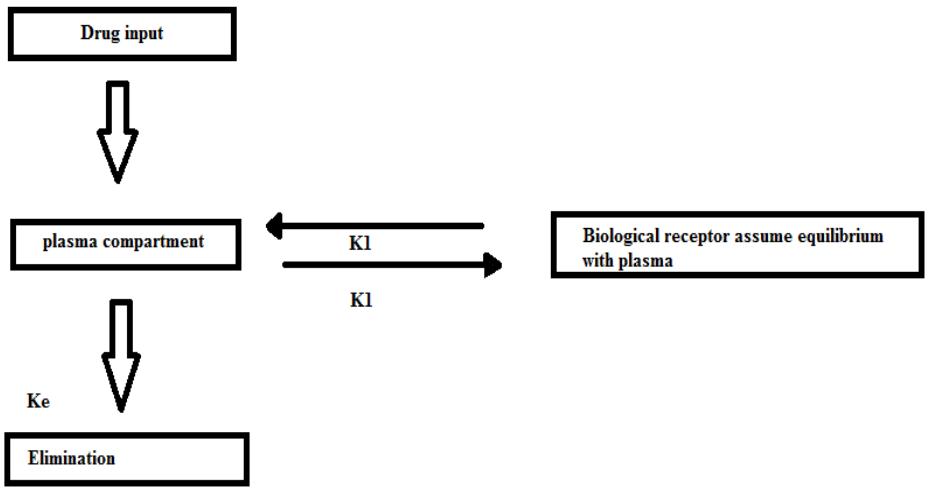

Figure 3: A simple pharmacokinetic model.

DRUGS SUITABLE FOR SUSTAINED RELEASE FORMULATION[6]

Not all the drug tend themselves to the formulation of sustained release product. The important factors that are to be considered in choice of a drug as candidate of SR preparation are as follows:

Biological half life

The pharmacological effect of some drugs with short half-lives is sustained by various mechanisms.

- The drug binds to the tissues. E.g., tissue bound ace inhibitors. for these drugs, less frequent dosing is needed even though the drug is having short half-lives

- The drugs with very short half-lives that is, less than two hours are poor candidate for SR preparation, because large quantities of drug required for such a formulation.
- The relationship between response and plasma/blood concentration is relative concentrations which are in the plateau region of dose response relationship E.g. Thiazides in hypertension.
- The drug is metabolized to pharmacological active metabolites which are more slowly cleared than the parent drug. E.g. quinapril, trandolapril, venlafaxine.

Therapeutic range

Drugs that are highly potent such as cardiac glycosides should not be considered for SR/CR preparation due to loss in flexibility in dosage regimen and potential sudden dose dumping.

Drug concentration level in blood is not necessarily equal to the quantity of the released from a device because drug absorption is determined largely by its solubility and availability of local blood flow in tissues.

Even if drug concentration in plasma were to remain reasonably constant, short term fluctuations will always be seen due to factors like physical activities, emotional situations (stress), eating, and sleeping.

1.2.2 TARGETED DRUG DELIVERY [9]

Targeted drug delivery refers to systemic administration of drug carrier to deliver it to specific cell types, tissues, or organs.

- **RATIONALE FOR TARGETED DRUG DELIVERY**

Targeting is intended to increase the specific distribution of drug and hence combined with lower dosing, to increase the therapeutic profile of a compound.

Most drug after administration in a conventional immediate or controlled release dosage form freely travel throughout the body, typically leading to uptake by cells, tissues or organs other than where their pharmacological receptors are located.

REASONS FOR SITE-SPECIFIC DELIVERY OF DRUGS

Pharmaceutical

Drug instability and drug solubility.

Biopharmaceutical

- Low absorption
- High membrane binding
- Biological instability

Pharmacokinetics

- Short half-life
- Large volume of distribution
- Low specificity

Clinical

- Low therapeutical index
- Anatomical or cellular barriers

Commercial

- Drug presentation (dosage form)

Types of drug release from particle carriers:

The drug release from the particle carries may be mainly based on physicochemical factors, but biological factors can influence drug release.

The release may be based on the following principle

- Diffusion
- Iron exchange involving particle diffusion and leasching
- Surface erosion
- Total sphere disintegration due to enzyme attack.
- Control of membrane permeability by use of either pH , heat, microwave or magnetic property

1.2.3.MODULATED DRUG DELIVERY

Modulated release implies a drug delivery device that release the drug at a variable rate controlled by

- Environmental conditions
- Bio feed back
- Sensor input
- External control device.

1.3.MICROPARTICLE[7,8]

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects.

There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microsphere as carriers for drugs.

The microparticulate delivery systems are considered and accepted as a reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.

Microsphere are characteristically free flowing powders and received much attention not only for prolonged release, but also for targeting of anticancer drug to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics gene and genetic material, safe, targeted and effective in vivo delivery and supplements as miniature Versions of diseased organ and tissues in the body.

1.3.1. POLYMER EMPLOYED AS MICROSPHERES

Microsphere used usually are polymers.

They are classified into two types:

1. Synthetic polymers
2. Natural polymers

SYNTHETIC POLYMERS

- Poly methyl methacrylate
- Poly methyl methacrylate copolymer
- Poly methyl cyanoacrylate
- Poly isobutyl cyanoacrylate
- Poly hexyl cyanoacrylate
- Poly acrylamide
- Poly (Na, N-L- lysinediylterephthalamide)
- Poly D, L-lactide
- Poly acryl dextran
- Poly acryl starch
- Poly lactic acid
- Poly lactic acid-poly glycolic acid copolymers
- Ethyl cellulose
- Eudragit RL
- Eudragit RS

NATURAL POLYMERS

- Albumin
- Gelatin
- Collagen
- Agarose
- Carrageenan
- Chitosan
- Starch
- Poly dextran
- Poly starch

PREREQUISITES FOR IDEAL MICROPARTICULATE CARRIERS

The material utilized for the preparation of microparticulates should ideally fulfill the following prerequisites:

- Longer duration of action
- Control of content release of therapeutic efficacy
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Bioresorbability
- Targetability
- Polyvalent

1.3.2. METHODS OF PREPARATION[8,12]

Preparation of microsphere should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life. Controlled particle size and dispersability in aqueous vehicle for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and susceptibility to chemical modification.

1. SINGLE EMULSION TECHNIQUE

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers.

The chemical cross linking agents used are glutaraldehyde, formaldehyde, di acid chloride etc. heat denaturation is not suitable for thermolabile substance. Chemical cross linking suffers the disadvantages of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation

2. DOUBLE EMULSION TECHNIQUE

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers.

The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVP). This result in the formation of a double emulsion.

The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction.

3. POLYMERIZATION TECHNIQUES:

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

- Normal polymerization
- Interfacial polymerization

Both are carried out in liquid phase

Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes.

- In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization.
- Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives.

- Emulsion polymerization differs from suspension polymerization as due to the presence of initiator in the aqueous phase, which later on diffuses to the surface of micelles.
- Bulk polymerization has an advantage of formation of pure polymers.

Interfacial polymerization;

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

4. PHASE SEPARATION COACERVATION TECHNIQUE

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of nonsolvent results in the solidification of polymer.

The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerizes globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particle since there is no defined state of equilibrium attainment.

5**. SPARY DRYING AND SPARY CONGEALING :**

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon then removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.

The polymer is firs dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. the drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is the atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 µm.

Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Very rapid solvent evaporation, however leads to the formation of porous microparticles.

6. SOLVENT EVAPORATION:

Solvent evaporate method is widely used for the preparation of micro particles, involvers removal of the organic phase by evaporation of microparticles, involves removal of the organic phase by evaporation of the organic solvent. In this method, polymer is dissolved in organic solvent, and then the drug is either dissolved or dispersed in the polymer solution. Then the polymer-drug mixture is dispersed in liquid manufacturing vehicle phase with agitation to obtain appropriate sized microspheres.

The process variables include rate of evaporation of solvent, temperature cycles and agitation rates. Choice of vehicle phase and selection of solvent greatly influence the properties.

DRUG LOADING AND DRUG RELEASING KINETICS

Drug loading

The active components are loaded over the microspheres principally using two methods,

- During the preparation of the microspheres

  or

- After the formation of the microspheres by incubating the with the drug protein.

The active component can be loaded by means of

- Physical entrapment
- Chemical linkage
- Surface adsorption

The entrapment largely depends on

Method of preparation

Nature of the drug or polymer (monomer if used)

Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. cross linking agent, surfactant stabilizers, etc) heat of polymerization, agitation intensity etc.

DRUG RELEASE

Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micro-morphology of the carrier and the properties.

Many theoretically possible mechanisms may be considered for the release of drug from the microparticulates.

- Liberation due to polymer erosion or degradation
- Self diffusion through the pore
- Release from the surface of the polymer
- Pulsed delivery initiated by the application of an oscillating or sonic field.

The drugs could be released through the microspheres by any of the three methods Osmotically driven burst mechanism Pore diffusion mechanism Erosion or the degradation of the polymer

In osmotically driven burst mechanism, water diffuse into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is main controlled by three factors the macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres.

The pore diffusion method is named so because as penetrating water front continue to diffuse towards the core.

The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix

FACTORS AFFECTING DRUG RELELASE FROM THE PARTICULATE SYSTEM

- **DRUG**
  - Position in microspheres
  - Molecular weight
  - Physicochemical properties
  - Concentration
  - Interaction with matrix
- **MICROSPHERES**
  - Type and amount of matrix poly
  - Size and density of the microspheres
  - Extent of cross linking, denaturation or polymerization Adjuvants

- **ENVIRONMENT**
  - pH
  - polarity
  - presence of enzyme

Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, i.e. whether it is reservoir type where the drug is present as a core, or matrix type in which the drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients.

Matrix type system

Release profile of the drug from the matrix type of the device critically depends on the state of the dug whether it is dissolved or dispersed in the polymer matrix.

In case of the drug dissolved in the polymeric matrix, the amount of drug and the nature of the polymer affect the release profile.

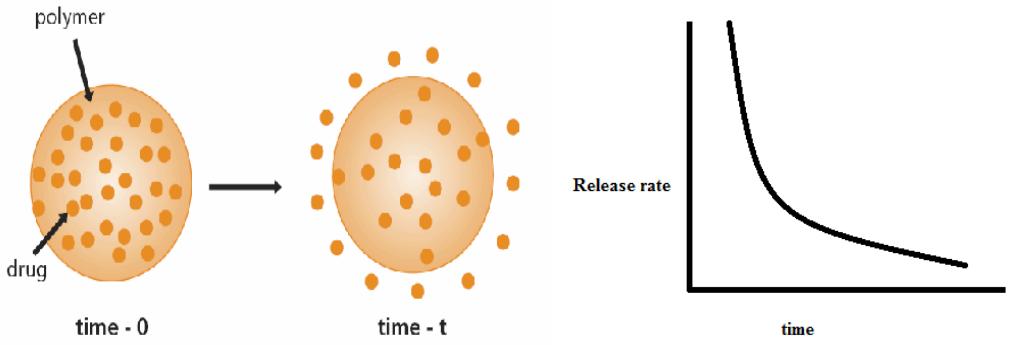

Figure 4: monolithic device and typical plot of drug release rate vs. time

Reservoir type system

Drug release from the reservoir type system with rate controlling membrane proceeds by first penetration of water through the membrane followed by dissolution of the drug in the penetrating dissolution fluid. The dissolved drug after partitioning through the membrane diffuses across the stagnant diffusion layer.

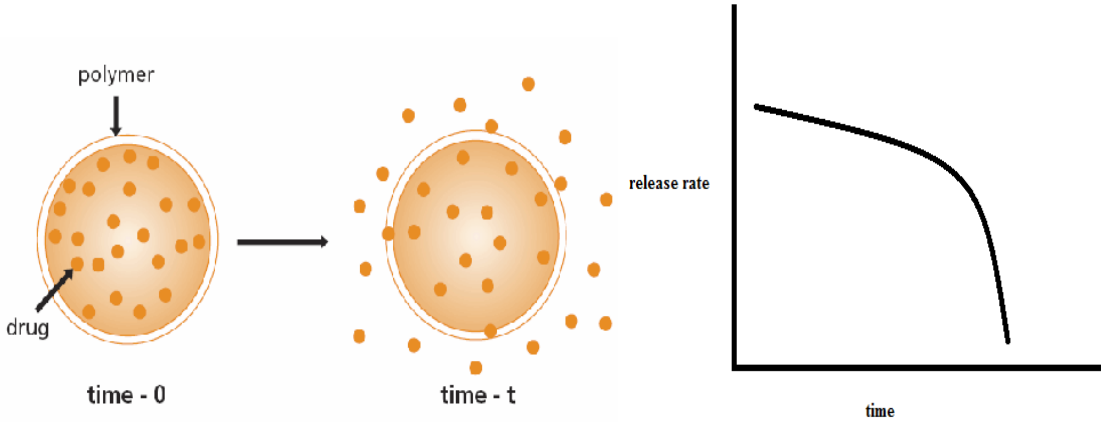

Figure 5: Reservoir device and typical plot of drug release rate Vs time

ADVANTAGES

Reliable means of deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.

Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.

Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.

Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor.

The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles *invivo.*

Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.

Blood flow determination: Relatively large microspheres (10-15 μm in Dm) are useful for regional blood flow studies in tissues and organs.

1.4. APPLICATIONS

1. Microspheres in vaccine delivery

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the required of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral rout may overcome the shortcoming of the conventional vaccine.

Microspheres as a carrier offer specific advances including:

- Improved antigenicity by adjuvant action
- Modulation of antigen release
- Stabilization of antigen

2. Targeting using microparticulate carriers

The concept of targeting i.e. site specific drug delivery is a well established dogma, which is gaining full attention. Placement of the particles indiscrete anatomical compartment leads their retention either because of the physical properties of the environment of biophysical interaction of the particles with the cellular content of the target tissue.

3. Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal

antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites.

The Mabs can be attached to microspheres by any o f the following methods

- Non specific adsorption
- Specific adsorption
- Direct coupling
- Coupling via reagents

4. Chemoembolisation

Chemoembilisation is an endovascular therapy, which involves the selective arterial embilisation of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent the theoretical advantage is that such embolisations will not only provide vascularocclusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour.

5.Imaging

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labeled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites.

6. Topical porous microspheres

Microsphonges are porous microsphere having myriad of interconnected voids of particle size range 5-300 µm. these microsponges having capacity to entrap wide range of active ingredients such as emollients fragrances, essential oils., are used as the topical carries system

7. Surface modified microsphere

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decreases their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance.

The most studied surface modifiers are :

- Antibodies and their fragments
- Proteins
- Mono-oligo- and polysaccharides
- Chelating compounds (EDTA, DTPA OR Desferroxamine)

1.5. PHYSICOCHEMICAL EVALUATION

CHARACTERIZATION

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

Table 1: METHODS FOR CHARACTERIZATION OF MICROSPHERES

SI.No	Parameter	Method
1.	Particle size and shape	Light microscopy (LM) Scanning electron microscopy (SEM) Conflocal fluorescence microscopy Laser light scattering Multi size coulte counter
2.	Surface elemental analysis	Electron spectroscopy ATRFT-IR
3.	Density	Helium compression pychnometry
4.	Crystallinity	x-ray diffraction differential Scanning calorimetry
5.	Surface charges	Electrophoresis Laser Doppler anemometry
6.	Hydrophobicity	Hydrophobic interaction chromatography Angle of contact measurement
7.	Molecular weight	Gel chromatograpy
8.	*Invitro* methods	Beaker method Interface diffusion method USP dissolution apparatus

1.6. ROUTES OF ADMINISTRATION OF MICROSPHERES

Microspheres can be administered through different routes such as oral, parentral, ocular etc.

Peroral administration

Microspheres can be designed for controlled release to the GI tract, the release of drug depend on the size of microparticles and the drug content within the microspheres. Microspheres of mucoadhesive polymer get attached to the mucus layerin GIT and hence prolong the gastric residence time and functionally offer a sustained drug release.

Parentral administration

Microspheres given by intravenous route distribute themselves according to their size range. The microparticulate carriers are rapidly cleared from the circulation mainly by means of RES system.

Ocular

Microparticulate system is a novel approach to increase the retention time of drug delivery device by changing them to gel form in the cul de sac of the eye.

Intranasal

Intranasal route is exploited for the delivery of peptides and proteins. The conventional dosage forms are rapidly cleared from the nasal mucosa. Bioadhesivemicrosphere have greater control over the surface character and the release pattern.

1.7. HYPERTENSION[11,12]

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as high blood pressure or shortened to HT, HTN or HPN. The word “hypertension”, by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either essential (primary) or secondary, Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure. It is common. About 90-95% of hypertension is essential hypertension. Secondary hypertension indicates that the high blood pressure is a result of (i.e., secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma).

Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated. Beginning at a systolic pressure (which is peak pressure in the arteries, which occurs near the end of the cardiac cycle when the ventricles are contracting) of 115 mmHg and diastolic pressure (which is minimum pressure in the arteries, which occurs near the beginning of the cardiac cycle when the ventricles are filled with blood) of 75 mmHg (commonly written as 115/75 mmHg), cardiovascular disease (CVD) risk doubles for each increment of 20/10 mmhg.

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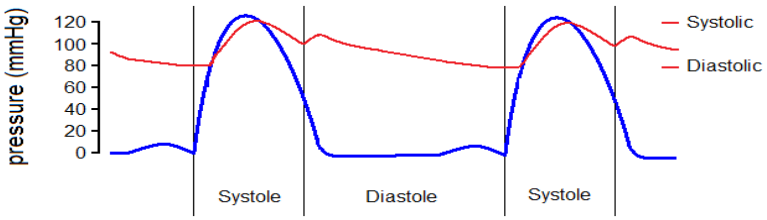


Figure 6: The variation in pressure in the left ventricle (blue line) and the aorta (red line) over two cardiac cycles ("heart beat"), showing the definitions of systolic and diastolic pressure.

A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is a common occurrence among the elderly. These readings are based on the average of seated blood pressure readings that were properly measured during 2 or more office visits. In individuals older than 50 years, hypertension is considered to be present 90 mmHg diastolic. Patients with blood pressures over 130/80 mmHg along with Type 1 or Type 2 diabetes, or kidney disease require further treatment.

Table 2: Classification of hypertensions

Classification	Systolic pressure		Diastolic pressure	
	mmHg	kPa (kN/m^2)	mmHg	kPa (kN/m^2)
Normal	90-119	12-15.9	60-79	8.0-10.5
prehypertension	120-139	16.0-18.5	80-89	10.7-11.9
Stage 1	140-159	18.7-21.2	90-99	12.0-13.2
Stage 2	=160	=21.3	=100	=13.3
Isolated systolic hypertension	=140	=18.7	<90	<12.0

Resistant hypertension is defined as the failure to reduce blood pressure to the appropriate level after taking a three-drug regimen (include thiazide diuretic)

Excessive elevation in blood pressure during exercise is called exercise hypertension. The upper normal systolic values during exercise reach levels between 200 and 230 mmHg. Exercise hypertension may be regarded as a precursor to established hypertension at rest.

SIGNS AND SYMPTOMS

Mild to moderate essential hypertension is greatly asymptomatic. Accelerated hypertension is associated with headache, somnolence, confusion, visual disturbances, and nausea and vomiting (hypertensive encephalopathy). Retinas are affected with narrowing of arterial diameter to less than 50% of venous diameter, copper or silver wire appearance, exudates, hemorrhages, or papilledema. Some signs and symptoms are especially important in infants and neonates such as failure to thrive, seizure, irritability or lethargy, and respiratory distress. While in children hypertension may cause headache, fatique, blurred vision, epistaxis, and bell palsy.

Sign and symptoms associated with pre-eclampsia and eclampsis, can be proteinuria, edema and hallmark of eclampsia which is convulsions, other cerebral signs may precede the convulsion such as nausea, vomiting, headaches, and blindness.

Initial assessment of the hypertensive patient should include a complete history and physical examination to confirm a diagnosis of hypertension. Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. elevated arterial pressure, headache. dizziness, palpitations, easy fatigability and impotence.

Angina pectoris [40]

Angina pectoris, or just angina, is temporary chest pain or discomfort caused by decreased blood flow to the heart muscle. Because of the decreased flow of blood, there is not enough oxygen to the heart muscle resulting in chest pain. Coronary artery disease , which can result in narrowing of the coronary arteries that carry blood and oxygen to the heart muscle, is one of the most common causes of angina. While angina is not a heart attack, it does signal an increased risk for a heart attack. Seek immediate medical attention if you experience any chest pain or discomfort.

There are two main types of angina

- stable

- unstable.

Stable angina, the most common type, develops during physical activity and usually lasts a short time (approximately five minutes or less) if the physical activity has ended. Unstable angina is less common and usually occurs during periods of rest. Unstable angina usually lasts longer and symptoms may be more severe.

Symptoms of angina include:

Chest pain or discomfort, such as tightening of the chest

Discomfort in the jaw, neck, arms, upper abdomen, shoulder or back

Fatigue, Sweating, Nausea, Dizziness

Diagnosing and evaluation

In order to diagnose the cause of angina, the following tests may be performed:

- Electrocardiogram (ECG)

- Blood tests
- Chest x-ray
- CT of the chest
- Coronary computed tomography (CT) angiography
- Magnetic resonance (MR) imaging/angiography
- Catheter angiography
- Echocardiogram
- Coronary artery bypass graft surgery (CABG)

DRUG PROFILE

AMLODIPINE BESYLATE

Chemical formula

A) 3-Ethyl 5-methyl ?(4RS-2-[(2-aminoethoxy)]-4-(2-chlorophenyl-6-methyl-1,4-dihydropyridien-3,5-dicariboxtlate benzensulphate.

OR

B) 3-ethyl 5-methyl 2-(2-aminomethoxymethyl)-4(chlorophenyl)-q,4-dihydro6-methylpyridine-3,5-dicarboxylate monobenzenesulphonate.

Chemical structure

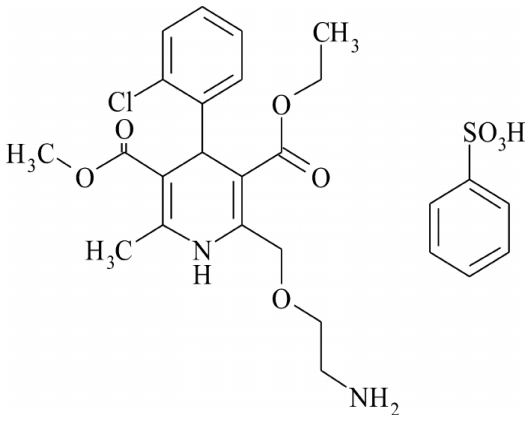


Figure 7: Structure of Amlodipine Besylate

Empirical formula	**:**	$C_{26}H_{31}CLN_2O_8S$
Molecular weight	**:**	567.1
Description	**:**	White or almost white powder
Melting point	**:**	195-2040°

Solubility	**:**	Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.
Therapeutic category:		Anti –anginal, Anti-hypertensive
Half life	**:**	30 – 35 hours

Mechanism of action:

Amlodipine besylate is a calcium channel blocking agent. It inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased after load. Another possible mechanism is that amlodipine inhibits vascular smooth muscle carbonic anhydrase activity with consecutive pH increase which may be involved in intracellular calcium influx through calcium channels.

Pharmacokinetics:

Absorption:

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hour post dose. Absolute bioavailability has been estimated to be between 60 and 80 %

Distribution: *In-vitro* studies have shown that approximate 97.5% of circulating amlodipine is bound to plasma proteins.

Metabolism: Amlodipine is extensively metabolized by the liver to inactive metabolites

Excretion: 10% of the parent compound and 60% of metabolites excreted in the urine

Indications: Hypertension and prophylaxis of angina.

Dosage and administration:

Adult recommended starting dose: 5 mg once daily with maximum dose 10 mg once daily. Small, fragile, or elderly patients or patients with hepatic insufficiency may be started on 2.5 mg once daily. Pediatric staring dose: 2.5 mg to 5 mg once daily.

Side effects:

- Amlodipine besylate may cause the following side effects. Most side effects are mild or moderate.
- Headache
- Swelling of legs or ankles
- Tiredness, extreme sleepiness
- Stomach pain, nausea
- Dizziness
- Flushing (hot or warm feeling in your face)
- Arrhythmia (irregular heartbeat)
- Heart palpitation (very fast heartbeat)

EXCIPIENTS PROFILE

Ethyl cellulose[17]

Structural formula

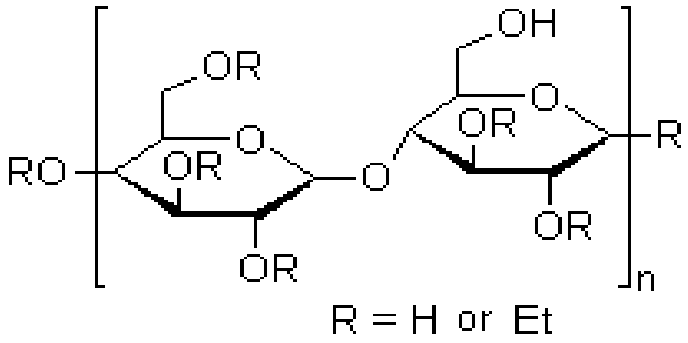


Figure 8: Structure of Ethyl Cellulose

Nonproprietary names

Bp : Ethylcellulose

PhEur : Ethylcellulose

USP : Ethylcellulose

Synonyms:

Aquacoat ECD; Aqualon; Ashacel; E462;Ethocel; Ethylcellulosum; Surelease.

Chemical name and CAS Registry Number

Cellulose ethyl ether

Empirical formula and Molecular weight

Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where n can vary to provide a wide

variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkage

Functional category

- Coating agent
- Flavouring agent
- Tablet filler
- Viscosity increasing agent

Applications in pharmaceutical formulation or technology:

Used in microencapsulation, sustained-release tablet coating, tablet coating, tablet granulation

Description

Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder

Typical properties

Density (bulk): 0.4/cm3

Glass transition temperature 129– 133 degree C (26)

Moisture content:

Ethylcelllulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

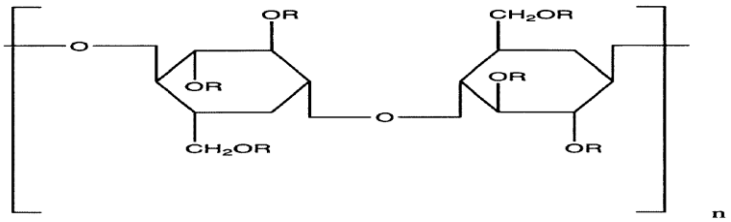
Solubility:

Ethylcellulose is practically insoluble in glycerin propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxy groups is freelysoluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Specific gravity	**:**	1.12-1.15g/cm3
Viscosity	**:**	46 cP, 5 % in toluene/ethanol 80:20
Density	**:**	1.4 g/ml at 25 ºC lit
Uses	**:**	used as thin film coating material for coating paper, vitamin and medical pill and thickeners in cosmetics and in industrial process and also used in food additives.

Hydroxyl Propyl Methyl Cellulos

Structural formula:



formula (II)

Figure 9: Structure of HPMC

Chemical name : cellulose hydroxyl propyl methyl ether.

Molecular mass **:** $OCH_2CH(OH)CH_3$

Molecular weight **:** 10,000-1500000

Melting point **:** 190-200°C

Physical state **:** HPMC is an odorless & tasteless or creamy white fibrous or granular powder.

Solubility:

Soluble in cold water, forming a viscous colloidal in soluble in hot water, chloroform, ethanol, dichloromethane, mixtures of water &alcohol.

Incompatibilities:

Incompatible with some oxidizing agents, organic ions to form insoluble precipitates.

Stability and storage conditions:

It is a stable, although it is hygroscopic after drying.

Stored in well closed container, in a cool & dry place.

Functional category:

- Bio adhesive material, coating agent, controlled release agent, film former, emulsifier, solubilizing & stabilizing agent, tablet binder, thickening agent.

Application of pharmaceutical formulation/ Technology

- It is widely used in oral, ophthalmic, nasal &topical pharmaceutical formulations.
- Tablet binder in film coating and as a matrix in extended release tablet formulations.
- In liquid orals which is used as a suspending or thickening agent.
- Lower viscosity grades are used in aqueous film coated solution, while higher viscosity grades are used with organic solvent.
- It is also used in cosmetic and food products.

Poly Vinyl Pyrrolidine

Structural Formula

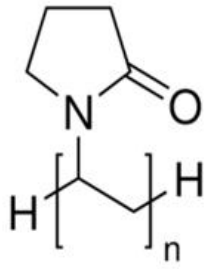


Figure 10: Structure of Poly Vinyl Pyrolidine

Nonproprietary Names **:** BP: Povidone, USP: Povidone

Synonyms **:** E1201, Kollidone, Plasdone, Polyvinylpyrrolidone.

Chemical name and

CAS Registry number **:** 1-ethyenyl-2-pyrrolidinone homopolymer [9003-39-8]

Emperical formula

& Molecular weight **:** $(C_6H_9NO)n$, 2500-3000,000

Functional category : Tablet binder, disintegrant, dissolution enhancer, suspending agent.

Applications in pharmaceutical formulation or technology:

Povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid dosage forms. In tableting povidone solutions are used as binders in wet granulation process. It is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydro alcoholic solutions. 0.5 – 5 % concentration is used in tablet binder.

Description:

Povidone occurs as a fine, white to creamy-white coloured, odorless, hygroscopic powder.

Stability & storage condition:

Povidone may be stored at a under ordinary without undergoing decomposition or degradation. Since the powder is hygroscopic, it should be stored in a air tight container in a cool, dry place.

Incompatibilities:

It is compatible in solution with a wide range inorganic salts, natural & synthetic resins & other chemicals

Eudragit RS 100

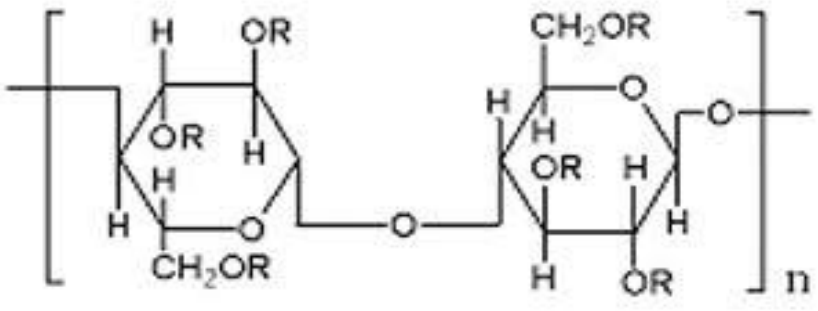


Figure 11: Structure of Eudragit RS 100

Eudragit RS 100 is copolymer of methacrylic acid estrs containing an amount of quarternary ammonium groups between 4.5 – 6.8%. Eudragit RS 100 is insoluble in water and digestive juices, but permeable and has pH-independent release profiles.

Class	**:**	"Ammonio Methacrylate Copolymer Type B" Ph.Eur.
Molecular weight	**:**	150,000.
Solubility	**:**	Miscible with methanol, ethanol and isopropyl alcohol (containing approx.3%water), as well as in acetone, cholorform, ethyl acetate and Methylene chloride in a ration of 1:1
Viscosity	**:**	Max. 15 mpa.s
Stability	**:**	stable under ordinary conditions of storage
Storage	**:**	protect from warm temperatures and against moisture. Keep in tightly closed containers.

Uses **:** Time-controlled release of active ingredients .

Therapeutically customized release profiles

Higher patient compliance due to reduced number of doses to be taken.

Applications :

1. Simple taste masking through gastric resistance to controlled drug release in all section of the intestine insoluble but permeable in digestic fluids.
2. Eudragit RS 100 polymer with alkaline enable controlled time release of the active ingredient by pH- indipendent swelling .
3. Delayed and sustained drug release.

LITERATURE REVIEW

Swethakallepu, et al.[19], have been reported a work on the Formulation and evaluation of Gastro Retentive Floating Microsphere of Nimodipine, The microsphere was prepared by solvent evaporation method. The result of *in-vitro* dissolution study. Microsphere was characterized for their micromeritic properties, floating behavior, entrapment efficiency, scanning electron microscopy (SEM), X-ray diffraction, differential scanning colorimetry, and *in-vitro* drug release it showed good flow properties. Size ranges of (90±1.02)-(145±1.34)µm. Microsphere were capable to float for 12 h. It can be concluded that the developed formulation is potential dosage form for nimodipine.

Joselinjoseph,et al[20]**,** have been studied the formulation and evaluation of floating microsphere of pantoprazole sodium. The floating microsphere of pantoprazole sodium wereprepared by solvent evaporation method using HPMC K 15 and ethyl cellulose as polymer. Seven different formulations were developed. The developed floating microspheres were evaluated for, percentage yield, particle size, entrapment efficiency, *in-vitro* buoyancy, scanning electron microscopy and drug release. Results show that as the concentration of polymer ethyl cellulose increase it affects the particle size, percentage yield, in vitro buoyancy and drug release of microsphere. The floating microsphere of pantoprazole sodium cane successfully designed for controlled drug delivery dosage forms.

Megha Sharma et al[21]**,** have reported the formulation, optimization, characterization and *in-vitro*evaluation of floating microsphere of Repaglinide. Drugs that are easily absorbed from the gastrointestinal tract (GIT)and having short half life are eliminated quickly from blood circulation and need frequent dosing such Repaglinide. Floating microsphere of Repaglinide was prepared by using ethylcellulose (EC) alone and in combination with HPMC by solvent diffusion-evaporation technique. Increase in stirring rate slightly increases the drug release and was found to be in the range of 70.2-86.3% for EC whereas 78.6-86.4 for EC:HPMC formulations. The mechanism of drug release was studied and

found to follows first order kinetics. The regression of optimized formulation were found to be 0.926 (E6) and 0.955 (H9).

NavneetGarud et al[22]**,** have reported the preparation and *in-vitro* evaluation of Metformin Microspheres using Non-Aqueous solvent Evaporation Technique. The effect of process variable, viz, drug polymer ration, stirring rate and type of polymer on the mean particle size drug entrapment efficiency, yield, drug content. It was observed that as the stirring speed increased from 600 to 1800 rpm, microsphere size decreased and hence drug release rate increased. Drug release rte at 1:2 drug:polymer for microspheres produced at a stirring rate of 1200 rpm. The formulation exhibited maximum prolonged drug release at gastrointestinal pH or atleast 15 h.

Ramesh Y.,et al[23]**,** have been prepared and evaluated the floating microspheres with Norfloxacin as model drug for prolongation of gastric residence time. The microspheres were prepared by the Non-Aqueous solvent diffusion method using polymers HPMC and EC SEM analysis. In vitro drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of the stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (10 h) and remained buoyant for > 12 h. the mean particle size increased and the drug release rate decreased at higher polymer concentration.

Vinodkumar et al[24]**,** have been studied the formulation and evaluation of floating microsphere of Ranitidine Hydrochloride. It inhibited histamine stimulation and gastirin stimulated acid secretion. The microspheres of each batch were subjected to various physiochemical studies i.e. particle size, bulk density, % yield, % buoyancy, drug entrapment efficiency etc. The compatibility of the drug with selected polymers was determined by FTIR spectrophotometric studies using FTIR Affinity -1. Thin layer was performed and studied comparative to the pure drug and its micro spherical formulations.

Mulugeta Fentie., et al[25]**,** have been studied the formulation of sustained release floating microsphere of furosemide from EC and HPMC polymer blends. Furesemide is a potent and commonly used loop diuretic. It is absorbed largely in the stomach hand upper small intestine. This narrow absorption window is responsible for its low bioavailability of about 50 % and variable and erratic absorption. Microspheres were prepared by the solvent evaporation method. The drug entrapment ranging from 86.2 % to 98.4%. Floating microsphere that effectively sustain the drug release more than 12 h and exhibit buoyancy of greater than 77% in 12 h were developed.

Mazumder.R., et al[26]**,** have been reported the formulation and evaluation of floating microsphere of amlodipine besylate. The floating microsphere were evaluated for size of microsphere, entrapment efficiency, swelling index, buoyancy studies and *in-vitro* release studies. The result indicated the optimized intragastric floating microsphere (F8) exhibited 97% release in 8 hrs. While the buoyance lag time was 20 sec and the intragastric floating microsphere remain buoyant for 20 hrs. *In vitro* drug release kinetics evaluated using the linear regression methods was using found to follow the Zero order kinetics. Optimized intragastric floating microsphere showed no significant change after storage at 40°C/75% relative humidity for 1 month.

SurendranathBetala.,et al[27]**,** have formulated the metoprolol sustained release microspheres. It was prepared by Ionic-Gelation method. The microspheres were evaluated for various characteristics like encapsulation efficiency, percentage yield, partial size and the *in vitro* release for 12 hours. The microspheres were found to be discrete, spherical and free-flowing. The microspheres were uniform in size, and the microencapsulation efficiency was in the range of 91.7% Microspheres had good spherical geometry.

Avinash Y Kaushik.,et al[28]**,** have prepared the valsartan floating microspheres and studied it's*in-vitro* characterization. solvent evaporation emulsification method using two polymers ethylcellulose and eudragit in different concentration and two different

surfactant poly vinyl alcohol and tween 80. *In-vitro* release and stability of formulation were also conducted. The valsartan floating microspheres F4 and F7 formulations followed first order kinetics and F8 formulation followed*higuchi* drug release kinetics with erosion as the dominant mechanisms of drug release. Ethylcellulose with poly vinyl alcohol and eudragit with tween 80 were formulations with good physical appearance. less concentration of polymers gives uniform floating microspheres in aspect of particle size, good floating ability and good flow property.

SurendranthBetala., et al[29]**,** have formulated and evaluated the sustained release microspheres of propranolol. Microspheres are prepared by Ionic-Gelation method using HPC & EC and sodium CMC for sustained release oral sustained dosage form was developed. The microspheres were evaluated for various characteristics like encapsulation efficiency, percentage yield, percentage size and the In vitro release for 12 hrs. The microspheres were found to discrete, spherical, and free-flowing. The microspheres were uniform in size, and the microencapsulation efficiency was in the range of 52.5-81.7% microspheres had good spherical geometry.

Sigimol Joseph et al[30]**,** describes the preparation of microspheres by solvent evaporation followed by *in-vitro* characterization of microspheres to evaluate the effect of method of preparation on physical properties and drug release profile of microspheres. *In-vitro* drug release rate for a microsphere was found to be sustained over 24 hours. Hence, it can be concluded that the Formulation prepared by solvent evaporation method, has potential to deliver Losartan potassium in a controlled manner in a regular fashion over extended period of time in comparison to all other formulations and can be adopted for a successful oral delivery of losartan potassium for safe management of hypertension.

Sharma Tejal et al[31]**,** prepared a floating drug delivery system of ranitidine. It was prepared by solvent evaporation (oil-in-water emulsion) technique using HPMC and EC as the rate controlling polymers. Particle size analysis, drug entrapment efficiency, surface topography, buouancy percentage and release studies were performed. Result

showed that the polymer ratio and stirring speed affected the size, incorporation efficiency and drug release of microspheres (>12 h), floating time (>12 h) and the best results were obtained at the ratio of HPMC:EC (1:6). The particle size of microspheres increased by the drug release rate from the microspheres decreased as the polymer concentration increased. So it is used for prolonged drug release in stomach for at least 12 hrs.

ShardenduPrakash et al[32]**,** was studied the development of floating microsphere of Gliclazide in order to achieve and extended retention in the upper gastrointestinal tract, The prepared microspheres were evaluated for particle size, micromeritic study, drug entrapment efficiency, in vitro buoyancy, swelling index and in vitro release & good flow properties. SEM confirmed spherical structure of the prepared microspheres. The best formulation F3 drug release kinetics were evaluated using Zero order, First order Higuchi model, Korsmeyer – Peppas model. It was observed that the Korsemeyer – Peppas model has a higher regression coefficient values indicating that the drug release was based on the erosion of polymeric chain matrix.

Shajijessy et al[33]**,** was developed the aceclofenac microsphere for floating pulsatile release intended for chronopharmacotherapy by emulsion solvent diffusion technique. The best batch exhibited a high entrapment efficiency of 90.1 % and mean particle size 118.66µm. polymers used for the preparation were Eudragit L100 and Eudragit S100 which gets solubilized at pH above 6 and 7 respectively. The floating microsphere provide two phase patter with initial lag time during floating in acidic medium followed by rapid release in phosphate buffer. This approach suggested the use of floating pulsatile microsphere as promising drug delivery for site and time specific release fromchronotheraphy of rheumatoid arthritis.

KaminiVasava et al[34]**,** was prepared a floating drug delivery system of Cephalexin. By emulsion solvent technique. Particle size analysis, drug encapsulation efficiency, surface topography, buoyancy percentage and release studies were performed. Results showed

that the polymer concentration and stirring speed affected the size, incorporation efficiency and drug release of microspheres (< 12 h) and its floating time (>12 h). The best results were obtained at the ratio of drug:EC (1:6). The mean particle size of prepared floating microspheres increased by the drug release rate from the microspheres decreased as the polymer concentration increased. Used for prolonged drug release in stomach for at least 12 hrs, thereby improving the bioavailability, prevents degradation in stomach and patient compliance.

Kapilkumar and AK Rai et al[35] were prepared and evaluate floating microspheres of curcumin for prolonged gastric residence time and increased drug bioavailability. Emulsion solvent method, using HPMC, EC, Eudragit S 100 polymer varying ratio. It was evaluated for flow properties, particle size, incorporation efficiency, as well as in-vitro floatability and drug release. The shape and surface morphology of the microsphere by optical SEM. The floating microspheres showed particle size, buoyancy, drug entrapment efficiency and yield in the ranges of 251 – 387 µm, 74.6 – 90.6 % and 45.5 – 82.0 %, respectively. Maximum drug release after 20 h was 47.1, 55.7, 69.4 and 81.3% for formulations F1,F2,F3 and F4, respectively. SEM

Swapnila V Shinde (Vanshiv) et al [36]**,** were develop the floating microspheres of Domperidone by emulsion solvent diffusion method using HPMC K 4 M, Ethyl cellulose. *In-vitro* drug release, FT-IR. The yield, particle size, buoyancy percentage, drug entrapment efficiency, and microspheres yielded 62.40 – 89.49 %. The particle size was distributed between 147 – 282.11 µm, Drug entrapment efficiency was 54.4 – 64.48 %, and Buoyancy percentage was 71 -87%. The best drug release profiles were seen with formulation F1 at the ratio of drug to polymer of, 1:1..

M. Najmudiin et al[37]**,** was prepared the floating microspheres of ketoprofen using Eudragit S 100 and Eudragit L 100 as polymer. Bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. It was prepared by emulsion solvent diffusion method using

Eudragit S 100 and Eudragit L 100 as polymer. Micromeritic properties, particle size, percentage yield, *in-vitro* buoyancy, incorporation efficiency, drug polymer compatibility (IR study), SEM and drug release of microspheres. Formulation EU_2 prepared with Eudragit S 100 drug:polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, *in-vitro* buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs.

ShankraiahM et al.[38], studied the development of new intra-gastric floating microspheres by emulsion solvent evaporation technique. The drug was encapsulated with HPMC and Eudragit S 100 in different polymers ratios. i.e. 1:1, 1:2, 1:3 prepared microspheres were evaluated for % entrapment, particle size, Buoyancy, dissolution study and drug release kinetics. The % yield of microspheres was high in HPMC batches over Eudragit RS 100 batches. The particle sizes of microspheres was increased by increasing the polymer concentration. % buoyancy of microspheres,63.38%-75.58% Microspheres of levofloxacin with HPMC showed enhanced release rate when compared to levofloxacin with Eudragit S 100.

Yuveraj Singh et al[39], were prepared and evaluated the floating microspheres of verapamil hydrochloride. Cellulose acetate, acrycoat S100 and eudragit S100 microspheres loaded with verapamil hydrochloride were prepared by solvent diffusion – evaporation method. Smooth surfaces, free-flowing and good-packing properties. The yield of was up to 70.51% and cellulose acetate microspheres entrapped the maximum amount of the drug. SEM confirmed their hollow structures with sizes in the range 251.80 to 350.75 µm. Microspheres exhibited prolonged drug release and remained buoyant for more than 12 h. radiographic images of dog stomach revealed that cellulose acetate microspheres loaded with barium sulphate floated on the gastric fluid for about 3.2 h. *In vitro* release studies demonstrated non-fickian diffusion of drug from the microspheres.

AIM AND SCOPE OF STUDY

- The purpose of this research work was to develop a novel retentive floating microsphere of amlodipine besylate.

- Amlodipine besylate has maximum solubility in acidic pH and thus most suitable to prolong release of drug in stomach so an attempt has been made to sustain the drug release by incorporation suitable polymers such as ethylcellulose and PVP.

- In the form of gastro retentive floating microspheres which after oral administration are designed to provide. The desired controlled and complete release of drug for prolonged period of time in the treatment of calcium channel block and used in the treatment of hypertension and angina pectoris. The maintenance of constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic response. Amlodipine besylate is used in the treatment of several disease of the cardiovascular system, especially hypertension.

- The main aim of the present study is to develop sustained release Amlodipine besylate Microsphere using Ethylcellulose , HPMC, PVP, Eudragit RS100 polymers by solvent evaporation method and to evaluate the suitability and potentiality of this sustained release drug delivery system through the determination of drug loading capacity, entrapment efficiency, flow properties and *in-vitro* release characteristic studies.

- Amlodipine besylate has half life of 30 to 35 hours. Multiple dosing needed to maintain a constant plasma concentration for a good therapeutic response and to improve patient compliance. This result in the frequent administration of a drug with higher dose causes unwanted side effects and dose dumpling. Microspheres are one of the promising drug delivery system to deliver the drug at a controlled rate over the period of time.

- Among various polymers, ethylcellulose, HPMC, PVP, Eudragit RS 100 are used in the formulation. Eudragit RS 100 is water insoluble and widely used as a wall material to sustain the drug release; this is due to its biocompatibility, good stability, easy of fabrication.

- Among the various method of preparation, solvent evaporation method has gained much attention due to its ease of fabrication without compromising the activity of the drug.

PLAN OF WORK

I. PREFORMULATION STUDIES

(i) Determination of solubility profile of Amlodipine besylate.

(ii) Compatibility studies (FT-IR)

II. FORMULATION OF AMLODIPINE BESYLATE FLOATNG MICROPARTICLE

III. EVALUATION OF AMLODIPINE BESYLATE FLOATING MICROPARTICLE

1. Determination of Percentage yield
2. Micromertic Properties
   - (i) Angle of Repose
   - (ii) Bulk Density and Tapped Density
   - (iii) Compressibility Index
   - (iv) Hausner's Ratio
3. Particle Size and Morphology Analysis (SEM)
4. Swelling Index (%)
5. Percentage of Drug content/ Drug loading amount (%)
6. Percentage of Drug entrapment (%)
7. *In-vitro* Buoyancy studies
8. *In-vitro* Drug Release

IV. STABILITY STUDIES

Stability studies for initial and after one month at 40^{o} C$\pm$ 2 and 75 % $\pm$ 5 % RH.

MATERIALS AND EQUIPMENTS

Table 3: MATERIALS

S.NO	CHEMICAL/MATERIAL	SOURCE
1	Amlodipine besylate	GIFT SAMPLE, Sai Meera Pharma, Chennai.
2	Ethylcellulose	S.D fine chemicals Ltd.
3	HPMC	S.D fine chemicals Ltd.
4	PVP	S.D fine chemicals Ltd.
5	Eudragit RS 100	S.D fine chemicals Ltd.
6	Ethanol	S.D fine chemicals Ltd.
7	Sodium lauryl sulphate (0.1%)	S.D fine chemicals Ltd.
8	Dichloromethane	S.D fine chemicals Ltd.

Table 4: EQUIPMENTS

S.NO	NAME OF THE INSTRUMENT	COMPANY
1	Mechanical stirrer	Remi equipment
2	UV spectrophotometer	Jasco V530
3	Optical microscope	Olympus
4	FT-IR Spectrophotometer	Karunya university, coimbatore
5	Scanning electron microscopy	Karunya university, coimbatore
6	Magnetic stirrer	Remi equpiments, Mumbai
7	Dissolution apparatus	Veego , VDA 6DR USP apparatus

METHODOLOGY

I. PREFORMULATION STUDIES

a. Solubility Profile

Determination of solubility profile of amlodipine besylate. The solubility profile of the selected drug (Amlodipine besylate) was determined.

Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

b. Fourier transform Infra-red spectroscopy

I.R. spectroscopy can be used to investigate and predict any physiochemical interactions between difference components in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients.

The aim of the present study was to find out the possible interaction between selected polymer, ethylcellulose, HPMC, PVP, Eudragit RS 100 and the drug Amlodipine besylate and also identify the compatibility between the drug and polymer.

10 mg of sample and 40 mg of KBr was taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet marker and was compressed at 10 kg/cm^2 using hydraulic press. The pellet was kept in a sample holder and scanned from 4000 cm-1 in Perkin Elmer FT-IR spectrophotometer.

Samples were prepared for pure polymer, pure drug, physical mixture of drug and polymer and drug loaded microparticles. The spectra obtained for these samples were compared and interpreted for the shifting of major functional peaks and disappearance of functional peaks if any.

II. FORMULATION OF AMLODOIPINE BESYLATE FLOATING MICROPARTICLES

In this present study, solvent evaporation technique was employed for preparation microsphere formulation. Amlodipine besylate microparticles were prepared by dissolving polymer ethylcellulose and HPMC in ethanol and dichloromethane. Then the drug amlodipine besylate was added to the polymer solution. The resulting mixture was then added drop by drop into 0.1% sodium lauryl sulphate while stirring continuously. Stirring rate was constant at 900 rpm and continued for 30 minutes until organic solvent evaporated completely.

The dispersed drug and polymer were transferred into fine droplets, which subsequently solidified into rigid microparticles due to solvent evaporation. The microparticles formed were collected by filtration, and washed 4 to 5 times with distilled water and dried at room temperature for 24 hours.

Nine batches of drug loaded microparticles were prepared by keeping drug ratio constant altering the different polymer with different ratio and formulations code as F_1,F_2,F_3,F_4,F_5,F_6,F_7,F_8,F_9.

S. No	Incredients	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Drug**	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
2	**Ethylcellulose**	0.5 g	4 g	0.3g	0.3	0.3 g	-	2 g	-	1 g
3	**HPMC E 50**	0.3g	0.3g	4 g	-	-	4 g	-	1 g	-
4	**Chitosan**	-	-	-	-	2 g	2 g	-	-	-
5	**PVP**	-	-	-	-	-	-	-	2 g	2 g
6	**Eudragit RS 100**	-	-	-	-	-	-	0.5 g	-	-
7	**Ethanol**	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml
8	**Dichloromethane**	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml
9	**Sodium lauryl sulphate (0.1%)**	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

Table 5: Formulation of Amlodipine Besylate Microparticles

III. PREPARATION OF STANDARD GRAPH OF AMLODIPINE BESYLATE USING PHOSPHATE BUFFER pH 7.4

Preparation of stock solution

10 mg of accurately weighed drug was dissolved and diluted to 100 mil with phosphate buffer pH 7.4 to produce 100 µg/ml.

Preparation of sample solution

Different dilutions of stock solution with phosphate buffer were made to obtain solution having concentration 5,10,15,20,25,30 µg/ml. absorbance was measured at 360 nm against phosphate buffer pH 7.4 as blank, using UV systronics-2202 spectrophotometer.

A standard curve was plotted with concentration on X-axis and absorbance on Y-axis.

IV. EVALUATION OF AMLODIPINE BESYLATE MICROPARTICLES

Actual drug content of microparticles was determined by UV-spectrophotometer (systronics-2202) 50 mg equivalent of drug loaded microsphere were dissolved in chloroform and extracted with 50 ml of phosphate buffer 7.4 and then analyzed at 360nm

a. Entrapment efficiency (%) = $\frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$

Buoyancy test

Microparticles (0.3g) were spread over the surface of a USP dissolution apparatus (type II) filled with 900 ml 0.1 mol. Hcl containing 0.01 % Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 8 hrs. The floating and the settled portion of floating microparticles were recoverd separately. The floating microparticles

were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the floating microparticles that remained flaoting and the total mass of the floating microparticles

$$\text{Percentage buoyancy} = \frac{\text{Microparticles remained floating}}{\text{Total mass of floating microparticles}} \times 100$$

$$\text{Drug loading (\%)} = \frac{\text{Actual drug content}}{\text{Weight of Microsparticles}} \times 100$$

$$\text{Percentage yield (\%)} = \frac{\text{Weight of Microsphere}}{\text{Total expected weight of Drug and polymer}} \times 100$$

Particle size and Morphology analysis

The particle size of microparticles was determined using optical microscopy method. Approximately 100 microparticles were counted for particle size using a calibrated optical microscope

Surface morphology of microsphere was determined by Scanning Electron Microscope (SEM). The microparticles were coated uniformly with gold-palladium by using Sputter Coater, after fixing the sample in individual stabs.

Swelling Index:

The swelling indexes of the formulated microparticles were performed pH 1.2 and phosphate buffer pH 7.4 at 37.5 ± 0.5°C for 8 hours. Drug loaded microparticles were equilibrated in different test tubes and at every one hour interval; microparticles were withdrawn filterd transferred into a small beaker and the weighed.

The swelling ratio was calculated from the followed expression,

$$\text{Swelling index} = \frac{W_f - W_0}{W_0} \times 100$$

Where, W1 = weight of micro particle observed at every time interval

W0 = initial weight of micro particles.

Micromeritic properties

i. Angle of repose

Flow properties of microsphere were determined by this method. Angle of repose of different formulation was measured according to a fixed funnel standing method.

$\Theta = \tan^{-1} h/r$

Where Θ is angle of repose, r is radius and h is the height

Angle of repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 6: Relationship between Flow properties and Angle of Repose

ii. Bulk density and Tapped density

Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample was poured in graduated cylinder and tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

iii. Carr's index

Compressibility Index (CI) or Carr's index value of microparticles was computed according to the following equation:

$$\text{Carr's index}(\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair-passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Table 7: Relationship between Percentage Compressibility and Flowability

iv. Hausner's ratio

Hausner'ratio of microsphere was determined by comparing the tapped density to the bulk density using the equation

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Hausner's ratio	Flowability
<1.25	Good
>1.25	Poor
1.25-1.5	Very

Table 8: Relationship between Hausner's ratio and Flowability

v. *In-vitro* dissolution study of Amlodipine besylate microsphere

Drug release from the microsphere was performed using the rotating basket method as specified in USPXXIV. *In-vitro* release profile was examined in Phosphate buffer pH 7.4 from 1- 8 hours.

Microparticles equivalent to 100 mg of drug were placed in the basket and the medium was maintained at 37°C and was kept at a rotation of 750 rpm. An aliquot of 10 ml were withdrawn periodically at intervals of one hour and same volume of fresh medium was replaced.

The concentration of drug released at time intervals was determined by measuring the absorbance at 360nm using UV spectrophotometer.

vi. Stability studies

The stability studies indicates the significant difference between the release patterns of microsphere at 40°C and RH for one month.

The stability studies were carried out at and optimized formulation, i.e, from F9 forumulation. The formulation was store at (40°C±2°C at 75% RH ± 5 %) for 1 months. Sample were withdrawn and retested for drug release and was compare with the formulation diffusion profile.

OBSERVATION DATA

S.NO	SOLVENT	SOLUBILITY
1	WATER	Slightly soluble
2	2,PROPANOL	Slightly soluble
3	METHANOL	Freely soluble
4	ALCOHOL	Sparingly soluble

Table 9: Solubility Profile of Amlodipine Besylate

S. No	polymer	Drug: polymer ratio	First day		After one week		After three week	
			25°C	40°C	25°C	40°C	25°C	40°C
1	Ethylcellulose	1:1	NC	NC	NC	NC	NC	NC
2	HPMC	1:1	NC	NC	NC	NC	NC	NC
3	PVP	1:1	NC	NC	NC	NC	NC	NC
4	Ethylcellulose HPMC	1:1:1	NC	NC	NC	NC	NC	NC

Table 10: Physical observation test for drug polymer compatibility studies

FOURIER TRANSFORM INFRARED SPECTROSCOPY

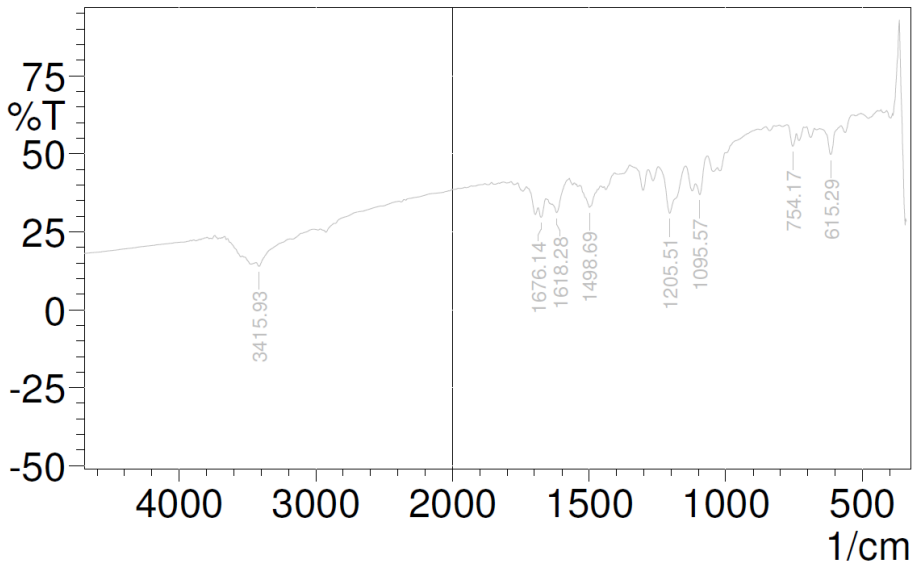


Figure 12: FT-IR Spectra of Amlodipine Besylate

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	49.807	8.675	650.01	578.64	18.18	1.56
2	754.17	52.441	5.04	777.31	740.67	9.306	0.594
3	1095.57	36.867	6.635	1111	1066.64	16.678	1.139
4	1205.51	30.914	15.075	1247.94	1147.65	41.19	7.372
5	1498.69	32.808	6.312	1535.34	1469.76	29.02	2.341
6	1618.28	31.129	5.02	1635.64	1571.99	28.06	1.17
7	1676.14	29.653	4.095	1685.79	1658.78	13.429	0.822
8	3415.93	13.913	1.841	3437.15	3188.33	179.432	-2.763

Table 11:FT-IR Spectra of Amlodipine Besylate

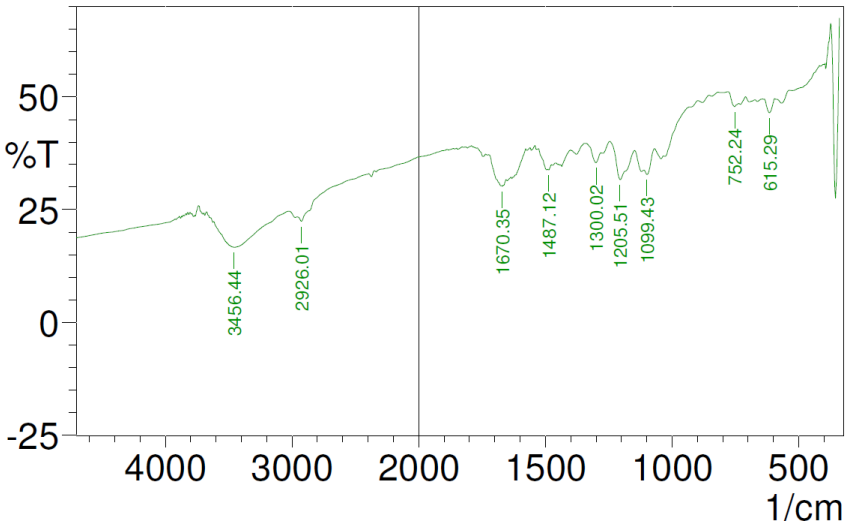


Figure 13: FTIR spectra of Amlodipine Besylate + Ethyl cellulose + Poly Vinyl Pyrolidone

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	46.512	3.043	636.51	596	12.967	0.616
2	752.24	47.88	1.616	779.24	736.81	13.146	0.311
3	1099.43	32.778	2.289	1111	1068.56	19.389	0.602
4	1205.51	31.664	7.657	1246.02	1147.65	44.445	4.361
5	1300.02	35.456	2.875	1338.6	1280.73	24.723	0.844
6	1487.12	33.802	0.362	1490.97	1475.54	7.182	0.033
7	1670.35	30.177	0.191	1672.28	1666.5	3.004	0.01
8	2926.01	22.425	1.583	2958.8	2517.1	243.977	-5.386
9	3456.44	16.647	1.005	3618.46	3427.51	140.243	4.197

Table 12: FTIR spectra of Amlodipine Besylate + Ethyl cellulose + Poly Vinyl Pyrolidone

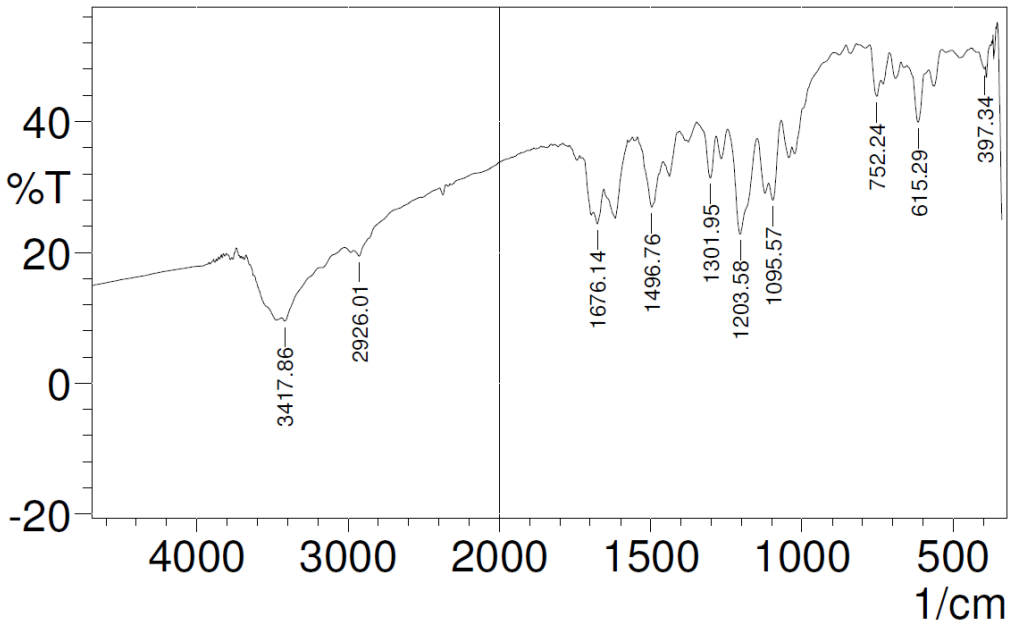


Figure 14: FTIR spectra of Amlodipine Besylate + Ethyl Cellulose

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	397.34	48.057	0.744	416.62	393.48	7.145	0.081
2	615.29	39.898	8.315	651.94	580.57	24.645	2.039
3	752.24	43.86	4.45	775.38	738.74	12.174	0.803
4	1095.57	27.968	6.113	1111	1068.56	20.875	1.562
5	1203.58	22.785	15.46	1246.02	1147.65	51.235	10.055
6	1301.95	31.41	6.961	1348.24	1284.59	28.073	1.934
7	1496.76	26.873	7.014	1543.05	1473.62	34.985	3.081
8	1676.14	24.329	3.182	1689.64	1654.92	20.171	0.897
9	2926.01	19.428	1.579	2964.59	2519.03	270.63	-5.352
10	3417.86	9.512	1.118	3439.08	3182.55	220.227	-4.597

Table 13: FTIR spectra of Amlodipine Besylate + Ethyl Cellulose

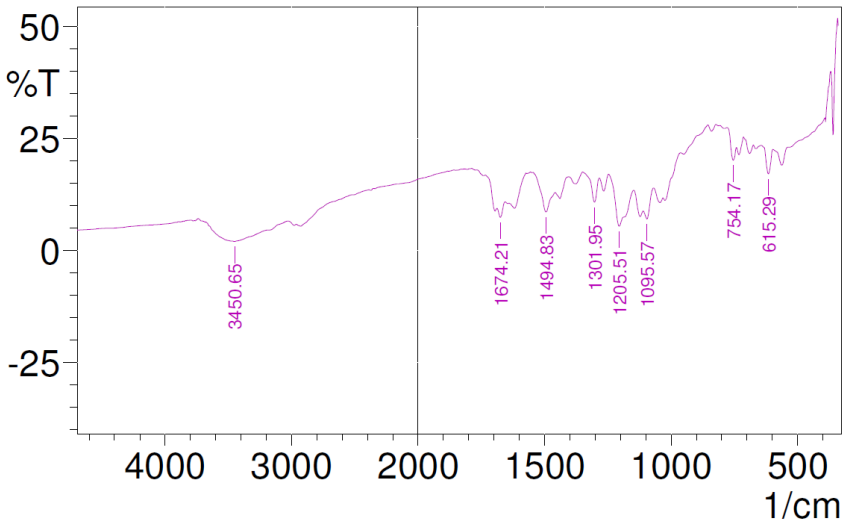


Figure 15: FTIR spectra of Amlodipine Besylate + Ethyl Cellulose + Hydroxy Propyl Methyl Cellulose

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	17.06	5.855	644.22	597.93	31.877	2.348
2	754.17	20.158	4.243	779.24	742.59	23.247	1.259
3	1095.57	7.015	3.623	1111	1068.56	43.41	2.807
4	1205.51	5.409	10.048	1247.94	1147.65	101.441	19.019
5	1301.95	10.771	5.701	1350.17	1284.59	54.706	3.87
6	1494.83	8.556	6.234	1544.98	1458.18	79.125	7.542
7	1674.21	7.374	2.626	1687.71	1656.85	32.706	1.93
8	3450.65	1.992	3.491	3678.25	3184.48	741.806	113.644

Table14: FTIR spectra of Amlodipine Besylate + Ethyl Cellulose + Hydroxy Propyl Methyl Cellulose

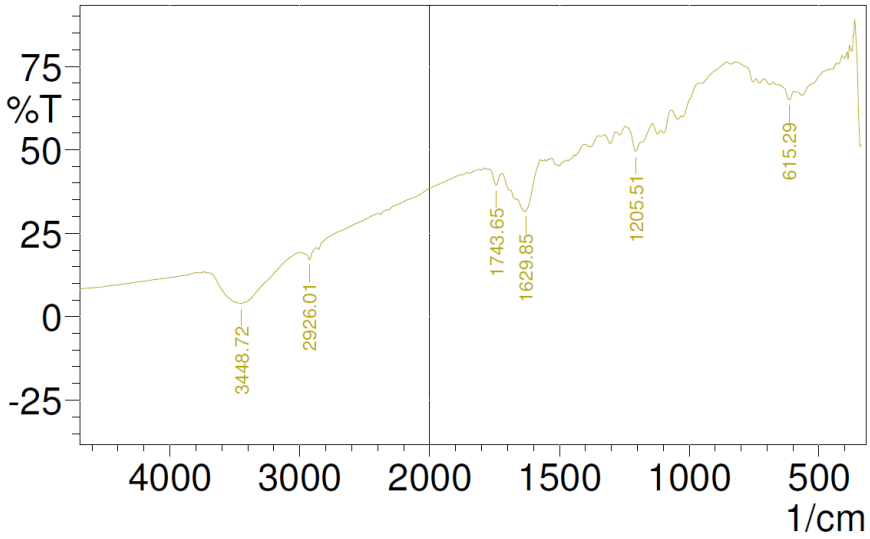


Figure 16: FTIR spectra of Amlodipine Besylate + Hydroxy Propyl Methyl Cellulose

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	65.013	3.109	655.8	597.93	9.904	0.406
2	1205.51	49.579	7.788	1246.02	1141.86	28.032	2.979
3	1629.85	31.602	1.061	1633.71	1573.91	24.882	0.198
4	1743.65	39.413	4.064	1770.65	1720.5	18.99	0.871
5	2926.01	17.12	2.79	2980.02	2870.08	79.614	2.552
6	3448.72	3.934	11.371	3695.61	3008.95	717.478	168.541

Table 15: FTIR spectra of Amlodipine Besylate + Hydroxy Propyl Methyl Cellulose

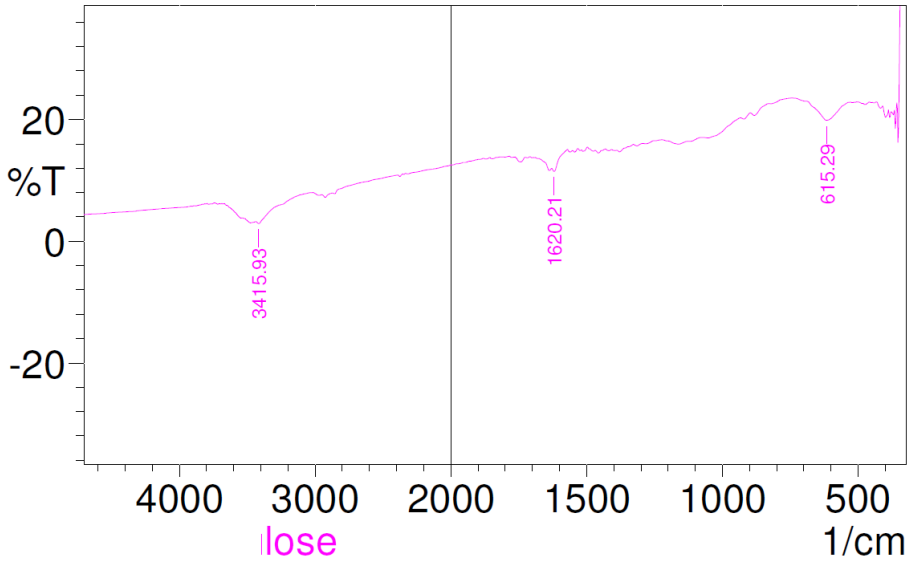


Figure 17: FTIR spectra of Ethyl Cellulose

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	19.88	3.06	690.52	536.21	103.3	4.62
2	1620.21	11.49	0.92	1627.92	1570.06	50.54	0.18
3	3415.93	2.88	0.54	3435.22	3016.67	517.08	-25.39

Table 16: FTIR spectra of Ethyl Cellulose

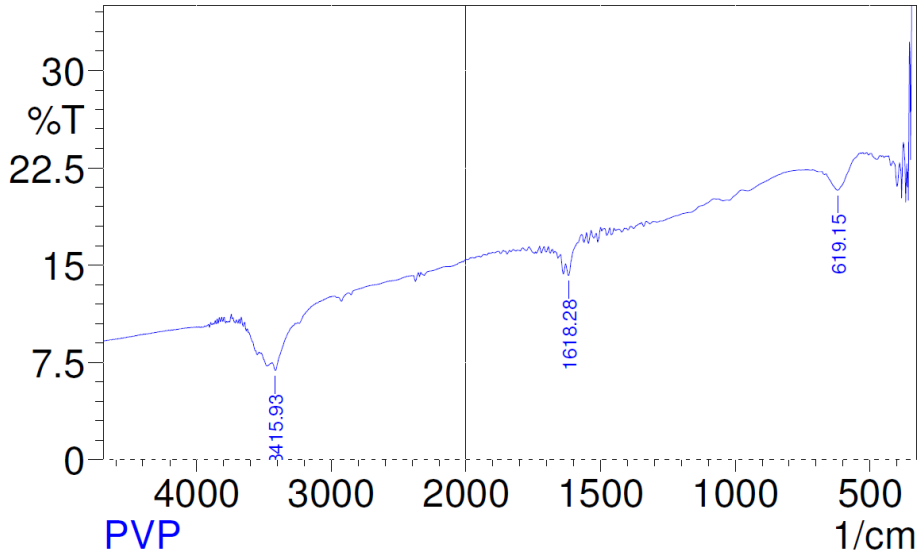


Figure 18: FTIR spectra of Poly Vinyl Pyrrolidone

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	619.15	20.77	1.81	661.58	534.28	83.81	2.16
2	1618.28	14.21	1.35	1629.85	1571.99	46.35	0.59
3	3415.93	6.89	1.01	3439.08	3265.49	183.58	1.01

Table 17: FTIR spectra of Poly Vinyl Pyrrolidone

STANDARD CALIBRATION CURVE OF AMLODIPINE BESILATE IN PHOSPHATE BUFFER pH 7.4

Table 18: Standard graph of Amlodipine Besylate

S.No	Concentration µg/ml	Absorbance
1	0	0
2	5	0.071
3	10	0.143
4	15	0.221
5	20	0.274
6	25	0.351
7	30	0.423

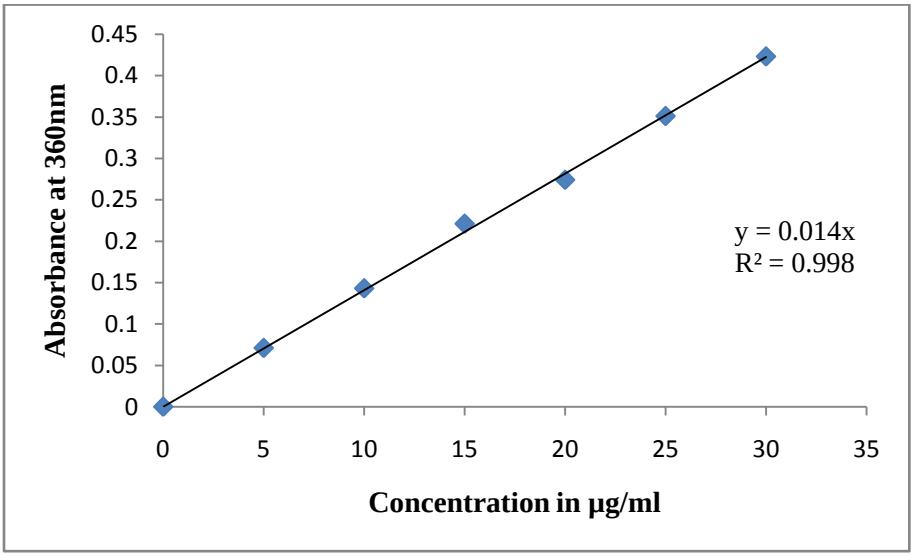


Figure 19:Standard graph of Amlodipine Besylate

Table 19: Percentage Yield of Amlodipine Besylate Microparticles

S.NO	FORMULATION CODE	PERCENTAGE YIELD (%)
1	F1	45
2	F2	95
3	F3	53
4	F4	65
5	F5	70
6	F6	75
7	F7	78
8	F8	82
9	F9	96

(±S.D.and no. of determinations = 3)

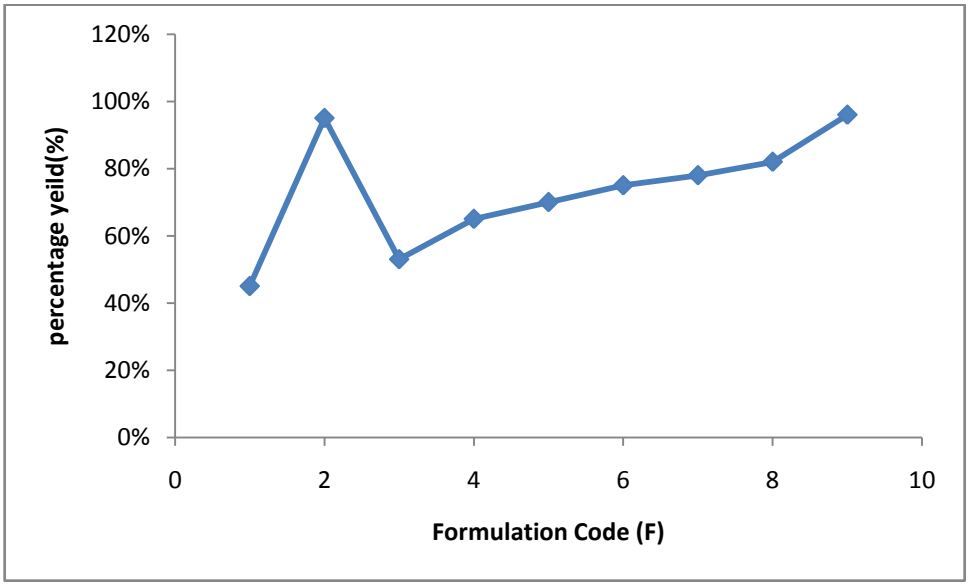


Figure 20 : Percentage yield of Amlodipine Besylate Microparticles

Table 20: Micromeritic Properties of Amlodipine Besylate Microparticles

S.NO	FORM. CODE	ANGLE OF REPOSE	BULK DENSITY	TAPPED DENSITY	CARR'S INDEX	HAUSNER'S RATIO
1	F1	20.42±0.20	0.78±0.64	0.84±0.73	10.1±0.84	1.05±0.54
2	F2	26.82±0.80	0.51±0.042	0.49±0.012	9.52±0.026	1.078±0.32
3	F3	20.66±0.36	0.79±0.62	0.83±0.72	7.73±0.29	1.14±0.011
4	F4	19.66±0.20	0.62±0.30	0.68±0.36	10.1±0.84	1.17±0.046
5	F5	19.11±0.20	0.73±0.46	0.67±0.32	10.05±0.54	1.16±0.032
6	F6	28.40±0.21	0.625±0.068	0.724±0.058	12.67±0.049	1.10±0.013
7	F7	32.00±0.63	0.641±0.52	0.769±0.074	16.65±0.064	1.15±0.018
8	F8	25.60±0.05	0.54±0.32	0.56±0.012	10.13±0.41	1.12±0.015
9	F9	24.92±0.32	0.49±0.013	0.55±0.014	9.12±0.012	1.122±0.032

(±S.D.and no. of determinations = 3)

Table 21: Particle Size of Amlodipine Besylate Microparticles

S.NO	FORMULATION CODE	PARTICLE SIZE µm
1	F1	185
2	F2	195
3	F3	253
4	F4	281
5	F5	321
6	F6	354
7	F7	343
8	F8	389
9	F9	482

(±S.D.and no. of determinations = 3)

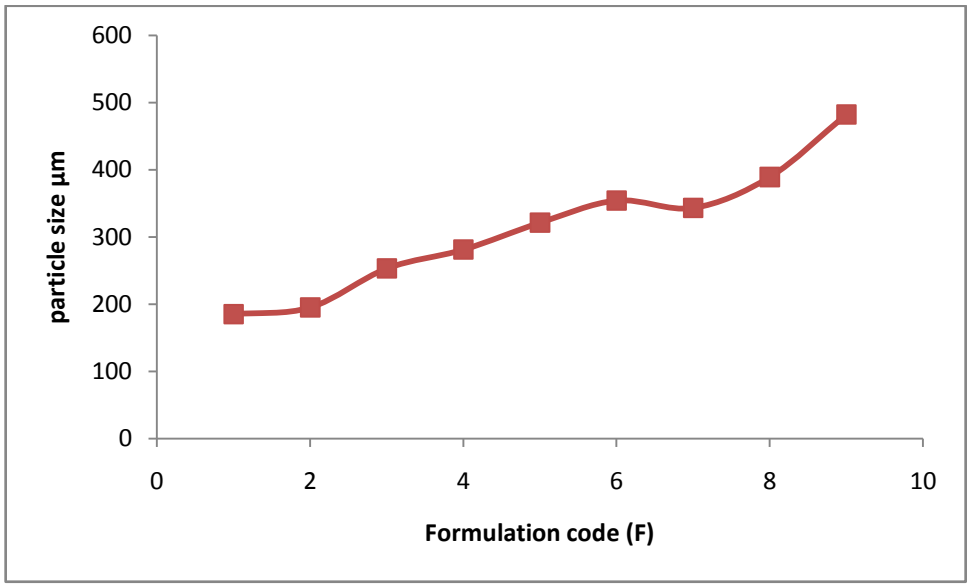


Figure 21: Particle Size of Amlodipine Besylate Microparticles

Table 22: Swelling Index(%) of Amlodipine Besylate Microparticles

S.No	Formulation code	Swelling index (%)
1	F1	190
2	F2	195
3	F3	189
4	F4	175
5	F5	165
6	F6	182
7	F7	185
8	F8	186
9	F9	196

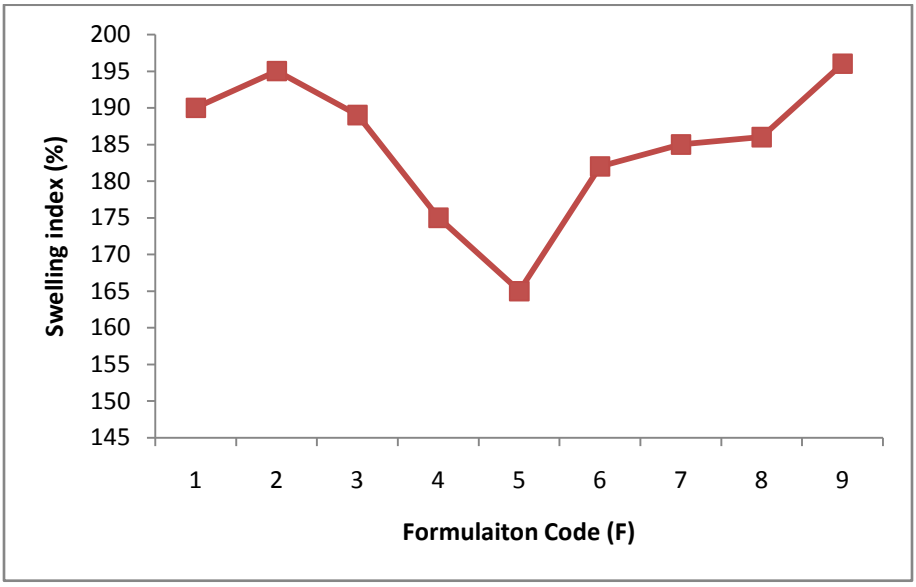


Figure 22: Swelling Index(%) of Amlodipine Besylate Microparticles

Table 23: Percentage Drug Loading of Amlodipine Besylate Microparticles

S. NO	FORMULATION CODE	DRUG LOADING (%)
1.	F1	80
2.	F2	95
3.	F3	75
4.	F4	89
5.	F5	90
6.	F6	85
7.	F7	85
8.	F8	90
9.	F9	96

(±S.D.and no. of determinations = 3)

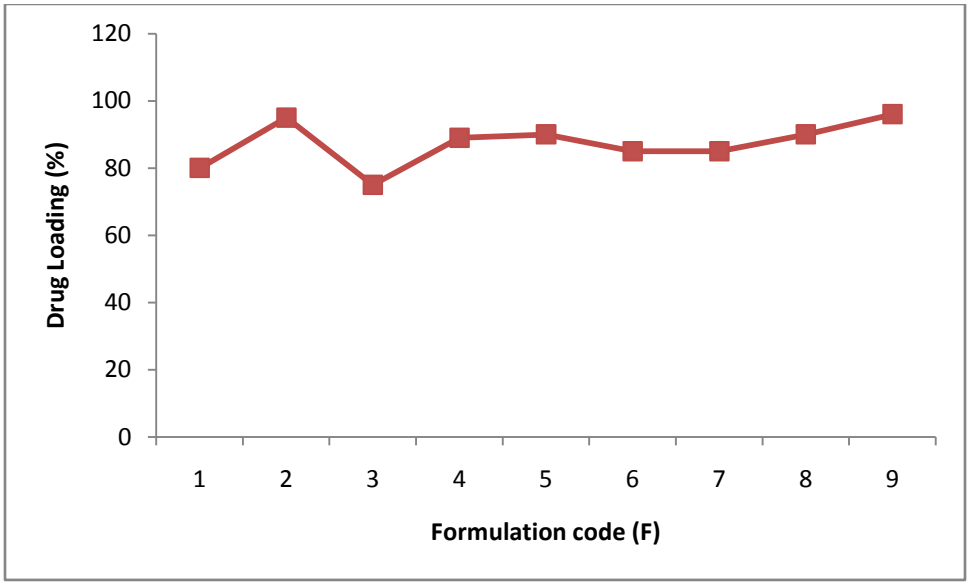


Figure 23: Percentage Drug Loading or Amlodipine Besylate

Table 24: Entrapment Efficiency of Amlodipine Besylate Microparticles

S.NO	FORMULATION CODE	ENTRAPMENT EFFICIENCY (%)
1	F1	25
2	F2	95
3	F3	30
4	F4	44
5	F5	53
6	F6	58
7	F7	65
8	F8	80
9	F9	96

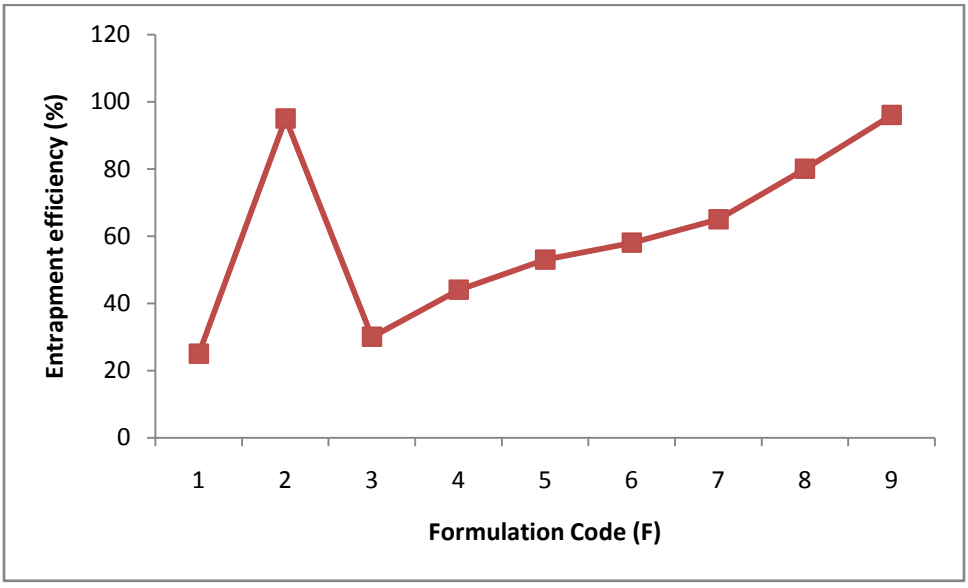


Figure 24: Entrapment Efficiency of Amlodipine Besylate Microparticles

Table 25: *In-Vitro* Buoyancy (%) Studies

S.No	Formulation code	Buoyancy (%)
1	F1	87.5
2	F2	96.0
3	F3	88.5
4	F4	83.5
5	F5	88.5
6	F6	88.2
7	F7	89.2
8	F8	91.21
9	F9	97.00

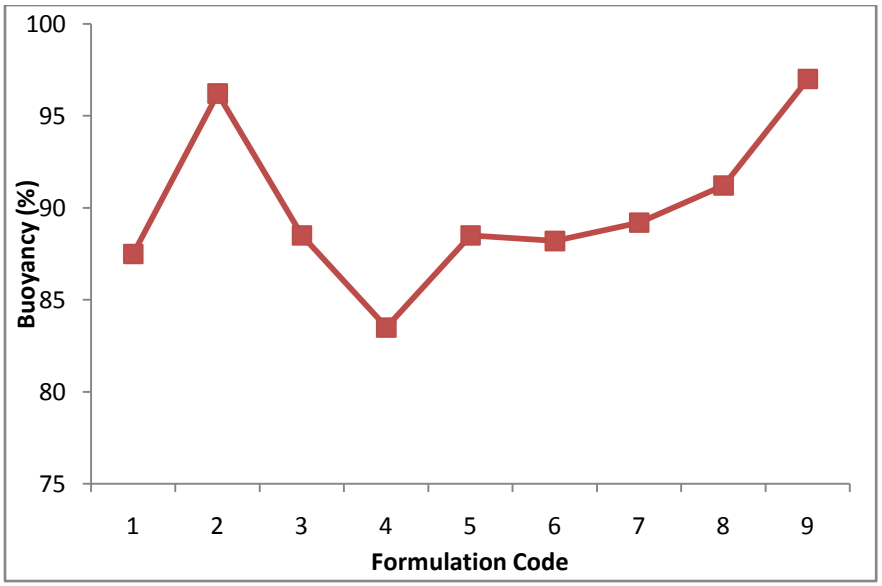


Figure 25: *In-Vitro* Buoyancy (%) Studies

TABLE 26: *In-Vitro* Dissolution Profile of Amlodipine Besylate Microsphere Mean Cumulative Percentage Drug Release (%)

S.No	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	14.84	11.92	14.01	10.18	10.91	11.65	10.11	10.25	11.82
2	2	19.20	29.82	20.02	25.14	27.20	20.05	30.11	28.52	30.12
3	3	24.26	42.01	23.01	38.26	43.05	30.01	42.45	39.42	43.15
4	4	28.96	59.02	26.05	42.01	55.06	40.05	55.42	40.14	57.89
5	5	32.27	68.01	31.08	45.01	65.01	52.06	60.14	52.15	69.12
6	6	38.97	79.03	35.04	58.03	74.06	68.17	85.12	61.27	78.95
7	7	42.01	87.05	42.05	60.02	85.23	70.18	87.15	75.38	89.01
8	8	42.05	95.03	42.06	60.05	87.41	72.19	87.26	79.16	96.89

(±S.D.and no. of determinations = 3)

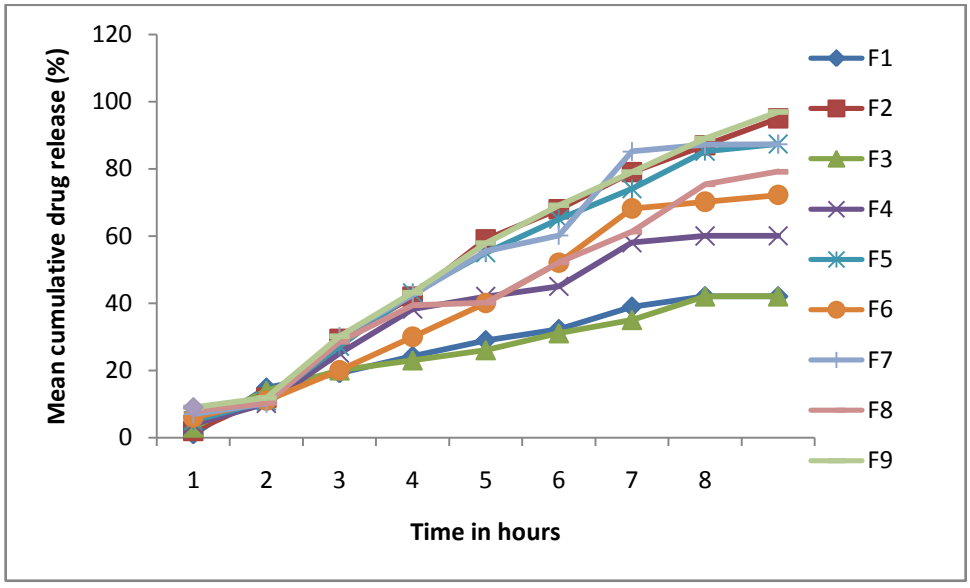


Figure 26 :*In-vitro* Dissolution Profile of Amlodipine Besylate Microparticle mean Cumulative Percentage Drug Release (%)

RESULT AND DISCUSSION

The principle objective of this research study was to formulate and evaluate sustained release microparticles of amlodipine besylate using ethylcellulose, HPMC, Eudragit RS 100 and PVP polymer by solvent evaporation technique method. Various batches were made form batch (F1 to F9).

To achieve the above objective, ethylcellulose and Poly vinyl pyrrolidine was found to be suitable polymer due to its biocompatibility, good stability, and ease of fabrication.

Solvent evaporation method was employed to formulate microsphere due to its ease of fabrication without compromising the activity of the drug. Sustained release microspheres obtained by this method were found to be spherical, discrete and free flowing in nature.

The prepared Microspheres were evaluated for percentage yield, Micromeritic properties such as Angle of repose, Bulk density, Tapped density, compressibility index, Hausner's ratio, particle size, Morphology analysis (SEM), swelling index (%), Drug content (%), Drug Entrapment efficiency(%), Buoyancy studies, *in-vitro* drug release and finally stability studies.

FOURIER TRANSFORM-INFRARED SPECTROSCOPY

FT-IR study was carried out to see whether there is any incompatibility between drug and polymer and also to know whether there is complete physical adsorption of drug on to the polymer matrix without any mutual interaction.

The results obtained from the IR studies are shown in Fig No.12 Amlodipine showed prominent peaks. The same peaks were also observed in the physical mixture of drug & polymer and drug loaded Microspheres.

After interpretation through the above spectra it was confirmed that there was no major shifting of functional peaks between the spectra of drug, polymer, physical mixture of drug and polymer and drug loaded microspheres.

Drug excipients interaction study

Drug excipients interaction was studied using (FT-IR) fourier transformed infrared spectroscopy. The characteristic peaks of the drug (fig 12) were observed at wave numbers 615.29cm^{-1}, 754.17 cm^{-1}, 1095.57 cm^{-1}, 1205.01cm^{-1},1498.69 cm^{-1} ,1618.28 cm^{-1}, 1676.14 cm^{-1},3415.93 cm^{-1}, in the functional group region of the pure drug spectrum. These characteristic peaks in the spectrum correspond to 615.29 cm^{-1} for stretching vibration of functional groups (OH, CH, CH3, CH2OH). These characteristic peaks also appear in the spectrum of amlodipine microparticles formulation at the same wave numbers indicating that there was no interaction between the drug and formulation excipients.

PERCENTAGE YIELD

The low percentage yield in some formulation may be due to microspheres lost during the washing process. Percentage yield of all formulations varies from F1 to F9 which are shown in Table No.19 and indicates that F9 shows highest percentage yield of 96%

MICROMERITIC PROPERTIES

Angle of repose

Angle of repose value of all the formulations were in the range of 20.42±0.20 to 25.60±0.05, which shows free flow nature of the prepared microsphere, the results were shown in table no.20.

Bulk density and Tapped density

It has been stated that, bulk density values less than 1.2 gm/cm^3 indicate good glow and values greater than 1.5 gm/cm3 indicate poor flow characteristic. It is seen from table No. 21 that the bulk density values are less than 1.2 gm/cm3 indicating good flow characteristics of the microspheres.

Compressibility index

The Carr's index of all the formulations was less than 20, i.e from 10.1±0.84 to 10.13±0.41, which inidicates good flow properties and compressibility

Hausner's ratio

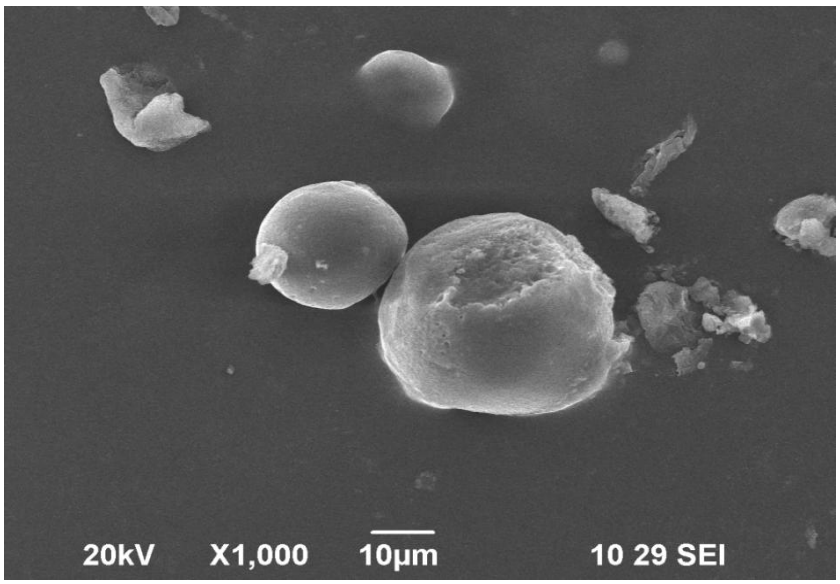
Hausner's ratio was ranging from 1.05±0.54 to 1.12±0.015 i.e., all the preparation showed that they had good flow properties. The improvement in flow properties suggests that the microspheres can be easily handled during processing. The results were shown in table no.20

PARTICLE SIZE AND MORPHOLOGY ANALYSIS (SEM)

Here, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases, viscosity increases, which influences the interaction between disperse phase and dispersion medium and affects the size concentration, there was increase in relative viscosity so as resulted in an increase in mean particle size. The particle size of drug loaded batches, ranges from 185 to 489µm. The mean particle size of all the formulations was shown in table No: 21

SURFACE MORPHOLOGY

SEM was performed on the prepared Amlodipine besylate microspheres to access their surface and morphological characteristics as shown in fig: 27 Scanning Electron Microphotographs indicate that microsphere were spherical and discrete.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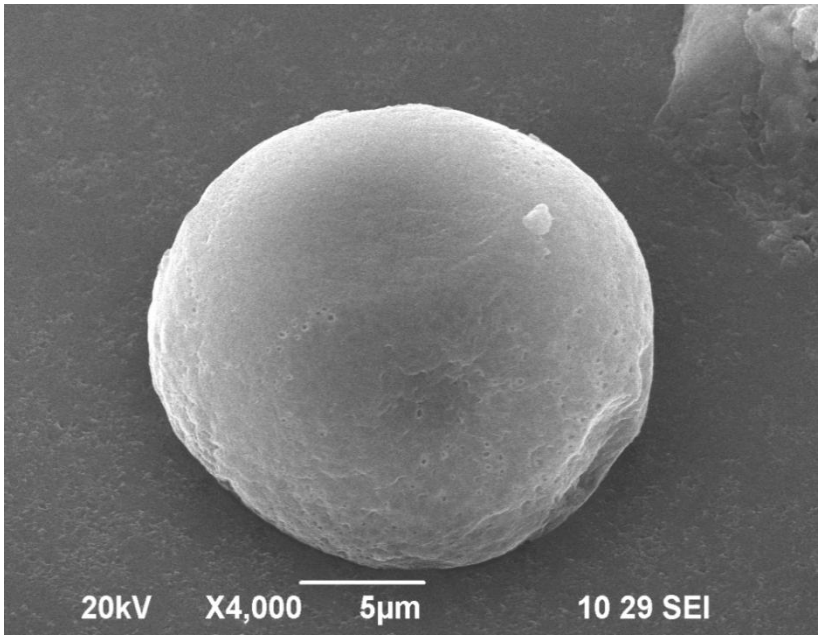
20kV X4,000 5µm 10 29 SEI

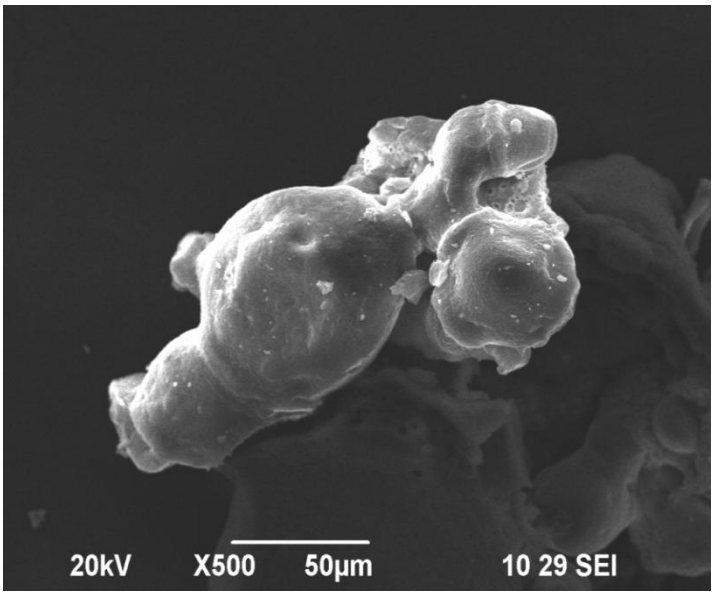

Figure: 27 SEM analysis for formulation F9

SWELLING INDEX (%)

The swelling index for all F1 to F9 formulations are ranges from 190 to 186%

DRUG CONTENT (%)

Loading efficiency of drug loaded batches was found to be 80% to 96 %. The drug loading efficiency of all formulations were shown in table No.23 which indicates that the highest drug loading was found to be F9 as 96%

DRUG ENTRAPMENT:

The microspheres exhibited an increase in drug entrapment with an increase in the proper ratio up to a particular concentration. A decrease in drug entrapment was observed after that point due to saturation capacity of the polymer. The entrapment efficiency of drug loaded batches, ranges from 25 to 95. The results were shown in table No.24

The maximum drug entrapped in the F9 formulation, 96% . The results are shown in table no.24

BUOYANCY STUDIES:

In this study the values ranges from 87.5 to 97.00

***IN-VITRO* DISSOLUTION STUDY**

Cumulative percentage release of amlodipine besylate loaded microsphere carried out in 1.2 pH HCl buffer for two hours and then 7.4 pH phosphate buffer upto 8, hours.

The release rate was decreased by increasing the polymer concentration and particle size.

The rapid release was obtained in formulation F9 due to low concentration of polymer and size of the particle results in higher contact of dissolution medium due to increased surface area.

Drug release from all the formulations was slow and sustained over 8 hours. By the end of 8 hours, F1, F2, F3, F4, F5, F6,F7, F8,F9 released 96.89 of loaded drug respectively. The polymer/drug F9 showed better sustained release pattern and drug entrapment and found to be most suitable among all the other formulations. *In-vitro* profiles of all the formulations have been shown in fig no.26

STABILITY STUDIES

The stability studies indicates the significant difference between the release patterns of microsphere at 40°C and RH and at room temperature for one month.

The stability studies were carried out at and optimized formulation, i.e, from F9 forumulation. The formulation was store at (40°C±2°C at 75% RH ± 5 %) for 1 months. Sample were withdrawn and retested for drug release and was compare with the formulation diffusion profile.

Table 27. Stability studies for formulated floating microparticles of Amlodipine Besylate

Characters	**Initial month**	**After 1 month**
Appearance	Spherical	Spherical
Solubility	Soluble in phosphate buffer	Solubile in phosphate buffer
Colour	Half white	Half white
Particle size	482	489
Swelling index	196	196
***In-vitro* drug release in hours**	**Mean cumulative release in percentage (%)**	
1	11.82	11.93
2	30.12	30.45
3	43.15	43.95
4	57.89	58.12
5	69.12	68.95
6	78.95	79.01
7	89.01	89.25
8	96.89	96.45

SUMMARY AND CONCLUSION

Floating amlodipine besylate microparticles using polymer ethylcellulose, HPMC, Poly vinyl pyrrolidine and Eudragit RS 100 was developed by solvent evaporation method and it was found to be a suitable floating oral drug delivery system in terms of particle size distribution, drug loading capacity and Sustained release amlodipine besylate microparticles obtained was spherical in shape, discrete and free flow in nature.

It can be concluded that,

- ✓ Polymer-drug ratio influence the particle size as well as drug release pattern of microsphere.
- ✓ Entrapment efficiency of drug loaded batches F1 to F9 were determined and it was found that F2 and F9 had a better drug entrapment efficiency of 95% and 96%
- ✓ Drug loading efficiency was better with F9 showed 96%
- ✓ Percentage yield from all the formulation were high and F9 showed good percentage yield of 96%
- ✓ Flow properties were determined for all the formulations F1 to F9. The result of Carr's index and angle of repose values indicated that all the formulations showed good flow properties.
- ✓ *In-vitro* drug release from all the formulations was found to be slow and sustained over the period of 8 hours was found to be 96.89%
- ✓ Stability studies of formulated Amlodipine microparticles was done at 40° C± 2°C and 75%±5 RH. Evaluating initial month and after one month founded that there is no significant changes in appearance, solubility, colour, particle size, swelling index, *in-vitro* drug release
- ✓ Decided to do *in-vivo* studies in future.

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