FORMULATION AND INVITRO EVALUATION OF SUSTAINED RELEASE TABLET OF QUINAPRIL HCL BY USING VARIOUS POLYMERS-A RESEARCH

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ABSTRUCT

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms.

KEYPOINTS: MEC, Eudragit L-100, Quinapril HCL,immediate-release dosage forms.

1. INTRODUCTION

1.1 ORAL DRUG DELIVERY

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according

to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized" . Several types of modified-release drug products are recognized:

1. *Extended-release drug products*. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.
2. *Delayed-release drug products*. A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.
3. *Targeted-release drug products*. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

1.2 ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

1.2.1 Advantages of Controlled Drug Delivery Systems:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects.

1.2.2 Disadvantages of Controlled Drug Delivery Systems:

- Increased variability among dosage units.
- Poor in vitro – in vivo correlation.
- Toxicity due to dose dumping may occur when more than usual fraction is being released.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- More rapid development of tolerance.
- Need for additional patient education and counselling.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

1.3 SELECTION OF DRUG CANDIDATE FOR SUSTAINED RELEASE DOSAGE FORM

The physico - chemical properties of the drug such as pKa, partition coefficient, biological half life, molecular weight, dose of the drug etc., have to be considered before selection.

Characteristics of drugs suitable for formulation as Sustained Release Products

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the gastrointestinal tract.
3. Administered in relatively small doses.
4. Possess good margin of safety.
5. Used for treatment of chronic therapy.

Characteristics of drugs unsuitable for formulation as Sustained Release Products

1. Not effectively absorbed in the lower intestine (Riboflavin).
2. Absorbed and excreted rapidly i.e. short biological half lives, less than one hour (Penicillin G, Furosemide).
3. Long biological half lives greater than 12 hours (Diazepam, Phenytoin).
4. Large doses required, 1gm (Sulphonamides)
5. Drugs with low therapeutic index (Phenobarbital, Digoxin).
6. Precise dosage titrated to individuals required (anticoagulants)
7. No clear advantage for sustained release formulation (griseofulvin)

1.4 Types of Oral Controlled Release Drug Delivery Systems

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems
- Diffusion controlled release systems
- Diffusion and dissolution systems
- Osmotically controlled release systems
- Gastroretentive drug delivery systems
- Electrically stimulated release devices
- Ion-exchange resins

1.4.1 DISSOLUTION CONTROLLED RELEASE SYSTEMS[6]

A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here the rate-limiting step is dissolution. This being true, sustained release preparation of drugs could be made by decreasing their rate of dissolution.

Dissolution controlled systems can be made either by

- Varying concentration of rate controlling coats or polymers (Matrix Dissolution Systems) or
- By administering the drug as a group of beads that have coating of different thickness (Encapsulated Dissolution Systems)

Matrix Dissolution Systems are prepared by compressing the tablet with a slowly soluble polymer carrier into tablet form. Wax matrices are prepared either by congealing or dispersion the drug - wax mixture in water.

1.4.2 Diffusion Controlled Release Systems

In these systems the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices-

1.4.2.1 Reservoir devices:

Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug.

The methods used to develop reservoir type devices include micro-encapsulation of drug particles and coating of tablets containing drug cores.

1.4.2.2 Matrix Devices:

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. The most common method of preparation is to mix the drug with the matrix material and then compress the mixture.The drug release from a porous or granular matrix can be described by

1.4.3 Diffusion and Dissolution Controlled Systems

In these systems the release rate of drug is determined by both the diffusion and dissolution mechanisms.

1.4.4 Osmotically Controlled Release Systems

The osmotic pump represents a newer concept in extended-release preparations. Drug delivery is controlled by the use of an osmotically controlled device that promotes a constant amount of water into the system, either by dissolving and releasing a constant amount of drug per unit time or by the use of a "push–pull" system that pushes the drug out at a constant rate as water flows into an expandable osmotic compartment. Drug is released via a single laser-drilled hole in the tablet.

1.4.5 Gastro retentive Drug Delivery Systems

Dosage forms that can be retained in stomach are called Gastro retentive Drug Delivery Systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

The approaches that have been pursued to increase the retention of an oral dosage form in the stomach include Bioadhesive systems, Swelling and expanding systems, High density systems and Low density (Floating) systems.

1.4.5.1 Bioadhesive Systems

Bioadhesion is the process whereby synthetic and natural macromolecules adhere to the biological membranes in the body and remain there for an extended period of time. If the membrane substrate is mucosal layer then the process is referred to as mucoadhesion. The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.

1.4.5.2 Swelling and Expanding Systems

These systems increase the residence time of the dosage form in the stomach. Particles greater than 10mm are unable to enter the duodenum and are retained in the stomach. The swelling systems incorporate hydrogels which are polymers that can swell up to 100 times their dry weight. The hydrogels used must be biodegradable.

1.4.5.3 High density systems

In High density systems the bulk density of the dosage form must exceed that of normal stomach and should be at least 1.40. In preparing such formulations, drug can be coated on a core with heavy, inert materials such as barium sulfate and titanium dioxide. The weighed pellet can then be covered with a diffusion controlled membrane.

1.4.5.4 Low density (Floating) systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so 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 GRT and a better control of fluctuations in plasma drug concentration. These systems are suitable for drugs that are poorly soluble or unstable in the intestinal medium.

1.4.6 Electrically Stimulated Release Devices

These are monolithic devices prepared by using polyelectrolyte gels which swell when an external electrical stimulus is applied, causing a change in pH. The release could be modulated, by the current, giving a pulsatile release profile. Precise control over the release of drug from devices implanted in the body, such as quantity, timing, is highly desirable in order to optimize drug therapy. Electrically-controllable drug release from polyelectrolyte hydrogels is helpful in achieving these goals.

Factors influencing the design and performance of Sustained release products

The design of controlled - release delivery system is subjected to several variables of considerable importance. Among these, the properties of the drug, the route of drug delivery, and the disease being treated and length of the therapy have major importance.

1. 6 Physicochemical factors

- Aqueous solubility
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and Diffusivity

1.7 Biological factors

- Absorption
- Distribution
- Elimination
- Biological half life and Duration of action
- Side effects and Margin of safety
- Dose size
- Disease state

1. 6 PHYSICOCHEMICAL FACTORS

- **Aqueous solubility:**

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membrane. The choice of mechanism for oral sustained release systems is limited by aqueous solubility of the drug. Diffusional systems will be poor choices for slightly soluble drugs since the driving force for diffusion; the concentration in aqueous solution will be low. Such drugs may be effectively incorporated in matrix system.

- **Partition coefficient:**

Partition coefficient ($K_{o/w}$) is defined as the ratio of the fraction of the drug in an oil phase to that of an adjacent aqueous phase.

Accordingly, compounds with a relatively high $K_{o/w}$ are predominantly lipid-soluble and consequently, have very low aqueous solubility. Furthermore, these compounds can usually persist in the body for long periods as they can localise in the lipid membranes of cells. (eg: Phenothiazines). Compounds with very low $K_{o/w}$ will have difficulty in penetrating membranes, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on partitioning characteristics of the drug. Drugs with a partition coefficient that is higher or lower than the optimum (i.e., 1000/1) in general, are poor candidates for formulation into SR dosage forms.

- **Drug stability:**

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. For drugs like Propantheline that are unstable in the stomach, the most appropriate controlling unit would be the one that releases its contents only in the intestine. The reverse in the case for drugs like Probanthine that are unstable in the environment of the

intestine, the most appropriate controlling unit in this case would be one that releases its contents only in the stomach. In general, drugs with significant stability problems in any particular area of the gastrointestinal tract are less suitable for formulation into sustained release systems.

- **Protein binding:**

Many drugs bind to plasma proteins with a significant influence on the duration of drug action. If a drug has binding properties with a particular protein, then the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a sustained release dosage form.

- **Molecular size and Diffusivity:**

Drugs in most of the sustained release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through these membranes is known as diffusivity (diffusion coefficient). This diffusivity is a function of its molecular size (or molecular weight) and is related by the equation.

1.7 Biological Factors

The design of sustained release products should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing.

2. LITERATURE REVIEW

Priya V Bhosale et.al.,(2015)

developed extended release matrix tablets of ranolazine, to reduce the frequency of administration and to improve the patient compliance; a once daily extended release formulation of ranolazine is desirable. The ranolazine 500 mg extended release matrix tablets were prepared by wet granulation method using different polymers. All the mentioned batches were prepared and granules were evaluated for pre-compression parameters such as

loss on drying, bulk density, tapped density, hasuner's ratio and compressibility index. Tablets were evaluated for weight variation, thickness, hardness and friability, were found to be within limits. The in-vitro release of ranolazine extended release tablets was studied in 900 ml of 0.1 N HCl as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37±0.5°C for 24 hrs. The (F8) formulation shown best results of 99.26% drug release in 24 hrs a complex salt of alginic acid.

Ju-Young Kim et.al.,(2015)

design and evaluate extended-release formulations of a model drug, nicorandil, in order to achieve the desired steady-state plasma concentration of drug in vivo. The dissolution test was employed using pH 1.2, 4.0, 6.8 buffer solution, or water, to measure the in vitro release behaviors of nicorandil formulations. A single dose (15 mg) of each formulation was orally administered to four beagle dogs under fasted conditions, and the pharmacokinetic parameters were calculated. The in vitro/in vivo relationship of the extended-release formulation was confirmed using in vitro dissolution profiles and plasma concentrations of drug in beagle dogs. Nicorandil was released completely within 30 min from the immediate-release tablets and released for 24 h from the extended-release tablets. The release rate of nicorandil was the rate-limiting step in the overall absorption of drug from the extendedrelease formulations.

Ramesh Namani et.al.,(2015)

Guaifenesin Extended release tablets were formulated and optimized at the polymer concentration ratio of 30:20 (HPMC: EC) at the coating percentage of an average weight build-up of 7.36%w/w. *In vitro* release studies complied with the innovator and the formulation was found to be equal. It was increased. Similarity factor (f_2) value was calculated for all formulations. The similarity factor (f2) of all the formulations ranged from 30 to 68.7. The similarity factor of is high when comparing to other formulations so, it is more similar to that of marketed formulation.

3. AIM AND OBJECTIVE

Aim:

To formulate extended release tablets of Quinapril HCL to improve its oral bioavailability and to reduce its dosing frequency

Objectives:

1. To optimize optimum concentration of various extended release polymers.
2. To perform various quality control evaluation parameters for the prepared tablets

4. PLAN OF WORK

To achieve the objectives of the work, the following work was planned and undertaken:

1. Literature survey
2. Preformulation studies
3. Selection of excipients
4. Formulation of SR tablets with different polymers
5. Selection of best formulation based on in-vitro drug release testing
6. Optimization of the selected formula
7. Evaluation
8. Comparison of in-vitro dissolution profiles.

5.1. DRUG PROFILE

Drug name : QUINAPRIL HCL

Iupac name : 9-[(2R,5S)-5-(hydroxymethyl)oxolan-2-yl]-6,9-dihydro-3H-purin-6-one

Synonyms : 9-[(2R,5S)-5-(Hydroxymethyl)tetrahydrofuran-2-yl]-1,9-dihydro-6H-purin-6-one , DDI, DdIno, Didanosina, Quinapril HCL, Didanosinum

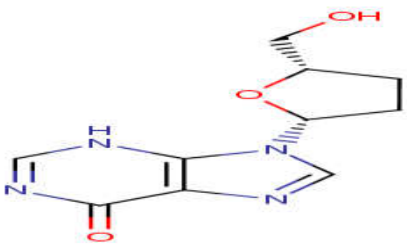
Solubility : Soluble in water (27.3 mg/mL at 25 °C and pH 6.2); soluble in dimethylsulfoxide; slightly soluble in ethanol and methanol; insoluble in chloroform

Description : A dideoxynucleoside compound in which the 3'-hydroxy group on the sugar moiety has been replaced by a hydrogen. This modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chains. Quinapril HCL is a potent inhibitor of HIV replication, acting as a chain-terminator of viral DNA by binding to reverse transcriptase; ddI is then metabolized to dideoxyadenosine triphosphate, its putative active metabolite.

Melting point : 160-163 °C

CAS NO : 69655-05-6

Structure :



Molecular formula : $C_{10}H_{12}N_4O_3$

Molecular weight : Average: 236.2273 Monoisotopic: 236.09094027 g/mol.

Bioavailability : 30 to 54%

Half-life : 30 minutes in plasma and more than 12 hours in intracellular environment.

Protein binding : Low (<5%)

Dosage forms : tablet,capsule

Dose : 10,25,50,100,150,250,400,500 mg.

Category : Anti-HIV Agents, Antimetabolites, Reverse Transcriptase Inhibitors

Pharmacodynamics :

Quinapril HCL is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Quinapril HCL differs from other nucleoside analogues, as it does not have any of the regular bases, instead it has hypoxanthine attached to the sugar ring. Quinapril HCL is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. Quinapril HCL is effective against HIV, and usually used in combination with other antiviral therapy. Switching from long term AZT treatment to Quinapril HCL has been shown to be beneficial. Quinapril HCL has weak acid stability and therefore, it is often combined with an antacid.

Mechanism of Action:

Quinapril HCL (ddI) is metabolized intracellularly by a series of cellular enzymes to its active moiety, dideoxyadenosine triphosphate (ddATP), which inhibits the HIV reverse transcriptase enzyme competitively by competing with natural dATP. It also acts as a chain terminator by its incorporation into viral DNA as the lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

Pharmacokinetic Properties:

Absorption: Rapidly absorbed (bioavailability 30-40%) with peak plasma concentrations appearing within 0.5 and 1.5 hrs.

Distribution: Binding of Quinapril HCL to plasma proteins in vitro was low (less than 5%). Based on data from in vitro and animal studies

Metabolism: Rapidly metabolized intracellularly to its active moiety, 2,3-dideoxyadenosine-5-triphosphate (ddA-TP). It is then further metabolized hepatically to yield hypoxanthine, xanthine, and uric acid.

Elimination: Based on data from in vitro and animal studies, it is presumed that the metabolism of Quinapril HCL in man occurs by the same pathways responsible for the elimination of endogenous purines. Purines are eliminated by the kidneys.

Adverse Effects:

diarrhea, nausea, vomiting, abdominal pain, fever, headache and rash. Peripheral neuropathy occurred in 21-26% of participants in key Quinapril HCL trials.Pancreatitis is rarely observed but has caused occasional fatalities, and has black box warning status. Other reported serious adverse events are retinal changes, optic neuritis and alterations of liver functions. The risk of some of these serious adverse events is increased by drinking alcohol.

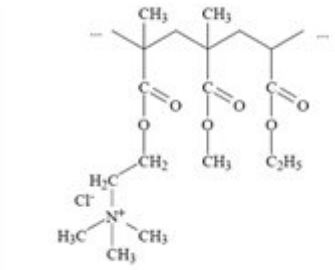
Storage:

Store at room temperature.

5.2 EUDRAGIT RLPO

Iupac name : Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2

Molecular structure:



Molecular weight: 32,000 g/mol

Functional category :film forming agent and in the oreparation of film forming agent.

Description : white powder with a faint amine-like odour.

Melting point : 259°C-268°C

Solubility : 1 g of the substances dissolves in 7 g aqueous methanol, ethanol and isopropyl alcohol (containing approx. 3 % water), as well as in acetone, ethyl acetate and methylene chloride to give clear to cloudy solutions. The substances are practically insoluble in petroleum ether, 1 N sodium hydroxide and water.

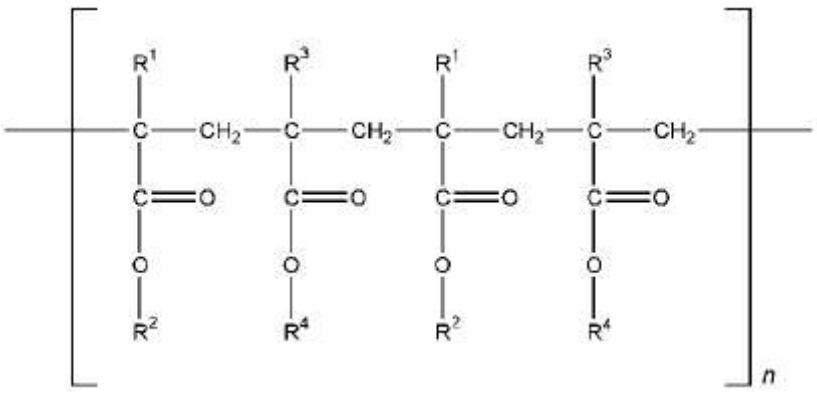
Applications : preparation of controlled release formulations

Stability: Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Storage Stability data are available upon request. Store at controlled room temperature (USP, General Notices). Protect against moisture. Any storage between 8 °C and 25 °C fulfils this requirement.

5.3. EUDRAGIT S 100

IUPAC name : Poly(methacylic acid-co-methyl methacrylate) 1:2

Structure:



For Eudragit S:

R1, R3 = CH3

R2 = H

R4 = CH3

Chemical name : Poly (methacrylic acid, methyl methacrylate) 1:2

Types : Eudragit S 12.5 ,Eudragit S 12.5 P

Description : Fine white powder or creamy-white granules

Solubility : soluble in acetone an alcohols.Soluble in intestinal fluid from pH 7

Density : 0.831–0.852 g/cm^3

Viscosity : 50–200 mPa

Stability : Dry powder polymer films are stable at temperatures less than30^{o}C. Above this temperature, powder tends to form lumps Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30^{o}C.

Uses : 1. Film forming agent

2. In the preparation of sustained release dosage forms.

6. METHODOLOGY

6.1. Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

b) Preparation calibration curve:

100mg of Quinapril HCL pure drug was dissolved in 100ml of 0.1 N HCl (stock solution)10ml of solution was taken and make up with100ml of 0.1 N HCl (100µg/ml).from this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20,25,30,35 and 40µg/ml of Quinapril HCL per ml of solution. The absorbance of the above dilutions was measured at 256 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

6.2. Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

6.3. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a

flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Angle of Repose	**Nature of Flow**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 6.1: Angle of Repose values (as per USP)

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$\text{Bulk Density} = M / V_o$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester

that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(tap - b) / tap] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Carr's index	**Properties**
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Table 6.2: Carr's index value (as per USP)

6.3. Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Quinapril HCL. Total weight of the tablet was considered as 600mg.

Procedure:

1) Quinapril HCL and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

6.4. Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core

and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 256 nm using UV-spectrophotometer.

7. RESULTS AND DISCUSSION

The present study was aimed to developing extended release tablets of Quinapril HCL using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

7.1. Analytical Method

Graphs of Quinapril HCL was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 256 nm and 260 nm respectively.

Table 7.1: Observations for graph of Quinapril HCL in 0.1N HCl (256nm)

Conc [µg/l]	Abs
5	0.104
10	0.205
15	0.302

20	0.411
25	0.503
30	0.608
35	0.710
40	0.808

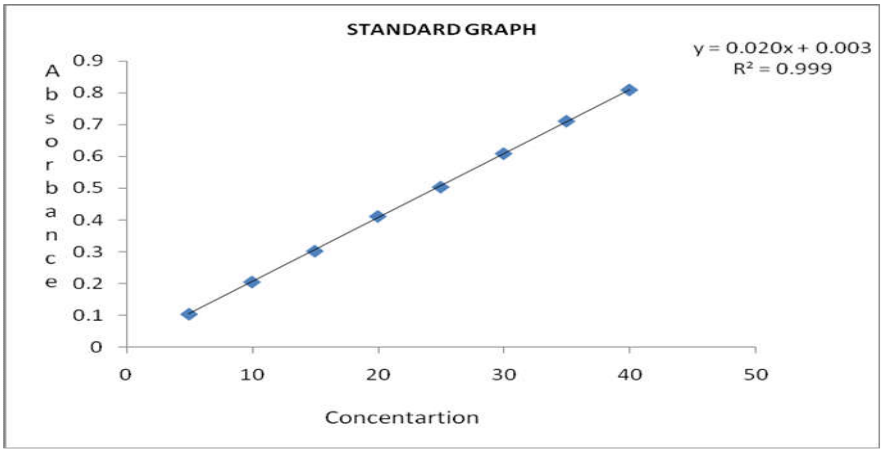


Figure 7.1: Standard graph of Quinapril HCL in 0.1N HCl

Table 7.2: Observations for graph of Quinapril HCL in p H 6.8 phosphate buffer (260nm)

Conc [µg/l]	Abs
5	0.098
10	0.195
15	0.256
20	0.392
25	0.490
30	0.595
35	0.690
40	0.776

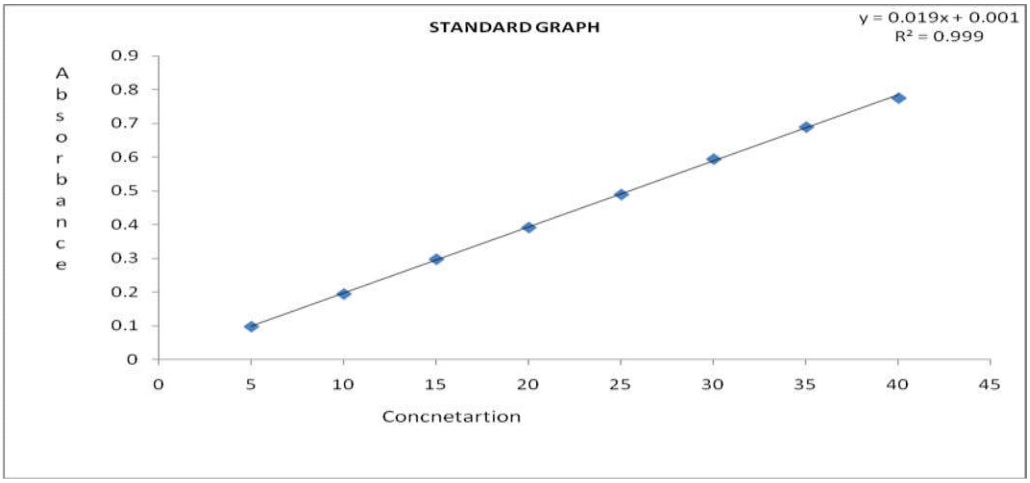


Figure 7.2: Standard graph of Quinapril HCL p H 6.8 phosphate buffer (260nm)

7.4. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

7.5. In-Vitro Drug Release Studies

Table 7.5: Dissolution Data of Quinapril HCL (F1, F2,F3 formulations).

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F1	F2	F3
0.5	4.55	5.65	19.59
1	14.33	9.65	29.97
2	23.75	15.43	37.89
3	29.54	20.43	45.9
4	35.53	25.87	56.38
5	43.65	36.55	62.2
6	59.26	48.65	69.06
7	75.43	61.93	75.52
8	79.33	66.85	79.88
9	85.47	79.54	88.6
10	87.66	83.87	90.09
11	89.54	85.44	93.22
12	92.54	89.58	94.25

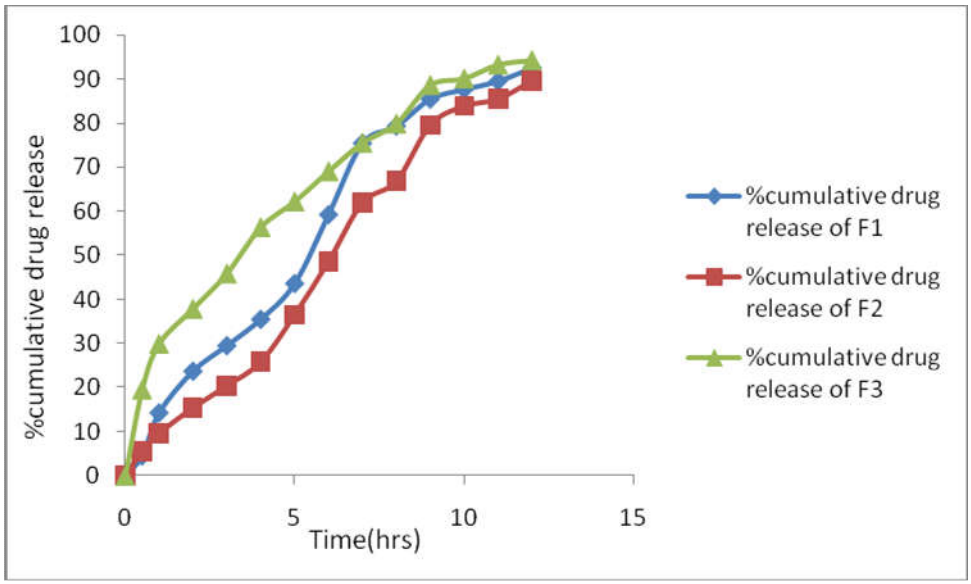


Fig 7.5: Dissolution profile of Quinapril HCL (F1, F2,F3 formulations).

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