FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF A SELECTIVE ANTIHYPERTENSIVE DRUG

By

GURUDATHA.S B.Pharm.,

Reg. no: 13PU081

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SENTHIL KUMAR. K **M.Pharm.,**

DEPARTMENT OF PHARMACEUTICS
SAC COLLEGE OF PHARMACY
B.G.NAGARA, KARNATAKA -571448

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RAJIV GANDHI UNIVERSITY OF HEALTH SCIENCES,

KARNATAKA, BANGALORE

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I hereby declare that this dissertation entitled FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF A SELECTIVE ANTIHYPERTENSIVE DRUG is a bonafide and genuine research work carried out by me under the guidance of **Mr. SENTHIL KUMAR. K** Associate Professor, Department of Pharmaceutics, SAC College of Pharmacy. B.G-Nagara.

Date:

Place: B.G-Nagara

GURUDATHA.S
B.Pharm
Department Of Pharmaceutics,
SAC College Of Pharmacy,
BG-Nagara-571448
Karnataka.

SRI ADICHUNCHANAGIRI COLLEGE OF PHARMACY
B.G.NAGARA-571448

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF A SELECTIVE ANTIHYPERTENSIVE DRUG was carried out by ***Mr.GURUDATHA.S*** in the laboratory of SAC College of Pharmacy, B.G.Nagara, under my direct supervision and guidance.

Date:

Place: B.G-Nagara

Mr. SENTHIL KUMAR. K
M. Pharm.,

Associate Professor,
Department of Pharmaceutics,
SAC College of Pharmacy,
B.G-Nagara-571448

SRI ADICHUNCHANAGIRI COLLEGE OF PHARMACY
B.G.NAGARA-571448

ENDORSEMENT BY THE HEAD OF THE DEPARTMENT

This is to certify that the dissertation entitled "FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF A SELECTIVE ANTIHYPERTENSIVE DRUG" is a bonafide research work carried out by ***Mr.GURUDATHA.S*** under the guidance of **Mr. SENTHIL KUMAR. K** Associate Professor, Department of Pharmaceutics, SAC College of Pharmacy, B.G.Nagara.

\

Date:

Place: B.G-Nagar

Dr. MOHAMMED GULZAR AHMED

M.Pharm., Ph.D.,

Professor and Head,
Dept. of Pharmaceutics,
SAC College of pharmacy
B.G-Nagara-571448

SRI ADICHUNCHANAGIRI COLLEGE OF PHARMACY
B.G.NAGARA-571448

ENDORSEMENT BY THE PRINCIPAL/HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled "FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF A SELECTIVE ANTIHYPERTENSIVE DRUG" is a bonafide research work carried out by ***Mr. GURUDATHA.S*** under the guidance of **Mr. SENTHIL KUMAR. K** Associate Professor**,** Department of Pharmaceutics, SAC College of Pharmacy, B.G-Nagara.

Date:

Place: B.G-Nagara

Dr. B. RAMESH

M. Pharm., Ph.D.,
Principal & Proffesor
SAC College of Pharmacy,
B.G-Nagara-571448.

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Date:

Place: B.G-Nagara

GURUDATHA.S B.Pharm

Department Of Pharmaceutics,

SAC College Of Pharmacy,

BG-Nagara-571448
Karnataka

Dedicated to my family members, & friends

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DATE:

PLACE: B.G. Nagara. *Gurudatha.S*

CONTENTS

ABSTRACT

The main aim of present work was to formulate and evaluate sustain release matrix tablets of Valsartan, an angiotensin II Receptor type 1 antagonist. Sustain release formulation are those which delivers the drug locally or systemically at a predetermined rate for a fixed period of time. The matrix tablet was prepared by direct compression method using by various concentration of chitosan and sodium alginate with combination of various release retardant polymer. The powder mixtures were subjected to various pre-compression parameters such as angle of repose, bulk density, tapped density and Carr's index shows satisfactory result and the compressed tablets are evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, *in-vitro* dissolution and stability studies. *In-vitro* dissolution studies were carried out for 24 hours using 0.1 N HCL for first 2 hours and pH 6.8 phosphate buffer for 24 hours and the result showed that formulations F_4 and F_7 showed good dissolution profile to control the drug release respectively. Formulation containing higher concentration of chitosan and sodium alginate along with polymers sustained the drug release for the period of 24 hours. The compatibility of the drug, polymers and other excipients were determined by FT-IR Spectroscopy. Results showed that the drug was compatible with polymers and other excipients. The release data was fitted to various mathematical models such as Zero-order, First-order, Higuchi equation and Korsmeyer-Peppas model to evaluate the kinetics and the drug release. The drug release followed first order and the mechanism was found to be non-Fickian. The stability studies were carried out for 3 months and result indicates that the selected formulations (F_4 and F_7) were stable.

Key words: Carbopol 934P, Chitosan, sodium alginate, sustain release matrix tablet, Valsartan.

LIST OF ABBREVIATIONS

ABBREVIATIONS	EXPANSIONS
%	Percentage
°C	Degree centigrade
µg	Microgram
λ_{max}	Maximum Wavelength
%CDR	Percentage cumulative drug release
Abs	Absorbance
Conc.	Concentration
Cm	Centimeter
hrs	Hour
ICH	International Conference on Harmonization
IP	Indian Pharmacopoeia
IR	Infra- red
Sec	Seconds
GIT	Gastro intestinal tract
FT-IR	Fourier Transform Infrared Spectroscopy
mm	Millimeter
gm	Gram
mg	Milligram
pH	Negative logarithm of hydrogen ion concentration
RH	Relative humidity
Min	Minute

ml	**Milliliter**
nm	**Nanometer**
$t_{1/2}$	**Half life**
UV	**Ultra violet**
Vs	**Versus**
w/w	**Weight by weight**
w/v	**Weight by volume**
SD	**Standard deviation**
MCC	**Micro-crystalline cellulose**
PVP	**Polyvinylpyrrolidone**
t_{max}	**Time taken for maximum concentration**

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Chapter 1

Introduction

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. Many of the drug delivery systems available in the market are oral drug delivery type systems.[1]

Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery. It does not pose the sterility problem and minimal risk of damage at the site of administration.[2]

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1) Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]

Design and formulation of oral sustained release drug delivery system:[4,5]

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal

motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal tract. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation.

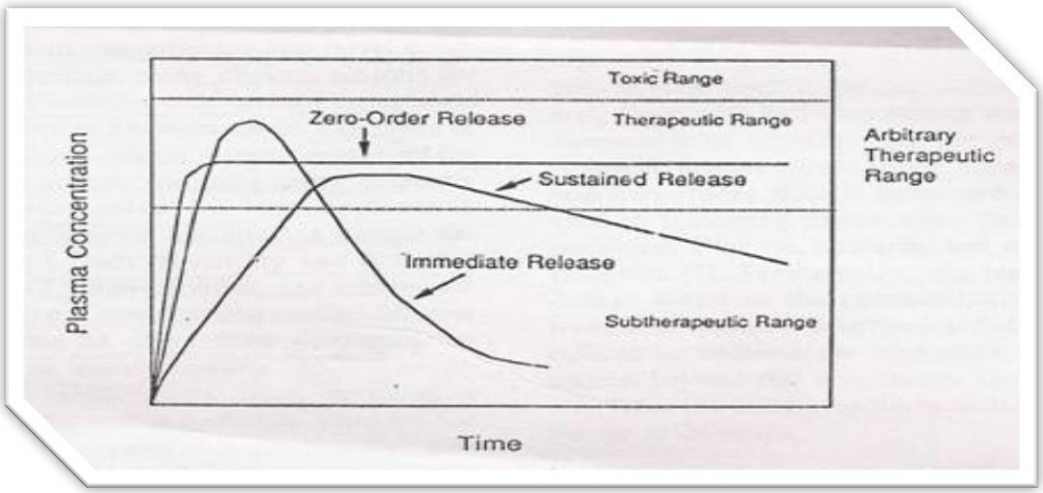


Fig 1: Plasma Concentration-profiles Vs Time (sustained release formulation and zero order formulation)

Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval.

Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet. A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio.

ADVANTAGES OF SUSTAIN RELEASE DOSAGE FORMS

1. Reduction in frequency of intakes.
2. Reduce side effects.
3. Uniform release of drug over time.
4. Better patient compliance.

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY

1. Increased cost.
2. Toxicity due to dose dumping.
3. Unpredictable and often poor *in vitro-in vivo* correlation.
4. Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
5. Increased potential for first- pass clearance.
6. Need for additional patient education and counseling.[6]

Methods used to achieve controlled release of orally administered drugs:

A. Diffusion controlled system:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. This system is of two types:

a) Reservoir type: A core of drug surrounded by polymer membrane, which controls the release rate, characterizes reservoir devices.

b) Matrix type: Matrix system is characterized by a homogenous dispersion of solid drug in a polymer mixture.

B. Dissolution controlled systems:

a) Reservoir type: Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure no.2, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals.

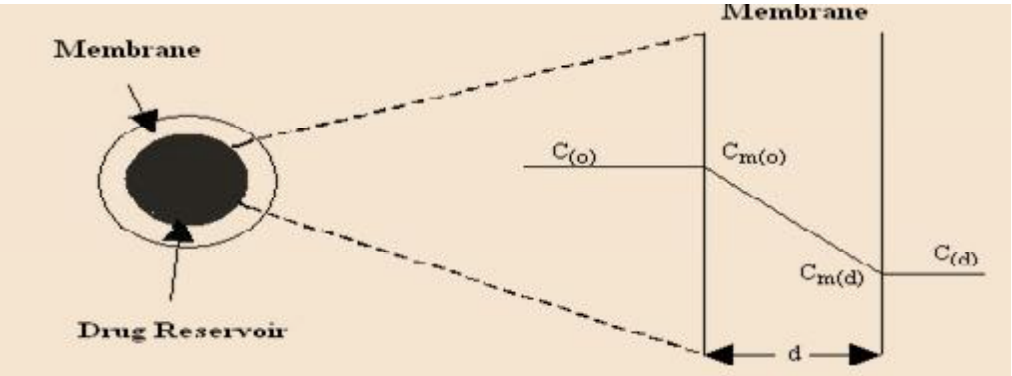


Fig 2: Schematic representation of diffusion controlled drug release reservoir system

b) Matrix type: The more common type of dissolution controlled dosage form as shown in figure 3. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

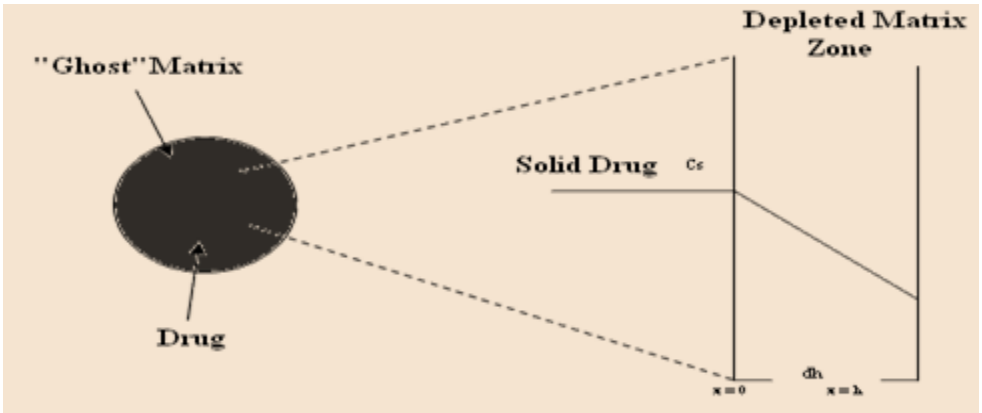


Fig 3: Schematic representation of diffusion controlled drug release matrix system

C. Bioerodible and combination of diffusion and dissolution systems:

It is characterized by a homogeneous dispersion of drug in an erodible matrix.

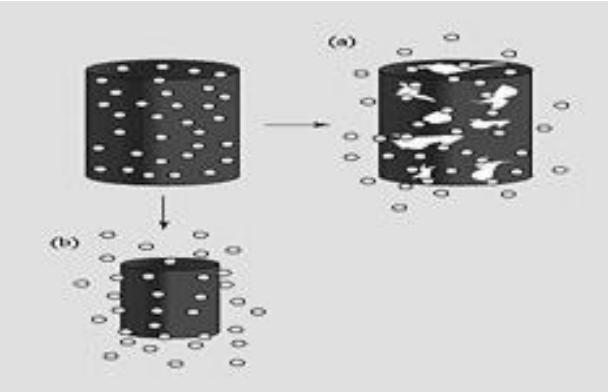


Fig 3: Drug delivery from (a) bulk-eroding and (b) surface-eroding Bio erodible systems

D. Methods using ion exchange: It is based on the drug resin complex formation when an ionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract.

E. Methods using osmotic pressure: It is characterized by drug surrounded by semi permeable membrane and release governed by osmotic pressure.

F. pH– Independent formulations: A buffered controlled release formulation as shown in figure 4, is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming polymer. When GI fluid permeates through the membrane the buffering agent adjusts the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

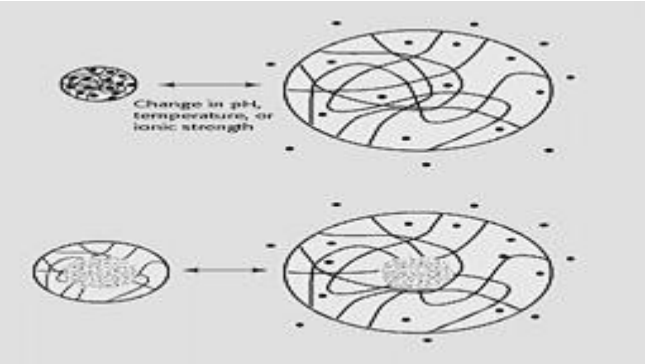


Fig 4: Drug delivery from environmentally pH sensitive release systems

G. Altered density formulations: Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High-density approach

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm

Low-density approach

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

Matrix tablets: One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression.[7]

Factors Affecting the Oral Sustain Release Dosage Form Design

A) Pharmacokinetics and pharmacodynamics factor:

1. Biological half-life

Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However this is limited in that drugs with very short biological half lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large.

2. Absorption

Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.

3. 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 n the time course of drug disposition. Thus for design of sustain release products, one must have information of disposition of drug.

4. Metabolism

The metabolic conversion to a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed

B) Drug properties relevant to sustain release formulation:

1. Dose size

A dose size of 500-1000mg is considered maximal for a conventional dosage form. This also holds true for sustain release dosage forms. Since dose size consideration serves to be a parameter for the safety involved in administration of large amounts with narrow therapeutic range.

2. Ionization, pKa and aqueous solubility

Most drugs are weak acids or bases and in order for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

3. Partition coefficient

Bioavailability of a drug is largely influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered as poor candidate for the sustain release formulation as it will be localized in the aqueous phase eg: Barbituric acid and vice a versa.

4. Drug stability

When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation. In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability.[8]

MATRIX TABLETS:

Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug release, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the release retardant. Alternatively drug and release retardant blend may be granulated prior to compression.[9]

ADVANTAGES OF MATRIX TABLET:

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.

  Ex: Morning relief of arthritis through bed time dosing.

DISADVANTAGES OF MATRIX TABLET:

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.[10]

Matrix tablet generally classified into different types:

a) Hydrophilic Matrix Tablet:

Hydrophilic matrix generally used to control the release rate of drug. The matrix can be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix materials. Water is required for the hydrophilic matrix to activate the release mechanism and explore several advantages, which includes simplicity of manufacture and excellent uniformity of matrix tablets. Use of matrix building material with fast polymer hydration capability is a best choice for formulation of a hydrophilic matrix tablet. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is suitable for formulation of water soluble drug.

b) Fat-wax Matrix Tablet:

Various technique used for incorporation of drug into fat wax granulation which involve spray congealing in air, blend congealing in an aqueous media with or without

the aid of surfactant and spray drying Technique. Bulk congealing method, a suspension of drug and melted fat wax is allowed to solidify and then comminuted for sustained-release granulations. Mixing of active ingredients waxy materials and fillers when the mixing is over this mixture converted into granule by compacting with s compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material. The drug which is embedded into a melt of fats and wax released by leaching and hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the GI tract. Addition of various surfactants to the formulation can also influence both the release rate of drug and the total drug proportion that can be incorporated into a matrix.

c) Plastic Matrix Tablet (Hydrophobic matrices):

Sustained release tablets based upon an inert compressed plastic matrix have been used widely. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with the drug particle.

d) Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to each other by functional groups and have unstable linkage in the backbone. It is biologically degraded or eroded by enzymes generated by surrounding living cells or by non enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

e) Mineral Matrices:

Mineral matrices consist of polymers which are obtained from various species of seaweeds. Example: Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.[11]

On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

- **Macro porous Systems:** In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.
- **Micro porous System:** Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.
- **Non-porous System:** Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.[12]

POLYMERS USED IN MATRIX TABLET:

- **Hydrogels:** Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)
- **Soluble polymers:** Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
- **Biodegradable polymers:** Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters
- **Non-biodegradable polymers:** Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).[13]

Mechanism of drug release from the matrix tablets:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

1) A pseudo-steady state is maintained during drug release.

2) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.

3) The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation:

dM/dh = C0. dh – Cs/2 …… (i)

Where, dM = Change in the amount of drug released per unit area.

dh = Change in the thickness of the zone of matrix that has been depleted of drug.

C0 = Total amount of drug in a unit volume of matrix.

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

dM = (Dm. Cs / h) dt..... (ii)

Where, Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix.

dt = Change in time.

By combining equation (i) and equation (ii) and integrating:

M = [Cs. Dm (2C0 –Cs) t] 1/2 ……... (iii)

When the amount of drug is in excess of the saturation concentration then:

M = [2Cs.Dm.C0.t] 1/2 …… (iv)

Equation (iii) and eq. (iv) relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

M = [Ds.Ca.p/T. (2Co – p.Ca) t] 1/2 …… (v)

Where, p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional pathlength

For pseudo steady state, the equation can be written as:

$$\mathbf{M = [2D.Ca .C0(p/T)t] 1/2 \ldots\ldots\ldots\ldots\ldots\ldots...(vi)}$$

The total porosity of the matrix can be calculated with the following equation:

$$\mathbf{p = pa + Ca/ \rho + Cex/\rho ex\ldots\ldots\ldots\ldots (vii)}$$

Where, p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients

For the purpose of data treatment, equation (vii) can be reduced to:

$$\mathbf{M = k. t 1/2} \ldots\ldots\ldots\ldots\ldots\ldots(vii)$$

Where, k = constant.

So the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion controlled.[14]

HYPERTENSION

High blood pressure is a major independent risk factor for cardiovascular disease and stroke; indeed, 5.8% of all deaths are directly linked with hypertension. All in all, hypertension is one of the five chronic diseases (psychological illnesses, diabetes, heart disease, asthma), which are responsible for half the expenditure of the health system.[15]

Hypertension (elevated blood pressure levels exceeding 140/90mmHg according to WHO criteria) is a common complex disorder, which affects 15–20% of adult population in Western societies. It is classified as primary (essential) or secondary hypertension. The

former type is used to describe hypertension without a known pathology. The diagnosis of essential hypertension is made when no other cause for increased blood pressure is found. This form of the disease constitutes about 90–95% of all hypertension cases; whereas in 5% of cases, the cause of hypertension is known to be secondary to conditions such as pheochromocytoma, primary hyperaldosteronism (Conn's syndrome), Cushing's syndrome (excessive glucocorticoids), renal diseases or drug induced.[16]

Hypertension, also referred to as high blood pressure, HTN or HPN, is a medical condition in which the blood pressure is chronically elevated. In current usage, the word "hypertension" without a qualifier normally refers to arterial hypertension.

Hypertension may also be referred as an increase in the blood pressure in any blood vessel, such as pulmonary or portal hypertension. It usually refers systolic arterial blood pressure. Hypertension is not a disease but is a physically finding.

Hypertension is defined as either:

- A systolic pressure consistently at 140 or higher.
- A diastolic pressure consistently at 90 or higher. The cut-offs from normal levels to high blood pressure, with varying degrees of severity, are as follows:
  - Optimal: systolic less than 120; diastolic less than 80
  - Normal: systolic less than 130, diastolic less than 85
  - High normal: systolic 130-139, diastolic 85-89
- High blood pressure
  - Stage 1 (mild) systolic 140-159, diastolic 90-99
  - Stage 2 (moderate) systolic 160-179, diastolic 100- 109
  - Stage 3 (severe) systolic 180-209, diastolic 110-119

Hypertension can be classified either essential (primary) or secondary. Essential hypertension indicates that no specific medical cause can be found to explain a patient's

condition. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumors (Pheochromocytoma and Paraganglioma). 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. Resistant hypertension is defined as the failure to reduce blood pressure to the appropriate level after taking a three-drug regimen. Hypertension is one of the most common complex disorders, with genetic heritability averaging 30 %.[17,18,19]

For essential hypertension mainly three following factors are responsible

1) Genetic factors

2) Racial factors

3) Risk factors modifying the course

1) Genetic factors: The role of familial aggregation, occurrence in twins has long been suspected.

2) Racial and environmental factors: Higher incidence of essential hypertension is in blacks than in whites. A number of environmental factors lik esalt intake, obesity, skilled occupation, higher living standards and patients in high stress have been implicated in the development of hypertension.

3) Risk factors: The essential hypertension that begins in the middle life is modified by a number of factors.

a) Age

b) Sex

c) Smoking

d) Obesity

e) Excess of alcoholic intake

f) Diabetes mellitus

For secondary hypertension mainly four factors are responsible:

1) Hypertension due to renal problems

2) Hypertension due to endocrine problems

3) Hypertension associated with coarctation of aorta

4) Neurogenic causes

Renal hypertension is produced by one of the following three inter-related mechanisms:

a) Activation of rennin angiotensin system

b) Sodium and water retention

c) Decreased release of vasodepressor.

Diagnosis:

The diagnosis of hypertension is based on repeated, reproducible measurements of elevated blood pressure. It serves primarily as prediction of consequences for the patient and includes a statement about the cause of hypertension. Since hypertension is usually asymptomatic until organ damage is imminent its diagnosis depends mainly on measurements of blood pressure and not on symptoms reported by patients.[20,21]

Recommended Dietary Approaches that Lower BP

Weight Loss: Weight is directly associated with BP. The importance of this relationship is evident by the high and increasing prevalence of overweight and obesity worldwide.

Reduced Salt Intake: On average as salt (sodium chloride) intake increases, so does BP. In addition to lowering BP, clinical trials have documented that reduced sodium intake

prevents hypertension (relative risk reduction of approximately 20% with or without concurrent weight loss), lowers BP in the setting of antihypertensive medications and improves hypertension control.

Increased Potassium Intake: High potassium intake is associated with lower BP. The extent of BP reduction from potassium depends on concurrent levels of salt intake and vice versa. Specifically, potassium lowers BP to a greater extent in the setting of a high salt intake compared with a low salt intake. Conversely, a reduced salt intake lowers BP to a greater extent when potassium intake is low rather than high.

Moderation of Alcohol Intake: Observational studies have documented a direct dose-dependent relationship between alcohol intake and BP, particularly above approximately 2 drinks per day.[22]

ANTIHYPERTENSIVE AGENTS:[23]

Antihypertensive agents are the drugs which lower the blood pressure in hypertensive patients. Proteins, peptides and recombinant drugs:

a. **Classification of antihypertensives**:
    1. **Diuretics:** Chlorthalidone, Clopamide, Indapamide
    2. **β Adrenergic blockers:** Acebutolol, Atenolol, Metoprolol, Propranolol, Timolol
    3. **Adrenergic blockers:** Terazosin, Prazosin, Doxazosin
    4. **α + β Adrenergic blockers:** Labetalol, Carvedilol
    5. **ACE inhibitors:** Perindopril, Captopril, Enalapril, Lisinopril, Fosinopril, Benazepril
    6. **Calcium channel blockers:** Amlodipine, Felodipine Nifedipine, Nimodipine, Verapamil

7. **Vasodilators:** Hydralazine, Minoxidil, Sodium nitroprusside
8. **Angiotensin-II receptor antagonists:** Candesartan, Losartan, Valsartan
9. **Central sympatholytics**: Clonidine, Methyldopa

Angiotensin-II receptor antagonists:

Excessive activation of the renin-angiotensin system (RAS), specifically angiotensin II, is a key component in the pathogenesis of hypertension, atherosclerosis, coronary artery disease, myocardial infarction, heart failure and nephropathy. The binding of angiotensin II to angiotensin II type 1 (AT_1) receptors produces vasoconstriction, increases aldosterone release and sympathetic activity, and mediates virtually all of the known adverse cardio vascular effects of angiotensin II. Angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) are a unique class of antihypertensive agents that selectively block AT_1 receptors in vascular smooth muscle, thereby preventing binding of angiotensin II, inhibiting the RAS and lowering BP.[24]

Blocking the AT_1 receptor mediates the blood pressure (BP) elevating effects of angiotensin, including vasoconstriction, release of aldosterone and antidiuretic hormone, sympathetic activation, and constriction of the efferent glomerular arterioles. Further, by not blocking the angiotensin type 2 (AT_2) receptors, the beneficial effects of stimulation of the AT_2 receptor are maintained, including vasodilation, tissue repair, and cell growth inhibition.[25]

Valsartan

Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure.

Valsartan is a potent and highly selective type I antagonist that lowers blood pressure in hypertensive patients.[26]

The aim of the present investigation was to formulate and evaluate the matrix tablets of an antihypertensive drug containing valsartan as an active agent.

Chapter 2

Objectives

2. OBJECTIVES

Need of the study:

The main aim of the present work was to formulate sustain release matrix tablets of Valsartan using various concentration of crosslinking agents like chitosan and sodium alginate and release retardant polymers.

Valsartan is an angiotensin II receptor antagonist, which acts by constricting blood vessels and activating aldosterone, which in turn results in reduced blood pressure. It is also used to treat congestive heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack. Due to its shorter half- life (5-6.5hrs) and frequent administration, Valsartan was selected as candidate for developing sustain released matrix tablets.

Tablets are considered as safe, cheap and stable dosage form with better patient compliance and convenience. Due to its shorter half-life, this drug is best candidate for formulation of sustain released dosage form tablets.

Objective of study:

The objective of this research work was to prepare and evaluate sustain release matrix tablets of Valsartan by direct compression method using various polymers and excipients.

- ✓ Determination of λ_{max} of Valsartan in 0.1 N NaOH.
- ✓ Determination of calibration curve of Valsartan in 0.1 N NaOH.
- ✓ Selection of various excipients.
- ✓ Drug-excipients compatibility study by using FTIR Spectroscopy.
- ✓ Formulation design of Valsartan sustain release matrix tablets.
- ✓ Evaluation of pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index and Haunser's ratio.

- ✓ Evaluation of post-compression parameters such as weight variation, thickness, hardness, friability, drug content, *in-vitro* drug release studies and *in-vitro* release kinetics studies.
- ✓ To carry out short term stability studies of optimized formulation at 25^{o}C/60% RH and 40^{o}C/75%RH.

Chapter 3

Review of Literature

3. REVIEW OF LITERATURE

3.1 Literature survey was carried out on the proposed topic by referring various scientific journals, online and offline also referred various text books available in college library. This survey reveals that no such articles were reported on the proposed work and some related articles are mentioned below.

Lakade SH et al., [27] have studied to develop hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) based Nicorandil matrix sustained release tablet for treating the anginal disorder which can release the drug up to 24 hours in predetermined rate. The *in-vitro* release rate profile of formulation F2 (Gaur gum) showed higher drug release rate than other formulation.

Shanmugam S et al.,[28] has formulated and evaluated the sustained release matrix tablets of Losartan potassium. The studies showed drug release from the tablets was sufficiently sustained and non-fickian transport of the drug from tablets was confirmed. The Losartan potassium sustained release tablets were stable at 40°C/75% RH up to 3 months period of study.

Krishnaiah YSR et al.,[29] have designed oral controlled drug delivery system for highly water soluble drugs using guar gum as a carrier in the form of three layered matrix tablet and concluded that guar gum is potential carrier in this system for a highly water soluble drugs.

Muhammad A et al.,[30] has done the formulation and *in-vitro* evaluation of Flurbiprofen controlled release matrix tablets using cellulose derivative polymers. The studies showed ethyl cellulose ether derivative polymer was effective release controlling polymer for Flurbiprofen matrix tablet. HPMC also retarded the release rate of drug when combined with ethyl cellulose.

Tabandeh H et al., [31] have prepared sustained-release matrix tablets of Aspirin using ethylcellulose, eudragit RS100, eudragit S 100 by direct compression method and reported

that ethyl cellulose with an little amount as little as 10 % in the formulation could make sustained-release Aspirin tablets.

Phani K et al.,[32] has prepared and evaluated the sustained release matrix tablets of Lornoxicam using tamarind seed polysaccharide(TSP). The studies showed that the tablets with highest binder concentration showed maximum hardness and minimum friability. After 24 hours tablets with 20% tamarind seed polysaccharide binder showed maximum drug release and tablets with 40% tamarind seed polysaccharide binder showed minimum drug release. With increasing the percentage of natural polymer, release rate decreased, though drug release pattern was mainly dependent on the type of polymer. Among all the formulations, the formulation which contains 20% TSP binder releases the drug which follows zero order kinetics via swelling, diffusion and erosion.

Yassin EH et al.,[33] formulated the novel sustained-release double-layer tablets of Lornoxicam by using cyclodextrin and xanthan gum combination. Each of the proposed DLTs (Double layered tablets) is composed a fast-release layer and a sustained-release layer, anticipating rapid drug release that start in the stomach to rapidly elevate the symptoms and continues in the intestine to maintain protected analgesic effect.

Nayak RK et al.,[34] has formulated and evaluated the sustained release matrix tablets of Lornoxicam. The tablet with guar gum in the ratio of drug: polymer (1:2) exhibited greater swelling index and better dissolution profile than those with pectin, xanthan gum, sodium alginate. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism was found to be non-fickian/anomalous according to Korsmeyer-Peppas equation.

Uddin M et al.,[35] formulated sustained release matrix tablet of Valsartan by direct compression method using Methocel K4M CR and Methocel K100M CR as polymer. They evaluated powder blend for its evaluation involves three micromeritic properties, physical

property studies of tablets and *in-vitro* release kinetics studies. The weight variation was observed to be within the prescribed limits for each formulation. *In-vitro* release studies were carried out using USP apparatus type II and dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 6.8 from 3 to 24 hours, maintained at 37±0.5°C. Kinetic modeling of *in-vitro* release profiles revealed that the drug release mechanism from all proposed formulations followed anomalous type or non-fickian transport. In this study formulation F8, F9 and F10 showed better drug release compared to other formulations. Drug release from the matrix occurred by combination of two mechanism, diffusion and erosion of tablet.

Vinit Sharma et al., [36] have developed Pregabalin sustained release matrix tablets prepared by using Hydroxy propyl methyl cellulose. The matrix tablets were prepared by direct compression method. Formulation F2, F3 to F5 failed to sustain release and among all the formulation, F4 shows 99.25% of drug release at the end of 12 hours. These results showed that above a particular concentration of MCC 101, HPMC K-100 and PVP K-30 are capable of providing sustained drug release.

Madhavi N et al., [37] developed sustained release matrix tablet of Phenytoin sodium using eudragit- RL100, eudragit-RS100, HPMC-E15, ethyl cellulose (N-14), chitosan and HPMC as release controlling factor. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Formulation F6 showed 60% of drug release for 12 hours. Criteria for selecting the most appropriate model were based on linearity (coefficient of correlation). Based on "n" value (0.168) the drug release was follows Fickian diffusion. Also the drug release mechanism was best explained by Higuchi order (correlation value is 0.9063) by using this polymer.

Varsha B. et al., [38] formulated and evaluated sustain release matrix tablets of Pregabalin by direct compression method using hydroxyl propyl methylcellulose (HPMC K-100),

polyvinylpyrrolidone (PVP K-30) and microcrystalline cellulose (MCC 101 and MCC 102) in varying ratios. Powder blends and prepared tablets were subjected to various pre-compression and post-compression evaluations respectively. Formulation F5 (which composed of HPMC K100 and MCC 102 in the ratio 1:3) and F7 (which composed of HPMC K100 and MCC 102 in the ratio 2:1) exhibited 93.03% and 95.80% of drug release respectively at the end of 12 hours. These findings revealed that by using MCC 102 and HPMC K-100, exhibited sustained release of Pregabalin for 12 hours.

Sajid et al., [39] developed sustained release matrix tablets of phenytoin sodium by the wet granulation method using water as granulating agent along with matrix materials like guar gum, sodium alginate, tragacanth and xanthan gum with varying percentage. The granules showed satisfactory flow properties, compressibility, and drug content. All the tablet formulations showed acceptable pharmacotechnical properties. In the further formulation development process, formulation F8 (55% guar gum with 10% acacia) exhibited satisfactory drug release up to 12 hours. The mechanism of drug release from all the formulations was diffusion coupled with erosion.

Subramaniam K et al.,[40] has formulated and evaluated the sustained release tablets of Aceclofenac using hydrophilic matrix system. Powder blends and prepared tablets were subjected to various pre-compression and post-compression evaluations respectively. The kinetic treatment of selected formulation (F8) showed that the release of drug follows zero order models. It is concluded that the formulation of sustained release tablet of Aceclofenac containing HPMC K100, mannitol and lactose (formulation F8) which are taken as ideal or optimized formulation of sustained release tablet for 24 hours release as it fulfills all the requirement of sustained release tablets.

Noorana et al., [41] designed twice daily mini-tablets formulation of pregabalin. For achieving the sustain release profile, various viscosity grades of hydroxyl propyl methylcellulose

polymer (HPMC K4M, K15M, K100M) were used. The mini-tablets were prepared by direct-compression method. The *in-vitro* formulation showed nearly 99.57 % of drug was sustained for a period of 12 hours. The stability study revealed that the formulations were found to be stable. It was concluded that matrix mini-tablets of Pregabalin along with HPMC can be used to improve its half-life and improve its bio-availability.

Emami J et al., [42] in the present study sustained-release matrix tablets of flutamide were prepared by direct compression method using different polymers. Cellulose ethers (HPMC and NaCMC), natural gums (guar and xanthan gums) and compressible eudragits (RSPO and RLPO) and their combinations were used in different ratios to examine their influence on tablet properties and drug release profile. Almost in all formulations, with increasing the percentage of polymer, release rate decreased, though drug release pattern was mainly dependent on the type of polymer. It was concluded that the formulations H_2F_4 (containing 25% HPMC) and S_3F_4 (containing around 40% RSPO) met the desired requirements for a sustained-release dosage form. These two formulations released their drug content with a first order kinetic.

Islam M S et al.,[43] has studied effect of polymers on sustained release Theophylline matrix tablets prepared by direct compression method using different release retardant polymers like HPMC, HPMCP, kollidon, Eudragit L 100 and Eudragit RL PO. Prepared matrix tablets showed satisfactory tableting properties. Matrix systems composed of Eudragit L 100 and Eudragit RL PO released almost 100% Theopylline within 5 hrs and 6 hrs of dissolution respectively.

Moin A et al., [44] formulated sustained release matrix tablets of Diltiazem by using microcrystalline cellulose, hydroxy propyl methyl cellulose (HPMC), locust bean gum and karaya gum. Matrix tablets of Diltiazem were prepared at different ratios of drug: gum (1:1, 1:2 and 1:4) and of the gum blends (karaya gum, karaya gum/locust bean gum, karaya

gum/hydroxy propyl methyl cellulose and karaya gum/locust bean gum/hydroxyl propyl methyl cellulose) by direct compression. The matrix tablets were evaluated for hardness, friability, *in-vitro* release and drug content. It was concluded that locust bean gum alone cannot efficiently control drug release, a suitable combination of the two natural gums (karaya and locust bean gum) may be successfully employed for formulating sustained release matrix tablets of diltiazem.

Ulla SN et al.,[45] has formulated and evaluated sustained release matrix tablets of Lornoxicam. Lornoxicam, a potent non-steroidal anti-inflammatory drug which has short half-life, makes the development of sustained release (SR) forms extremely advantageous. However, due to its weak acidic nature, its release from SR delivery systems is limited to the lower gastrointestinal tract which consequently leads to a delayed onset of its analgesic action. Therefore, the present investigation of this study was to develop Lornoxicam SR matrix tablets that provide complete drug release that starts in the stomach to rapidly alleviate the painful symptoms and continues in the intestine to maintain analgesic effect. Various formulations were developed by using release rate controlling and gel forming polymers like HPMC (K4M, K15M, K100M) by direct compression method.

Sharma VK et al.,[46] has formulated floating sustained release matrix tablets using hydroxyl propyl methyl cellulose (HPMC) K15M as matrix forming polymer and sodium bicarbonate as a gas generator. Meloxicam was used as model drug. It was observed that the buoyancy lasted for up to 24 hrs and supported by in-vitro dissolution studies. Floating drug delivery system can be successfully formulated by direct compression technique and combination of polymers.

Rao V et al., [47] have formulated and evaluated the release profile of matrix tablets of losartan potassium prepared by using different concentrations of chitosan and trisodium citrate as cross-linking agent with combination of HPMC K100M, carbopol 934P, and xanthan gum as

polymers. Matrix tablets were prepared by direct compression. It was found that among the 12 formulations F11 (99.72%) and F12 (98.70%) showed good dissolution profile to control the drug release. The above results concluded that by combining different classes of polymers an acceptable release profile can be obtained in the fluctuating *in-vivo* environment.

Michael M C et al.,[48] has studied the physico-chemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. The results of this study demonstrated that the Guaifenesin release rate was dependent upon the particle size of ethyl cellulose and the processing conditions employed to prepare the tablets. The Guaifenesin release rate was slower in tablets prepared with the "fine" ethyl cellulose particle size fraction due to the presence of fewer soluble drug clusters within the matrix. Tablets prepared by hot-melt extrusion exhibited considerably slower drug release relative to those prepared by direct compression method.

Rakesh PP et al., [49] formulated and evaluated sustained release matrix tablet of Tizanidine Hydrochloride by direct compression technique. Tizanidine hydrochloride tablets were prepared by melt direct compression technique using xanthum gum, guar gum, glyceryl behenate, glyceryl monostearate and stearic acid in different proportion. Sustained release tablets of Tizanidine prolong the time for absorption as well as bioavailability and thus better patient compliance can be achieved.

Ahmad QJ *et al.*,[50] has prepared bi-layer tablet of Lornoxicam (LOR) for the effective treatment of arthiritis. LOR was formulated as immediate release layer and sustained release layer using hydrophilic matrix (hydroxypropylmethylcellulose [HPMC K15M]). The effect of concentration of hydrophilic matrix (HPMC K15M), binder (polyvinyl- pyrrolidone [PVP K30]) and dissolution study of sustained release layer showed that an increasing amount of HPMC or PVP K30 results in reduced Lornoxicam release. The hydrophilic matrix of HPMC

could control the Lornoxicam release effectively for 24 hours. It is evident from the result that a matrix tablets prepared with HPMC and binding agent (PVP, 4% w/v) is a better system for once-daily sustained release of a highly water-insoluble drug like Lornoxicam.

Basavaraj *et al.*,[51] designed and characterized sustained release matrix tablets of Aceclofenac containing tamarind seed polysaccharide seed kernel of *Tamrindus indica* belonging to family leguminaceae. It is practically insoluble in water so it is suitable to develop sustained release matrix tablet using hydrophilic polymer. Aceclofenac is non-steroidal anti-inflammatory drug (NSAID) used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is newer derivative of Diclofenac and having less GIT complication, with short biological half-life 4 hrs, so developed formulation provides the advantages of sustained release formulations. The tamarind seed polysaccharide (TSP) was extracted from tamarind kernel powder and this polysaccharide was utilized in the formulation of matrix tablets containing Aceclofenac by wet granulation technique and evaluated for its drug release characteristics. TSP is a hydrophilic and rate controlling polymer. The matrix tablets were found to be effective in sustaining the drug release up to 12 hours so, that the controlled released profile is maintained for an extended period.

Chapter 4

Materials & Methods

4. MATERIALS AND METHODS

4.1. MATERIALS

Table 1: List of chemicals

SI.NO	MATERIALS	COMPANY NAME
1.	Valsartan	Yarrow Chem Products, Mumbai
2.	Carbapol 934P	S.D fine chem limited, Mumbai
3.	Chitosan	S.D fine chem limited, Mumbai
4.	Sodium alginate	S.D fine chem limited, Mumbai
5.	Polyvinyl pyrrolidone K30	S.D fine chem limited, Mumbai
6.	Magnesium stearate	S.D fine chem limited, Mumbai
7.	Talc	S.D fine chem limited, Mumbai
8.	Micro crystalline cellulose	S.D fine chem limited, Mumbai

Table 2: List of the Equipments

SL.NO	EQUIPMENT	MODEL/COMPANY
1.	Electronic analytical balances and precision scales	Acculab Sartorius group
2.	UV-Visible spectrophotometer	Spectrophotometer UV-1800, Shimadzu, Japan
3.	Fourier transform infrared spectrophotometer	Thermo Nicolet
4.	PH meter	Techno scientific products
5.	Multi tablet Punching machine	LAB PRESS, Cip Machinaries Ltd. Ahmedabad
6.	Roche Friabilator	PSM Industries, Benguluru
7.	Hardness tester	Monsanto hardness tester
8.	Electrical weighing balance	Essae-Teraoka
9.	Dissolution test apparatus	Lab India
10.	Stability chamber (106 Model)	LABTOP, SKY Lab Instruments and Engineering Pvt. Ltd.

4.2 DRUG PROFILE

VALSARTAN[17, 52]

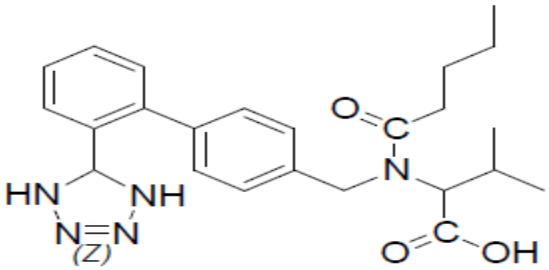
Introduction

Valsartan is a potent, orally active nonpeptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension. It was first developed by Novartis and has a wide market in the developed and the developing countries. It is also available in combination with other antihypertensive drugs. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. The drug is a very good target for the generic industries. It is soluble in the neutral pH range. It belongs to the BCS class III drug classified as low permeability and high solubility drug. Valsartan is soluble in acetonitrile and methanol. The drug is rapidly absorbed orally and has limited volume of distribution and is extensively bound to plasma proteins. Valsartan is not extensively metabolized and is mainly excreted by non-renal routes. Valsartan is effective in treatment of pediatric, adolescents and the elderly patients with mild to moderate hypertension. Monotherapy with Valsartan with 80 mg as the starting dose has shown considerable efficacy in patients with CHF and renal impairment along with hypertension and add on therapy helped control BP in large population of patients with severe hypertension not responding sufficiently to β-blockers, ACE inhibitors or diuretics. The importance of aggressive blood pressure control is undisputed, but the therapeutic focus is now extending to end-organ protection as a treatment goal of equal importance to BP reduction. Thus, the value of ARBs like Valsartan in slowing the progression of kidney disease due to high blood pressure or diabetes has very positive medical as well as commercial implications.

Physicochemical properties

Valsartan is 3-methyl-2-[pentanoyl-[[4-[2-(2*H*-tetrazoyl-5-yl)phenyl]phenyl]methyl] amino] -butanoic acid with empirical formula $C_{24}H_{29}N_5O_3$. Its molecular weight is 435.519 g/mol. Valsartan is a white coloured powder that is freely soluble in ethanol, methanol, acetonitrile and sparingly soluble in water. Valsartan appears in the melting range of 105-110˚C and the specific rotation [α]D/20 in methanol being 68˚. The partition coefficient of Valsartan is 0.033 (log P=1.499), suggesting that the compound is hydrophilic at physiological pH. The compound is stable under storage in dry conditions.

Structural formula



Pharmacology

Valsartan belongs to the family of angiotensin II type1 receptor (AT1) antagonists and this action exert effects on blood pressure (BP) reduction, as well as decreases vascular smooth muscle contraction, inhibits sympathetic outflow, improves renal function and also leads to reduction in progression of atherosclerosis lesions. Also blockade of AT1 receptor by valsartan leads to increase in local angiotensin II concentration that stimulates the unblocked AT2 receptor. The increase in AT2 receptor stimulation causes vasodilation through local production of bradykinin which in turn leads to a signalling cascade that increases the production of nitric oxide and cyclic guanosine 3'-5'-monophosphate at the endothelial level that provides protection against vascular dysfunction.

Pharmacokinetic profile

Absorption: Valsartan is rapidly absorbed orally. After oral administration of Valsartan 80mg capsule and solution formulation in 12 healthy volunteers, maximum plasma concentrations (Cmax) of Valsartan (1.64mg/l and 3.25 mg/l) were respectively reached in ~ 1-2 h. Plasma levels and the area under the plasma concentration time curve were not linearly related to dose, indicating a saturable first pass metabolism. The absorption occurs by a passive diffusion process. Food has not been reported to affect the absorption of valsartan. Hence, it can be administered with or without food.

Distribution: Valsartan has only limited distribution outside the plasma compartment and is extensively bound to the plasma proteins (94-97%) and hence is only limited distributed outside plasma compartment. Because of the presence of carboxylic groups Valsartan is soluble in neutral pH range and is mainly present in the ionized form at physiological pH. The volume of distribution at steady state is about 17l.

Metabolism and Elimination: Valsartan does not require any metabolism in the body to become active. After the oral administration of 80 mg of [14C]-radiolabelled valsartan only one

pharmacologically inactive metabolite was found in plasma nearly about 11%.

Valsartan is mainly excreted in faeces via biliary excretion and hence it is not recommended for patients with hepatic dysfunction and biliary cirrhosis. After the administration of an i.v. dose in healthy volunteers, plasma clearance of Valsartan was found to be ~2 l/h. Renal Clearance (0.62 l/h) was found to be only 30% of the total plasma clearance. Hence, it is clear that Valsartan is eliminated mostly by non-renal routes. It is only slightly metabolized and excreted mainly unchanged in bile (<80%) and urine (20%).

Therapeutic efficacy:

Hypertension: Efficacy had been studied from nine double-masked, randomized, placebo-controlled, parallel studies on 4067 patients. Patients with mild-to-moderate hypertension were given a range of doses of valsartan 10-320 mg once daily or placebo. The integrated analysis resulted in a linear relationship between increasing dose of valsartan 10 to 320 mg and blood pressure-lowering efficacy.

Chronic Heart Failure: Valsartan had favourable acute and chronic neurohormonal and haemodynamic actions in CHF according to a large randomized, double blind placebo conducted on a 5010 group of patients and had no effect on mortality among patients but patients receiving valsartan showed 13.2% reduction in morbidity. This study proved the fact that valsartan is a good treatment for patients with hypertension receiving ACE inhibitors as Valsartan has shown to decrease hospitalization (27.5%) in such patients.

Renal Impairment: A study was conducted in a randomized, double-blinded group of patients with chronic renal failure and hypertension. It showed that Valsartan (80 mg) considerably lowered the mean arterial blood pressure, when compared to placebo. It had no effect on the GFR (glomerular filtration rate) or renal blood flow when compared to placebo, but showed significant reduction in Proteinuria (26%) and albuminuria (41%).

Chronic Heart Failure: In general, Angiotensin receptor blockers like Valsartan are more effective inhibitors of the renin-angiotensin-aldosterone system than ACE inhibitors. Valsartan appears to be better tolerated in context with side effects like cough and angioedema as seen with the ACE inhibitors.

Post myocardial infarction: A study named VALIANT (valsartan in acute myocardial infarction) conducted on patients with LV systolic dysfunction, HF, or both following an acute myocardial infarction, compares the efficacy and safety of long-term treatment with Valsartan, Captopril and their combination in 14,703 high risk patients after MI. It is a

multi-centre, double blind, randomized, active controlled parallel group study. The study showed no differences in mortality among patients being treated with captopril 50 mg TID, Valsartan 160 mg BID, or the combination of Valsartan 80 mg BID with Captopril 50 mg TID.

Diabetes Mellitus: Valsartan (80 mg) gives similar response as compared to Amlodipine (5 mg) in blood pressure reduction. But Valsartan shows a significantly greater reduction in urinary albumin excretion ratio when compared to amlodipine.

Left Ventricular Hypertrophy: In a randomized double-blind study of 69 previously untreated hypertensive people, it was shown that Valsartan (80 mg daily for 8 months) reduced left ventricular mass index by 21 g/m^2 as compared to 10 g/m^2 with atenolol.

Side-effects: Dizziness (11.7%), headache and migraine (10.3%) followed thereafter. Epistaxis (0.5%), fatigue (10%), rash (1.1%) appeared the labelled adverse drug reactions associated with Valsartan. Joint stiffness, muscle cramps, myalgia added to the list. Renal functions along with creatinine clearance, electrolyte excretion and uric acid excretion are not influenced on administration of valsartan. Other reported side effects of the drug are dose-related orthostatic hypotension, rash, hyperkalemia (5%), respiratory tract disorders, nausea, vomiting (1.4%), intolerance, diarrhoea, dyspnoea, impotence/ejaculation failure, dyspepsia and oedema.

Contraindications: Valsartan is contraindicated in patients with severe hepatic impairment, liver cirrhosis, biliary obstruction and also contraindicated throughout pregnancy and lactation as the drug acts directly on the renin-angiotensin system.

Drug Interactions: Valsartan is contraindicated with NSAIDs and cephalosporin as it causes increased risk of renal impairment and hyperkalemia. With general anaesthetics, clozapine, dopamine agonists and other hypertensives valsartan causes increased risk of

hypotension. Hyperkalemia can be caused during valsartan therapy with potassium-sparing diuretics, potassium supplements, ACE inhibitors and heparin.

Dosage: Valsartan is available in the dose range of 10, 20, 40, 80, 160, and 320 mg. All doses of Valsartan have been found to be safe and tolerable.

4.3 EXCIPIENTS PROFILE

4.3.1 CARBOPOL[53, 54]

Non-proprietary names: BP: Carbomer, USPNF: Carbomer

Synonyms: Acritamer; acrylic acid polymer; carbomer; carboxyvinyl polymer; polyacrylic acid

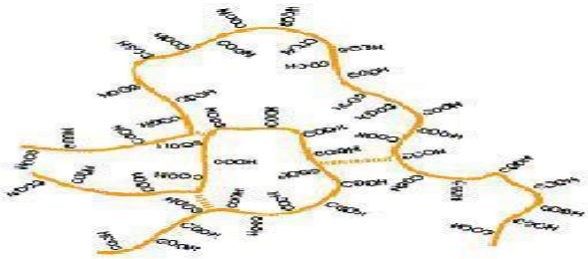
Chemical names: Carboxypolymethylene

Empirical formula: 【$-CH_2-CH-$】N-COOH

Molecular weight: Approx. 3×10^6

Description: A fluffy, white, acidic, dry powder.

Structure:



Structure of Carbopol

Solubility: It is soluble in water and forms viscous colloidal solution, insoluble in alcohol, ether and chloroform, but soluble in ethanol and glycerin after neutralization.

Typical properties:

- pH of 1.0% water dispersion: 2.5 - 3.0
- Density (bulk):1.76 g/cm^3
- Density (tapped): 1.4 g/cm^3

- Viscosity: 45,000 - 80,000 cps

Melting point: Decomposition occurs at 260°C

Functional categories: Suspending and/ or viscosity increasing agent, tablet binder, coating agent, adhesive anhydrous ointment ingredient, film former and emulsion stabilizer.

Viscosity (dynamic): Carbopol disperse in water to form acidic colloidal solutions of low viscosity which when neutralized produce highly viscous gels. 1g of carpools may be neutralized by approximately 0.4 g of sodium hydroxide; viscosity is reduced if the pH is less than pH 3 or greater than pH 12. Viscosity is also reduced in the presence of electrolytes. Gels rapidly loose viscosity on exposure to light, but this can be minimized in the presence of antioxidant.

Incompatibilities: Carbopol is decolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids and high concentration of electrolytes. Trace level of iron and other transition metals can catalytically degrade carbomer dispersions. Intense heat may be generated if carbopol is in contact with a strongly basic material such as ammonia, potassium hydroxide, sodium hydroxide, or strongly basic amines.

Storage conditions: 40-85 °F (5-30 °C)

Applications in pharmaceutical formulation or technology:

The readily water swellable Carbopol polymers are used in a diverse range of pharmaceutical applications to provide:

- Binder in tablet formulations (Controlled release in tablets).
- Bio adhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.

- Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topical.

4.3.2 CHITOSAN[55, 56]

It is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). Chitosan is produced commercially by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (such as crabs and shrimp) and cell walls of fungi.

Non -proprietary names: BP: chitosan hydrochloride

PhEur: Chitosani hydrochloridum

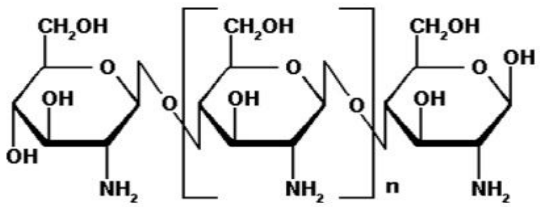
Synonyms: 2-Amino-2deoxy-(1,4) -d-glucopranan, deacetylated chitin.

Chemical name : Poly-(1-4)-2-Amino-2-deoxy-ß-D-Glucan.

Molecular weight: On average, the molecular weight between 3800 and 20,000 Daltons.

Molecular Formula: $(C_6H_{11}O_4N)_n$

Structural Formula:



Structure of Chitosan

Functional category: Coating agent, disintegrant, film forming agent, mucoadhesive, tablet binder, viscosity increasing agent.

Description: Off-white to pale yellow powder and characteristic odor.

Melting Point: Melting point range between 132-135°C.

Stability and Storage: Chitosan should be stored in a tightly closed container in a cool and dry place, at temperature of 2-8°C.

Incompatibilities: Chitosan is incompatible with strong oxidizing agents.

Safety: Chitosan is generally as a non-toxic and non-irritant material and biodegradable. It is biocompatible with healthy and infected skin.

Applications in Pharmaceutical Formulation:

- ❖ Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations.
- ❖ It is used in controlled drug delivery, mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery and colonic drug delivery systems.
- ❖ Chitosan has been processed into several pharmaceutical forms including gels, films, beads, tablets, microspheres and coating for liposomes.

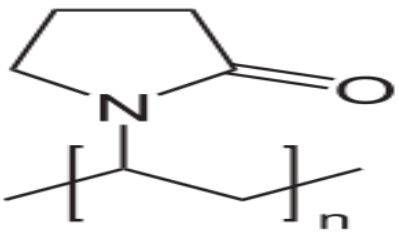
4.3.3 P0LYVINYLPYRROLIDONE[57]

Synonym: Plasdone k-30, luviskol k-30, plasdone, povidone, polyvinylpyrrolidone p, polyvinylpyrrolidone k-30, polyvinylpyrrolidone; poly (1-(2-oxo-1-pyrrolidinyl)ethylene); povidone k-30; poly(n-vinylbutyrolactam); poly(1-vinylpyrrolidinone)

Chemical name: Poly (1-vinyl-2-pyrrolidinone)

Chemical formula: $(C_6H_9NO)n$

Structure:



Functional category: Suspending agent, tablet binder.

Molar mass: 2.500-2.5000.000g.mol^{-1}

Density: 1.2 g/cm^3

Melting point: 150-180^{0}C

Boiling point: 193^{0}C

Description: It is a fine, white to creamy-white colored, odorless, hygroscopic, amorphous powder.

Incompatibility: Reactive with oxidizing agents.

Solubility: Soluble in cold water, soluble in chloroform, alcohol, chlorinated hydrocarbons, amines, nitro paraffin's, lower weight fatty acids.

Application: PVP K series can be used as film forming agent, viscosity enhancement agent, lubricator and adhesive. In tabulating, PVP solutions are used as binders in wet granulation process. PVP is also added to powder blends in the dry forms and granulated *in-situ* by addition of water, alcohol or hydro alcoholic solutions. PVP solutions are used in coating of tablets. It is also used as a suspending, stabilizing or viscosity increasing agents in topical and oral suspensions and solutions.

Stability and storage conditions: PVP darkens to some extent on heating at 150^{o}C, with a reduction in aqueous solubility. PVP may be stored under ordinary conditions without undergoing decomposition or degradation. It stored in an airtight container in a cool place, dry place.

Safety: When consumed orally, PVP may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. PVP has no irritant effect on the skin and causes no sensitization.

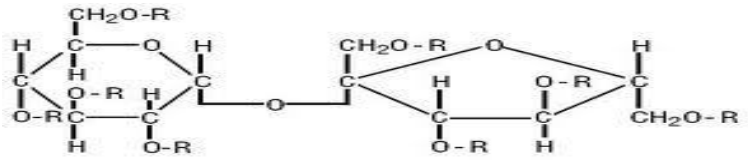
4.3.4 MICROCRYSTALLINE CELLULOSE[57]

Non-proprietary names: BP-Microcrystalline cellulose, USP/NF - Microcrystalline cellulose

Synonyms: Avicel, Cellulose gel, Crtstalline cellulose, E460, Emcocel, Fibrocel, Tabulose.

Empirical formula: $(C_6H_{10}O_5)_n$ where $n \approx 220$

Structural formula:



Molecular weight: 36000

Description: Microcrystalline cellulose is purified, partially depolymerized cellulose that occur as a white, odorless, tasteless, crystalline powder composed of porous particles.

Functional category: Adsorbent; suspending agents; tablet and capsule diluent, tablet disintegrates.

Application in pharmaceutical formulation: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/ diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression process.

Stability and Storage conditions: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool place.

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agent.

Safety: Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively non-toxic and non-irritant material.

Table no.3: Uses of microcrystalline cellulose

USE	CONCENTRATION (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule diluents	20-90
Tablet disintegrants	5-15
Tablet diluents	20-90

4.3.5 MAGNESIUM STEARATE[57]

Non-proprietary Names: BP: Magnesium stearate EP: Magnesium stearate

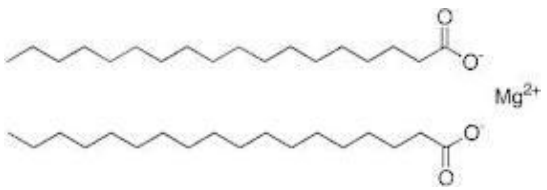
Synonyms: Metallic stearate, Magnesium salt.

Chemical Name: Octadecanoic acid magnesium salt.

Molecular Weight: 591.34.

Molecular Formula: $C_{36}H_{70}MgO_4$.

Structural Formula:



Functional Category: Tablet and capsule lubricant.

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

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Density (true): 1.092 g/cm^3

Flowability: Poorly flowing, cohesive powder.

Melting Piont: 117-150^{0}C for commercial samples and 126-130^{0}C for high purity magnesium stearate.

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

Stability and Storage: It is stable chemical substance. It should be stored in a well closed , air tight container in a cool and dry place.

Incompatibilities: It is incompatible with strong acids and iron salts. It should not be included in the formulations containing aspirin, some vitamins, and most of the alkaloidal salts.

Safety: It is one of the mostly used pharmaceutical excipient. It is non-toxic, when injected through oral route. Upon consumption of large amount produces laxative effect and can irritate mucosal layer of G.I.T.

Applications in pharmaceutical formulations and technology:

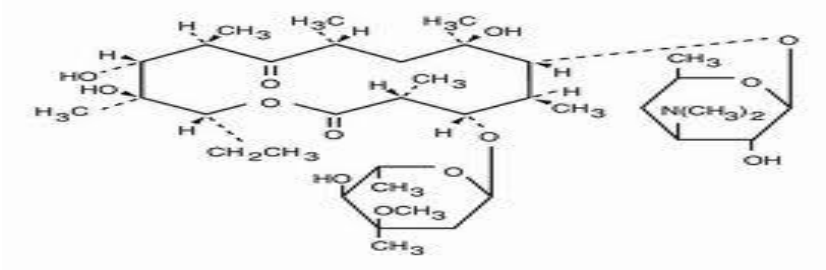
- It was extensively used in cosmetic and food formulations.
- It is primarly used as a lubricant in tablets and capsules fabricating processes at a concentrations of 0.25-2%.
- It is used to prepare barrier creams.

4.3.6 TALC[58]

Nonproprietary Names: BP: Purified talc JP: Talc PhEur: Talcum USP: Talc

Empirical Formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Structural formula:



Description: Talc is a purified, hydrated, magnesium silicate, it may contain small variable amounts of aluminium silicate and iron.

Functional Category: Anti-caking agent, Glidant, tablet and capsule diluent, tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

- Talc is widely used in oral solid dosage formulations as a lubricant and diluents.
- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended release pellets and as an adsorbent.

4.4 Preparation of sustain release matrix tablets by direct compression method [59]

Valsartan matrix tablets were prepared by direct compression method. The corresponding amount of drug and excipients were accurately weighed and mixed properly and the matrix tablets were prepared by direct compression using punching machine. Each tablet contains 80 mg of Valsartan.

Table no 4: Selected excipients for prototype formulation

Sl.NO	EXCIPIENT	FUNCTION
1	Carbopol	Release rate retardant
2	Polyvinylpyrrolidone K30	Binder
3	Micro Crystalline Cellulose	Diluent
4	Magnesium stearate	Lubricant
5	Talc	Glidant

Table no 5: Formulation development of valsartan by direct compression technique

FORMULA CODE	F1	F2	F3	F4	F5	F6	F7
Valsartan	80	80	80	80	80	80	80
Carbopol	100	100	100	100	100	100	100
Chitosan	--	5	10	15	--	--	--
Sodium alginate	--	--	--	--	5	10	15
PVP K 30	5	5	5	5	5	5	5
Magnesium Stearate	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2
Micro crystalline cellulose QS to	**250**	**250**	**250**	**250**	**250**	**250**	**250**

***All quantities are in milligrams (mg) only.**

4.5 PRE-FORMULATION STUDIES

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced.

4.5.1. Analytical Method used in the Determination of Valsartan.

The UV spectrophotometric method was developed for the analysis of the drug using Shimadzu 1800 spectrophotometer.

Preparation of 6.8 pH phosphate buffer solution:

A) Preparation of 0.2 M potassium dihydrogen phosphate

27.22gm of potassium dihydrogen phosphate was weighed and diluted up to 1000 ml with distilled water to get 0.2M potassium dihydrogen phosphate.

B) Preparation of 0.2 M NaOH

8 gm Sodium hydroxide was weighed and diluted up to 1000 ml with distilled water to get 0.2M sodium hydroxide solution.

Preparation of 6.8 pH phosphate buffer solution:

50 ml of the 0.2M potassium dihydrogen phosphate solution was taken from the stock solution in a 200 ml volumetric flask and 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then distilled water was used to make up the volume.

4.5.2 Determination of λ_{max}

1% w/v Valsartan was prepared in 0.1 N NaOH and scanned for maximum absorbance in UV double beam spectrophotometer (Shimandzu-1800) in the range from 200 to 400 nm, using 0.1 N as blank. The λmax of the drug was found to be 249 nm.

4.5.3 Standard Curve for Valsartan

100 mg of Valsartan was accurately weighed and dissolved in 100 ml of 0.1 N NaOH to prepare first stock solution. 10ml of above solution was taken and diluted to 100 ml with the same solvent to prepare II stock solution. The aliquot amount of stock solution II was further diluted with 0.1 N NaOH to get 5µg, 10µg, 15µg, 20µg, 25µg and 30µg of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 249 nm against 0.1 N NaOH as blank. The graph was plotted for absorbance vs concentration.

4.5.4 Compatibility study using FT-IR: [61]

A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration that promote the consistent release and bioavailability of the drug and protect it from degradation.

Infrared spectroscopy was conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm-1. The interaction between drug-excipients was observed from IR-Spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug.

Procedure: Weighed amount of drug (3 mg) was mixed with 100mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer. Similar procedure is followed for all relevant excipients used.

4.6 EVALUATION OF PRE-FORMULATION PARAMETERS

Melting point: Melting point of drug was determined by capillary method in triplicate.

Determination of angle of repose [62, 63]

Angle of repose is an indication of the frictional forces excited between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontal plane:

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

Where, **θ** = the angle of repose, **h** = height of the heap of the powder and **r** = radius of the heap of the powder

Table no.06: ANGLE OF REPOSE

SL.NO	ANGLE OF REPOSE(θ)	TYPE OF FLOW
1.	< 20	Excellent
2.	20-30	Good
3.	30-40	Passable
4.	>40	Very poor

Procedure: Weighed quantities of powder (mix blend) were poured through the funnel from the fixed height onto the graph paper. The height of the heap was measured. The circumference of the heap was marked by pencil. The area of the circle formed was calculated on the basis of large squares and small squares present inside the circle and angle of repose was then calculated on the parameter "r" which was found out from the area of circle.

Determination of Bulk Density and Tapped Density [63, 64]

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following formulae.

Bulk density = W / VO

Tapped density = W / VF

Where, W = weight of the powder mixture, VO = initial volume of the powder mixture and

VF = final volume of the powder mixture.[52]

Carr's compressibility Index (CI): [63, 54]

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$CI = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Table no.07: COMPRESSIBILITY INDEX

SL NO	% COMPRESSIBILITY INDEX	PROPERTIES
1.	5-12	Free flowing
2.	12-16	Good
3.	18-21	Fair
4.	23-35	Poor
5.	33-38	Very poor
6.	>40	Extremely poor

Hausner's Ratio:[63]

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Table no. 08 : HAUSNER'S RATIO

SL.NO	HAUSNER'S RATIO	PROPERTY
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive flowing

POST-COMPRESSION EVALUATION PARAMETERS

4.7 Evaluation of Valsartan sustain release matrix tablets:

Tablets were subjected to various evaluation parameters including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and *in-vitro* drug release with different media.

Weight variation [63, 65]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the **Table no 9.**

Table 09: WEIGHT VARIATION LIMIT

Sl. No.	Average weight of tablet (mg)	Maximum % difference allowed
1.	130 or less	10
2.	130-324	7.5
3.	324<	5

Tablet hardness:[63]

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability:[65]

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method: 20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.[52] Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Tablet thickness:[63]

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Callipers. It was determined by checking the thickness of ten tablets of each formulation batch.

Drug content uniformity:[59]

10 tablets were weighed from each batch and average weight is calculated. All tablets were crushed and powder equivalent to 80 mg drug was dissolved in phosphate buffer 6.8 and the volume was made up to 100 ml with pH 6.8 phosphate buffer. From the stock

solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH 6.8 phosphate buffers. Solution was filtered and absorbance was measured spectrophotometrically at 249 nm against pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

***In-vitro* dissolution studies** [35, 59]

The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. Dissolution media was 0.1 N HCl for first 2 hrs and phosphate buffer pH 6.8 for remaining hrs and temperature was maintained at 37 ± 0.5^0C. A 5ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 249 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

TABLE 10: Details data of dissolution test:

Dissolution test apparatus	USP type II
Speed	50 rpm
Stirrer	Paddle type
Volume of medium	900 ml
Volume withdrawn	5 ml
Medium used	6.8 phosphate buffer
Temperature	37±0.5ºC

Mathematical modelling of drug release profile: [66, 67]

Investigation for the drug release from the Valsartan sustain release matrix tablets was done by studying the release data with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to Korsmeyer Peppas model.

a) Zero order kinetics:

When the data is plotted as cumulative % drug release versus time, if the plot is linear then the data obeys zero- order release Kinetics, with a slope equal to K^0.

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

$$\mathbf{A_t = A_0 - K_0 t}$$

Where,

A_t= Drug release at time't'.

A_0= Initial drug concentration.

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

b) First order Kinetics:

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

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

$$\mathbf{Log\ C = log\ C_0 - K_t / 2.303}$$

Where,

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

C_0 = Initial concentration of drug.

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

c) Higuchi's model:

When the data is plotted as cumulative drug release versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

Drug release from the formulation by diffusion has been described by following Higuchi's classical diffusion equation:

$$Q = [D_\varepsilon / \varepsilon (2A - \varepsilon C_S) C_S t]^{1/2}$$

Where,

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

D = Diffusion co-efficient of the drug in the matrix.

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

C_S = Solubility of the drug in the matrix.

ε = Porosity of the matrix.

t = Tortuosity.

d) Korsmeyer equation/ Peppa's model:

When the data is plotted as log of drug released versus time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y- intercept. To study the mechanism of drug release, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_a = Kt^n$$

Where,

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

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

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

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

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

For Fickian release 'n' = 0.5 while for anomalous (non- Fickian) transport 'n' ranges between 0.5 and 1.0.

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

SL. No	'n' value	Drug release mechanism	Rate as a function of time
1.	0.45	Fickian release	$t^{-0.5}$
2.	0.45 <n = 0.89	Non- Fickian transport	t^{n-1}
3.	0.89	Class II transport	Zero order release
4.	Higher than 0.89	Super case II transport	t^{n-1}

Stability studies: [68]

Stability of a drug has been defined as ''the ability of a particular formulation in a specific condition, to remain within its physical, chemical, therapeutical and toxicological specifications''. The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence of various environmental conditions such as temperature, humidity, light. From this study we know about recommended storage condition, re-test periods and shelf-life of the drug can be established.

Stability studies are important for the following reasons.

1. This is an assurance given by the manufacturer that the patient would receive a uniform dose throughout the shelf life.
2. The drug control administration insists on manufacturers on conducting the stability studies, identity, strength, purity and quality of the drug for an extended period of time in the conditions of normal storage.
3. Stability testing prevents the possibility of marketing an unstable product. Both physical and chemical degradation of drug can result in unstable product.[57]

Purpose of stability studies: Stability studies are done to understand how to design a product and its packaging, such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and used.

Storage conditions: The selected formulations were subjected for three month stability study as per ICH guidelines**.** The selected formulations were placed in a wide mouth glass bottles, mouth of the bottle was tightly closed and packed in aluminum foils. In the present study, stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a specific period of 3 months for the selected formulations.

Chapter 5

Discussion

5. RESULTS AND DISCUSSION

5.1. Determination of λ_{max} of Valsartan

The λ_{max} of the Valsartan was found to be 249 nm in 0.1 N NaOH.

5.2. Calibration curve of Valsartan

The absorbance of Valsartan was measured in a UV spectrophotometer at 249 nm against 0.1 N NaOH as blank. The absorbance so obtained was tabulated (**table no.12**) and graph was obtained by plotting absorbance Vs concentration (**figure no.5**).

Table no.12: Spectrophotometric data for the estimation of Valsartan in 0.1 N NaOH

SL. No.	Concentration (µg/ml)	Absorbance at 249 nm				
		Trail-1	Trail-2	Trail-3	Average	S.D.
1	0	0	0	0	0	0
2	5	0.0125	0.0153	0.0153	0.00952	0.00306
3	10	0.0222	0.022	0.0219	0.0189	0.0088
4	15	0.0259	0.0258	0.0258	0.0258	0.00077
5	20	0.0320	0.0331	0.0329	0.0360	0.00351
6	25	0.0369	0.0376	0.0378	0.04174	0.00422
7	30	0.0432	0.0433	0.0434	0.0533	0.00412

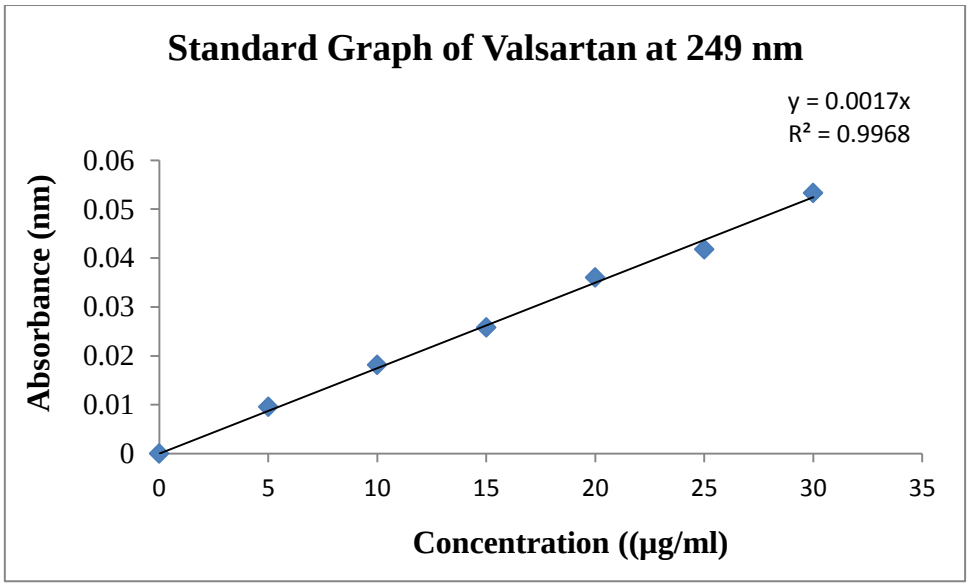


Figure 5: Calibration Curve of Valsartan in 0.1 N NaOH

Compatibility studies using FT-IR

Infra-red spectrum of drug, polymers and mixture of both were determined by KBr disks method. Samples were prepared in KBr disks by means of a hydrostatic press at 5 tons pressure for 5 min and obtained spectra were shown in the **figure no: 6-9**

All the characteristic peaks of Valsartan were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. From the results, it was concluded that there was no interference of the functional group as the principle peaks of the Valsartan were found to be unaltered in the drug- polymer physical mixtures, indicating that they were compatible chemically. The spectrum confirmed that there is no significant change in the chemical integrity of the drug.

Table 13: Interpretations of IR-spectrum

Ingredients	Functional groups with wave number (cm^{-1})				
	N-H (s)	N-O (b)	C-H(b)	C-O(s)	O-H (b)
Valsartan	1651.12	1558.54	1427.37	1280.78	840.99
Valsartan + Chitosan	--	1550.82	1388.79	1273.06	895.00
Valsartan + sodium alginate	1643.41	1550.82	1396.56	1273.06	856.42
Valsartan + Carbapol	--	1550.82	1396.51	1273.06	856.42
Valsartan + Physical mixtures	1705	1550.82	1388.79	1273.06	864.14

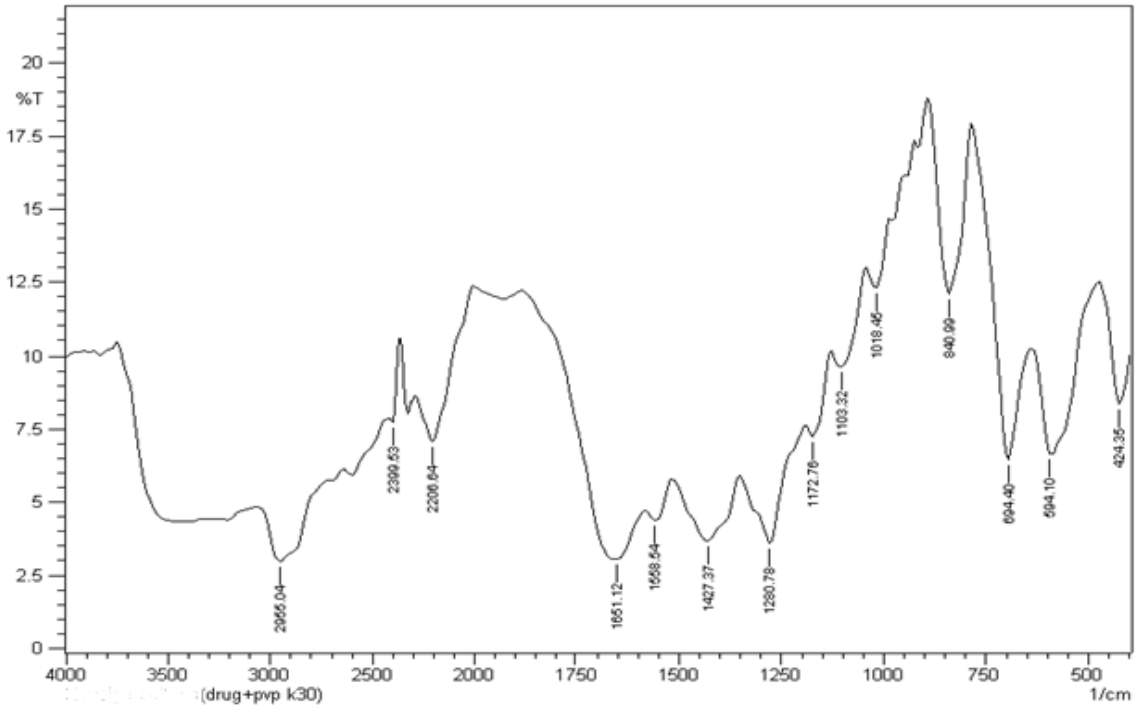


Figure 6: IR Spectrum of Pure Drug Valsartan

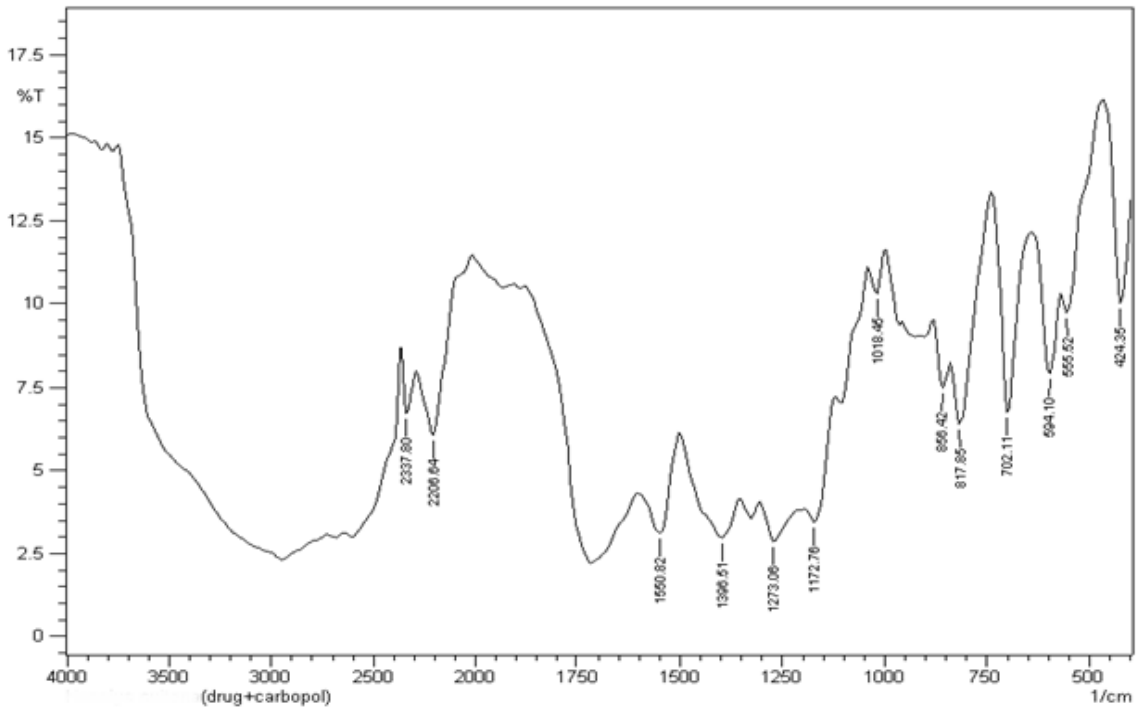


Figure 7: IR Spectrum of carbopol

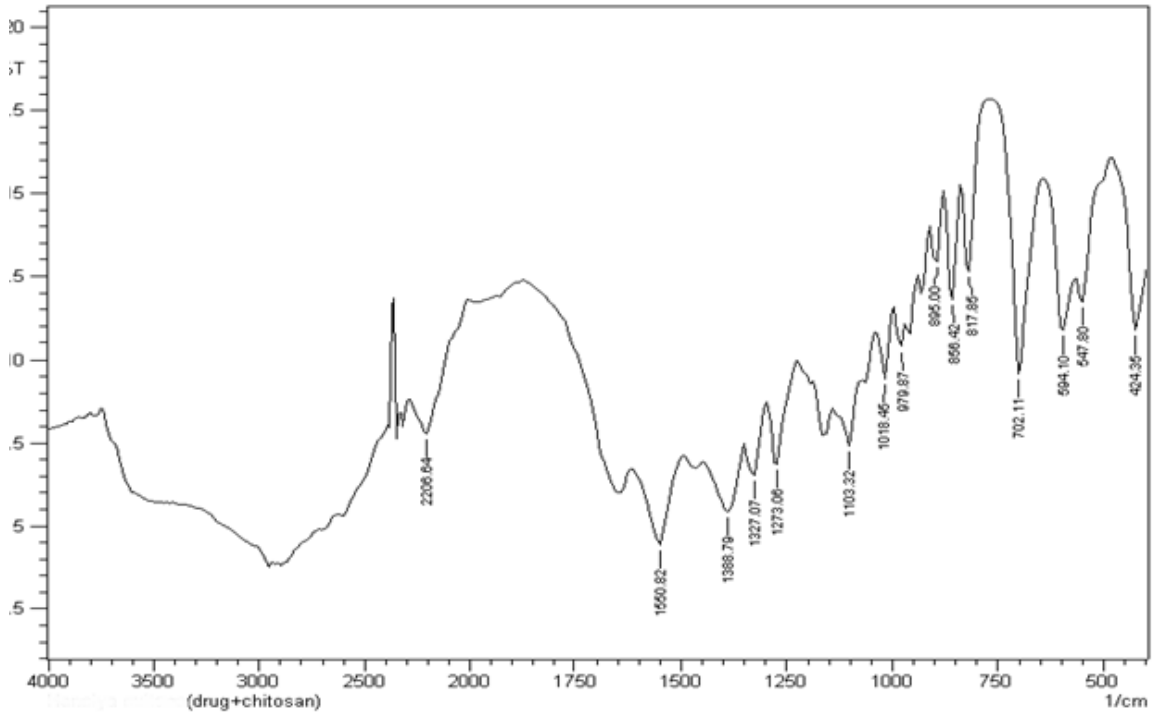


Figure 8: IR Spectrum of Chitosan

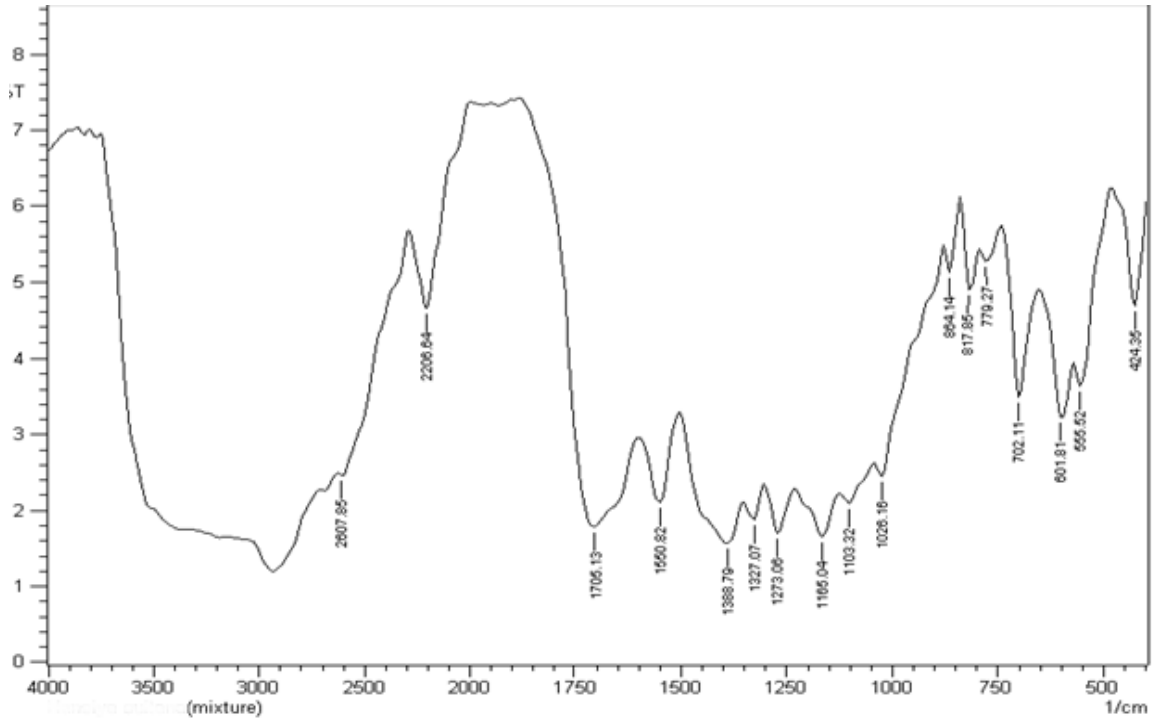


Figure 9: IR Spectrum of Drug + Physical mixtures

FORMULATION DESIGN:

The main aim of present study was to formulate sustain release matrix tablets of Valsartan using chitosan in order to improve its therapeutic efficacy and decrease the adverse effects by minimizing the dosing frequency.

In this case nine formulations of sustain released matrix tablets were prepared by using different polymers such as Chitosan, Sodium alginate, Carbapol, MCC and PVP K_{30} in different ratios. The detailed composition of each formulation is given in the **table no 5.**

The powder mixture was subjected to pre-compression and post-compression evaluation before and after compression.

Evaluation Parameters:

Evaluation of powder blended characteristics of matrix tablet formulation of Valsartan

For each type of formulation, blends of Valsartan and other excipients were prepared and evaluated for various parameters such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. Bulk density was found in the range of 0.355-0.3850 g/cm^3 and the tapped density between 0.4101- 0.4880g/cm^3 indicating both parameters were found to be within the limits. Using the above two density data, Carr's compressibility index were calculated. The compressibility index and Hausner's ratio was found in the range of 7.27-18.42 % and 1.053-1.24 respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range of 25.33-31.43°. The results of angle of repose showed all powder blends exhibited good to acceptable flow property. The results of pre-compression parameters are shown in **table no** 14.

Table no.14: Evaluation parameters of pre-formulation characteristics of powder blend

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.3716±0.0011	0.4101±0.0025	7.27±0.659	1.177±0.0076	29.73±0.41
F2	0.3803±0.0005	0.4120±0.0026	7.58±0.514	1.053± 0.0060	25.33±0.63
F3	0.3843±0.0015	0.4120±0.005	7.43±0.760	1.059±0.0088	28.44±0.35
F4	0.376±0.0020	0.4270±0.0037	13.78±0.386	1.073±0.0053	27.48±0.52
F5	0.355±0.0017	0.4600±0.0024	17.31±0.794	1.224±0.011	31.34±0.13
F6	0.3810±0.0045	0.4880±0.0065	18.42±0.120	1.24±0.0020	28.26±0.43
F7	0.3850±0.0081	0.4384±0.133	10.88±0.030	1.123±0.0021	27.27±0.42

Physical evaluation of tablets

After compression various quality control tests were carried out, which demonstrated following organoleptic properties *viz*. colour, odour and shape. All formulations **(F1 to F7)** were found to be white in colour, odourless and concave round flat with break-line on one side.

Table no.15: Organoleptic properties of prepared tablets

Formulation code	Color	Odour	Shape
F1	White color	odourless	Concave, round and flat with break-line on one side
F2	White color	odourless	Concave, round and flat with break-line on one side
F3	White color	odourless	Concave, round and flat with break-line on one side
F4	White color	odourless	Concave, round and flat with break-line on one side
F5	White color	odourless	Concave, round and flat with break-line on one side
F6	White color	odourless	Concave, round and flat with break-line on one side
F7	White color	odourless	Concave, round and flat with break-line on one side

Table no.16: Post-compression parameters results

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	7.82±0.012	3.9±0.09	250.89±0.12	7.3±0.04	0.61±0.007	98.25±0.044
F2	7.80±0.002	4.0±0.02	253.88±0.60	7.8±0.03	0.52±0.005	100.31±0.037
F3	7.85±0.007	4.2±0.01	251.12±0.52	8.0±0.07	0.58±0.031	98.54±0.07
F4	7.84±0.022	3.9±0.07	249.81±0.13	6.5±0.04	0.72±0.016	99.67±0.087
F5	8.0±0.015	4.0±0.04	250.80±0.32	6.8±0.08	0.665±0.09	99.37±0.058
F6	7.94±0.010	3.8±0.09	248.92±0.44	7.1±0.03	0.714±0.01	98.97±0.073
F7	7.97±0.016	4.1±0.01	252.61±0.60	6.0±0.05	0.447±0.00	101.61±0.08

Discussion about the physical parameters such as

A. Thickness of tablets

B. Hardness

C. Friability

D. Weight Variation

E. Drug content

A. Thickness of tablets

All the formulations were evaluated for their thickness using "Vernier callipers" as per procedure in methodology section 4 and the results are shown in **table no 16.** The average thickness for all the formulations was found in the range of 3.8-4.2 mm which is within the allowed limit of deviation i.e. 5% of the standard value. Also the crown diameter of all the tablet formulation was in the range of 8.0-7.8 mm.

B. Hardness

Tablet hardness is one of the critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before its administration. All the controlled release matrix tablet formulations of Valsartan were evaluated for their hardness as per procedure in methodology section 4 and the results were dissipated in **table no 16**. Hardness test was performed by "Monsanto hardness tester". All

the formulations have an average hardness in between 6.0 to 8.0 kg/cm^2. This ensures good handling characteristics of all formulation batches.

C. Friability

Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. Friability of prepared tablets was determined by using "Roche friabilator". The entire controlled release matrix tablet formulations were evaluated for their percentage friability and the results are shown in **table no 16**. The average percentage friability for all the formulations was found in between 0.447% to 0.72%, which is found within the pharmacopoeial limit (i.e. less than 1%). So the maximum friability was 0.72% observed for F_4 and the minimum friability 0.447% observed for F_7.

D. Weight variation test:

As the powder material was free-flowing, tablets obtained were uniform in weight due to uniform die fill with acceptable variation as per IP standards. The weight variation for all formulations was found in the range of 249.92 to 253.88 mg and results were dissipated in **table no 16**. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits (<5%). The weights of all the tablets were found to be uniform with low standard deviation values.

E. Drug content:

The percentage of the drug content for formulation F1 to F7 was found to be between 98.25%w/w and 101.61%w/w. It complies with official specifications. The results were shown in **table no 16**.

***In-vitro* drug release study:**

In this study carbopol was chosen as polymer and it was combined with chitosan and sodium alginate to explore their sustain release capability. The *in-vitro* release data for chitosan-carbopol and sodium alginate-carbopol based Valsartan sustain released matrix

tablets are represented in **table 17** and illustrated in **figure 10.** The *in-vitro* release of Valsartan, from prepared matrix tablets formulations was mainly affected by dissolution medium, concentration of chitosan, concentration of sodium alginate and concentration of polymers. *The in-vitro* release of Valsartan form prepared matrix tablets also depends on swelling behaviour of the tablets, higher the tablet swells comparative the lesser amount of drug release. The *in-vitro* release study was performed in 0.1 N HCl for initial first 2 hrs, and then the medium was replaced by phosphate buffer pH 6.8) and study was continued for 24 hour. The *in-vitro* release of Valsartan was higher in first 6-7 hours in all formulations. After 1 hour, approximately 10.29%- 18.34% of Valsartan from chitosan-carbapol tablets, 16.90%-21.91% from sodium alginate-carbapol, 25.12% from tablets containing only release retardant polymer has been released. Initially amount of drug release was higher but after 6-7 hrs drug release was retarded. Formulation F_1 do not contains any crosslinking agent, so almost all drugs was released at the end of 12 hrs. Formulation F_2, F_3, F_5, and F_7 containing lower concentration of chitosan and sodium alginate showed almost all drug release within 16 hrs, 20 hrs, 16 hrs and 18 hrs respectively. Thus these formulations were not considered as good formulation as the maximum amount of drug was released before desire period of time i.e. 24 hrs. The ionic interaction between crosslinking agents and negatively charged polymers was greatly reduced at this pH 6.8 and forms a loose network with increase porous surface which allows great part of dissolution media. Formulation F_4 and F_7 containing highest concentration of chitosan and sodium alginate respectively along with carbopol gum respectively prolong the release of Valsartan to 24 hrs which might be due to the fact that the self-assembled poly electrolyte complexes film was formed on the surface of cross linking agent-polymer based system. Swelling study also showed that formulation which contains higher concentration of cross linking agent showed higher swelling capacity and prolonged the drug release to 24 hrs.

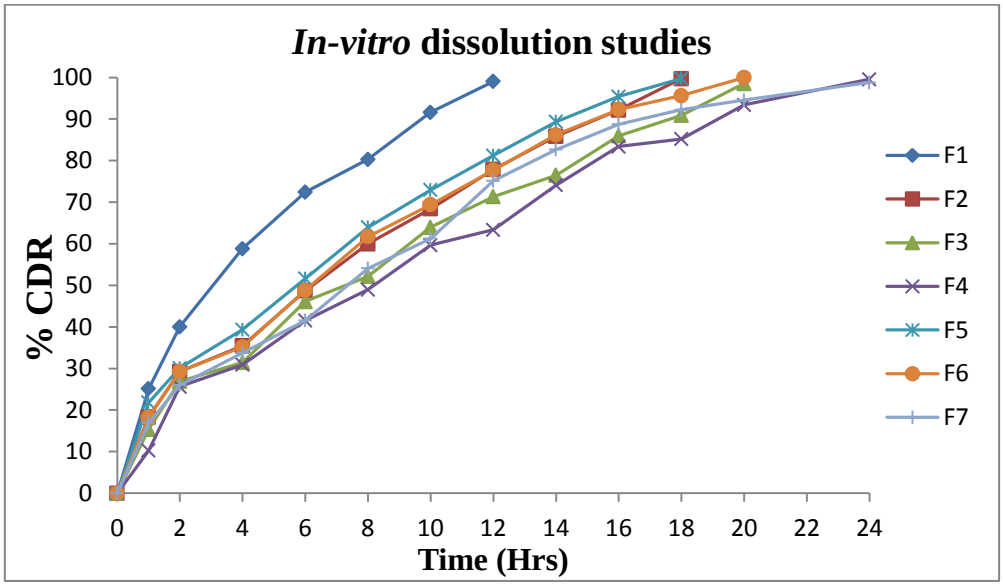


Figure 10: Comparative dissolution profile of the formulations F_1 to F_7

Time (Hrs)	Cumulative Percentage Drug Release						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
0	0	0	0	0	0	0	0
1	25.12±0.09	18.34±0.43	15.386±0.33	10.29±0.55	21.91±0.54	18.25±0.32	16.90±0.85
2	40.02±0.12	29.24±0.21	26.905±0.45	25.64±0.62	30.92±0.43	29.25±0.22	25.99±0.42
4	58.82±0.14	35.45±0.33	31.465±0.21	30.94±0.53	39.33±0.54	35.20±0.64	33.71±0.79
6	72.41±0.14	48.71±0.2	46.137±0.13	41.54±0.45	51.64±0.51	48.82±0.73	41.55±0.54
8	80.03±0.28	59.99±0.54	52.186±0.43	48.96±0.38	63.93±0.65	61.73±0.85	54.08±0.64
10	91.61±0.34	68.41±0.55	63.97±0.42	59.68±0.42	72.96±0.72	69.40±0.88	61.27±0.53
12	99.07±0.12	77.09±0.22	71.33±0.54	63.38±0.38	81.23±0.42	77.73±0.95	75.14±0.43
14	--	85.86±0.26	76.50±0.65	74.11±0.43	89.37±0.45	86.24±0.76	82.67±0.48
16	--	92.15±0.33	85.96±0.66	83.39±0.14	95.39±0.62	92.28±0.87	88.75±0.48
18	--	99.71±0.42	90.88±0.59	85.21±0.11	99.77±0.11	95.62±0.73	92.23±0.48
20	--	--	98.54±0.43	93.39±0.14	--	99.99±0.61	94.54±0.48
24	--	--	--	99.54±0.11	--	--	98.78±0.48

Table 17: *In-vitro* drug release profile of Valsartan sustain release matrix tablets

Release kinetic studies:

The *in-vitro* drug release data of all formulations were analysed for determining kinetics of drug release. The obtained data were fitted to zero order kinetics, first order kinetics and Higuchi model. The highest correlation coefficient (r^2) obtained from these method gives an idea about model best fitted to the release data. From the results of kinetic studies, the examination of correlation coefficient 'r' indicated that the drug release followed **first order release kinetics**. It was found that the value of 'r' for first order ranged from **0.981-0.992**, which is near to **1** when compared to Higuchi square root ranged from **0.892-0.958** and zero order ranged from **0.895-0.969.** So, it was understood to be following first order release pattern followed by all formulations. Further, to understand the drug release mechanism, the data were fitted into Korsmeyer Peppas exponential model $\mathbf{M_t / M_a = Kt^n}$. Where $\mathbf{M_t / M_a}$ is the fraction of drug released after time **'t'** and **'k'** is kinetic constant and **'n'** release exponent which characterizes the drug transport mechanism. The release exponent (n) ranges in between **0.483-0.7911**. For all the formulations F_1 to F_9 the values for **'n'** ranged above **0.89** which indicates that all the formulations followed **non-fickian** release mechanism. The relative complexity of the prepared formulations may indicate that the drug release mechanism was possibly controlled by the combination of diffusion and erosion.

Table no. 18: Release exponent values and release rate constant values for different formulations

Batch	Zero order	First order	Higuchi's plots	Korsmeyer-Peppas plots		Best fit Model	Drug release mechanism
	R^2	R^2	R^2	R^2	N		
F_1	0.9293	0.982	0.9116	0.912	0.597	First order	Non-Fickian
F_2	0.969	0.974	0.8944	0.915	0.594	First order	Non-Fickian
F_3	0.916	0.984	0.9217	0.899	0.6077	First order	Non-Fickian
F_4	0.946	0.978	0.8926	0.892	0.577	First order	Non-Fickian
F_5	0.944	0.992	0.9581	0.902	0.488	First order	Non-Fickian
F_6	0.895	0.958	0.9022	0.929	0.7911	First order	Non-Fickian
F_7	0.896	0.981	0.9258	0.938	0.4838	First order	Non-Fickian

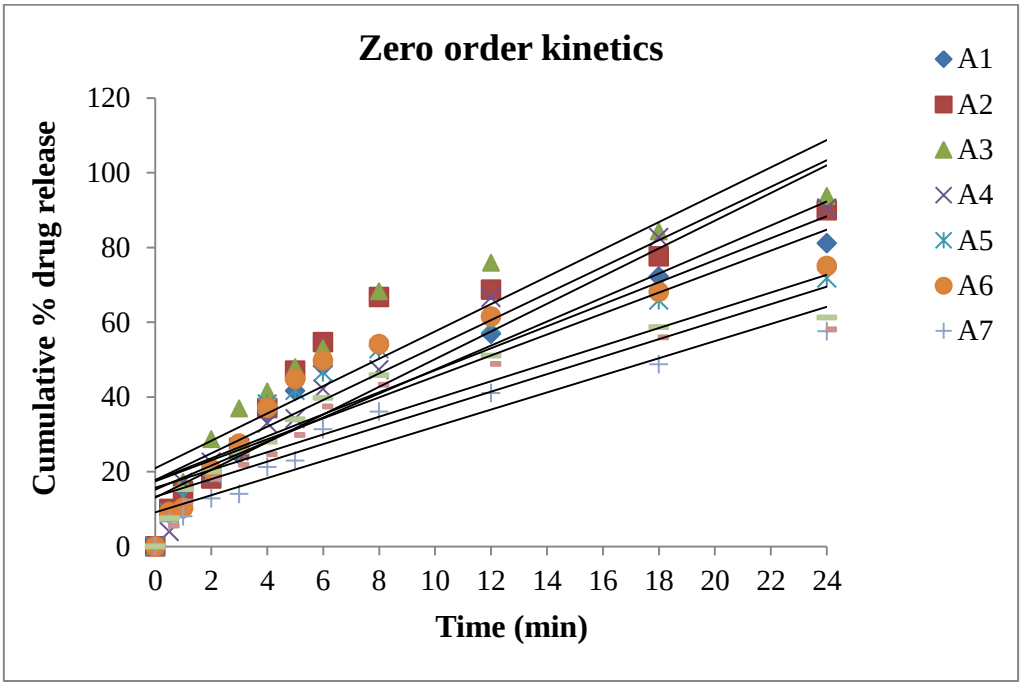


Figure 11: Comparative Zero Order release profile of formulations F_1 to F_7

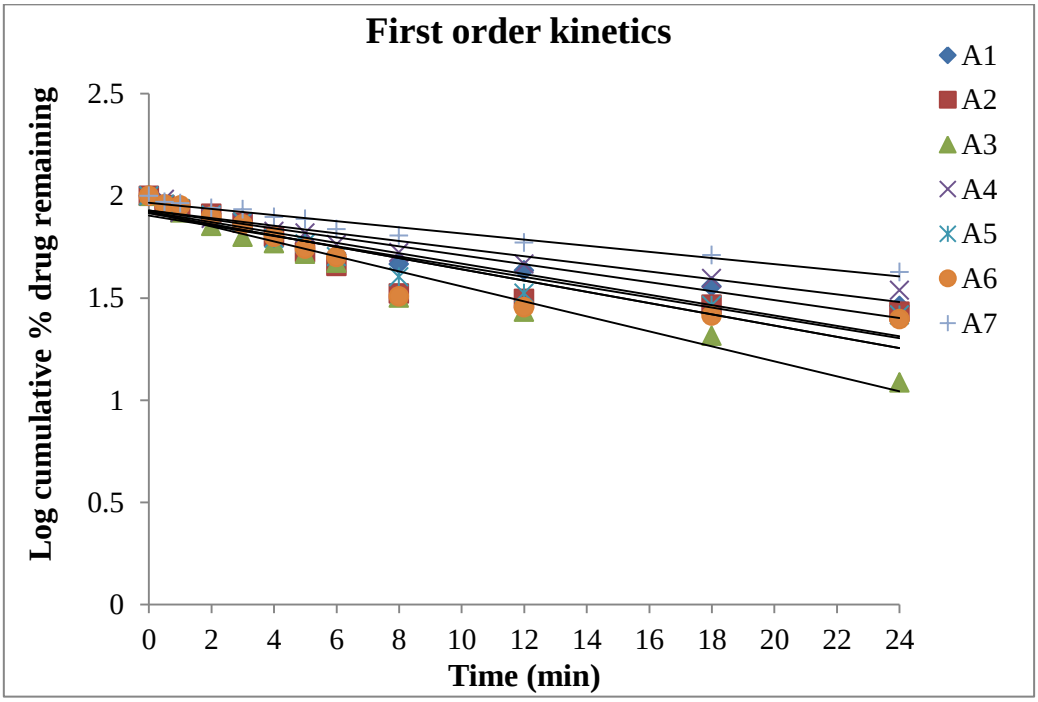


Figure 12: Comparative First Order release profile of formulations F_1 to F_7

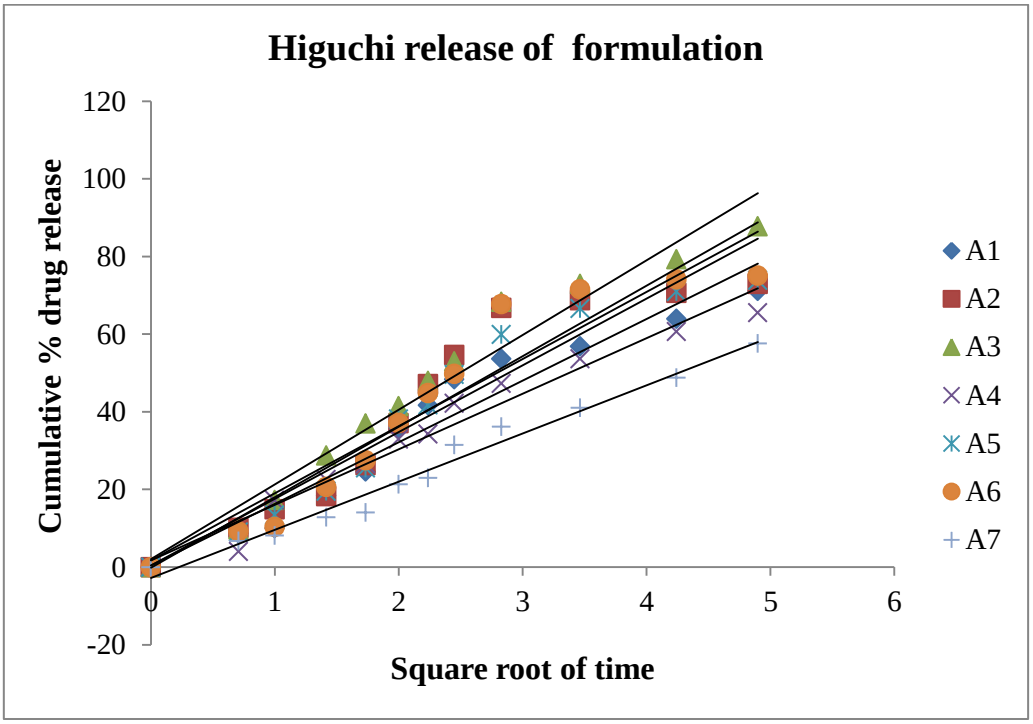


Figure 13: Comparative Higuchi release profile of formulations F_1 to F_7

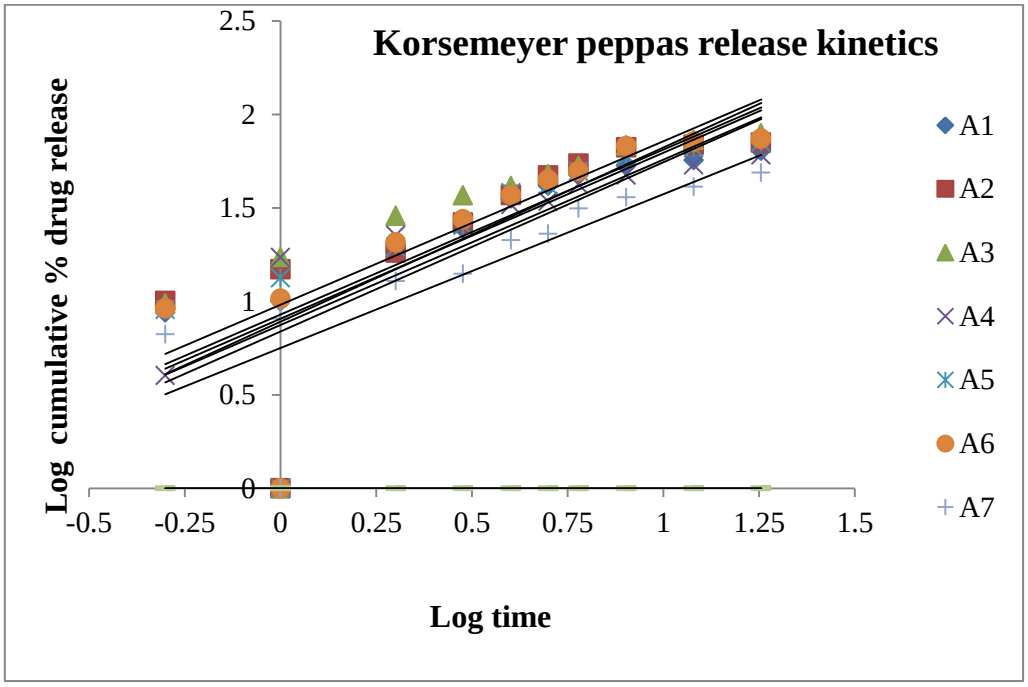


Figure 14: Comparative Korsemeyer peppas release profile of formulations F_1 to F_7

Stability studies:

Based on the results of *in-vitro* drug release two best formulations F_4 and F_7 were selected for three month stability studies at 25ºC/60% RH and at 45ºC/75% RH. The stability studies were conducted according to the method described in section four. The selected formulations were evaluated for physical appearance, hardness, friability, and drug content and *in-vitro* drug release. The results showed that there was no significant change in physical appearance, hardness, friability, drug content and drug release profile throughout the study period. Three months of stability studies revealed that; there was no any significant degradation of the drug. Thus prepared formulations were physically and chemically stable. The result of stability studies were tabulated in **table no 19**

Table 19: Results of stability studies for formulation F_4 stored at 25ºC/60% and 45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_4				Formulation F_4			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	% Drug content	% CDR
Initial	8.0±0.07	0.58±0.1	99.67±0.3	99.5±0.4	8.0±0.07	0.58±0.2	99.6±0.3	99.5±0.2
After 1 month	7.9±0.12	0.60±0.3	98.84±0.1	99.2±0.4	7.7±0.098	0.61±0.1	98.7±0.2	99.0±0.3
After 2 month	7.8±0.46	0.65±0.2	97.97±0.2	98.6±0.4	7.5±0.07	0.64±0.3	97.4±0.3	98.3±0.2
After 3 month	7.6±0.13	0.62±0.1	97.76±0.3	98.0±0.4	7.4±0.07	0.66±0.1	97.1±0.3	97.8±0.2

Table 20: Results of stability studies for formulation F_7 stored at 25ºC/60% and 45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_7				Formulation F_7			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	Drug content	% CDR
Initial	6.6±0.06	0.54±0.2	101.6±0.3	98.6±0.5	6.6±0.09	0.54±0.3	96.8±0.3	98.7±0.5
After 1 month	6.5±0.16	0.57±0.3	99.6±0.1	98.5±0.5	6.4±0.11	0.55±0.1	96.5±0.3	98.5±0.5
After 2 month	6.3±0.21	0.60±0.4	99.4±0.2	98.1±0.5	6.2±0.21	0.59±0.1	96.2±0.3	97.8±0.2
After 3 month	6.2±0.15	0.62±0.3	98.3±0.6	97.6±0.5	6.0±0.23	0.61±0.3	96.0±0.3	97.4±0.3

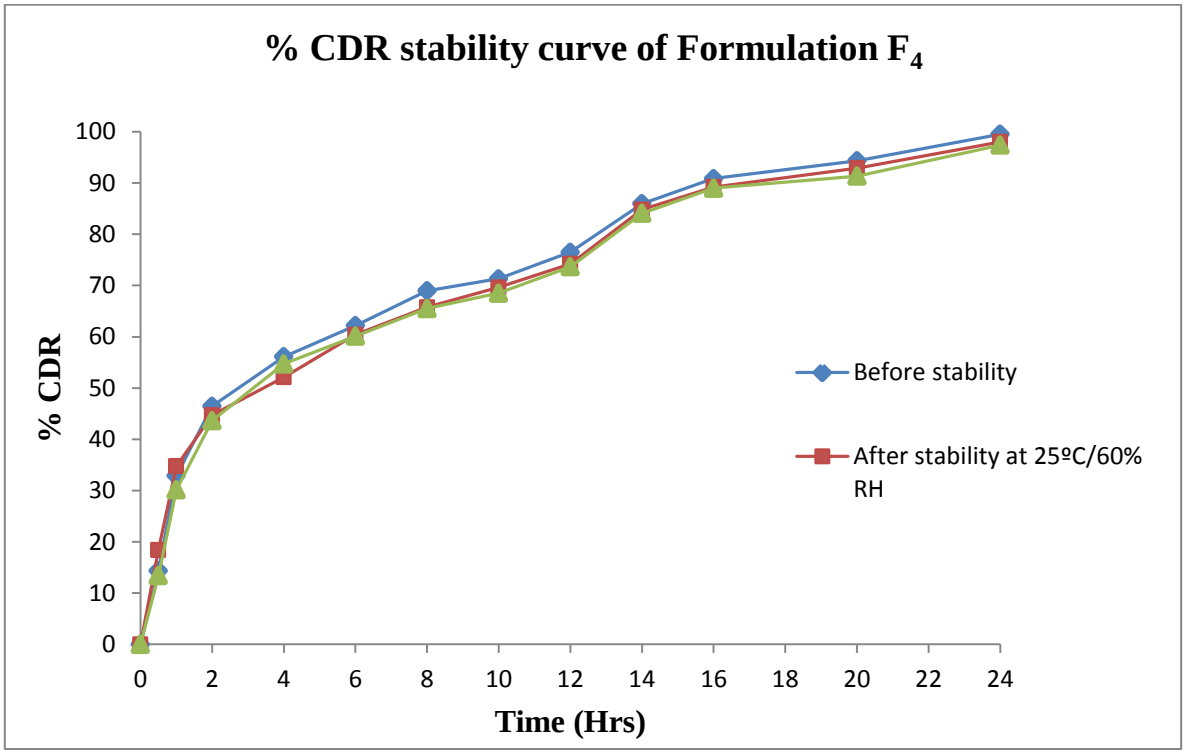


Figure15: Dissolution rate profile of formulation F_4 before and after stability.

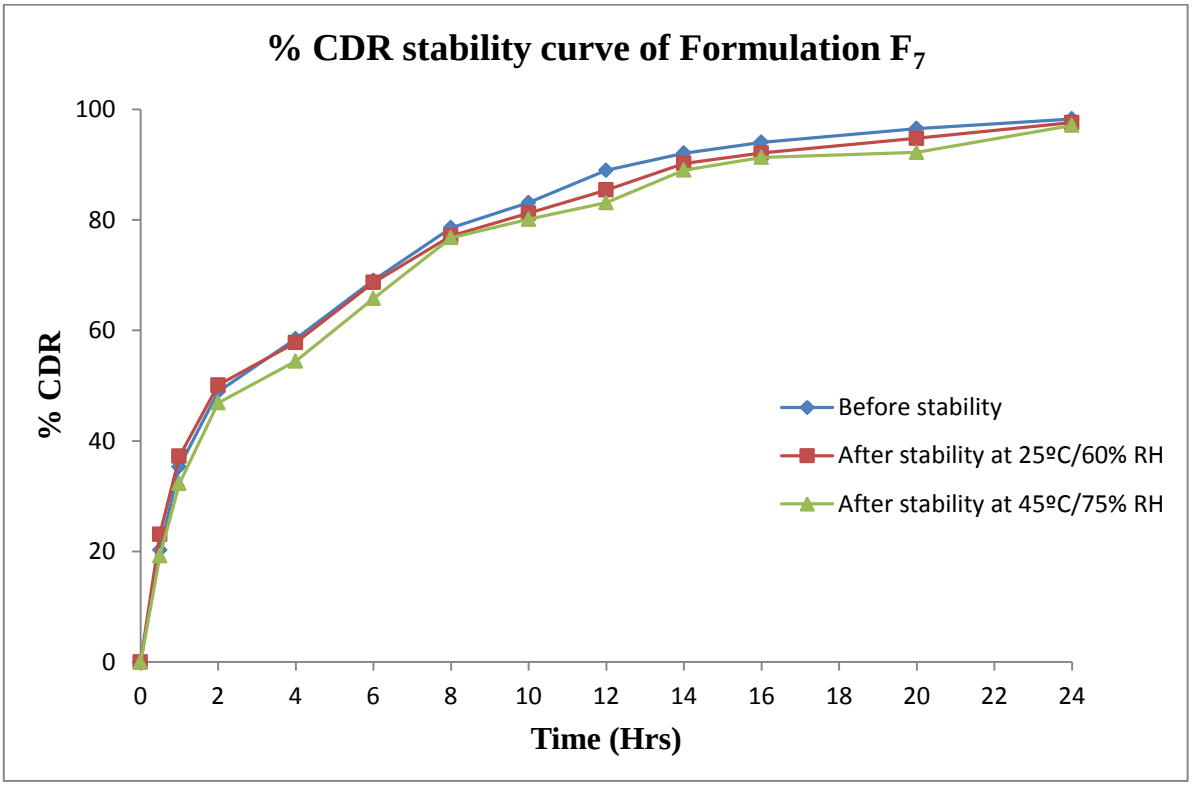


Figure16: Dissolution rate profile of formulation F_7 before and after stability.

Chapter 6

Conclusion

6. CONCLUSION

Valsartan is a potent, orally active non peptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension. The objective of the present study was to investigate the possibility of sustaining the valsartan release from matrix tablet prepared by using different concentration of cross linking agents and polymers.

The following conclusions can be drawn from the result obtained.

- The pre-formulation studies like angle of repose, bulk density, tapped density Haunser's ratio and Carr's index of all formulations were found to be within the standard limits.
- FTIR studies revealed that there was no chemical interaction between drug and other excipients.
- The powder mixtures were compressed into tablet and evaluated for post-compression parameters like weight variation, thickness, hardness, friability and drug content. All the formulation batches showed acceptable results.
- The *in-vitro* drug release was studied with USP Type-II dissolution apparatus in both simulated gastric fluid and intestine fluid for a period of 24 hours. Results showed that formulations containing higher concentration of chitosan i.e. F_4 (99.54%) and sodium alginate i.e. F_7 (98.78%) sustained the drug release over a period of 24 hours.
- The *in-vitro* drug release follows first order and indicated that non-Fickian could be the mechanism of drug release.
- Stability studies showed that the tablets formulations were stable throughout the stability period.
- It was concluded that the polymer and cross linking agents plays a major role in the formulation of sustain release matrix tablets of Valsartan. Finally, the study revealed that the release of drug was low when the matrix tablet contained higher concentration of cross linking agents and polymers also showed similar diffusion and erosion kinetics.

Chapter 7

Summary

7. SUMMARY

Valsartan is an angiotensin II receptor antagonist, which acts by constricting blood vessels and activating aldosterone, which in turn results in reduced blood pressure. It is also used to treat congestive heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack. Due to its shorter half- life (5-6.5hrs) and frequent administration, Valsartan was selected as candidate for developing sustain released matrix tablets.

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. Sustain release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration 2-3 times.

The use of polymers in sustaining the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustain release can be achieved by using carbopol 934P along with cross-linking agents and other excipients used were PVP K30 as binding agent, MCC as a direct compressible agent, talc and magnesium stearate as a glidant and lubricating agent respectively.

- Drug and excipients were subjected for compatibility study using FT-IR, which suggested that there was no interaction between drug and excipients.
- All the formulations were subjected for various pre-compression studies such as angle of repose, bulk density, tapped density, Carr's index, Haunser's ratio and results revealed that the powder mixtures showed good to acceptable flow and compressibility properties.
- All the formulations were subjected for various post-compression studies such as weight variation, hardness, thickness, friability, drug content and *in-vitro* dissolution studies. The hardness and thickness of prepared tablets were found in the range of 6.0 to8.0 kg/cm^2

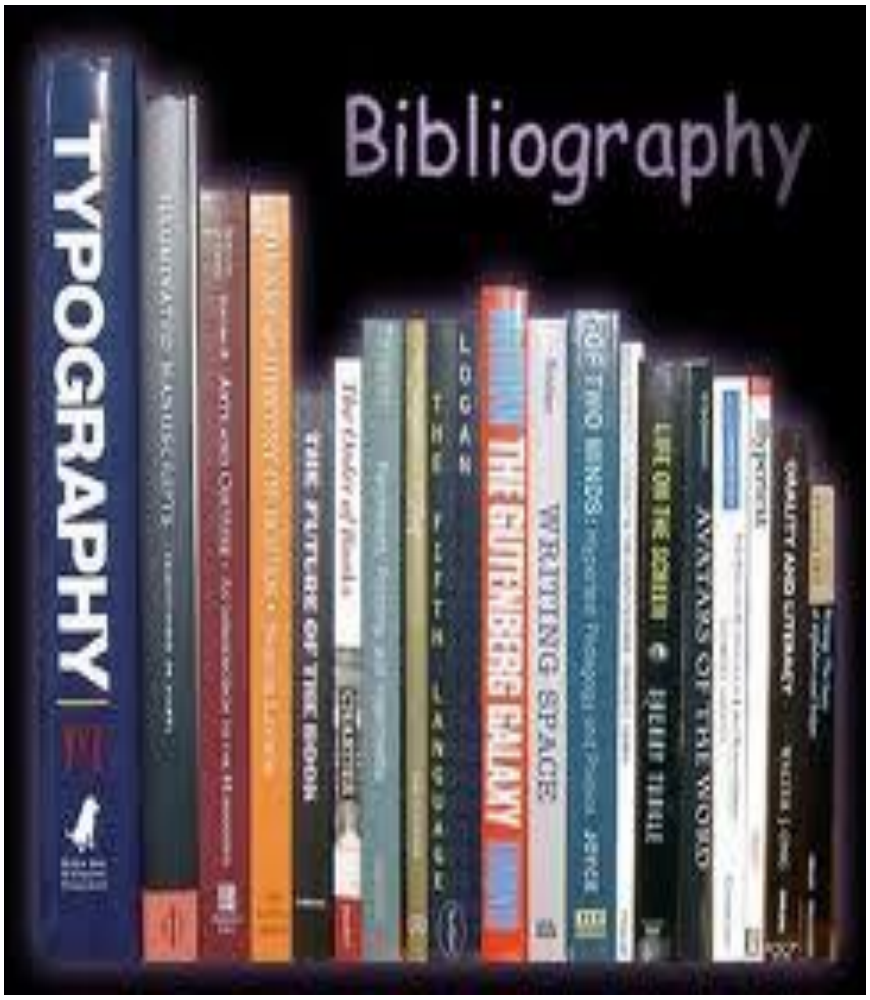
and 7.8.0-8.0 mm and all other parameters were within the standard official specifications.

- The results of *in-vitro* dissolution study indicated that the drug release from formulation F_4 and F_7 showed 99.54% and 98.78% respectively at the end of 24 hours in sustain manner.
- To analyze the mechanism of drug release from the matrices, the *in-vitro* drug release data were fitted to Zero order, First order, Higuchi and Korsmeyer's-Peppas model.

  It was observed that the release of drug followed first order and the mechanism was found to be non-Fickian.
- The best formulations F_4 and F_7 were subjected to 3 months stability studies and results showed there was no significant change in the hardness, friability, drug content and *in-vitro* drug release. Thus it was found that prepared tablets were physico-chemically stable throughout stability period.

  Thus it can be summarised that the stable matrix tablet dosage form of Valsartan has been developed for sustain release in the treatment of hypertension.

Chapter 8



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