# Development and Assessment of Sustained Release Matrix Tablet of Antihypertensive Drug

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**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.**

## I. INTRODUCTION

Oral route of drug administration is the most widely accepted and preferred route for drug delivery because of its convenience, safety, cost-effectiveness, and high patient compliance. The majority of pharmaceutical dosage forms available in the market are intended for oral administration. Historically, oral drug delivery has remained the dominant route owing to ease of administration, accurate dosage, and better acceptance by patients of all age groups. Moreover, oral dosage forms do not require sterile conditions and generally pose minimal risk of infection or tissue damage at the site of administration. Most of the conventional oral dosage forms available in the market are immediate release (IR) formulations, which are designed to release the drug rapidly after administration. These formulations are useful when rapid onset of action is required. However, immediate release dosage forms suffer from several limitations. Drugs having a short biological half-life require frequent dosing, which may lead to poor patient compliance. In addition, conventional dosage forms often produce a peak–valley plasma concentration-time profile, where high peak concentrations may cause side effects and low trough levels may result in sub-therapeutic effects. Such fluctuations in plasma drug levels make it difficult to maintain steady-state drug concentration and may increase the risk of toxicity, especially for drugs having a narrow therapeutic index. To overcome these drawbacks, significant advancements in pharmaceutical technology have led to the development of modified release drug delivery systems, particularly sustained release (SR) and controlled release systems. Sustained release drug

delivery systems are designed to release the drug over an extended period of time, thereby maintaining relatively constant plasma drug levels, reducing dosing frequency, minimizing side effects, and improving patient compliance. Ideally, a sustained release system should deliver the drug at a constant (zero-order) rate, producing a plasma concentration-time profile similar to that obtained after intravenous constant rate infusion. Although true zero-order release is difficult to achieve in practice, many sustained release systems attempt to approximate this ideal behavior. The oral route remains the most suitable and practical route for the development of sustained release formulations. However, while designing an oral sustained release dosage form, several physiological factors must be considered, such as variations in gastrointestinal pH, gastric emptying time, intestinal motility, presence of enzymes, and food effects. The majority of oral sustained release systems depend on diffusion, dissolution, erosion, or a combination of these mechanisms to control the rate of drug release into the gastrointestinal tract. Sustained release dosage forms are defined as those formulations which are capable of releasing the drug over a prolonged period of time in order to maintain therapeutic drug concentration in the systemic circulation. In contrast, delayed release dosage forms are designed to release the drug after a certain lag time, for example, enteric-coated tablets which prevent drug release in the stomach but allow release in the intestine. Repeat-action tablets represent another approach, where multiple doses of drug are incorporated into a single dosage form and released at predetermined intervals. Sustained release dosage forms offer several advantages such as reduction in dosing frequency, improved patient compliance, reduced fluctuations in plasma drug concentration, better control of therapeutic effect, and reduction in side effects. However, these systems also have certain disadvantages including higher cost of formulation, risk of dose dumping, possible variability in in vitro–in vivo correlation, and the need for careful patient counseling to avoid misuse such as chewing or crushing of tablets. Various methods have been employed to achieve controlled or sustained release of drugs from oral dosage forms. These include diffusion-controlled systems, dissolution-controlled systems, bioerodible systems, ion-exchange systems, osmotic pressure-controlled systems, pH-independent formulations, and altered density formulations. Among these, matrix-based systems have gained wide popularity because of their simplicity, ease of manufacture, cost-effectiveness, and ability to provide reproducible drug release profiles. Matrix tablets represent one of the simplest and most commonly used approaches for developing sustained release oral dosage forms. In matrix tablets, the drug is uniformly dispersed within a polymeric matrix, and the release of drug occurs either by diffusion through the polymer network, by erosion of the matrix, or by a combination of both mechanisms. Depending on the nature of the polymer used, matrix systems can be classified as hydrophilic matrices, hydrophobic (plastic) matrices, fat-wax matrices, biodegradable matrices, and mineral matrices. Hydrophilic matrices, in particular, are widely used because of their ability to swell in the presence of gastrointestinal fluids and form a gel layer that controls the release of drug. The drug release from matrix tablets is influenced by several factors such as the type and concentration of polymer, drug solubility, tablet porosity, and gastrointestinal conditions. Despite some limitations, matrix tablets remain a preferred choice for sustained release formulations due to their versatility, manufacturing simplicity, and proven clinical performance. Designing an oral sustained release dosage form also requires careful consideration of pharmacokinetic and pharmacodynamic properties of the drug. Important factors include biological half-life, absorption rate, distribution, metabolism, and elimination. Drugs with a biological half-life of about 2–8 hours are generally considered suitable candidates for sustained release formulations. In addition, drug-related properties such as dose size, solubility, ionization (pKa), partition coefficient, and stability in gastrointestinal conditions play a crucial role in determining the feasibility of sustained release formulation. Hypertension is one of the most common chronic cardiovascular disorders and is a major risk factor for stroke, myocardial infarction, heart failure, and renal diseases. According to global health statistics, hypertension contributes significantly to morbidity and mortality worldwide. It is often referred to as a “silent killer” because it may remain asymptomatic for many years while progressively damaging vital organs such as the heart, kidneys, brain, and blood vessels. Therefore, long-term and effective management of blood pressure is essential to reduce cardiovascular risk and improve

patient outcomes. Several classes of drugs are used in the management of hypertension, including diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, and angiotensin II receptor blockers (ARBs). Among these, angiotensin II receptor blockers (ARBs) have gained widespread acceptance because of their efficacy, good tolerability, and lower incidence of side effects such as cough and angioedema commonly associated with ACE inhibitors. Valsartan is a potent and selective angiotensin II type 1 (AT1) receptor antagonist widely used in the treatment of hypertension, chronic heart failure, and in patients after myocardial infarction. By blocking the AT1 receptor, valsartan inhibits the vasoconstrictor and aldosterone-secreting effects of angiotensin II, resulting in reduction of blood pressure and improvement in cardiovascular function. Additionally, blockade of AT1 receptors allows stimulation of AT2 receptors, which contributes to vasodilation and protective effects on the cardiovascular system. Valsartan belongs to BCS Class III, characterized by high solubility and low permeability. It is rapidly absorbed after oral administration, extensively bound to plasma proteins, and primarily eliminated via biliary excretion with minimal renal clearance. Although valsartan is effective, its pharmacokinetic profile and the need for long-term therapy make it a suitable candidate for development of a sustained release dosage form. A sustained release formulation of valsartan can help in maintaining consistent plasma drug levels, reducing dosing frequency, improving patient compliance, and enhancing overall therapeutic efficacy.

## II. REVIEW OF LITERATURE

2.1 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

## III. 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. | nces and precision scales | Acculab Sartorius group |
| 2. | UV-Visible spectrophotometer | hotometer UV-1800, Shimadzu, Japan |
| 3. | Fourier transform infrared spectrophotometer | Thermo Nicolet |
| 4. | PH meter | Techno scientific products |
| 5. | Multi tablet Punching machine | ESS, 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) | TOP, SKY Lab Instruments and Engineering Pvt. Ltd. |

## IV. DRUG PROFILE

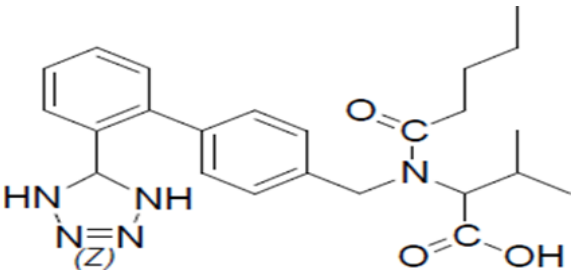
VALSARTAN

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.

## 4.2 EXCIPIENTS PROFILE

### 4.2.1 CARBOPOL

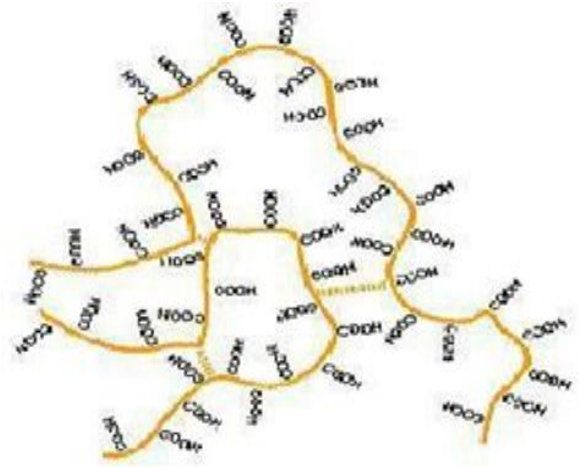
Non-proprietary names: BP: Carbomer, USPNF: Carbomer

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

Chemical names: Carboxypolymethylene Empirical formula: 【-$CH_2$-CH-】N-COOH Molecular weight: Approx. $3\times10^6$

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.

4.2.2 CHITOSAN

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

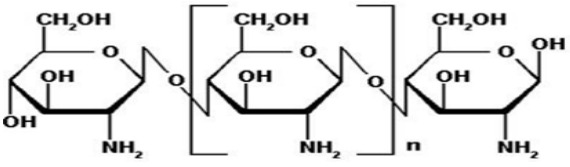
PhEur: Chitosani hydrochloridum

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.

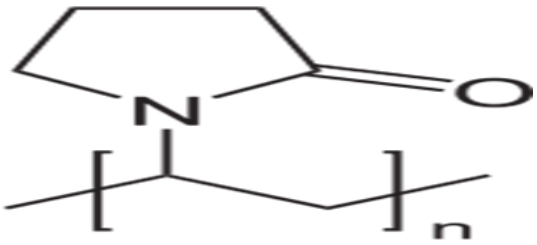
4.2.3 P0LYVINYLPYRROLIDONE

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.

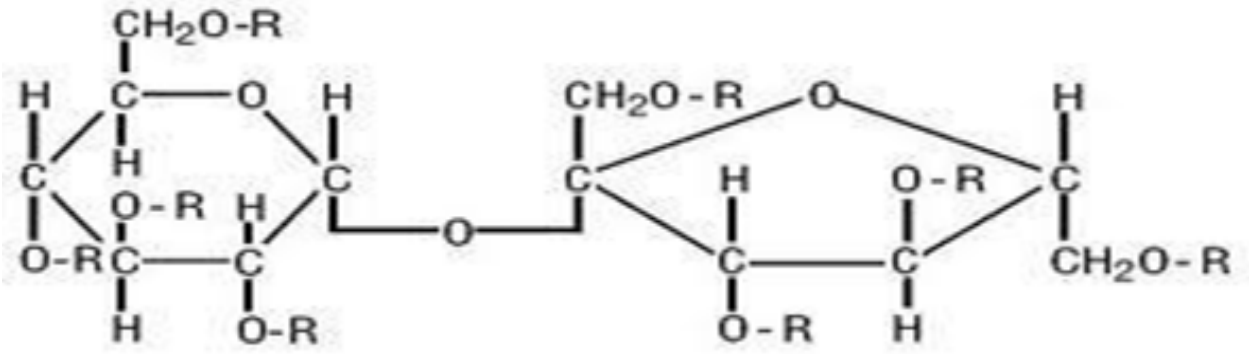
MICROCRYSTALLINE CELLULOSE

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 ≈ 220

Structural formula:




4.2.4 MAGNESIUM STEARATE

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

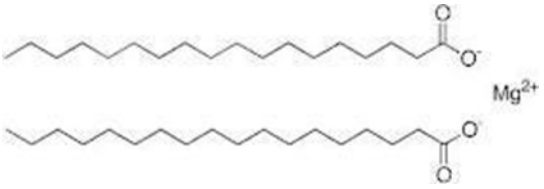
Synonyms: Metallic stearate, Magnesium salt.

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.

## III. RESULTS AND DISCUSSION

### 5.1. Determination of $\lambda_{max}$ of Valsartan

The $\lambda_{max}$ 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 and graph was obtained by plotting absorbance Vs concentration

Table no.3: 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 |

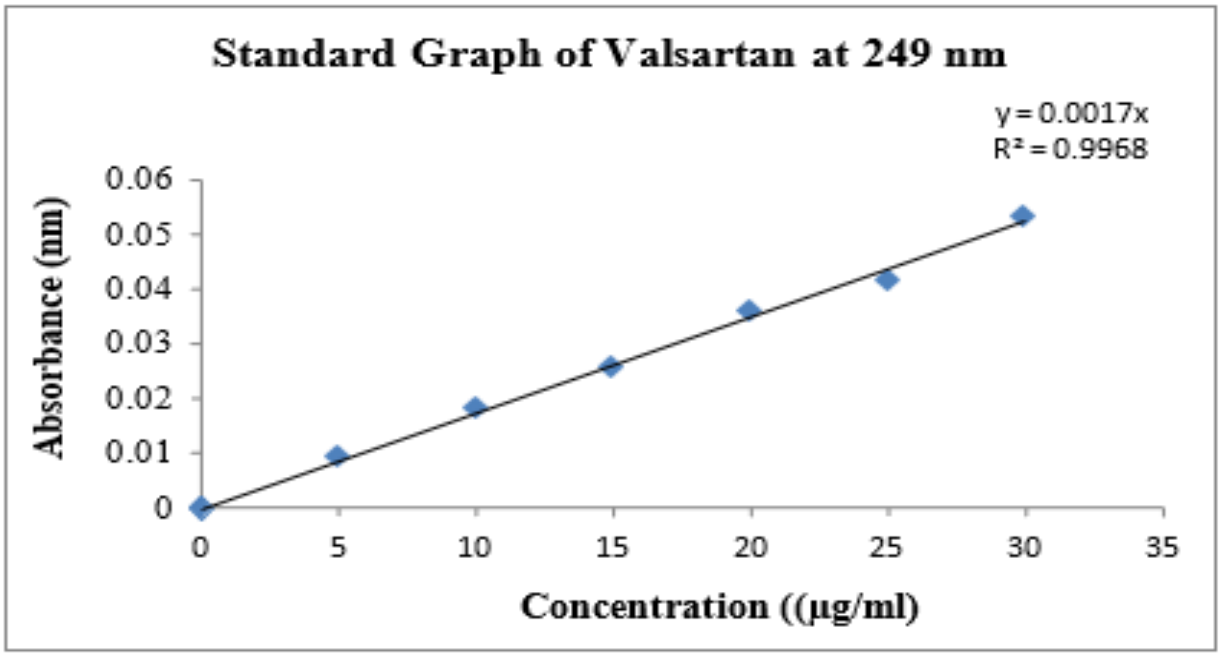



**Figure : Calibration Curve of Valsartan in 0.1 N NaOH**

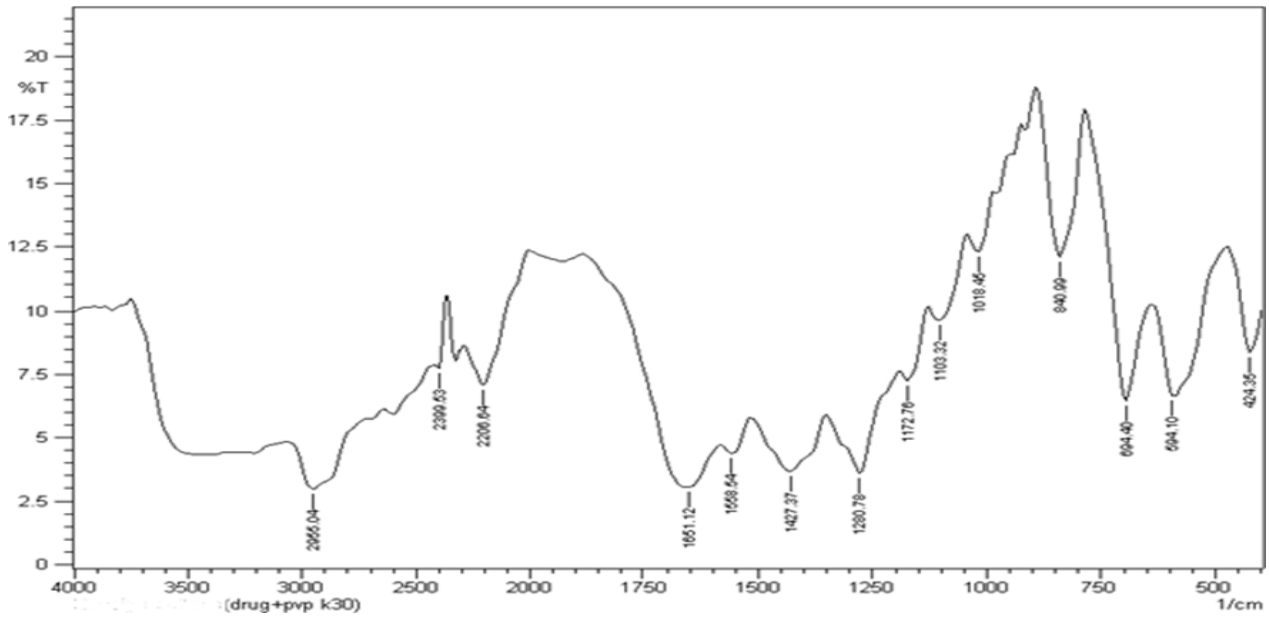



Figure: IR Spectrum of Pure Drug Valsartan

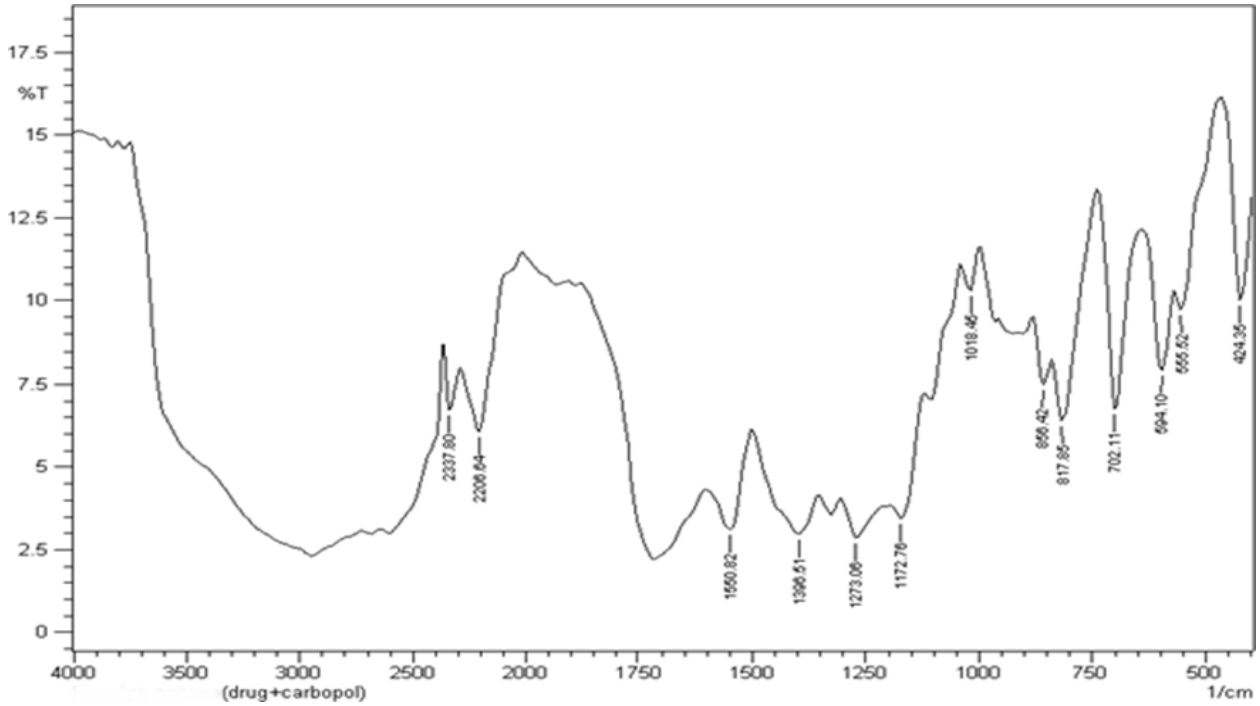



Figure: IR Spectrum of Carbopol

## V. 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. 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.

Table no.4: 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.5: 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 |

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 $M_t / M_a = Kt^n$. Where $M_t / M_a$ 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. 6: Release exponent values and release rate constant values for different formulations

| Batch | Zero order | irst order | uchi'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 |

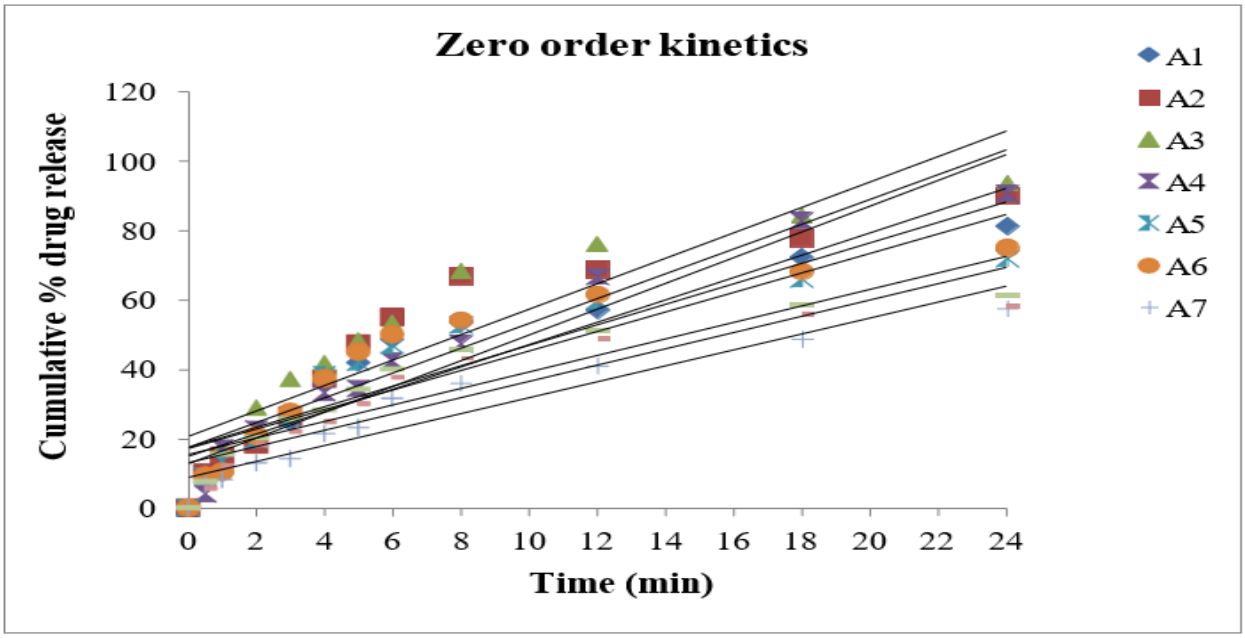



**Figure: Comparative Zero Order release profile of formulations $F_1$ to $F_7$**

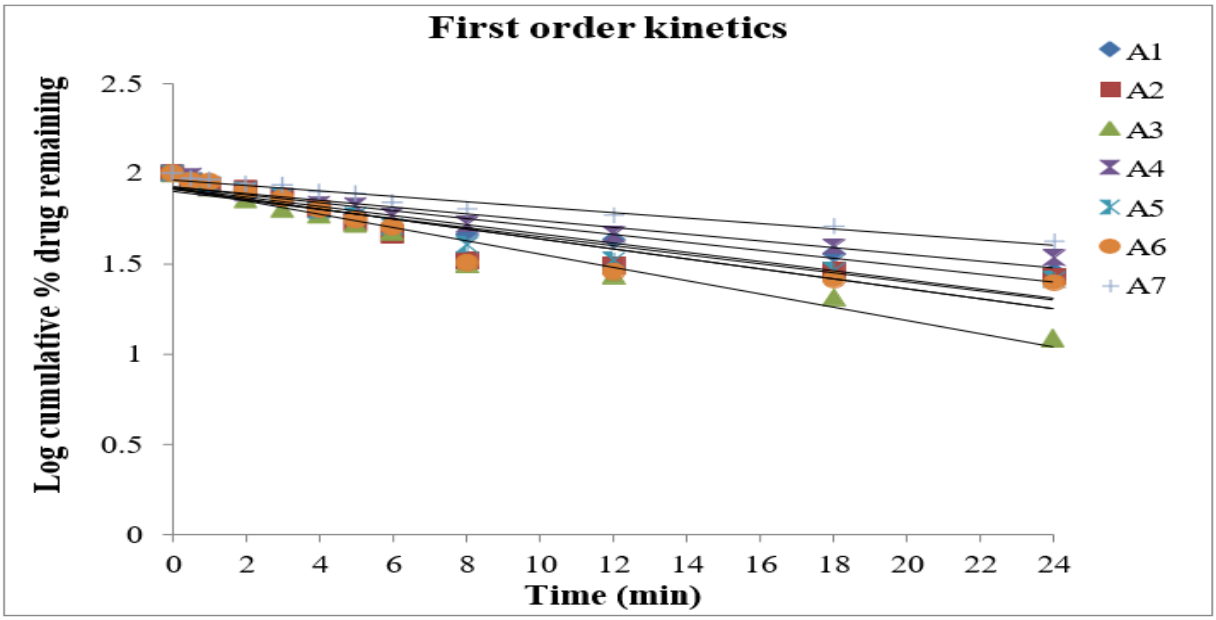



**Figure: Comparative First Order release profile of formulations $F_1$ to $F_7$**

## VI. 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.

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