# *FORMULATION DEVELOPMENT AND EVALUATION OF TABLET CONTAINING ANTIHYPERTENSIVE DRUG USING JACKFRUIT MUCILAGE*

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**MASTER OF PHARMACY**
In
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**MAY-2015**

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## ABSTRACT

The aim of the current research work was to isolate and evaluate Jackfruit mucilage to develop Verapamil HCl tablets using varying concentration of jackfruit mucilage. Tablets containing 40mg drug were prepared by wet granulation method. Compatibility study was carried out by using FTIR and confirmed that no chemical interaction took place during entrapment process. Pre-compression parameters like Bulk density, Tapped density ,Carr's index, Hausner's ratio, and angle of repose were evaluated and post-compression parameters like Friability, Hardness, Thickness, Diameter, Weight variation, Disintegration, and Drug content estimation and Dissolution were evaluated and the results were within the acceptable official limits. *In-vitro* drug release was carried out by using USP dissolution rate apparatus type- II using two different dissolution media (0.1 N HCl and phosphate buffer of pH 6.8). *In-vitro* drug release shows, as the concentration of jackfruit mucilage increases, drug release decreases. The drug release follows first order kinetics and mechanisms was found to be super case II. the stability studies were carried out for two months. In conclusion result suggested that formulation containing jackfruit mucilage delayed the drug release could therapeutically better than conventional dosage form leading to improved efficacy and better patient compliance.

**Key words ;** sustained release tablet, Verapamil HCl, Jackfruit mucilage, Wet granulation.

# LIST OF ABBREVATION

| | |
|---|---|
| % | Percentage |
| °C | Degree centigrade |
| µg | Microgram |
| $\lambda_{max}$ | Maximum wavelength |
| % CDR | Percentage cumulative drug release |
| Abs | Absorbance |
| Conc | Cocentration |
| cm | centimeter |
| Cmax | Maximum concentration |
| Hr | Hour |
| RPM | Revolution per minutes |
| ICH | International conference on harmonization |
| IP | Indian pharmacopeia |
| IR | Infra red |
| Kg | Kilogram |
| Sec | Second |
| $t_{max}$ | Time of peak concentration |
| AUC | Area under curve |
| GIT | Gastro intestinal tract |

| | |
|---|---|
| FTIR | Fourier Transform infrared Spectroscopy |
| Mm | Milimeter |
| gm | Gram |
| Mg | Miligram |
| pH | Negative logarithm of hydrogen ion concentration |
| RH | Relative humidity |
| Min | Minute |
| Ml | Mililiter |
| nm | Nanometer |
| $t_{1/2}$ | Half life |
| USP | United state pharmacopeia |
| UV | Ultra violet |
| Vs | Verses |
| w/w | Weight by weight |
| w/v | Weight by volume |

# TABLE OF CONTENTS


| CHAPTER NO | CHAPTER NAME | PAGE NO |
|---|---|---|
| **1** | INTRODUCTION | 1-24 |
| **2** | OBJECTIVES | 25-28 |
| **3** | REVIEW OF LITERATURE | 29-38 |
| **4** | MATERIALS AND METHODS | 39-64 |
| **5** | RESULTS | 65-76 |
| **6** | DISCUSSION | 77-81 |
| **7** | CONCLUSION | 82-83 |
| **8** | SUMMARY | 84-85 |
| **9** | BIBLIOGRAPHY | 86-93 |

## LIST OF TABLES


| Table No | Title | PgNo |
|---|---|---|
| 1 | Physicochemical Parameters for Drug Selection | 4 |
| 2 | Pharmacokinetic Parameters for Drug Selection | 4 |
| 3 | Taxonomy of Artocarpus heterophyllus | 22 |
| 4 | Potential Medicinal Values of Artocarpus heterophyllus | 23 |
| 5 | List of chemicals used | 39 |
| 6 | Details of Equipment's used | 40 |
| 7 | Properties of Verapamil HCl | 41 |
| 8 | Pharmacology of Verapamil HCl | 42 |
| 9 | Pharmacokinetics of Verapamil HCl | 43 |
| 10 | Interaction of Verapamil HCl wiyh other drugs | 44 |
| 11 | Adverse reaction of Verapamil HCl | 45 |
| 12 | Profile form of Magnesium stearate | 46 |
| 13 | Profile form of Talc | 47 |
| 14 | Profile form of Microcrystalline cellulose | 48 |
| 15 | Profile form of Dicalcium phosphate | 49 |
| 16 | Profile form of Bentonite | 50 |
| 17 | Formulation design | 54 |
| 18 | Formulation development | 55 |
| 19 | Effect of Carr's Index and Hausner's Ratio on flow property | 57 |
| 20 | Effect of Angle of repose (□) on Flow property | 58 |
| 21 | Weight variation tolerances of uncoated tablets | 60 |
| 22 | Mechanism of Drug Release as per Korsmeyer Equation/ Peppa's Model | 63 |
| 23 | Spectrophotometric determination of Verapamil HCl in 0.1N HCl | 67 |
| 24 | Spectrophotometric determination of Verapamil HCl in 6.8 pH buffer | 68 |
| 25 | Viscosity of Jackfruit mucilage | 69 |
| 26 | Pre-compression parameters results | 70 |
| 27 | Physico-chemical parameters of tablets | 70 |
| 28 | Post-Compression Parameter results | 71 |
| 29 | *In-vitro* drug release profile | 72 |
| 30 | Results of Kinetic data of various models for release study | 73 |
| 31 | Results of stability studies for F4 formulation at 40$^{0}$C/75% RH | 76 |

## LIST OF FIGURES


| Sl No | Title | Page No |
|---|---|---|
| 1 | Plasma concentration-profiles Vs time. | 2 |
| 2 | Complications of hypertension. | 11 |
| 3 | Pathophysiological mechanism of hypertension. | 13 |
| 4 | Mechanism of action of antihypertensive –drugs. | 19 |
| 5 | Structure of Verapamil Hcl. | 41 |

## LIST OF SPECTRA


| Sl No | Title | Page No |
|---|---|---|
| 1 | FT-IR spectra of Verapamil HCl drug | 65 |
| 2 | FT-IR spectra of Jackfruit mucilage | 66 |
| 3 | FT-IR spectra of Verapamil HCL+ Jackfruit mucilage | 66 |


## LIST OF GRAPHS


| Sl No | Title | Page No |
|---|---|---|
| 1 | Calibration Curve of Verapamil HCl in 0.1 N HCl | 67 |
| 2 | Calibration Curve of Verapamil HCl in 6.8 phosphate buffre | 68 |
| 3 | Viscosity of Jackfruit mucilage | 69 |
| 4 | *In-vitro* Cumulative percentage drug released V/S Time for Formulations F1 to F6 | 73 |
| 5 | Plot of % Cum. Drug Released Vs. Time | 74 |
| 6 | Plot of Log % Cum. Drug Retained Vs. Time | 74 |
| 7 | Plot of % Cum. Drug Released Vs. √Time | 75 |
| 8 | Plot of Log % Cum. Drug Released Vs. Log Time | 76 |

## 1. 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]Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst these the controlled release/sustained release dosage form have become extremely popular in modern therapeutics.[3] The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design.[4] It is important especially in the case of antihypertensive agents to maintain constant blood level, as otherwise dose dumping may cause hypotension. Constant blood level can be maintained by formulating sustained release tablet.[5]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 requires 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 over medication 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.[6]

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal.[7]

**Design and formulation of oral sustained release drug delivery system:**

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.[8,9]

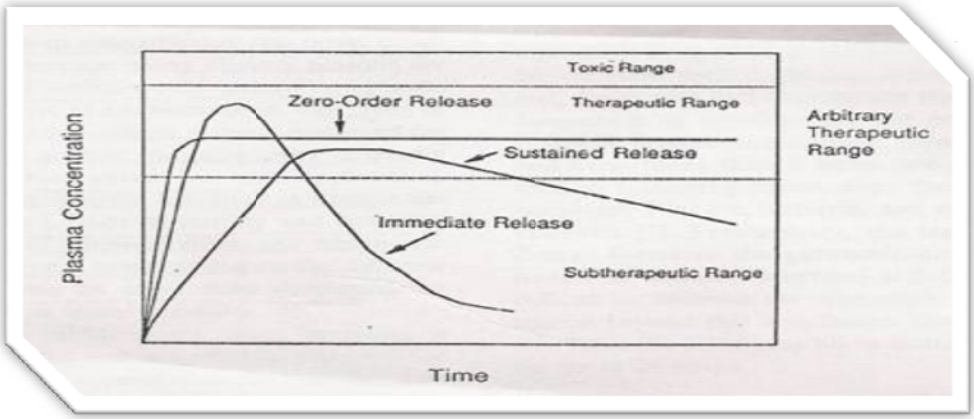



**Fig 1:** Plasma concentration-profiles Vs time (sustained release formulation and zero order formulation)

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.[10]

**ADVANTAGES OF SUSTAIN RELEASE DOSAGE FORMS**

1. Reduction in frequency of drug intakes.
2. Reduce side effects.
3. Uniform release of drug.
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 ormasticating, alcohol intake).
5. Increased potential for first- pass clearance.
6. Need for additional patient education and counseling.[11]

**DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS:**

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the GIT the general

absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient.

**Table No 1**:Physicochemical parameters for drug selection.

| S. No | Parameters | Preferred value |
|---|---|---|
| **1** | Apparent partition co-efficient | High |
| **2** | Molecular weight/size | >1000 |
| **3** | Solubility | >0.1mg/ml for pH 7.8 |
| **4** | General absorbability | From all GI segments |
| **5** | Release | Should not be influenced by pH and enzymes |

**Table No 2**:Pharmacokinetics properties for drug selection.

| S.No | Parameters | Comments |
|---|---|---|
| **1** | Elimination half life | Preferably between 0.5 and 8hrs |
| **2** | Elimination rate constant | Required for design |
| **3** | Total clearance | Should not be dose dependent |
| **4** | Absolute bio-availability | Should b 75% or more |
| **5** | Apparent volume of distribution (Vd) | The larger Vd and MEC, the larger will be the required dose size |
| **6** | Intrinsic absorption rate | Must be greater than release rate |

## VARIOUS MECHANISMS OF MEDICAMENT RELEASE

### 1. Diffusion rate limiting:

Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system.In practice, we can follow either of the two methods.

a. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion.

b. The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.

### 2. Dissolution rate limiting:

The drugs with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water soluble drugs, it is possible to incorporate a water insoluble carrier to reduce dissolution of the drug particles are coated with this type of materials e.g.Polyethylene Glycol. One may skip the use of disintegrating agent to promote delayed release**.**

### 3. Osmotic pressure rate limiting:

Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the drug and increases the internal pressure which pumps the drug solution out of the aperture and releases

the drug in gastric environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But, it declines to zero once the concentration drops below saturation**.**

**4. Release controlled by ion exchange:**

Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site.[12 13, 14.]

**CLASSIFICATION OF ORAL SUSTAINED OR CONTROLLED RELEASE SYSTEMS**

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release. these systems are classified as follows:

1. Continuous release systems

2. Delayed transit and continuous release systems

3. Delayed release systems

**1.Continuous release systems**

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

**2. Delayed transit and continuous release systems**

These systems are designed to prolong their residence in the GIT along with their release. Often the dosage form is fabricated to detain in the stomach and hence the drug present should be stable to gastric pH. Systems included in this category are mucoadhesive systems and size based systems.

**3. Delayed release systems** The design of such systems involves release of drug only at specific site in the GIT. The drugs contained in such a system are those that are:

a. Known to cause gastric distress

b. Destroyed in the stomach or by intestinal enzymes.

c. Meant to extent local effect at a specific GI site.

d. Absorbed from a specific intestinal site.[15]

**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 life 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 on 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 co-efficient**

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 co-efficient of the drug. Drugs having low partition coefficient are considered as poor

Candidate for the sustained release formulation as it will be localized in the aqueous phase. Eg Barbituric acid.

**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, where as in contrast the drug unstable in intestine will face problem of less bioavailability.[8]

**Hypertension**

There are many diseases that are caused due to genetic disorders, hypertension is one among them.

**Defination**: Hypertension or high blood pressure, is a chronic medical condition in which the blood pressure in the arteries is higher than it should be. This requires the heart to work harder than normal to circulate blood through the blood vessels.

The pressure in the arteries changes depending on what the heart is doing. When the heart contracts, pumping blood into the arteries, the pressure increases. When the heart relaxes, the pressure decreases. When blood pressure is measured, the highest pressure (when the heart is contracting) is called systole, and the lowest pressure (when the heart is relaxing) is called diastole. Systolic blood pressure is difficult to control in clinical practice, which is a better predictor of cardiovascular risk than diastolic blood pressure, systolic blood pressure increases linearly from 30 years, while diastolic blood pressure decreases from 50 years. [17]

Blood pressure is measured with a number followed by “mmHg”, which stands for “millimetres of mercury”.[18]

Hypertension is a very common disorder, particularly past middle age. It is not a disease in itself, but it is a important risk for cardio vascular mortality and morbidity. The cut off monometric reading between normotensives and hypertension is arbitrary for practical purposes hypertension could be that level of B.P at or above which long-term antihypertensive treatment will reduce cardio vascular mortality. Hypertension is one of the major precursors of atherosclerotic vascular disease which is the leading cause of death in the united state and other western nations. Atherosclerosis involving the coronary cerebral and peripheral circulations is responsible for approximately half of all death in this country each year, with coronary heart failure accounting for two-thirds of the mortality. The national health survey indicates that above 50% of men and 75% of women with coronary disease have hypertension. The result of a number of epidemiological studies indicates that the risk of every manifestation of coronary heart disease, including angina, coronary insufficiency, myocardinal infraction, and sudden death is significantly related to the antecedent level of both systolic and diastolic blood pressure. Recent survey indicate that the great majority of the hypertensive populations are either unaware of their disease or are receiving inadequate treatment. Hypertension is a leading risk factor for heart disease, stroke, kidney failure. Hypertesion has a mechanical effect on the heart which result in an increase in work load and oxygen requirement of the myocardium, as well as atherosclerosis, congestive heart failure and many arterial changes.

There is increasing evidence that the mechanical effects of hypertension on heart as well as on the arteries can have an unfavorable effect on the course of coronary artery disease. These effects of hypertension which include the precipitation of coronary insufficiency and congestive heart failure are diagramed as below.

**Complication of Hypertension**

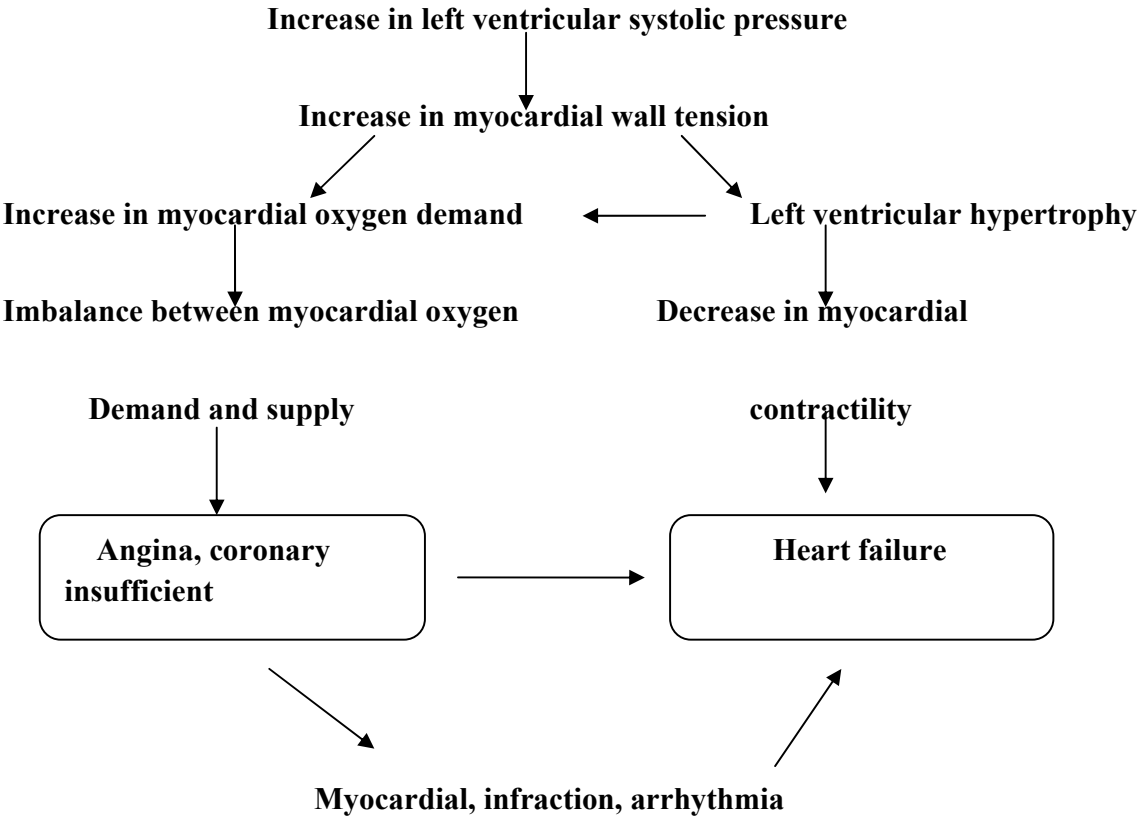



**Fig 2**: complication of hypertension

Congestive heart failure is major complication of hypertension which may occur in presence or absence of coronary artery disease. It is usually preceded by left ventricular hypertrophy and appears to result mainly from the excessive work load placed upon the heart by the elevated arterial pressure. However, complicating arteriosclerotic heart disease may also contribute to congestive heart failure transitory left ventricular failure preceded by a rise in blood pressure has been described during an attack of angina pectoris. Changes in blood pressure can alter the balance between myocardial oxygen supply and demand and imbalance which can result in myocardial ischemia.

It is generally agreed that the major hemodynamic variables directly related to myocardial oxygen requirements include

1. The intramyocardial tension
2. The heart rate
3. The contractile state of ventricle

The arterial changes characteristic of hypertension include

1. Increased thickness and rigidity of the arteries
2. Hyperplasia and hypertrophy of arterial smooth muscle cells
3. Increased deposition of acid mucopolysaccharides, collagen and elastin in the arteries
4. Increased in the arterial content of sodium, chloride, potassium, calcium and water

There is a substantial evidence in man and experimental animals that a substained elevation of arterial blood pressure regardless of its cause aggravates and accelerates atherosclerosis. A number of investigators have studied coronary atherosclerosis in autopsy material from normatensive and hypertensive man and concluded that coronary atherosclerosis is more severe in hypertensive than normotensive man. Me gill and Robertson and strong have evaluated the extent and type of atherosclerotic lesions is coronary arteries and aortas collected from various areas of the world. They have found that the hypertensive as compared to the normotensives had more extensive fibrous plaques or “raised lesions” as well as a slight but significant increase in the extent of fatty streaks in the coronary arteries and abdominal aorta. [19]

**Pathophysiology:**

Many pathophysiologic factors have been implicated in the genesis of essential hypertension: increased sympathetic nervous system activity, perhaps related to heightened exposure or

response to psychosocial stress; overproduction of sodium-retaining hormones and vasoconstrictors; long-term high sodium intake; inadequate dietary intake of potassium and calcium; increased or inappropriate renin secretion with resultant increased production of angiotensin II and aldosterone; deficiencies of vasodilators, such as prostacyclin, nitric oxide (NO), and the natriuretic peptides; alterations in expression of the kallikrein– kinin system that affect vascular tone and renal salt handling; abnormalities of resistance vessels, including selective lesions in the renal microvasculature; diabetes mellitus; insulin resistance; obesity increased activity of vascular growth factors; alterations in adrenergic receptors that influence heart rate, inotropic properties of the heart, and vascular tone; and altered cellular ion transport.

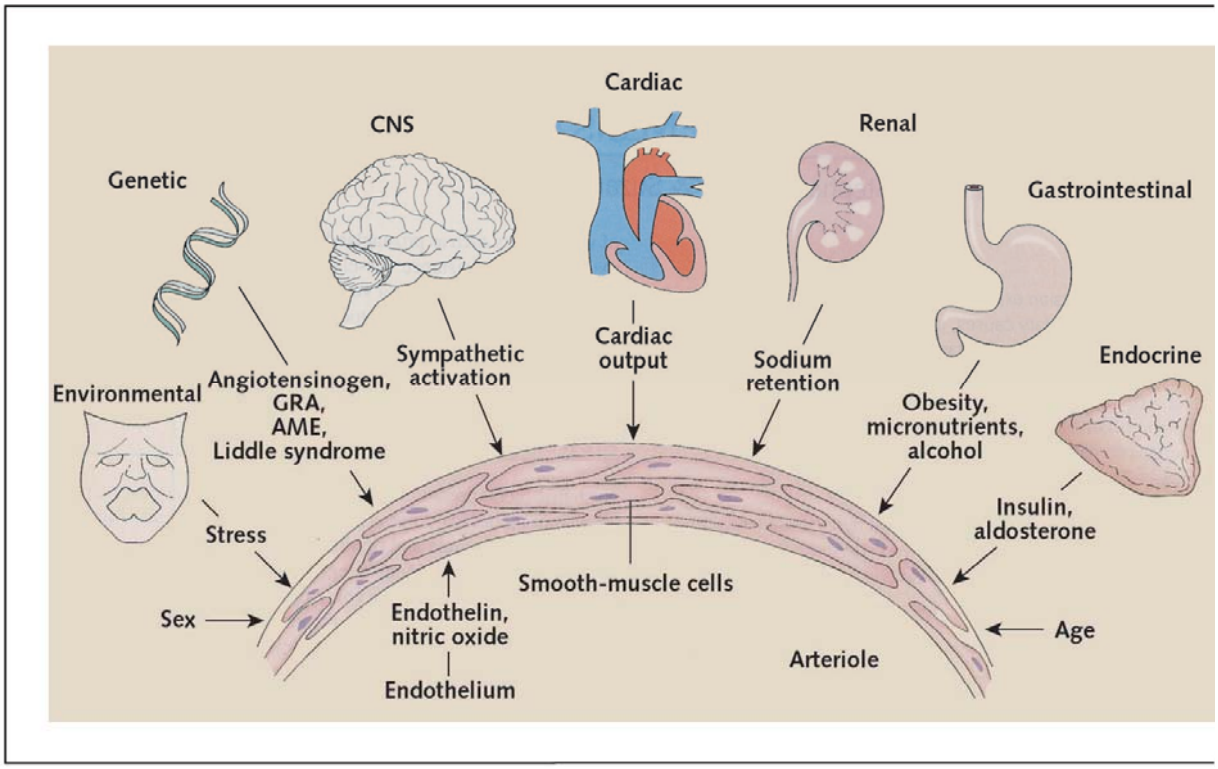



**Fig:3** Pathophysiological mechanisms of hypertension.

In youth, the pulse pressure generated by the left ventricle is relatively low and the waves reflected by the peripheral vasculature occur mainly after the end of systole, thus increasing pressure during the early part of diastole and improving coronary perfusion. With ageing, stiffening of the aorta and elastic arteries increase the pulse pressure. Reflected wave moves from early diastole to late systole. This result in increase in left ventricular afterload and contribute to the left ventricular hypertrophy. The widening of the pulse pressure with ageing is strong predictor of coronary heart disease. Considerable evidence indicate that resetting of pressure natriuresis plays a key role in causing hypertension.[20]

**Types of hypertension:-**

There are two major types of hypertension and four less frequent found types.

The two major types are:

- Primary or essential hypertension
- Secondary hypertension

**The other types include:-**

- Malignant hypertension
- Isolated systolic hypertension
- White coat hypertension
- Resistant hypertension

**Primary hypertension:-** This type is also called essential hypertension, and it is by for the most common type of hypertension, and is diagnosed in about 95% of cases. Essential hypertension has no obvious of yet identifiable cause.

**Secondary hypertension:-**

This may be caused by:

- Kidney damage or impaired function
- Tumours or over activity of the adrenal gland
- Thyroid dysfunction
- Pregnancy related condition
- Drinks and food.

**Malignant hypertension:-**

This is the severe form of hypertension. It rapidly leads to organ damage, unless properly treated. It is fatal within five years for the majority of patient.

**Isolated systolic hypertension:-**

In this case the systolic blood pressure, is consistently above 160mm Hg, and the diastolic below 90mm Hg. This may occur in older people, and results from the age-related stiffening of the arteries. The loss of elasticity in arteries, like the aorta, is mostly due to arteriosclerosis.

**White coat hypertension:-**

Also called anxiety induced hypertension. It means blood pressure is only high when tested by a health professional. It confirmed by repeated reading outside of the clinical setting. It does not need to be treated. However, regular follow-up is recommended to ensure that persistent hypertension has not developed.

**Resistant hypertension:-**

If blood pressure cannot be reduce to below 140/90mm Hg despite a triple-drug regime resistant hypertension is considered.[21,22]

**Etiological factors :**

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 like salt 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

**Other factors are responsible for hypertension**:

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. [23]

**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.[24,25]

**Life Adaptations:**

People with hypertension should take note of the following in their daily lives:

I. Quit smoking.

2. Reduce salt intake. Eat less preserving and processed food such as sausages, pickles and potato chips.

3. Drink less caffeinated beverages like strong tea, coffee and coke.

4. Do moderate exercise regularly.

5. Keep optimal body weight.

6.Learn self-relaxation because anxiety loss of temper and overstrain all give rise to increased blood pressure.

**Antihypertensive drug:**

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

Patients with hypertension must take antihypertensive drugs on a long-term basis. Although such drugs cannot give a radical cure, they can prevent heart failure, kidney failure and acute stroke induced by hypertension and delay the development of atherosclerosis by controlling the blood pressure. Generally speaking, antihypertensive drugs must be taken for life.

**Classification of antihypertensives**:

1. **Diuretics:** Chlorthalidone, Clopamide, Indapamide
2. **β Adrenergic blockers:** Acebutolol, Atenolol, Metoprolol, Propranolol, Timolol
3. **Adrenergic blockers:** Terazosin, Prazosin, Doxazosin
4. **a + β Adrenergic blockers:** Labetalol, Carvedilol
5. **ACE inhibitors:** Perindopril, Captopril, Enalapril, Lisinopril, Fosinopril, Benazepril
6. **Calcium channel blockers:** Amlodipine, FelodipineNifedipine, Nimodipine, Verapamil
7. **Vasodilators:** Hydralazine, Minoxidil, Sodium nitroprusside
8. **Angiotensin-II receptor antagonists:** Candesartan, Losartan, Valsartan
9. **Central sympatholytics**: Clonidine, Methyldopa.[27]

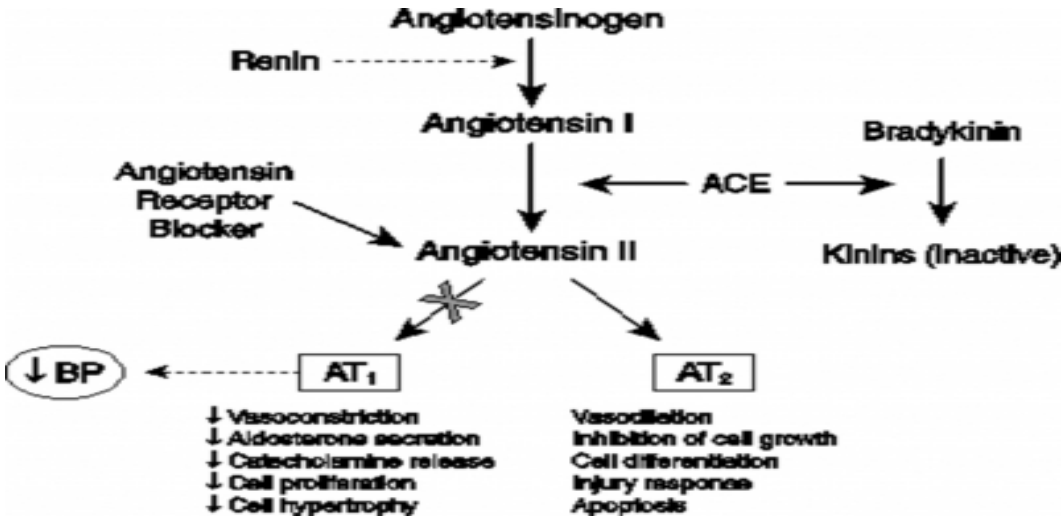



**Figure 4**: Mechanism of action of an anti-hypertensive drug

**Mechanism of action of verapamil HCL:**

Verapamil HCL is belong to the class of calcium channel blocker. Calcium channel blockers (CCBs) or calcium antagonists, are among the most widely used drugs in cardiovascular medicine with roles not only in hypertension but also in angina and (for some CCBs) tachyarrhythmias**.** CCBs promote vasodilator activity (and reduce blood pressure) by reducing calcium influx into vascular smooth muscle cells by interfering with voltage-operated calcium channels (and to a lesser extent receptor-operated channels) in the cell membrane. Interference with intracellular calcium influx is also important in cardiac muscle, cardiac conduction tissue and gastrointestinal smooth muscle. In cardiac tissues, CCBs have potential for negative inotropic, chronotropic and dromotropic activity while the gastrointestinal effects predispose to constipation. These effects vary with different agents according to ability to penetrate cardiac and other tissues, relative affinity for calcium channels in different tissues and the influence of reflux cardiac stimulation secondary to peripheral vasodilation. [28]

**Side Effects of the Drugs:**

Side effects of antihypertensive drugs vary with individual drugs. Common side effects include the following temporary reactions:

1. Headache, weakness or fatigue.
2. Dizziness upon rising quickly from a sitting or lying position.
3. Numbness or sharp pain in fingers or toes.
4. Cold hands and feet.
5. Dr y eyes, mouth and throat.
6. Nightmares or sleeping difficulties
7. ACE inhibitor may cause cough in patients and should inform the doctor immediately if this occurs.
8. Patients who have asthma should consult doctor before using beta-adrenoceptor antagonists.[29]

**1.3 Mucilages as Natural Polymer:**

Mucilages are naturally occurring, high molecular weight Polyuroides consisting of sugars and Uronic acid units. They are normal physiological metabolism products formed within the cell/deposited on it in layers[30.] Mucilages are most commonly used adjuvant in pharmaceutical preparations. They swell in water and form a gel, such phenomenon is ofte called as rheology synergism[31]. Mucilages found in rhizomes, roots and seed endosperm may act primarily as energy reserves where as foliar mucilages appear not to serve as storage carbohydrates[32]. Plant mucilages are well known, since ancient times, for their medicinal use. In recent years, plant mucilages have evoked tremendous interest due to their diverse applications in pharmacy, for formulation of both solid and liquid dosage forms. Plant mucilages are pharmaceutically

important polysaccharides with a wide range of applications such as thickeners, binding agents, water retention agents, emulsion stabilizers, suspending agents, disintegrants, gelling agents, and film formers[33].Mucilages find applications in tablet formulation as binders because of their adhesive nature. They impart cohesiveness to the powder mass and convert them into granules, which are further compressed into tablets. They can swell upto 5times their original volume and this swelling leads to breakage of tablets into smaller pieces, which in turn improves the dissolution rate thereby making them a favorable candidate as disintegrating agents[34]. In several cases, the polysaccharides, resins or the tannins present in the gums are responsible for imparting release retardant properties to the dosage form. Natural polymers are remain attractive primarily because they are capable of chemical modification, having high drug holding capacity and thermal stability. Natural polymers are easily available and have some advantages when employed in controlled release drug delivery system such as bio-acceptability, bio-compatibility, bio-degrability and non-toxicity.[35]

**Overview of Jackfruit**

The scientific name of Jackfruit tree is *Artocarpus heterophyllus*. It is one of the most significant trees in tropical homegardens and perhaps the most widespread tree in the genus Artocarpus. It is a medium-size evergreen tree typically reaching 8–25 m (26–82 ft) in height with evergreen, alternate, glossy and leathery leaves to 22.5 cm (9 in) in length. Jackfruit's place of origin is believed to be indigenous to the rain forests of the Western Ghats. Today, it is cultivated at low elevations throughout India, Sri Lanka, Myanmar, southern China, Malaya, East Indies, Queensland, Mauritius, Kenya, Uganda and former Zanzibar, Pacific islands and Brazil [12]. Many parts of the plant including the bark, roots, leaves, and fruit are attributed with medicinal properties. It is reported in Ayurveda to possess antibacterial, anti-inflammatory,

antidiabetic, antioxidant and immunomodulatory properties. It is an important source of compounds like morin, dihydromorin, cynomacurin, artocarpin, isoartocarpin, cyloartocarpin, artocarpesin, oxydihydroartocarpesin, artocarpetin, norartocarpetin, cycloartinone, betulinic acid, artocarpanone and heterophylol which have therapeutic properties . The root is a remedy for skin diseases and asthma and the extract is taken in cases of fever and diarrhea. The ashes of the leaves, burned together with corn and coconut shells are used alone or mixed with coconut oil to heal ulcers. Mixed with vinegar, the latex promotes healing of abscesses, snakebite and glandular swellings. Heated leaves alone are placed on wounds and the bark is made into poultices. The seed starch is given to relieve biliousness and the roasted seeds are regarded as aphrodisiac. In Chinese medicine the pulp and seeds are considered tonic and nutritious [36].

**Table No.3:** Taxonomy of *Artocarpus heterophyllus*[37]

| **Kingdom** | **Plantae** |
|---|---|
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Order | Rosales |
| Family | Moraceae |
| Genus | Artocarpus |
| Species | A.heterophyllus |

**Phytochemistry of Jackfruit:**

A. *heterophyllus* contains various chemical constituents as several flavone colorings, morin, dihydromorin, cynomacurin, artocarpin, isoartocarpin, cyloartocarpin, artocarpesin,

oxydihydroartocarpesin, artocarpetin, norartocarpetin, cycloartinone, and artocarpanone. The heartwood of jackfruit on analysis yields moisture (6.7%), glucosides (38.0%), lipids (0.7%), protein (1.7%), and cellulose (59.0 %) (Perkin and Cope 1895). The jackfruit also contains free sugar (sucrose), fatty acids, ellagic acid, and amino acids like arginine, cystine, histidine, leucine, lysine, metheonine, theonine, tryptophan, and others.. Bark from the main trunk contains betullic acid and two new flavone pigments including cycloheterophyllin ($C_{30}H_{30}O_7$). Heterophylol, a phenolic compound with a novel skeleton, was obtained from *A.heterophyllus*. The leaves and stem have shown the presence of sapogenins, cycloartenone, cycloartenol, β-sitosterol, and tannins, and they have shown estrogenic activity. The root contains β-sitosterol, ursolic acid, betulinic acid, and cycloartenone.[38] It is a nutritious fruit, rich in vitamin A, B, C, Potassium, Calcium, Iron, Protein, and Carbohydrates. Potassium rich in Jackfruit may help to regulate blood pressure. Jackfruit contains lignans, isoflavons, saponins.[3]

**Table No 4**:Potencial Medicinal values of Artocarpus heterophyllus.

| Traditional Uses | Pharmacological Activities | Side Effects |
|---|---|---|
| To treat constipation<br>Remedy for snake bite<br>to reduce fever<br>to cure wound,<br>Swelling, diarrhea,<br>skin disease,<br>pharyngitis,<br>glandular Swellings, | Anti-inflammatoory<br>Anti-diabetes<br>Anti-oxidant<br>Anti- hypertensive<br>Anti- antiaging<br>Anti- ulcer<br>Anti- cancer | May increase coagulation<br>in people suffering from<br>blood disorder.<br>May have<br>immunostimulative effect<br>in patients undergoing<br>immunosuppression<br>theraphy. |

Even though jackfruit mucilage have some side effect it can use as binding agent to delay the drug release It is important especially in the case of antihypertensive agents to maintain constant blood level, as otherwise dose dumping may cause hypotension. Constant blood level can be maintained by formulating sustained release tablet, using natural tablet retardant polymer since they are non-toxic, chemically stable, bio-degradable.

Present work therefore planned to developed a oral sustained release tablet of antihypertensive drug by using Jackfruit mucilage as one of the exceipient.

## 2. OBJECTIVES

The main aim of the present work was to formulate and evaluate Oral the sustained release tablet containing antihypertensive drug by using jackfruit mucilage as binding agent.i.e to study the effect of jackfruit mucilage in sustained release tablet.

### 2.1 Need for study:-

Oral route of administration is the most convenient, widely utilized, and preferred route of drug delivery for systemic action. However, when administered orally many therapeutic agents are subjected to extensive pre-systemic elimination by gastrointestinal degradation or first-pass metabolism as a result of which low systemic bio-availability and short duration of therapeutic activity and formulation of inactive or toxic metabolites.

Sustained release dosage form is useful especially for achieving controlled plasma level of drug as well as improving bio-availability. Natural polymers are remain attractive primarily because they are capable of chemical modification, having high drug holding capacity and thermal stability. Natural polymers are easily available and have some advantages when employed in sustained release drug delivery system such as bio-acceptability, bio-compatibility, bio-degrability and non-toxicity. Mucilage are most commonly used adjuvant in pharmaceutical preparation as binding, disintegrating, suspending, emulsifying and sustaining agent, because of their low cost, readily availability and non-toxicity.

It is important especially in the case of antihypertensive agents to maintain constant blood level, as otherwise dose dumping may cause hypotension. Constant blood level can be maintained by formulating sustained release tablet, using natural tablet retardant polymer since they are non-toxic, chemically stable, bio-degradable.

Present work therefore planned to developed a oral sustained release tablet of antihypertensive drug by using Jackfruit mucilage as one of the binding agent.

**2.2 Objectives of the present Study:**

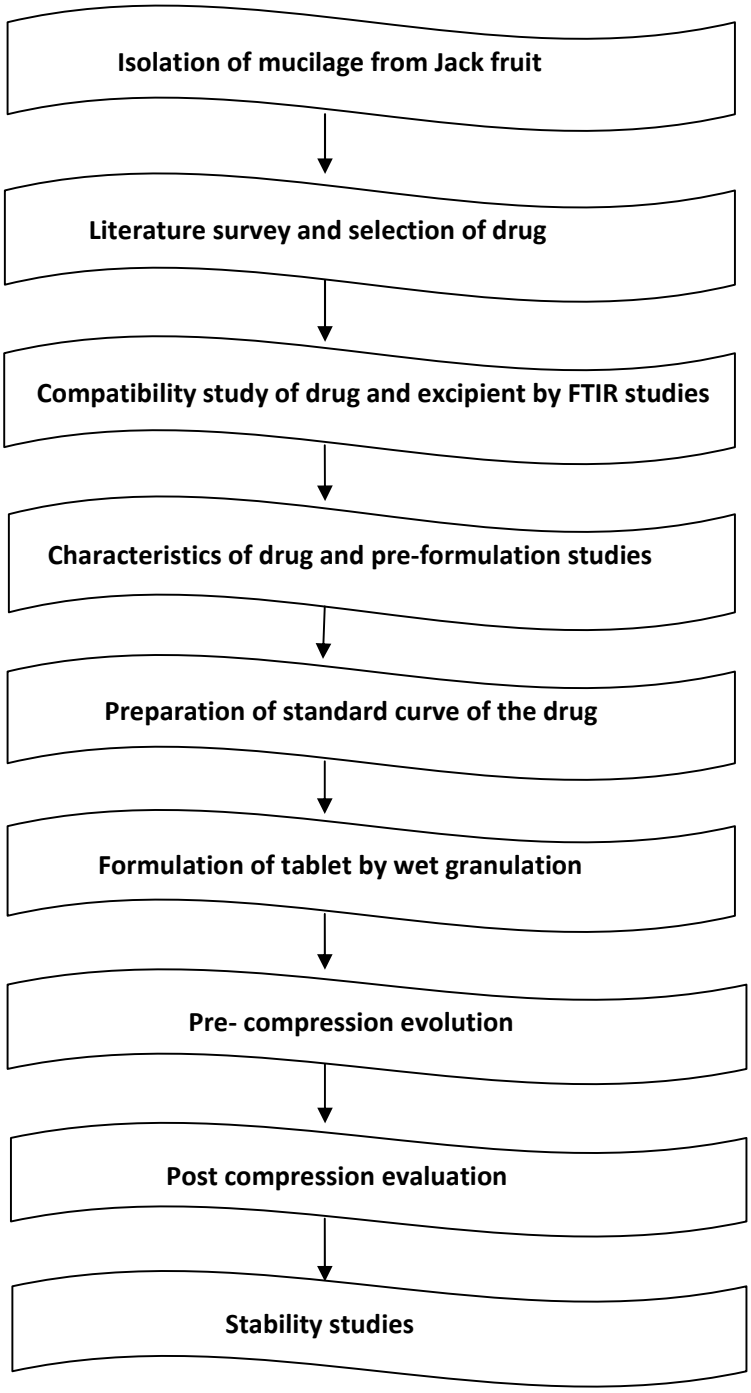
1. To isolate and investigate the suitability of the Jackfruit mucilage as binding agent.
2. To carry out the compatibility studies for possible drug and binding agent interactions by FT-IR studies.
3. To prepare sustained release dosage form containing Anti-hypertensive agent.
4. To carry out various *in-vitro* evaluation parameters.
5. Treatment of dissolution data with various mathematical models.
6. To carry out short-term stability study for best selected formulations.

**2.3 Plan of the work:**

1. To isolate mucilage from Jackfruit.
2. To carry out the compatibility studies for possible drug and mucilage interactions by FTIR studies.
3. Literature survey
4. Selection of drug candidate for sustained release dosage form based on Physical and Biopharmaceutical properties.
5. Procurement of drug and excipients.
6. To carry out Pre-formulation studies like Drug excipient compatibility melting point, angle of repose, bulk density, tapped density, Carr's Index and Hausner's ratio.
7. Determination of $\lambda_{max}$for Verapamil HCl in 0.1N HCl (pH 1.2) and phosphate buffer pH 6.8

8. Preparation of standard calibration curve of Verapamil HCl using 0.1N HCl and phosphate buffer pH 6.8
9. To develop experimental designing for formulation and characterization of Verapamil HCl.
10. Development of sustained release tablets of Verapamil HCl by using Jackfruit mucilage and other exicipient by wet granulation method.
11. Evaluation of the formulations for weight variation, hardness, friability, drug content and *in-vitro* disintegrationrelease studies.
12. To study*in-vitro*dissolution of Verapamil HCl tablets in 2different mediums 0.1N HCL (pH 1.2) and Phosphate buffer (pH 6.8)
13. To fit the resultant data to various kinetic models by curve fitting analysis.
14. To suggest a suitable mechanism of drug release based on the curve fitting analysis.
15. To carry out short-term stability study for best selected formulation.

**2.4 Brief Outline of the work:**



## 3. REVIEW OF LITERATURE

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.

**M.A. Shende et al.,**[41] Development of sustained release Diltiazem hydrochloride matrices through Jackfruit mucilage. Sustained release tablets of Diltiazem hydrochloride were developed by using natural polymers and gums like Jackfruit mucilage and tamarind polysaccharide to achieve controlled plasma level of drug as well as to improve bio-availability. Tablets were prepared by direct compression method using response surface methodology. Different batches of tablets were prepared by using different concentration of jackfruit mucilage and tamarind polysaccharide. Batches of the tablet containing 15% Jackfruit mucilage and 12.5% tamarind polysaccharide shows better controlled release of tablets.

**Narkhede sachin B.et al.,** [42] Formulation of Paracetamol tablets by using Jackfruit starch as binding agent. starch was isolated from Jackfruit, isolated starch was macerated and filtered, finally it is dried in vacuum dryer at 40°C. Granules were prepared by wet granulation method with different concentration of starch like 4,6,8%. This study concluded that as the concentration of binding agent increase disintegration time of tablet also increase and friability decrease.

**Vidya sabale el al.,**[37] Isolation and characterization of Jackfruit mucilage and its comparative evaluation as a mucoadhesive and controlled release component in buccal tablets. Aqueous extraction of mucilage from Jackfruit pulp and characterization of various physicochemical parameter including mucoadhesive components. Three batches of tablets were prepared by wet granulation method using three different mucodhesive component by changing the proportion of

mucoadhesive component (1:2:3) resulting in nine different formulation. *In-vitro* studies shows ,as the concentration of the isolated natural mucoadhesive agent increase in the formulation sustained action of drug also increase, but changing the mucoahesive component not changes the permeability behavior. Present study concluded that development of buccal tablets containing natural mucilage have a potential in sustained release action.

**Vinaya O.G. et al.,** [43] Development of oral sustained release tablet of Theophylline. Theophylline have higher incidence of side effects, the aim of this experiment is to develop sustained release Theophylline tablet to overcome such side effects by using Jackfruit latex. Latex was collected from the peduncle of slightly upper ripe Jackfruit. A flow property of latex powder was predicted. Matrix tablet of Theophylline with kollidon SR were prepared by dry granulation method. Drug release profile identical to that of the optimized formulation was determined, this optimized formulation showed an extended drug release for a period of 10hours.Tablet subjected to short term stability studies, and it showed good stability. This concluded that Jackfruit latex can be use in the formulation of oral sustained release tablets.

**Prakash pawan et al.,** [44] Role of natural polymer in sustained release drug delivery system. In recent year different dosage form have been developed by using natural, semi-synthetic, synthetic and gummy exudates. Among these natural polymers such as acacia, agar, gelatin, guar gum are most widely used in various pharmaceutical dosage form to get an effective product. Natural polymers are used as emulsifying agent, adjuvant ,adhesive in packing. Apart from this natural polymers are used in retarding drug release. Natural materials have advantages over synthetic materials such as they are chemically inert, non-toxic, less expensive, bio-degradable and widely available.

**Shantaveer V.Salger et al.,**[9] Development of propranolol as a sustained release matrix tablet, where hydroxypropyl methyl cellulose K100M used as rate retarding polymer, lactose and dibasic calcium phosphate as diluents as co- excipients. Amount of polymer and co- excepients plays an important role in release rate of drug. Lactose enhances the release rate of drug on the other hand dibasic calcium phosphate slowdowns the release rate of drug. Granules are prepare by the wet granulation method. This experiment concluded that the development of sustain release matrix tablet of propranolol hydrochloride help to achieve steady state blood level and it is therapeutically effective and non toxic for an extended period of time.

**Vidya D.waghnet al.,** [45] Formulation development and evaluation of extended release tablets of Metoprolol succinate. Metoprolol succinate is an antihypertensive drug use in management of hypertension. Multiple dosing due to lower half life is the main disadvantage hence this study has been carried out to formulate the metoprolol succinate tablet which provide prolong release of drug, this was attempted by preparing matrix tablet using HPMC K4M, HPMC K100M ,carbopol 971 and polyethylene oxide polymer by wet granulation method. Different batches of tablets were prepared by using different polymer among these batches carbopol containing batch showed ideal drug release for 20hours.Hence carbopol 971 was selected as base polymer along with polyethylene oxide, HPMC K4M,HPMC K100M to formulate sustained release tablets of Metoprolol succinate.

**G. Ganesh kumar et al.,** [46] Preparation and evaluation of sustained release matrix tablet of valsartan using natural polymers. Valsartan was formulated as sustained release matrix tablet to avoid frequency of dosing by modifying the rate of drug absorption. Various natural polymers such as pectin, guar gum, xanthan gum were used because natural gums are biodegradable, non-toxic which is hydrated and swell on contact with aqueous medium.SR matrix tablets of

valsartan were prepared by using different drug polymer ratio. Lactose was used as diluent , magnesium stearate was incorporated as lubricant. This study concluded that a better controlled drug release was obtained with matrix tablet made up of guar gum than with pectin and xanthan gum.

**Y.Rajajayarao p et al.,** [47] Formulation and evaluation of oral sustained release matrix tablet of Nifedipine tablets. Nefedipine is formulated in the form of sustained release matrix tablet by using HPMC, HEC eudraget RS100 as hydrophilic polymer, ethylcellulose as release retardant and lactose as filler. Type and concentration of polymer influence rate of drug release. HPMC and ethylcellulose successfully sustained the release of Nifedipine for a period of 17hours.Single polymer could not control the rate of drug release, only the combination of HPMC and ethylcellulose can control the rate of drug release. Because interaction between ethylcellulose chain ionic polymer rand HPMC chain non-ionic polymer increases the water uptake capacity and gel viscosity, leading to better control over the release.

**Durgacharan.A Bhagwat et al.,** [48] Sustained release matrices of Verapami hydrochloride using glyceryl monosterate and stearic acid. Glyceryl monostearate and stearic acid are used in formulation of sustained release dosage form of Verapamil hydrochloride. Drug release was studied by using USP-1 with PH 1.2 for one hour and PH 6.8 for seven hour. Drug release profile compared with marketed formulation and specification given in USP for extended release of Verampamil hydrochlodide tablets. During dissolution study other parameters were also studied like effect of different ratio of waxy substance on release pattern of drug and effect of release enhancer such as MCC and lactose. They concluded that matrices formulated from combination of monosterate and stearic acid gets more retardant than the matrices formulated from glyceryl monosterate alone or stearic acid alone. As the concentration of waxy substance increases release

of drug from matrices decreases. Effect of release enhancer showed that use of lactose produces a higher release of drug compare to MCC.

**V. Kalvimoorthi, *et al.,*** [49] Conducted a study in which six formulations of delayed release tablets were prepared by the direct compression method and simple pan coating using Drug coat N-100 and Hydroxy propyl methylcellulose phthalate (HPMCP) as enteric coating polymers. The *in-vitro* drug release was carried in pH 1.2 HCl and pH 6.8 phosphate buffer using USP dissolution Apparatus II at 100 rpm. They concluded that $F_4$ batch was considered to be the best enteric formula it shows 84.23% drug release at end of 45 min in the phosphate buffer.

**P. Suresh Kumar, *et al..,*** [50] Attempts were made in the present investigation to prepare a stable composition of delayed release tablets of Rabeprazole sodium. They concluded that the prepared formulation offers effective resistance in acidic environment and starts its release in the alkaline environment of small intestine. Thus, Instacoat EN-HPMCP A34G00031 Yellow can be successfully employed to retard the release pattern of Rabeprazole sodium thereby enhancing the therapeutic efficacy.

**Shanmugam S et al.,** [51] Purpose of this study is to 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.

**Tabandeh H et al.,** [52] Purpose of this study is to 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., [53]** preparation and evaluation of 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.

**Nayak RK et al.,[54]** Formulated and evaluated the sustained release matrix tablets of Lornoxicam. The tablet with guar gum in the ration 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,.[55]** 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.,**[56] 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 a particular concentration of MCC 101, HPMC K-100 and PVP K-30 are capable of providing sustained drug release.

**Basavaraj*et al.,***[57] Designed and characterized sustained release matrix tablets of Aceclofenac containing tamarind seed polysaccharide seed kernel of *Tamrindusindica* belonging to family leguminacy. 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 upto 12 hours so, that the controlled released profile is maintained for an extended period.

**M.D.Sajid et al.,**[58] 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.,**[59] 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. 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, manitol 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.

**EmamiJ et al.,** [60] 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 $S_2F_4$ (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.

**Rajiya Begum G et al.,**[61] The aim of the present work was to prepare and evaluate the sustained release tablet of Chlorzoxazone by using varying concentration of natural gums such as Acacia, Guar gum, Tragacanth. tablets were prepared by direct compression method and evaluated for weight variation, hardness, friability, thickness, drug content uniformity and *in-vitro* drug release .Based on *in-vitro* drug $F_3$, $F_6$, and $F_9$ showed sustained release effect upto 12 hours.

**Moin A et al.,**[62] 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.

**Rakesh PP et al.,**[63] Formulation and evaluation of 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.

**Lakade SH et al., [64]** 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.

## 4. MATERIALS AND METHODS

### 4.1 MATERIALS USED:

**Tables No 5:** List of chemicals used

| Sl NO | Materials | Name of the Supplier |
|---|---|---|
| 1 | Verapamil HCl | Yarrow Chem Products Mumbai |
| 2 | Microcrystalline cellulose | S.D. Fine Chemical Ltd,Mumbai |
| 3 | Dicalcium phosphate | S.D. Fine Chemical Ltd,Mumbai |
| 4 | Talc | S.D. Fine Chemical Ltd,Mumbai. |
| 5 | Magnesium stearate | S.D. Fine Chemical Ltd,Mumbai |
| 6 | Bentonite | S.D. Fine Chemical Ltd,Mumbai |
| 7 | Starch paste | S.D. Fine Chemical Ltd,Mumbai |

**4.2 EQUIPMENT USED:**

**Table No 6:** Details of Equipment's used

| Sl NO | Instrument | Manufacturer |
|---|---|---|
| 1 | Electronic balance | Acculab |
| 2 | Hot air oven | Kaavil electro mechanical industries,Kerala, India |
| 3 | UV-Visible spectrophotometer | Spectrophotometer UV -1800, Shimadzu, Japan |
| 4 | FT-IR Spectrometer | Thermo nicolet 380,India |
| 5 | Tablet punching Machine | LAB PRESS, Cip Machineries Pvt.Ltd Ahmadabad, India |
| 6 | Roche Friabilator | PSM industries, Banglore, India |
| 7 | Monsantro Hardness tester | Techno scientific products, Banglore , India |
| 8 | Disintegration test apparatus | SiiSerwell Instruments INC, Banglore, India |
| 9 | Dissolution test apparatus | Lab india instruments Pvt.Ltd,DS 8000, Navimumbai, India |
| 10 | Stability chamber(106 Model) | LABTOP,SKY Lab Instruments & Engineering Pvt.Ltd. India |
| 11 | Brook field viscometer | Brook field DV2TRV |

### 4.3. DRUG PROFILE[65,66.]

**Name:** Verapamil HCl

**Structure:**

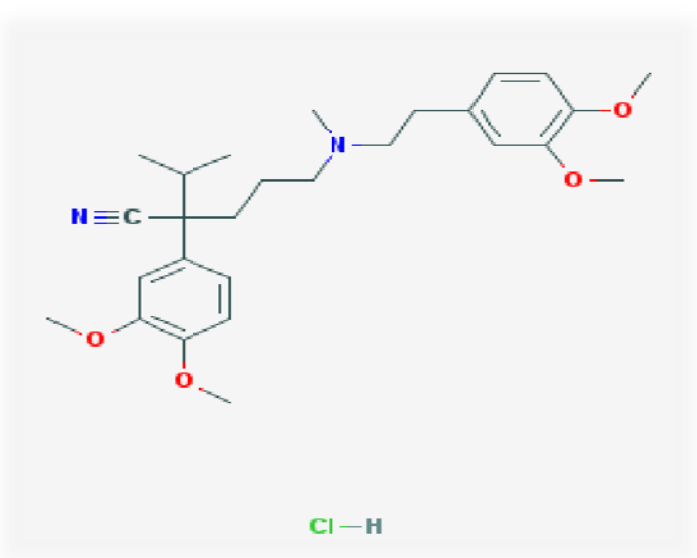



**Figure No. 5 :** Structure of Verapamil HCl

**Table No 7:**:Properties of Verapamil HCl

| | |
|---|---|
| **Synonym** | Veracim, Veramex, Calan, Isoptin**.** |
| **Chemical** | 2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile;hydrochloride |
| **CAS Number** | 36622-28-3 |
| **Category** | Anti-hypertensive, treatment of chest pain, in certain heart rhythm disorders. |
| **Molecular formula** | C27H39ClN2O4 |
| **Molecular weight** | 491.06 |
| **Appearance** | Amorphous powder |
| **Physical state** | Solid |

| | |
|---|---|
| **Color** | White |
| **Odour** | Characteristic |
| **Solubilty** | Soluble in water(7g/100ml), 100% ethanol(26mg/ml).Sparingly soluble in chloroform |
| **Melting point** | 126-129°C |
| **Refractive index** | $n^{25}$ D 1.54 |
| **Pka (Strongest acidic)** | <-1.74 |
| **Pka (Strongest basic)** | 9.68 |

**Table No 8:**Pharmacology of Verapamil HCl

| | |
|---|---|
| **Indication** | For the treatment of hypertension, angina, and cluster headache prophylaxis |
| **Pharmacodynamics** | Verapamil is an L-type calcium channel blocker that also has antiarrythmic activity. The R-enantiomer is more effective at reducing blood pressure compared to the S-enantiomer. However, the S-enantiomer is 20 times more potent than the R-enantiomer at prolonging the PR interval in treating arrhythmias. |
| **Mechanism of action** | Verapamil inhibits voltage-dependent calcium channels. Specifically, its effect on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thuis reducing heart rate and blood pressure. Verapamil's mechanism of effect in cluster headache is thought to be linked to its calcium-channel blocker effect, but which channel subtypes are involved is presently not known**.** |
| **Absorption** | 90% |

| | |
|---|---|
| **Volume of distribution** | Protein binding |
| **Metabolism** | Hepatic metabolism |
| **Route of elimination** | Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug. |
| **Half life** | 2.8-7.4 hours |
| **Toxicity** | $LD_{50}$=8 mg/kg (i.v. in mice) |

**Table No 9:**Pharmacokinetics of Verapamil HCl

| | |
|---|---|
| **Absorption** | More than 90% of an oral dose is absorbed. Bioavailability ranges from 20% to 35%. $T_{max}$ is 1 to 2 h (immediate-release), 7 to 9 h ( Verelan ), and 11 h ( Covera-HS and Verelan PM ). |
| **Distribution** | Rapid early distribution phase (half-life approximately 4 min). 90% protein bound**.** |
| **Metabolism** | Rapidly metabolized. Extensive metabolism in the liver with 12 metabolites identified, most only in trace amounts. Major metabolites are N- and O-dealkylated products of verapamil**.** |
| **Elimination** | Elimination half-life is approximately 3 to 7 h (single oral dose), 4.5 to 12 h (multiple oral dose), or 2 to 5 h (IV). Approximately 70% of dose is excreted in the urine and 16% or more in feces within 5 days. Approximately 3% to 4% is excreted as unchanged drug. |

**Table No 10:**Interaction of Verapamil HCl with other drugs

| | | |
|---|---|---|
| **DRUG** | Acetylsalicylic acid | Calcium Channel Blockers (Nondihydropyridine) may enhance the anticoagulant effect of Salicylates**.** |
| | Afatinib | P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib |
| | Alfuzosin | May enhance the hypotensive effect of Antihypertensives |
| | Aliskiren | Verapamil may increase the serum concentration of Aliskiren. |
| | Amifostine | Antihypertensives may enhance the hypotensive effect of Amifostine. |
| | Amiodarone | Calcium Channel Blockers (Nondihydropyridine) may enhance the bradycardic effect of Amiodarone. Sinus arrest has been reported. |
| | Amobarbital | Barbiturates may increase the metabolism of Calcium Channel Blockers. |
| | Apixaban | CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Apixaban. |
| | Aprepitant | May increase the serum concentration of CYP3A4 Substrates. |
| | Aripiprazole | CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Aripiprazole. |

| | |
|---|---|
| **Food** | The drug should be administered with food. |
| **Dose and administration** | Initiate therapy with 180 mg /day. Lower initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil.<br>If adequate response is not obtained with 180 mg of verapamil hydrochloride extended-release tablets, the dose may be titrated upward in the following manner:<br>240 mg each morning,<br>180 mg each morning plus 180 mg each evening; or 240 mg each morning plus 120 mg each evening,<br>240 mg every 12 hours. |
| **Storage** | Tightly closed container at room temperature (approximately 25°C); generally should be protected from light and moisture. |

**Table No11:** Adverse reaction of Verapamil HCl

| | |
|---|---|
| **Cardio vascula system** | Chest pain, Slow and irregular heart beat |
| **Respiratory system** | Shortness of breath ,Coughing that produce a pink frothy sputum, difficult, fast, noisy breathing, sometimes with wheezing |
| **CNS** | Confusion, Dizziness, |
| **Eyes** | Blurred vision. |
| **Skin** | Pale skin, Burning, Itching, Tingling feeling |

4.4.EXCIPIENT PROFILE:

**Table No 12:** Magnesium stearate[67,68]

| | |
|---|---|
| **Non-proprietary names** | BP: Magnesium stearate<br>USP/NF: Magnesium stearate |
| **Synonyms** | Magnesium octadecanoate, octadecanoic acid, magnesium salt |
| **Description** | Very fine, light white, precipitated or milled, impalpable powder of low<br>bulk density, having a faint odor of stearic acid and a characteristic taste.<br>The powder is greasy to touch and readily adhere to skin. |
| **Chemical names**<br>**CAS Number** | Octadecanoic acid magnesium salt<br>557-04-0 |
| **Emoherical forula**<br>**CAS Number** | C36H70Mgo4<br>591.34 |
| **Melting point** | 117-150ºC (commercial samples)<br>126-130 ºC (high purity magnesium stearate) |
| **Solubility** | Practically insoluble in ethanol, ethanol (95%), ether and water, slightly<br>soluble in warm benzene and warm ethanol (95%). |
| **Functional Category** | Tablet and capsule lubricant |
| **Incompatibilities** | Strong acids, alkalis and iron salt |
| **Safety** | It is widely used as pharmaceutical excipient and is generally regarded<br>as being nontoxic |
| **Application** | It is widely used in cosmetic, foods, and pharmaceutical formulations. It<br>is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. it is also used in barrier<br>creams. |

**Table No 13:**Talc[69,70]

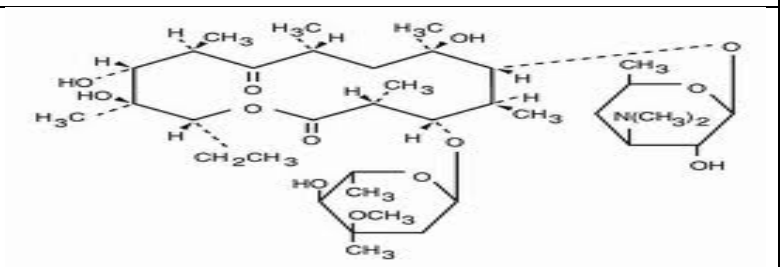
| | |
|---|---|
| **Non-proprietary names** | BP: Purified talc<br>USP: Talc |
| **Synonyms** | Altalc, E553b, hydrous magnesium calcium silicate, Luzenac Pharma, Purtalc, steatite, purified French chalk. |
| **Description** | Very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. |
| **Structural Formula** |  |
| **Chemical names**<br>**CAS Number** | Talc<br>14807-96-6 |
| **Empirical formula** | $Mg_6(Si_2O_5)_4(OH)_4$ |
| **Functional Category** | Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant. |
| **Stability and storage conditions** | It is stable material and may be sterilized by heating at $160^0$C for not less than 1 hour. It should be stored in a well-closed container in a cool, dry place. |
| **Incompatibilities** | Quaternary ammonium compounds |
| **Application** | It is widely used oral solid dosage formulations as a lubricant and diluent. It is also used as lubricant in tablet formulation, in a novel powder coating for extended-release pellets and as an adsorbant. |

**Table No 14:**Microcrystalline cellulose[71]

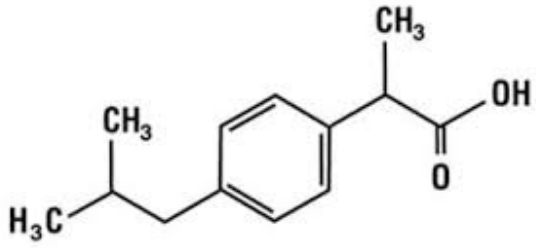
| | |
|---|---|
| **Non-proprietary names** | BP:Microcrystalline cellulose<br>USP:Microcrystalline cellulose |
| **Synonyms** | Avicel, cellulose gel, Vivacel |
| **Description** | White,odourless, tasteless, crystalline powder composed of porous particles |
| **Structural Formula** |  |
| **Chemical names**<br>**CAS Number** | Cellulose<br>9004-34-6 |
| **Empirical formula** | $(C_6H_{10}O_5)n$ Where n =220 |
| **Functional Category** | Adsorbent,Suspending agent, Diluent in tablet and capsule,Disentigrate |
| **Stability and storage conditions** | It is stable.Should be stored in well closed container in cool place |
| **Incompatibilities** | Strong oxidizing agent |
| **Application** | Widely used in pharmaceutics, primarily as binder,diluents**.** |
| **Safety** | Relatively non-toxic and non-irritant |

**Table No 15**:Dicalcium phosphate[72]

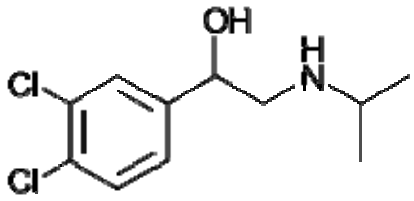
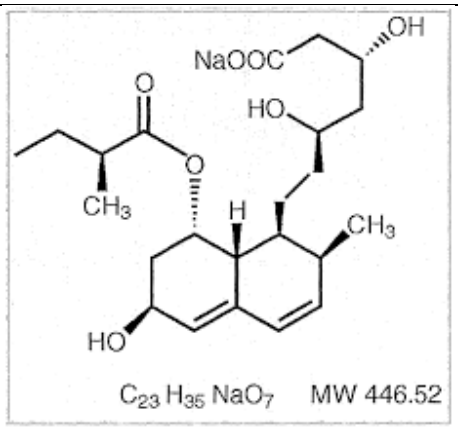
| | |
|---|---|
| **Non-proprietary names** | USP: Dicalcium phosphate unhydrous<br>B.P.: Dibasic calcium phosphate |
| **Synonyms** | Dibasic calcium phosphate dehydrate<br>Calcii hydrogenophosphas dihydrous |
| **Description** | White, odourless, tasteless. Soluble in dil HCl and dil nitric acid. Insoluble in cold water |
| **Structural Formula** |  |
| **Chemical names**<br>**CAS Number** | Calcium hydrogen phosphate dehydrate<br>7789-77-7 |
| **Empirical formula** | $CaHPO_4.2H_2O$ |
| **Functional Category** | In the manufacturing of tablet, it delay the drug release. |
| **Stability and storage conditions** | It is a stable material. Should be store at room temperature |
| **Incompatibilities** | Strong acid,strong base and nitrates |
| **Application** | Used ad excipients in the manufacturing of of medicine and nutaceutical product. As a bioavailable source of calcium and phosphorous in nutrient supplement |

**Table No 16:**Bentinite:[73]

| | |
|---|---|
| **Non-proprietary names** | Colloidal hydrated aluminium silicate. |
| **Synonyms** | Wilkinite Wilkonite Otylite. |
| **Description** | Grey colour powder,characteristic odour, insoluble in water |
| **Structural Formula** |  |
| **Chemical names**<br>**CAS Number** | Hydrated aluminium silicate<br>1302-78-9 |
| **Empirical formula** | $Al_2o_34sio_2H_2o$ |
| **Functional Category** | Adsorbent, Binding agent. |
| **Stability and storage conditions** | It is stable.it should be stored in opaque, glass or PET plastic, air tight, non-metalic container |
| **Incompatibilities** | No specific or group of materials are likely to react to produce a hazardous solution |
| **Application** | Drilling mud,binder,purification, ground water barrier. |
| **Melting point** | >450ºC |

## 4.5 METHODOLOGY

### 4.5.1 PRE-FORMULATION CHARACTERIZATION

Pre-formulation 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 bio-available dosage form.

. **A. Melting Point determination:**

The melting temperature of drugs was determined using capillary method.

**B. Compatibility study using FT-IR:**

A successful stable and effective formulation of a 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. Compatibility study was carried out for Drug and Jackfruit mucilage.

**C. Development of analytical method**

**i. Preparation of 0.1 N HCL solution:**

8.5ml of 35% hydrochloric acid was accurately measured and transferred into a 1000ml volumetric flask and the volume was made up to the mark with distilled water.

**ii. Preparation of 6.8 pH phosphate buffer solution:**

50 ml of the 0.2M potassium dihydrogen orthophosphate 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.

**iii. Preparation of standard Verapamil HCl solution**

accuretly weight 100mg of verapamil HCl was transfer into 100ml volumetric flask and dissolved in small quantity of methanol. Finally make up to the volume with 0.1 N HCl. Stock solution so prepared was containing 100 microgram of drug per ml of solvent.

**iv. Determination of wavelength of maximum absorbance**

Standard Verapamil HC solution (1ml) was pipetted in 100 ml volumetric flask. Then the volume was adjusted to the mark with 0.1N HCl. The solution was scanned and absorbance was measured in the range of 200-400 nm against blank on Shimadhzu 1800 UV-Visible spectrophotometer. The blank was prepared in similar manner in which volume of standard drug solution was replaced by equal volume of 0.1 N HCl.

**v. Preparation of standard calibration curve of Verapamil HCl in 0.1N HCl**

**Preparation of standard solution**

100 mg of Verapamil HCl was accurately weighed in to 100ml volumetric flask and dissolved in small quantity of 0.1 N HCl. The volume was made up to the mark with the 0.1 N HCl to get a concentration of 1000µg/ml (SS-I). From this 1ml was withdrawn and diluted to 100ml to get a concentration of 10µg/ml (SS-II).

**Preparation of working standard solutions:**

From (SS-II) aliquot 1ml,, 2ml, 3ml, 4ml, 5ml were pipetted into 10ml volumetric flasks. The volume was made up with 0.1N HCl to get the final concentration of 1, 2, 3, 4, 5 µg/ml respectively.

The $\lambda_{max}$ was found to be 278 nm from UV spectrum of Verapamil HCl in 0.1N HCl, during scanning from 200-400 nm. Absorbance was measured at 278 nm against 0.1N HCl as blank on a UV-Visible Spectrophotometer (UV-1800 SHIMADZU). The observations were recorded in Table No 24. and the calibration curve was prepared by plotting absorbance versus concentration of Verapamil HCl as shown in graph no.1

**vi. Preparation of standard calibration curve of Verapamil HCl in 6.8 pH**

**Preparation of standard solution:**

100 mg of Verapamil HCl was accurately weighed in to 100ml volumetric flask and dissolved in small quantity of phosphate buffer pH 6.8. The volume was made up to the mark with the phosphate buffer pH 6.8 to get a concentration of 1000µg/ml (SS-I). From this 1ml was withdrawn and diluted to 100ml to get a concentration of 10µg/ml (SS-II).

**Preparation of working standard solutions:**

From (SS-II) aliquots 1ml, 2ml, 3ml, 4ml, and 5ml were pipetted into 10ml volumetric flasks. The volume was made up with the phosphate buffer pH 6.8 to get the final concentration of 1, 2, 3, 4 and 5µg/ml respectively.

The $\lambda_{max}$ was found to be 278 nm from UV spectrum of Verapamil HCl in 0.1N HCL, during scanning from 200-400 nm. Absorbance was measured at 278 nm against phosphate buffer pH 6.8 as blank on a UV-Visible Spectrophotometer (UV-1800 SHIMADZU). The observations were recorded in Table No 25. and the calibration curve was prepared by plotting absorbance versus concentration of Verapamil HCl as shown in graph no.2

**D. Isolation of mucilage from Jackfruit:**

The fresh fruits were obtained from the loacal market, in the month of June. The fruits were thoroughly washed with water to remove dirt and debris. The seeds which were present inside the fruit were removed. Pulps of the fruits were made into slices and dried in oven at 35ºC till it dried completely. collected, grounded , passed through a # 80 sieve, and in desiccator till use.

**E. Determination of Jackfruit mucilage viscosity:** Viscosity of 3% aqueous solution jackfruit mucilage was determined by using Brooke field viscometer at different rpm.[73]

**4.5.2. FORMULATION DESIGN**

**Table No.17:** Selected Ingredients for formulation with function

| Sl.no | EXICIPIENT | FUNCTION |
|---|---|---|
| 1 | Verapamil HCl | Model drug |
| 2 | Microcrystalline cellulose | Diluent |
| 3 | Dicalcium phosphate | Diluent |
| 4 | Magnesium Stearate | Lubricant |
| 5 | Talc | Glidant |
| 6 | Bentonite | Adsorbent |
| 7 | Jackfruit mucilage | Binder |
| 8 | Starch paste | Binder |

**Table No.18:** Formulation developed

| Sl.no | Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| **1** | Verapamil HCl | **40** | **40** | **40** | **40** | **40** | **40** |
| **2** | Microcrystalline cellulose | **55** | **45** | **40** | **35** | **30** | **30** |
| **3** | Dicalcium phosophate | **45** | **25** | **25** | **25** | **25** | **20** |
| **4** | Magnesium staerate | **5** | **2** | **2** | **2** | **2** | **2** |
| **5** | Talc | **5** | **2** | **2** | **2** | **2** | **2** |
| **6** | Bentonite | **_** | **26** | **26** | **26** | **26** | **26** |
| **7** | Jackfruit mucilage | **_** | **10** | **15** | **20** | **25** | **30** |
| **8** | Starch paste | **q. s** | **q. s** | **q. s** | **q. s** | **q. s** | **q. s** |
| **9** | Total tablet weight | **150** | **150** | **150** | **150** | **150** | **150** |

### 4.5.3. PREPARATION OF VERAPAMIL HCL TABLETS BY WET GRANULATION METHOD

Wet granulation method was used for all tablet production. Calculation was made for 100 tablets in each batch.

**i. Preparation of starch paste:** Starch past was prepared by adding a required quantity of starch powder to the boiling water on water bath till it gives paste consistency. This mixture was then used as binder solution in the preparation of granules.

**ii. Preparation of damp mass:** In each case, accurately weighed quantities of Verapamil HCl, Microcrystalline cellulose, Dicalcium phosphate, Magnesium stearate, Bentonite and Jackfruit mucilage, were mixed in a mortar and the starch paste was added to obtain a damp coherent mass. The damp mass was sieved with 1.7mm sieve and dried at 37ºC in oven for 30mins.

**iii. Punching of Tablets:** The dried granular mass was passed through a 1.0 mm sieve to obtain uniform sized granules. The different batches of the granules were then mixed with calculated equal quantities of Talc, and then were compressed into tablets on a pilot press machine (Lab Press Multi punch machine, India) using 12 mm diameter, flat faced punches at a pressure of approximately 5kgs/cm.$^2$

**4.5.4. PRE COMPRESSION CHARACTERIZATION**

**i. Bulk density (Bd)**

The term bulk density refers to a measure used to describe a packing of particles. The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm$^3$ (V). The standard method (USP) was adopted for measurement of bulk density of granuls and following equation was used for calculation.

$$Bd = M/V$$

Where, M = weight of samples in grams, V= bulk volume of powder in cm$^3$

**ii. Tapped density (Td)**

The tapped density or poured density attained after mechanically tapping a container containing the powder sample. The standard method described in USP was followed and tapped density was calculated using equation given below:

$$Td = M/ Vp$$

Where, M = weight of samples in grams and Vp = final tapped volume of powder in cm$^3$

**iii. Carr's index(CI)**

An indirect method of measuring powder flow from bulk densities was developed by Carr's. A low Carr's index implies a good initial packing arrangement, with less volume of voids. As the value of these indices increases, the flow of the powder decreases. Carr's index of each sample was calculated according to equation given below:

$$CI = 100 (Td - Bd) / Td$$

**vi. Hausner's ratio(HR)**

Hausner's ratio measures the powder ability to settle and permit an assessment of the relative importance of interparticulate interactions. Hausner's ratio is calculated as the ratio of bulk density to tapped density.

$$HR = V_0 / V_f$$

Where, $V_0$: unsettled apparent volume, $V_f$: final tapped volume

**Table No.19**: Effect of Carr's Index and Hausner's Ratio on flow property

| Carr's Index (%) | Flow Character | Hausner's Ratio |
|---|---|---|
| ≤10 | Excellent | 1.00–1.11 |
| 11-15 | Good | 1.12–1.18 |
| 16-20 | Fair | 1.19-1.25 |
| 21-25 | Passable | 1.26-1.34 |
| 26-31 | Poor | 1.35-1.45 |
| 32-37 | Very poor | 1.46-1.59 |
| >38 | Very very poor | >1.60 |

**v. Angle of Repose**

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the fixed height funnel method. The angle of repose was calculated by substituting the values of the base radius 'r' and pile height 'h' in the following equation.

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, h and r are the height and radius of the powder cone respectively.

**Table No.21:** Effect of Angle of repose (□) on Flow property

| Angle of Repose (□) | Type of Flow |
|---|---|
| <20 | Excellent |
| 20-30 | Good |
| 30-34 | Passable |
| >35 | Very poor |

**4.5.5. POST COMPRESSION CHARACTERIZATION**

**i. Appearance:**

Organoleptic properties such as color and odor were evaluated. Ten tablets from each batch were randomly selected and their colors were visually compared and odour was checked.

**ii. Dimensions:**

Thickness and diameter of the tablet was measured using Digital Vernier caliper. Five tablets of the formulation were picked randomly and measured individually.

**iii. Hardness:**

Hardness was measured using fpizer hardness tester. For each batch five tablets were used.

**iv. Friability:**

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. The tablets were de-dusted and weighed again. The percentage friability was calculated using the formula:

$F = \{1-(W_t/W)\} \times 100$

Where, F = Friability in percentage

W = Initial weight of tablets

$W_t$ = Weight of tablets after friabiation.

**v. Drug content estimation**[42]

Sustained release tablets of Verapamil HCl equivalent to 150 mg are weighed and dissolved in little amount of methanol in100ml volumetric flask, sonicate for 5min and volume is made upto 100 ml with the 0.1N HCl and filtered through membrane filter. Subsequent dilutions are made and absorbance is measured at 278 nm against blank (0.1N HCl) and drug content is calculated using standard curve. Each test is performed in triplicate.

$$\%\ \text{drug content} = \frac{\text{actual drug content in tablet}}{\text{theoretical amount of drug in tablet}} \times 100$$

**vi. Weight variation test:** 20 tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met; if not more than two of the individual weights deviate from the average weight by not more than existing 5%.

$$\text{weight variation} = \frac{\text{Average weight} - \text{tablet weight}}{\text{tablet weight}} \times 100$$

**Table 21:** Weight variation tolerances for uncoated tablets

| Sl.no | Average weight of tablets in mg | Max % differences allowed |
|---|---|---|
| 1 | 130 or less | 10% |
| 2 | 130-324 | 7.5% |
| 3 | More than 324 | 5% |

**vii. Disintegration test**

The disintegration time was measured using disintegration test apparatus as per the USP. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no.10) were immersed in water bah a 37± 2°C. The time required for complete disintegration of the tablet in each tube was determined.

**viii. *In-vitro* dissolution studies:**

Dissolution of the tablets was carried out on USP XXIII dissolution type II apparatus using paddle. The dissolution medium consisted of 900 ml of pH 1.2 buffer (0.1N HCl) for first two hours and the phosphate buffer pH 6.8 from 3- 12 hours maintained and the temperature of the medium was set at 37±0.5□ C. The rotational speed of the paddle was set at 50 rpm. 5ml of sample was withdrawn at predetermined time interval of 1 hour up to 10 hour and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10ml with pH 6.8.filtered and analyzed on UV spectrophotometer at 278nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

**Details 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 : pH 0.1N HCl (pH 1.2) and phosphate buffer pH6.8

Temperature : 37±0.5ºC.

**4.5.6. Data analysis:**

To analyze the mechanism of release and release rate kinetics of the dosage form the data obtained were fitted into Zero order, First order, Higuchi matrix and Korsmeyer's and peppas models. Based on the 'R'-value the best fit model was selected.

- **Zero order kinetics:**

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation

$Q_t = Q_0 + K_0 t$

$Q_t$= amount of drug dissolved in time t

$Q_0$ = initial amount of the drug in the solution

$K_0$= zero order release constant

❖ **First order kinetics:**

To study the first order release rate kinetics the release rate data were fitted to the following equation:

Log $Q_t$= log $Q_0$+ + $K_1$t/2

Where,

$Q_t$= amount of drug released in time t

$Q_0$= initial amount of drug in the solution

$K_1$= first order release constant.

❖ **Higuchi model:**

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated into semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media and the equation is:

$$Q_t = K_H.t^{1/2}$$

Where, $Q_t$= amount of drug released in time t.

$K_H$= Higuchi dissolution constant.

❖ **Krosmeyer and Peppas release model:**

To study this model the release rate data are fitted to the following equation:

$$Mt / M_\infty = K \cdot t^n$$

Where, Mt / $M_\infty$= fraction of drug release

K = release constant

t = release time and

n = diffusional coefficient.

**Table No.22:** Mechanism of Drug Release as per Korsmeyer Equation/ Peppa's Model

| Sl. No | 'n' value | Drug release |
|---|---|---|
| 1. | 0.45 | Fickian release |
| 2. | 0.45 <n<0.89 | Non- Fickian release |
| 3. | n>0.89 | Case II transport |

### 4.5.7. STABILITY STUDIES

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 various environmental conditions such as temperature, humidity, light. From this study we know about recommended storage conditions, re-test periods and self-life of the drug can be established.

**A.Importance of stability studies**

Stability studies are important for the following reasons.

This is an assurance given by the manufacturer that the patient would receive a uniform dose throughout the shelf life.

1.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.

2.Stability testing prevents the possibility of marketing an unstable product. Both physical and chemical degradation of drug can result in unstable product.

**B.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.

The optimized formulation was subjected for stability study. The selected formulations were packed in aluminum foil in tightly closed container. They were then stored at 40ºC / 75% RH and evaluated for their physical appearance, drug content and dissolution.

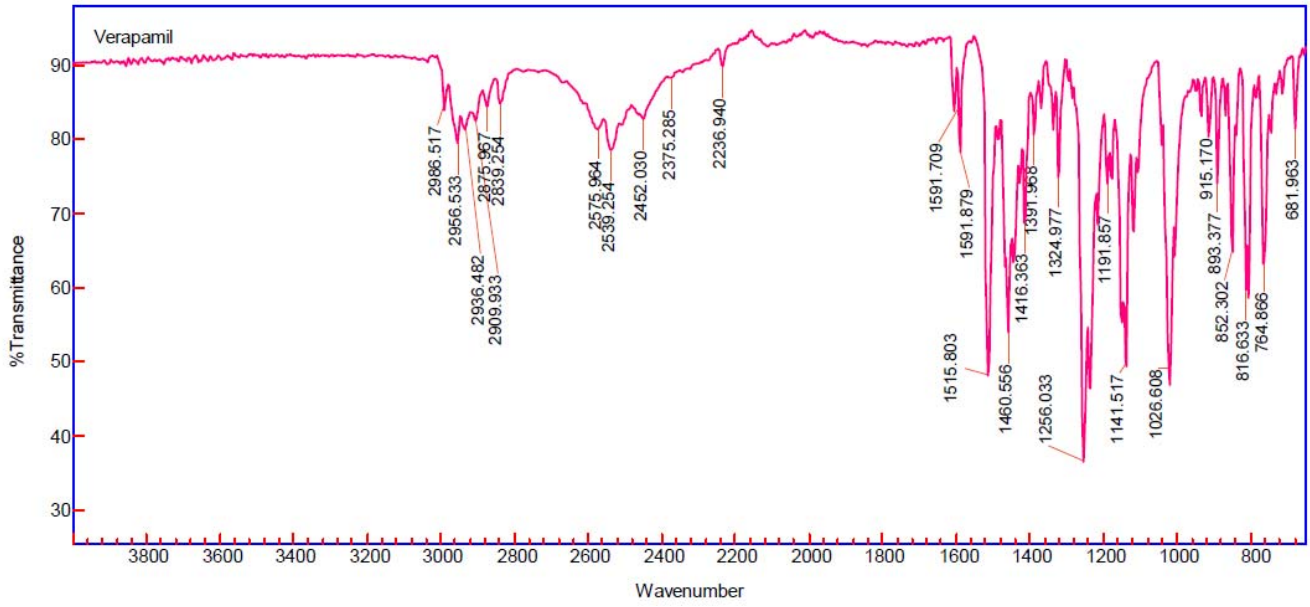
# 5. RESULTS

## 5.1 PRE-FORMULATION CHARACTERIZATION

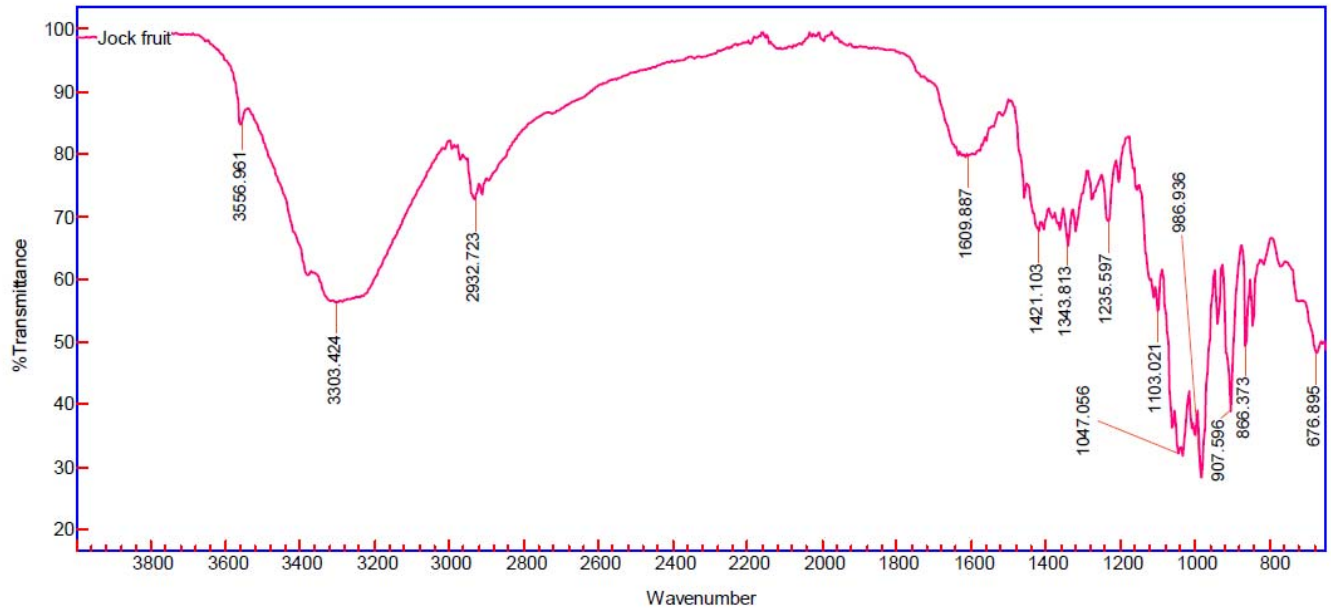
### A. Melting Point determination:

The melting point of Verapamil HCl was found to be 132°C

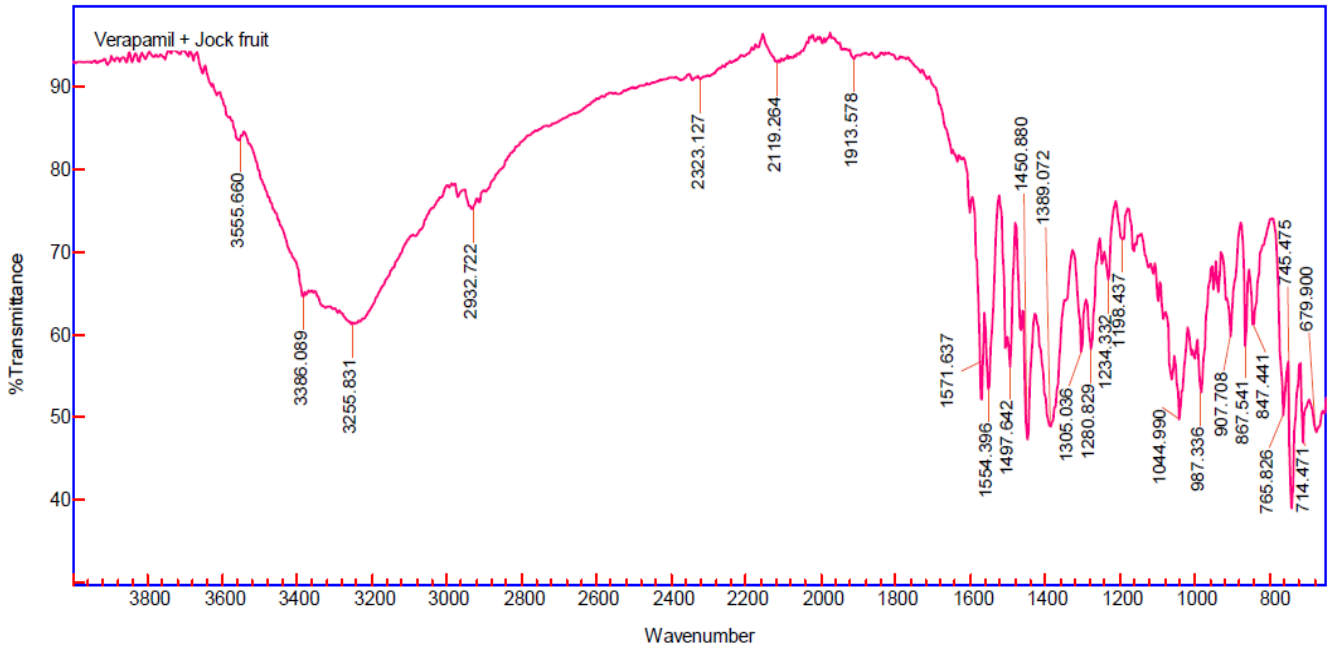
### B. Drug - Excipients Compatibility:




**Spectra No 1:**FT-IR spectra of verapamil HCl




**Spectra No 2**: FT-IR Spectra of Jackfruit mucilage




**Spectra No 3:** FT-IR Spectra off Verapamil HCl + Jackfruit mucilage

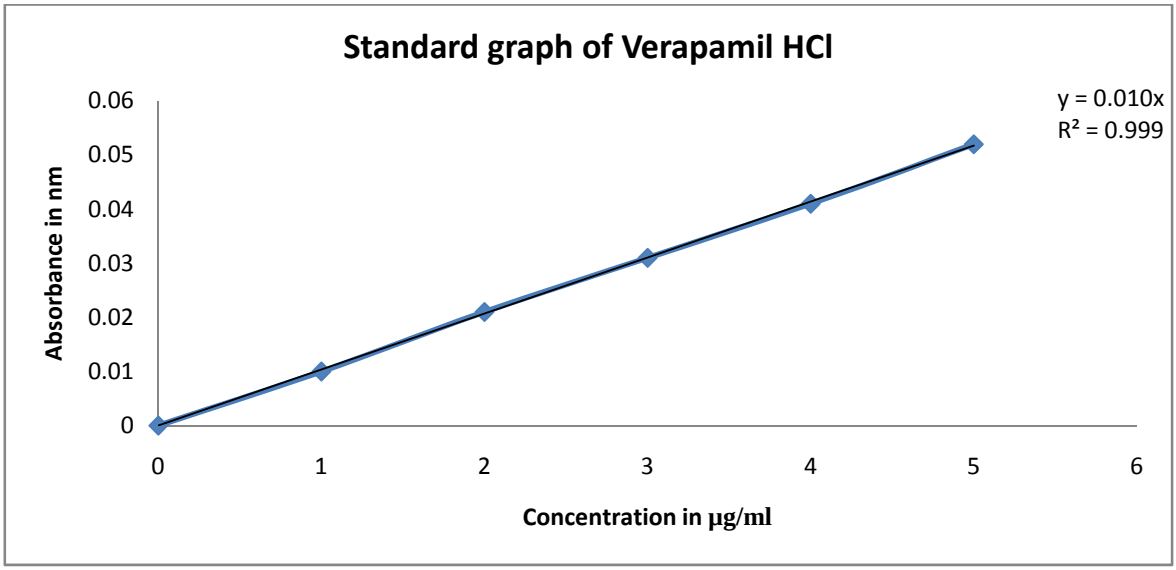
## C. Development of analytical method

### i. Standard Calibration curve for Verapamil HCl in 0.1N HCl

The $\lambda_{max}$ of the Verapamil HCl was found to be 278nm in 0.1 N HCl.

**Table No.23**: Spectrophotometric Data for the Estimation of Verapamil HCl in 0.1N HCl.

| Sl No | Conc (µg/ml) | Abs |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 1 | 0.01 |
| 3 | 2 | 0.021 |
| 4 | 3 | 0.031 |
| 5 | 4 | 0.042 |
| 6 | 5 | 0.052 |



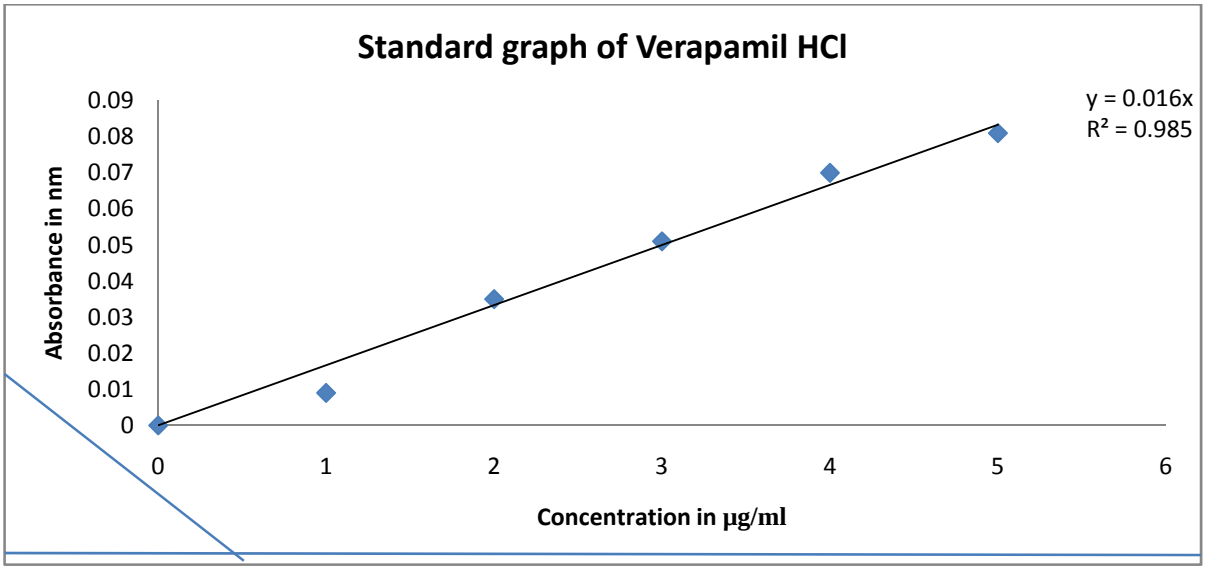

**Graph No.1:** Calibration Curve of Verapamil HCL in 0.1N HCL.

**ii. Standard Calibration curve for Verapamil HCl in 6.8 Phosphate Buffer**

The $\lambda_{max}$ of the Verapamil HCl was found to be 278nm in pH 6.8

**Table No.24:** Spectrophotometric Data for the Estimation of Verapamil HCl IN 6.8pH Phosphate buffer.

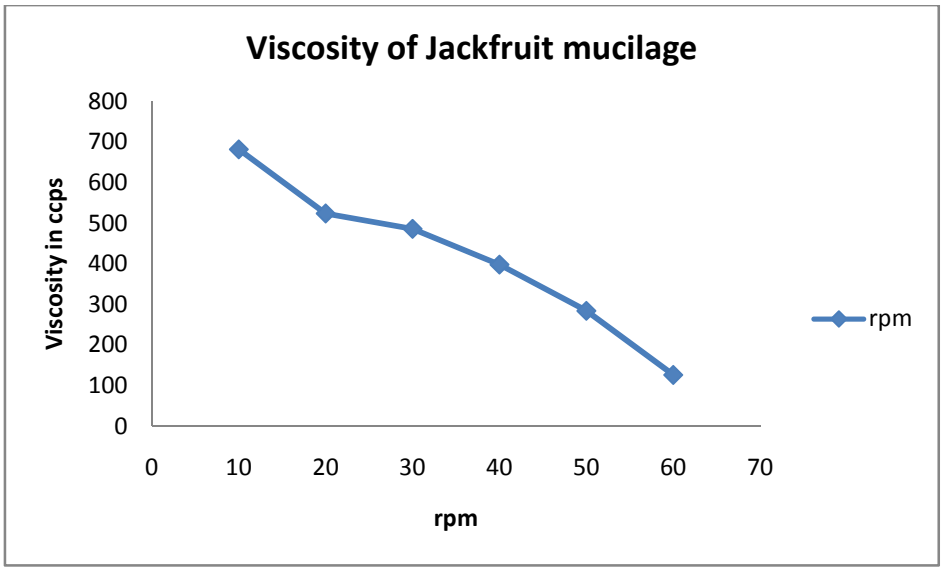
| Sl No | Conc (µg/ml) | Abs |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 1 | 0.009 |
| 3 | 2 | 0.035 |
| 4 | 3 | 0.051 |
| 5 | 4 | 0.070 |
| 6 | 5 | 0.081 |




**Graph No.2:** Calibration Curve of Verapamil HCL in 6.8 Phosphate buffer.

**D.Viscosity of Jackfruit mucilage: Table No.25**

| Sl NO | Viscosity in cps | Rpm |
|---|---|---|
| 1 | 682 | 10 |
| 2 | 524 | 20 |
| 3 | 486 | 30 |
| 4 | 398 | 40 |
| 5 | 284 | 50 |
| 6 | 126 | 60 |




**Graph No:3** Viscosity of Jackfruit mucilage

**5.2. Evaluation Parameters:**

**5.2.2. Pre-compression Parameters**

**Table No.26:** Pre-compression parameters results.

| Code | Bulk density ($g/cm^3$) | Tapped density ($g/cm^3$) | Carr's index% | Hausner's ratio | Angle of repose(°) |
|---|---|---|---|---|---|
| **F1** | 0.521±0.094 | 0.625±0.120 | 17.24±0.03 | 1.19 | 28.56±0.04 |
| **F2** | 0.529±0.101 | 0.626±0.034 | 16.64±0.094 | 1.14 | 26.19±0.067 |
| **F3** | 0.528±0.074 | 0.627±0.069 | 16.37±0.065 | 1.17 | 23.89±0.051 |
| **F4** | 0.523±0.089 | 0.632±0.091 | 13.49±0.074 | 1.20 | 25.21±0.079 |
| **F5** | 0.521±0.093 | 0.623±0.113 | 14.83±0.093 | 1.19 | 27.97±0.084 |
| **F6** | 0.476±0.112 | 0.555±0.108 | 14.23±0.034 | 1.16 | 24.61±0.099 |

**5.2.3. Post-compression Parameters**

**Table No 27:** Physicochemical Properties of tablets:

| Formulation code | Color | Shape | Odor |
|---|---|---|---|
| F1 | White color | Flat and circular | Odorless |
| F2 | Cream colour | Flat and circular | Odorless |
| F3 | Cream color | Flat and circular | Odorless |
| F4 | Cream color | Flat and circular | Odorless |
| F5 | Cream color | Flat and circular | Odorless |
| F6 | Cream color | Flat and circular | Odorless |

**Table No.28:** Post-Compression Parameter results

| Code | Weight variation (mg) | Hardness ($kg/cm^2$) | Thickness (mm) | Friability (%) | Drug content (%) | Disintegration Time |
|---|---|---|---|---|---|---|
| **F1** | 148.91±0.22 | 4.02±0.10 | 3.12±0.01 | 0.39±0.15 | 93.51±0.57 | 25min |
| **F2** | 145.12±0.36 | 5.05±0.09 | 3.14±0.03 | 0.36±0.11 | 95.00±0.42 | 36min |
| **F3** | 154.10±0.49 | 5.01±0.04 | 3.11±0.03 | 0.33±0.09 | 96.85±0.32 | 48min |
| **F4** | 152.30±0.41 | 5.07±0.007 | 3.44±0.02 | 0.43±0.62 | 95.79±0.27 | 60min |
| **F5** | 146.60±0.32 | 5.07±0.05 | 3.16±0.01 | 0.42±0.44 | 97.01±0.89 | 72min |
| **F6** | 149.20±0.91 | 6.06±0.03 | 3.18±0.04 | 0.32±0.53 | 96.15±0.42 | 88min |

### 5.2.4 *In-vitro* Drug release profile of all the formulations:

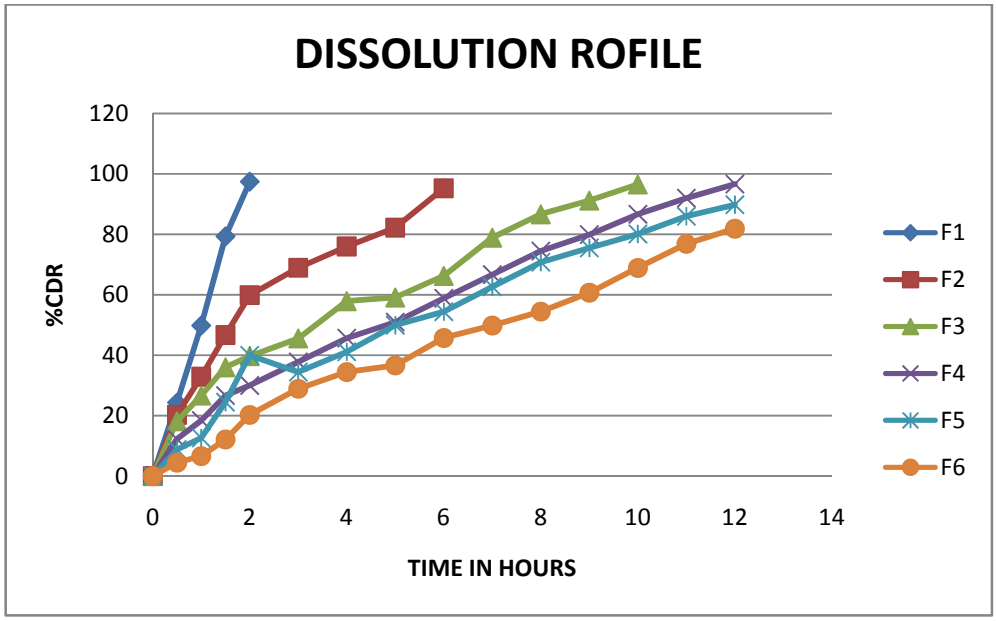
Volume of dissolution media:900 ml

0.1 N HCl for first 2 hrs

phosphate buffer PH 6.8 upto 10 hrs.

**Table No.29:** *In-vitro* drug release profile

| SL.NO | TIME (hrs) | % CUMULATIVE DRUG RELEASE(CDR) | | | | | |
|---|---|---|---|---|---|---|---|
| | | FORMULATION CODE | | | | | |
| | | F1 | F2 | F3 | F4 | F5 | F6 |
| 1 | 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 0.5 | 24.32 | 20.23 | 18.14 | 12.24 | 8.78 | 4.45 |
| 3 | 1 | 49.83 | 32.88 | 26.66 | 18.42 | 12.61 | 6.62 |
| 4 | 1.5 | 79.33 | 46.67 | 35.98 | 26.66 | 24.48 | 12.12 |
| 5 | 2 | 97.43 | 59.89 | 39.68 | 29.98 | 28.45 | 20.24 |
| 6 | 3 | - | 68.98 | 45.55 | 37.78 | 34.44 | 28.89 |
| 7 | 4 | - | 75.98 | 57.89 | 45.67 | 41.11 | 34.44 |
| 8 | 5 | - | 82.23 | 59.11 | 50.98 | 49.92 | 36.62 |
| 9 | 6 | - | 95.27 | 66.24 | 58.84 | 54.42 | 45.72 |
| 10 | 7 | - | - | 78.89 | 66.67 | 62.66 | 49.85 |
| 11 | 8 | - | - | 86.66 | 74.48 | 70.77 | 54.44 |
| 12 | 9 | - | - | 91.17 | 79.94 | 75.55 | 60.69 |
| 13 | 10 | - | - | 96.52 | 86.66 | 80.12 | 68.89 |
| 14 | 11 | - | - | - | 92.01 | 85.99 | 76.86 |
| 15 | 12 | - | | - | 96.66 | 89.82 | 81.89 |

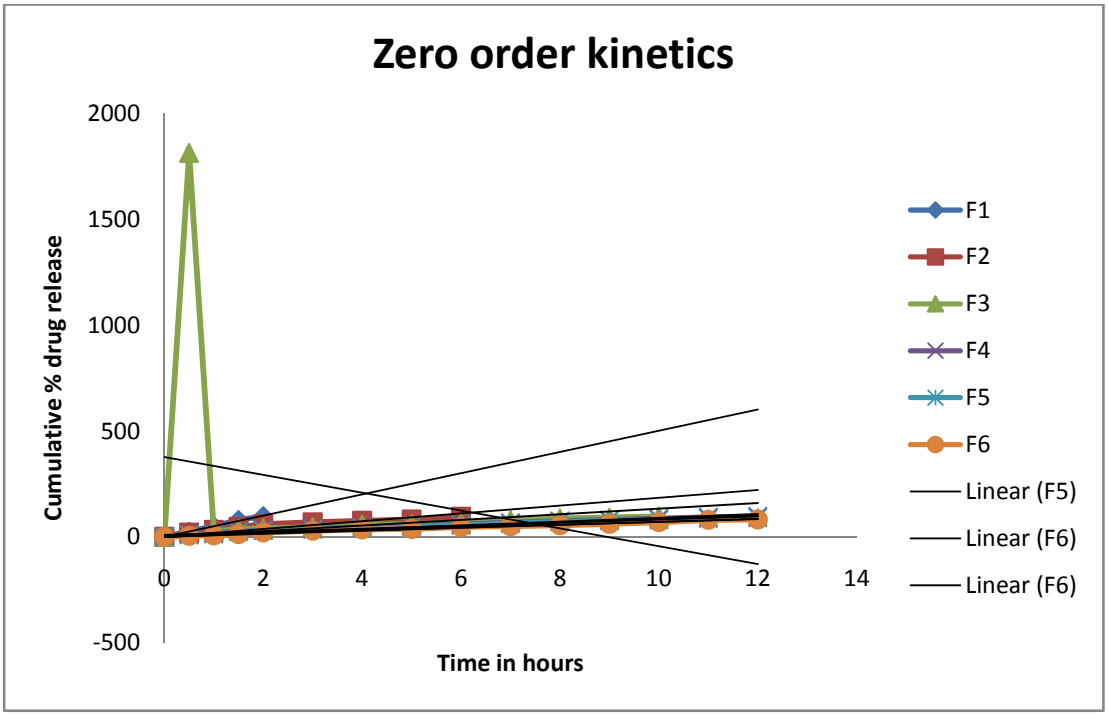



**Graph No.4:** *In-vitro* Cumulative percentage drug released V/S Time for Formulations F1 to F6

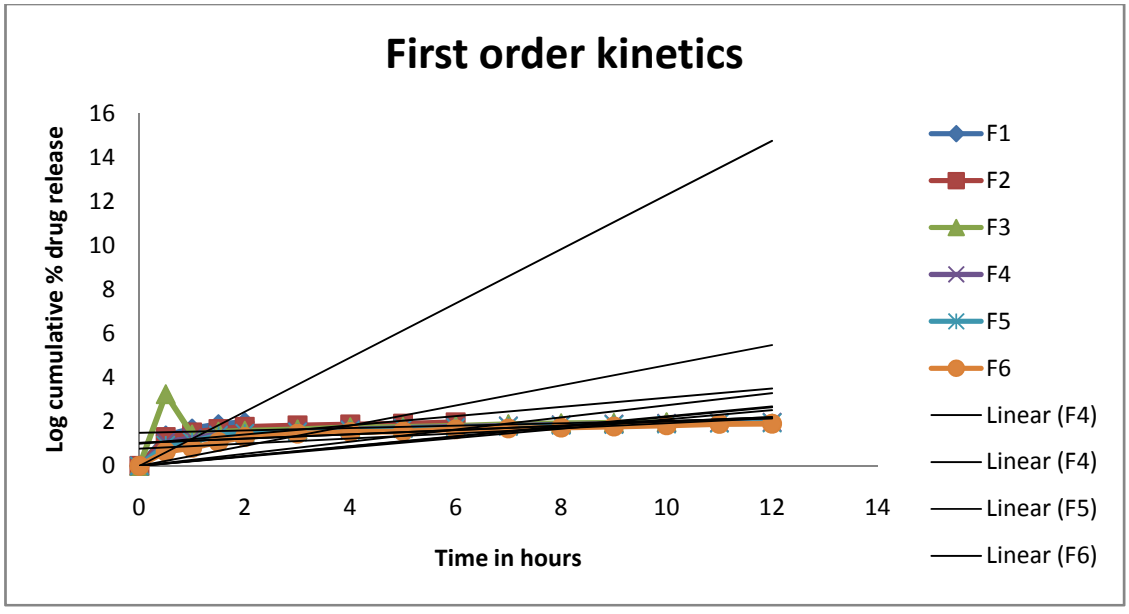
### 5.2.5 Kinetic Release Study

**Table No 30: Results** of Kinetic data of various models for release study

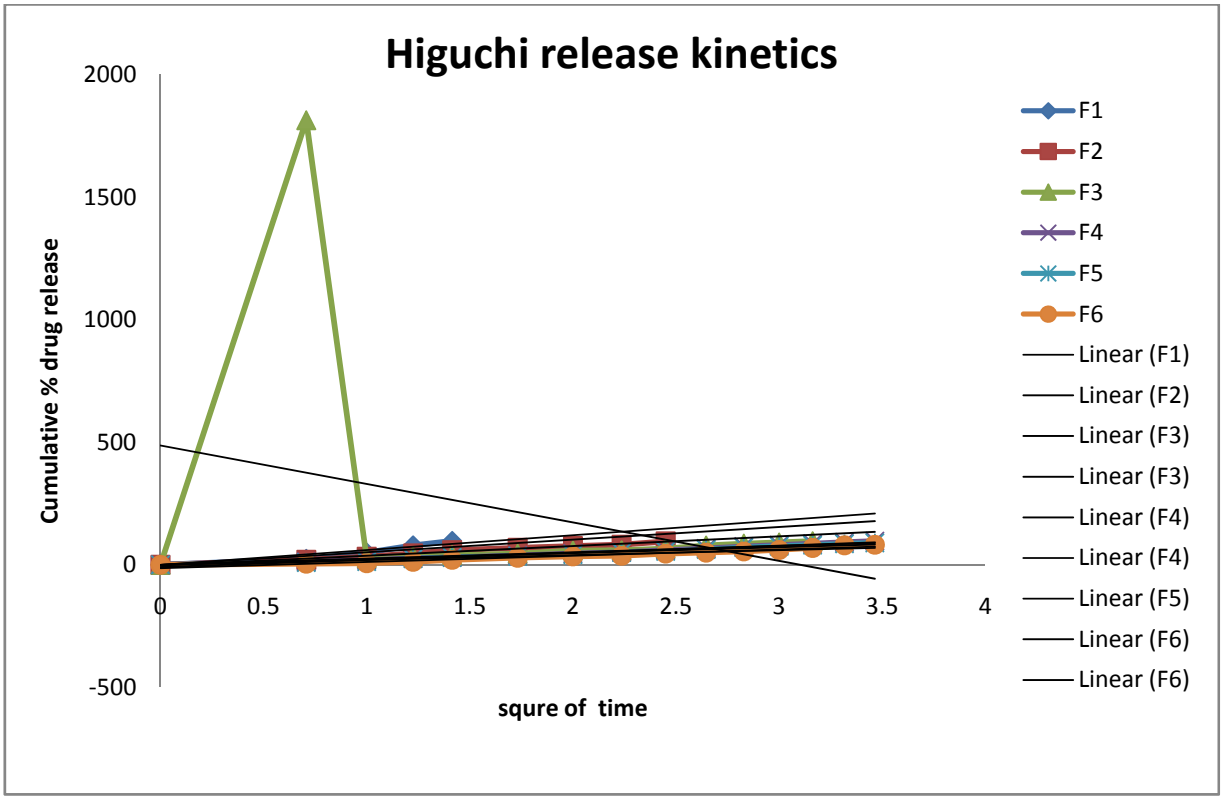
| Formulation code | Zero order release plots | First order release Plots | Higuchi's plots | Korsmeyer'sand Peppas plots | |
|---|---|---|---|---|---|
| | Regression coefficient ($R^2$) | Regression coefficient ($R^2$) | Regression coefficient ($R^2$) | Regression coefficient ($R^2$) | Exponential value (n) |
| F1 | 0.995 | 0.998 | 0.945 | 0.534 | 1.312 |
| F2 | 0.706 | 0.987 | 0.897 | 0.765 | 1.050 |
| F3 | 0.882 | 0.988 | 0.901 | 0.861 | 1.066 |
| F4 | 0.989 | 0.991 | 0.916 | 0.914 | 1.008 |
| F5 | 0.889 | 0.921 | 0.712 | 0.911 | 0.983 |
| F6 | 0.854 | 0.951 | 0.813 | 0.906 | 1.085 |



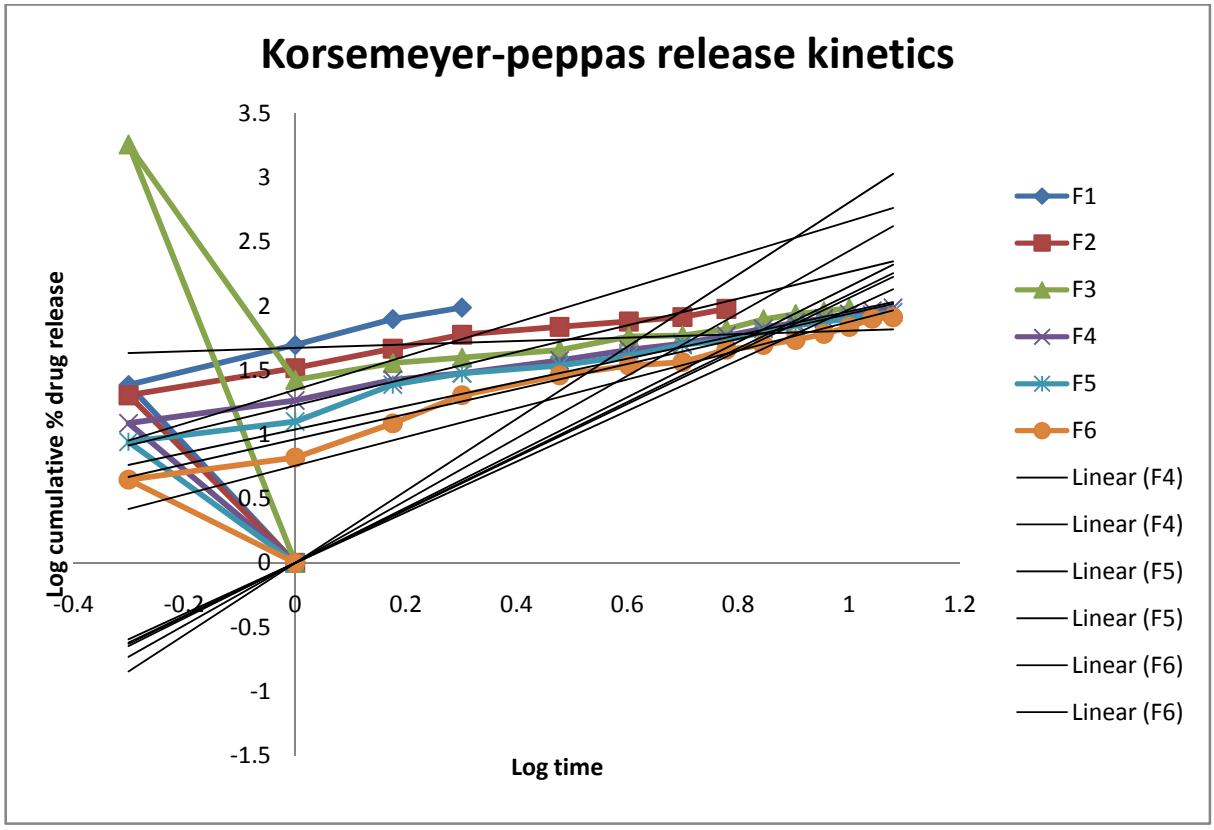

**Graph No.5:** Plot of Cum. % Drug Released Vs. Time




**Graph No.6:** Plot of Log % Cum. Drug Retained Vs. Time




**Graph NO 7:** Cumulative % drug release Vs Square of time




**Graph No 8:** Log cumulative % drug release Vs Log time.

### 5.2.6 Stability Studies

**Table No. 31:** Results of Stability studies for F4 formulation at 40ºC/75%RH

| Time | Evaluation parameters | | | |
|---|---|---|---|---|
| | Color | Hardness | Drug content | %CDR |
| 15 days | Cream | 5.07 | 95.79 | 98.89 |
| 30 days | Cream | 5.05 | 95.54 | 98.73 |
| 45 days | Cream | 5.01 | 95.34 | 98.66 |
| 60 days | Cream | 5.00 | 94.99 | 98.24 |

# 6. DISCUSSION

## 6.1 Melting point:

The melting point of the obtained drug sample was found to be $132^0$C which is within the reported range of 131-$133^0$C. It complies with the purity of the drug sample.

## 6.2 FT- IR Studies:

The FT-IR spectroscopy is a useful tool for identifying both organic and inorganic chemicals.

It can be utilized to quantify some components of an unknown mixture and can be used to analyze liquids, solids and gases.

The FTIR spectrum of the Verapamil HCl pure drug was found to be similar to the standard spectrum of Verapamil HCl as in I.P. The individual FT-IR spectra of the pure drug Verapamil HCl, as well as the combination spectra of the drug and mucilage are shown in the Spectra No.1, Spectra No.2, and Spectra No.3.

The FT-IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between drug and mucilage, hence stable formulation could be prepared.

## 6.3 Analysis of Verapamil HCl

### 6.3.1 Scanning of Verapamil HCl

Verapamil HCl was dissolved in both pH 1.2 and pH 6.8, further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (shimadzu 1800) in the range from 200 to 400 nm, using pH 1.2 and pH 6.8 as blank. The λmax of drug was found to be 278 nm.

### 6.3.2 Calibration curve of Verapamil HCl in 0.1 N HCl

The absorbance was measured in UV spectrophotometer at 278nm against 0.1N HCl. The absorbance so obtained were tabulated as in Table No.14 .Calibration curve was plotted and shown in Graph No.1 and standard calibration curve with slope 0.010 and regression value $R^2$ of 0.999 was obtained.

### 6.3.3 Calibration curve of Verapamil HCl in 6.8 pH buffer

The absorbance was measured in UV spectrophotometer at 278nm against 6.8 pH buffer. The absorbance so obtained was tabulated as in Table No.15. Calibration curve was plotted and shown in Graph No.2. and standard calibration curve with slope 0.016and regression value $R^2$ of 0.985 was obtained.

**6.4 Viscosity of Jackfruit mucilage:** As the number of rotation decreases viscosity of mucilage increase.

### 6.5 Evaluation of Pre-compression Parameters:

The results of all formulations F1 to F9 are shown in Table No.26, which were evaluated for variable parameters such as bulk density, tapped density, angle of repose, % Compressibility index, Hausner's ratio.

- **Bulk density**: Bulk density of all formulation was in between 0.476 to 0.529.
- **Tapped density**: Tapped density of all formulation was in between 0.55 to0.632.
- **Carr's index:** Carr's index was between 13.49 to17.24 indicating all formulations were found to be within the limits.
- **Hausner's Ratio:** Hausner's ratio was between 1.14 to 1.20.

**Angle of repose:** Angle of repose of all formulations was between 23º to 28° indicating reasonable flow property and all formulations were found to fit with respect to flow property. **6.7**

**6.6 Evaluation of Physicochemical Properties:**

All formulations F1 to F7 were evaluated for variable physiochemical properties such as color, odor and shape. All the formulations were found to cream in color, odorless and flat and circular in shape. Results were tabulated as in Table No.27.

**6.7 Evaluation of Post-compression Parameters:**

The formulations F1 to F7 were evaluated for variable parameters such as weight variation, hardness, friability, thickness, drug content and disintegration and results are tabulated in Table No.28.

- **Weight variation:** The results of weight variation of tablets for all formulations was found to be in the range of 145.12 to154.10 mg indicating that the weight variation is within the pharmacopoeia limits.
- **Hardness:** Hardness was found to be in the range of 4.02 to 6.06±0.03
- **Thickness:** Thickness of all formulations found to be in the range of 3.12 to 3.19.
- **Friability:** Friability ranges from 0.32 to 0.43 indicating that the friability of all formulations was less than 1%.
- **Drug content:** The percentage drug content of all formulations was found in the range of 93.51 to 97.01, which was all within the acceptable limits of official standards.
- **Disintegration Time:** Disintegration time of all formulation was found in between 25 min to 88 min.

**6.8 *In-vitro* drug release:** The *in-vitro* release study was carried out in two different dissolution media namely 0.1N HCl (acidic buffer pH 1.2) for 2 hrs and then medium was replaced by simulated intestinal fluid for next 10hrs (phosphate buffer 6.8pH).

The amount of drug released from formulations F1, F2, F3, F4, F5 and F6 in 0.1N HCl after 2hrs were 97.43%, 59.89%, 39.68%,29.98%,28..45%, 20.24 respectively. Formulation F1 showed almost all percentage of drug release at the end of 2hrs because of absences of retardant mucilage, F2 release 95.27% of drug in 6hrs, F3 release 96.52% of drug in 10 hrs F4,F5,F6 release 96.66%,89.82%,81.89% of drug after 12 hrs respectively.

Results showed that the drug release from the formulations decreased with increase in the amount of mucilage added in each formulation. Formulation F6 shows slow drug release compared to all formulations. Based upon the drug release profile formulation F4 was considered as optimized formulation as it releases 96..66% drug at the end of 12 hrs.

The *in-vitro* drug release data of all formulations are shown in Table No.29 and GraphNo.4

**6.9 Release kinetics:**

The results obtained from in-vitro drug release were plotted a four different mathematical models of data treatment as follows:

1. % Cum. Drug Release Vs. Time (Zero order rate kinetics).
2. Log % Cum. Drug Retained Vs. Time (First order rate kinetics).
3. % Cum. Drug release was plotted against √T (root time). (Higuchi model)
4. Log % Cum. Drug Release Vs. Log Time (Peppas exponential equation)

The curve fitting results of the release rate profile of the designed formulation are shown in the Graph No.5,6,7 and 8 which gave an idea on the release rate and the mechanism of release.

The values were compared with each other for kinetic model and drug equation as shown in Table

No.30 based on the highest regression values ($r^2$), fitting of the release rate data to various models revealed that all the formulations (F1 to F6) follows first order release kinetics with regression values ranging from 0.945 to 0.998.

All the formulations were subjected to Korsmeyer-Peppas plots, 'n' value ranges from 1.050 to 1.312 indicating that the drug release was by super case II mechanism.

**6.10 Stability studies:**

Stability study was conducted for the formulations F4 at 40℃/75 RH for 2 months. Then the tablets were analyses for physical change, drug content estimation and *in-vitro* dissolution studies at an interval of 15, 30, 45 and 60 days. Results showed that there was no change in case of physical appearance, no significant differences in the physical appearance, hardness, drug content and dissolution study, hence prepared tablets were found stable throughout the study period.

The results of stability studies are given in the Table No.31.

## 6. CONCLUSION

Sustained release dosage form is promising alternative to conventional drug delivery system, which provide continuous release of their active ingredient for prolong period of time. The present study reports a novel attempt to isolate plant based mucilage i.e. Jack fruit. The obtained mucilage was utilized as binder in different concentration to formulate sustained release tablets of the Verapamil HCl. Sustained release tablets of the Verapamil HCl were prepared by wet granulation method. Various evaluation parameters were assessed, with a view to obtain sustained release of Verapamil HCl.

Details regarding isolation of Jackfruit mucilage and formulation and evaluation of sustained release tablets of Verapamil HCl have been discussed in previous chapters. From the study following conclusions could be drawn,

- Biocompatible Jackfruit mucilage was isolated and it was used as binder to formulate sustained release tablet.
- The FT-IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between drug and mucilage.
- Pre-compression parameters like bulk density, tapped density, angle of repose, Hauser's ratio are in the range of given in official standard, indicated that granules prepared by wet granulation method were free flowing.
- The after compression, prepared tablets were evaluated for hardness, friability, weight variation, disintegration time, and drug content and results obtained were within the acceptable official limits.
- Cumulative percentage drug release significantly decreased with increase in natural mucilage concentration.

- The overall curve fitting into various mathematical models were found to be on an average and were best fitted to first order kinetic model and the drug release from the formulation was by super case II mechanism mechanism.
- Based upon the results of *in-vitro* release study, formulations F4 was selected as optimum formulation and it was subjected to stability studies for 60 days.
- The stability studies showed no significant change in the physical appearance, hardness, drug content, and *in-vitro* drug release characteristics of the prepared tablet, hence prepared tablet formulation was stable.

**SCOPE OF THE STUDY:**

This type of the study showed that natural mucilage could be better alternative of synthetic polymer in tern of its utility and cost.

Further detailed stability studies and *in-vivo* bioavailability studies are to be done to establish the efficacy of these formulations.

- *In-vitro–in-vivo* correlations are to required to establish the guarantee of efficacy and bioavailability of the formulation.

## 8. SUMMARY

The present study reports an attempt to isolate Jackfruit mucilage and to formulate and evaluate sustained release tablets of the Verapamil HCl by using various concentration of Jackfruit mucilage as natural binding agent.

Sustained release dosage form is one of the best alternatives to conventional dosage form, when conventional dosage form is not satisfactory in terms of therapeutic efficacy and other problems.

The use of polymer in sustaining the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustain release can be achieved by formulating drugs using jackfruit mucilage since it is a natural polymer it is having various advantages over synthetic polymers. Natural polymers are attractive primarily because they are capable of chemical modification, having high drug holding capacity and thermal stability. Natural polymers are easily available and have some advantages when employed in sustained release drug delivery system such as bio-acceptability, bio-compatibility, bio-degrability and non-toxicity. and other excipients used were Microcrystlline cellulose, Dicalcium phosphate, Talc, Magnesium stearate, Bentonite.

- Drug and mucilage were subjected for compatibility study using FT-IR, which suggested that there was no interaction between drug and mucilage.
- 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 showed good to acceptable result.
- *In-vitro* dissolution studies indicated that drug release decrease as the concentration of Jackfruit mucilage increase. Formulation F4 considered as best formulation since it release 96.66% of drug in 12hrs.
- 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 . super case II mechanism.
- The best formulations F4 was subjected to 2 months stability studies and results showed there was no significant change in the physical appearence , hardness, 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 summarized that the stable sustained release tablet dosage form of Verapamil HCl could be successfully developed using jackfruit mucilage as binder and prepared tablet showed sustain release action in the treatment of hypertension.

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