

Formulation and Evaluation of Inlay Tablet Dosage form of Metformin & Glimepiride as Sustain Release

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INTRODUCTION

Drug therapy has a profound influence on the health statistics all over the world. The effective and rational use of the drug constitutes one of the most important of the health programmer. Today all the world allopathic systems of medicine dominates the "Traditional medicine and healing art" due to its strong link with modern sciences & technology. Drug delivery has metamorphosed from the concept of pill to molecular medicine in the past 100 years. Better appreciation and integration of system has been developed a lead to improve therapeutic efficacy. Drug research has evolved and matured through phases beginning from pill to pharmaceutical dosage form.

1.1 Oral drug delivery system¹

Oral route is the most convenient and usually the safest and least expensive, it is the one most often used.

Advantages

- Convenient - portable, no pain, easy to take.
- Cheap - no need to sterilize (but must be hygienic of course), compact, multi-dose bottles, automated machines produce tablets in large quantities.
- Variety - fast release tablets, capsules, enteric coated, layered tablets, slow release, suspensions, mixtures.

1.2 Mechanism of absorption¹:

- ❖ By passive diffusion through the lipid bilayer, neutral, liposoluble molecules but not those completely insoluble in water.
- ❖ By secondary active transport, amino acids and sugars, certain peptides.
- ❖ By complex mechanisms, elements in the form of ions, cations and anions, such as sodium, potassium, calcium, chlorine.

The oral route can be used for a local or general treatment:

- Local treatment: gastrointestinal protectants of the digestive tract itself, treatment of an intestinal infection or a parasitosis. In this case, one wishes, in general, that the drug will not be absorbed or only poorly absorbed.
- General treatment: it is the usual route of administration of drugs and digestive absorption is followed of their diffusion in the body.

1.3 Tablets as a dosage form¹:

- Tablet is a solid dosage forms each containing a unit dose of one or more medicaments with or without suitable excipients.
- Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Some are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants or passeries may also be presented in form of tablet.
- Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration.

Advantages:

- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Accuracy of dose is maintained since tablet is a solid unit dosage form. Tailor made release profile can be achieved.
- Longer expiry period and minimum microbial spillage owing to lower moisture content.
- As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.
- Ease of packaging (blister or strip) and easy handling over liquid dosage form.
- Easy to transport in bulk. Emergency supply supplies can be carried by patients.
- Organoleptic properties (taste, appearance and odor) are best improved by coating of tablet.
- Product identification is easy and markings done with the help of grooved punches and printing with edible ink.
- Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable, etc.
- In composition to parenteral dosage form, a doctor or a nurse is not required for administration. I.e. self-administration is possible.
- In comparison to capsules, tablets are more tamperproof.

Disadvantages:

- It is difficult to convert a high dose poorly.

- Compressible API into a tablet of suitable size for human use.
- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
- Slow onset of action as compared to parenterals, liquid orals and capsules.
- The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less.
- Difficult to swallow for kids, terminally ill and geriatric patients.
- Patients undergoing radiotherapy cannot swallow tablet.

1.4 Multi-layer tablet⁶

These novel delivery systems have been essential not only for formulating new products but also it helping pharmaceutical companies extend patent.

There are several resins to consider multi-layer tablets.

Incompatible matrices. Many matrices are incompatible with one another .but with multi-layer tablet; formulations are inserting an inert barrier layer between the incompatible matrices to prevent an interaction.

Novel formulations. Multiple layers keep the modified release portion that is immediately bio-available, which allows the patents to take just one tablet per day instead of multiple doses throughout the day.

Marketing advantage. It makes dosing more convenient. The unique product appearance of multi-layer tablet offers other marketing advantages, and manufacturers of mints and other candies have used multi-layer technology to introduce products that grab attention and to put a new spin on an ordinary product.

Life-cycle strategy. Multi-layer technology allows companies to re formulate single-API tablets in to tablets that contain two or more APIs, thus extending patents and fending of competition.

Multi-layer and core tablets allow incompatible drug or granulations to be combined and allow companies to create unique brand. With research leading every day to discovery of new products, manufacturers face and increasing need for this technology.

1.5 Inlay tablet¹

A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. Tablet compressing was done with core rod tooling in which only one surface of core is expose to outside and other drug is incorporated in cup portion. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it .The main body portion may consist of an uncoated granulation which is compressed around the enteric coated inlay portion In this modification the main body portion of the tablet is first released and assimilated in the gastrointestinal tract while the enteric coating protects the inlay portion for a predetermined period of time so as to provide time delayed or sustained medication.

1.5.1 Advantages of Inlay Tablet dosage form¹

- Dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release can be prepared.
- Plasma level can be maintained constant and within the therapeutic window throughout the period of treatment.
- Adverse effects due to sub therapeutic plasma concentration can be avoided.
- The burst effect, namely, large release within a short period of time, is common in highly soluble drugs, and shall be avoided, as it may lead to high concentration of active ingredients in the blood stream.
- Has the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media .Dosage frequency of highly water soluble drugs can be reduced providing same efficacy.
- Tablets of different shape such as triangular, rectangular, or capsule shaped tablets can be manufactured.
- Advantages of inlay tablets over other compressed tablets:
- Less coating material is required.
- Core is visible, so coreless tablets can be easily detected.
- Reduction in coating forms a thinner tablet and thus freedom from capping of top coating.
- The layered tablet is preferred over compression coated tablet as the surface contact is less and the production is simple and more rapid.

1.5.2 Disadvantages of Inlay dosage form²

- It is difficult to compression process because double compression process is done for two different layers.
- It is Time consuming formulation.

1.6 Compression techniques Inlay Tablet³

Formulations of the present invention can be made by conventional Inlay tablet or compression coating techniques. This technology facilitates the control of API by altering the thickness of outer coating. Capability to precisely position multiple cores allows the manufacture of tablet product with variety of pulsatile drug delivery profile

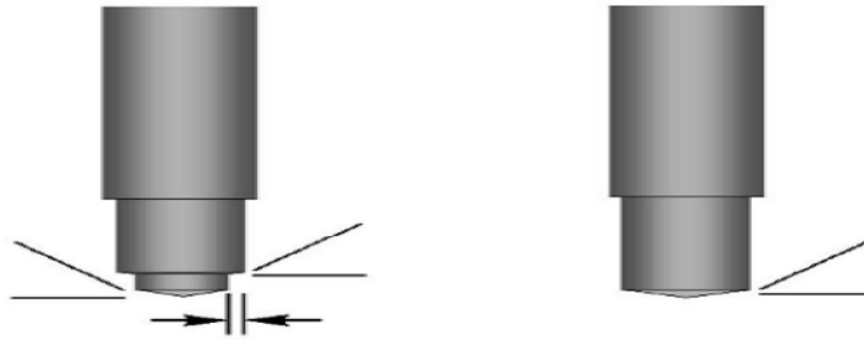


Fig.1.6.1 Upper punches for producing prototype compression-coated tablets on a Carver press:

- (a) Construction of the punch used to make a cup and
 (b) Construction of a punch used for the final compression.

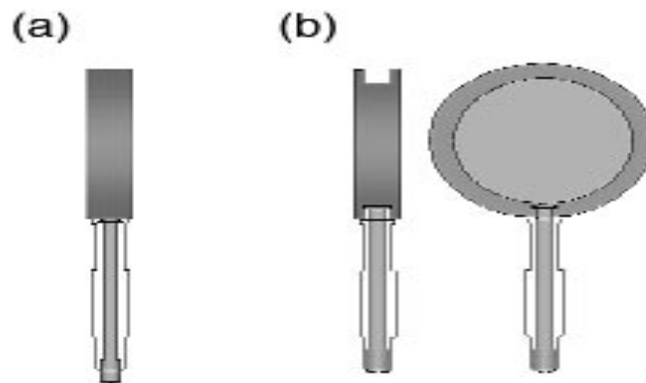


Fig.1.6.2 Schematic of a hollow upper punch with a core rod showing

- (a) The side view of a punch tip in the extended position and a traditional solid roller.
 (b) The side and front views of a punch tip in the retracted position and a recessed roller.

1.7 Novel One Step Dry Coating (OSDRC) technique³.

1.7.1 What is OSDRC?³

OSDRC is one step dry coating technology that opens a door to a new world of pharmaceutical tablet manufacturing.

- ✓ OSDRC is the great innovation towards compression coated tablets and inlay tablets.
- ✓ OSDRC provides unique, high quality products at low cost.
- ✓ OSDRC is novel variable double punch tableting technology, simply by changing the punch of rotary tablet compression machine, product development scientists can create new formulations and tablet configurations that are not possible with current tablet manufacturing technology.

1.7.2 Technology Attributes³

- ✓ OSDRC includes variable double punches those can manufacture compression coated or inlay tablet in a single step and can go beyond the parameters of current tableting machines.
- ✓ This technology has ability to manufacture this compression coated and inlay tablet configuration at a rate of up to 100,000 tablets per hour with the avoidance of problem faced with conventional manufacturing process such as misalignment of cores, mass variability and cross contamination.
- ✓ This variable double punch rotary tableting machine has up to 54 double punches and two or three feeders.
- ✓ Because the tablet is prepared in a single step while the punches make one rotation on a turret there is no longer any need for separate step to deliver a core tablet. Because the core tablet is held in place by lower punch until the final compression, thus misalignment does not occur.
- ✓ There are many types of tablet configurations can be made with OSDRC, depending only on double punch variations.
- ✓ OSDRC allow the formulators to freely control the size, shape, thickness and position of core tablet as well as that of outer cup tablet.
- ✓ This facilitates the manufacturing of completely new types of drug products that were not possible with conventional technology.
- ✓ In addition of this one can include cameras, automation and advance in process control functions to provide precision, high speed tableting, also prevent cross contamination of powders, auto sampling and auto exclusion mechanism can meet Good Manufacturing Practice (GMP) standards.

❖ This technology not only produces higher quality cored tablets than previously possible, but also enables development of various new solid dosage forms; it also allows product development scientists to device new novel dosage forms.

1) Divided Core Tablets³

There also possible to make divided tablets with separate cores in one step operation, which is not possible with current technology. For example divided enteric coated tablets are the world's first dividable enteric coated tablets.

Dividable core tablets so called because the core fully encased in the coating even when the tablet is divide, even though the release profile is remain unaffected by dividing the table.

2) Cored Tablets with Poorly Compressible Cores³

By using this technology there is no need of separate manufacturing of core tablet even using of powders with poor compressibility as the core matrix.

As it possible to directly encase core pharmaceutical ingredients with the outer covering, these ingredients can be used in oral rapid disintegration tablets.

Pellets can also be used instead of powder as core material, drugs normally formulated as capsule dosage form can be formulated as tablet dosage form.

3) Sugar and Film Coating can be Replaced³

Tablet with extremely thin coat can be produce in one step, thus sugar and film coating can be replaced which substantially reduce manufacturing steps and cost.

4) Core and Coat Shapes are also Variable³

The shape, thickness and tablet configuration of core and coat can be varied simply by changing the punches.

5) Triple-Layered Tablets⁴

Triple-layered tablets are comprised of an inner drug core layer which is sandwiched between two surrounding barrier layers. These barrier layers may also contain drug and serve as matrices to release drug in various release patterns.

6) Core-in-Cup Devices⁵

Danckwerts developed a core-in-cup tablet system that was able to provide zero order drug release of aqueous-soluble and aqueous-insoluble drugs. The system consisted of a disc-shaped matrix core that was compression-coated on one surface as well as at the circumference in order to form a cup around the core.

7) Procise Technology (Geometrically altered drug delivery system)⁵

It is composed of a core which contains uniformly dispersed drug with a core hole in the middle. It has been made known that, altering the geometry of the core can change the drug release kinetics into zero order or even first order if desired the core's entire surface besides the surface of the cylindrical face is surrounded by a permeable inactive coat so that drug release occurs slowly from the cylindrical area.

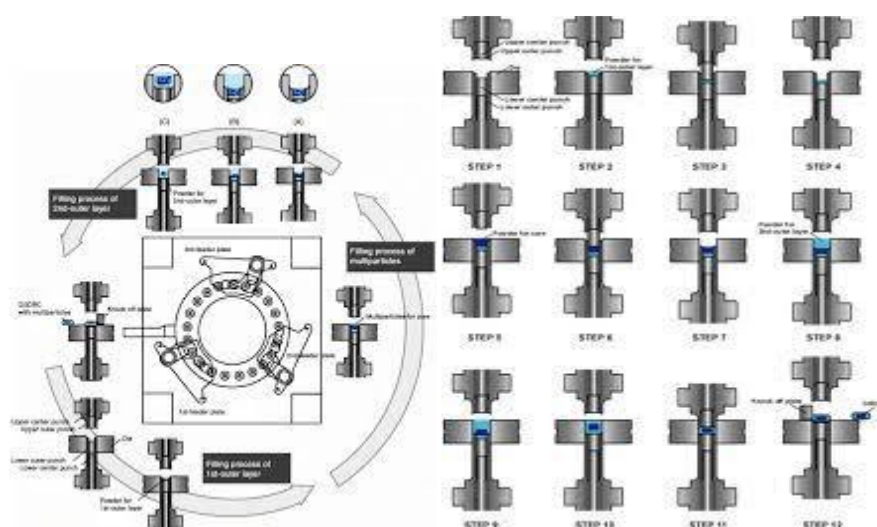


Fig1.7.1 Step involve in Inlay Tablet

1.8 Applications of Inlay Tablets¹:

1. Novel Controlled Release Formulation for Highly Water Soluble Drug TramadolHCl:

- Tramadol, a synthetic opioid, is a dual action analgesic agent. Despite a good oral bioavailability (75%) and moderate elimination half life (5.5 hrs), Tramadol needs frequent oral dosing throughout the day (50 mg/4-6 hrs).
- High aqueous solubility causes the rapid diffusion of drug from sustained release formulations.
- A novel and robust controlled release formulation of Tramadol HCl to reduce the dosing frequency can be prepared.
- Developed formulation of Tramadol HCl showed controlled release in-vitro behavior with a release profile of less than 15% for initial two hours (retarding initial burst) followed by a controlled complete release in controlled manner.
- Developed formulation could be novel alternative to traditional immediate release formulations of tramadol is stable, convenient to manufacture and cost effective for commercial use.

2. Preparation of Compound pseudoephedrine hydrochloride sustained-release inlays tablets:

Compound pseudoephedrine hydrochloride sustained-release inlay tablets exhibit prominent sustained-release and rapid release characteristics in vitro.

Compound pseudoephedrine hydrochloride sustained-release inlay tablets were prepared by twice-compressing technology using HPMC as the matrix of sustained-release part. 3.Naproxen sodium released more than 75% in 0.5 hr, while pseudoephedrinehydrochloride released 7%±3.6% in 0.5 hrs, 15.8%±2.3% in 1 hr, 49.5%±3.9% in 4 hr and more than 85% in 8 hr.

3. A hypnotic tablet with Pentobarbital and Mephenesin:

The outer layer with uncoated granulations is promptly disintegratable for immediate hypnotic effect and the inlay portion with an enteric coating or envelope around begins to disintegrate after three to four hours to maintain or continue the desired effect.

4. An appetite depressant tablet with Amphetamine sulfate and Amobarbital:

In the outer layer the particles of the granulation are enteric coated to provide slow release over a period of ten to twelve hours. The inlay portion is formed from an uncoated readily disintegratable granulation for immediate therapeutic effectiveness.

1.9 Controlled release drug delivery system^{5,6}

Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improved shelf life of the product. In recent years, considerable attention has been focused on development of sustained release drug delivery systems. The rationale for the development of controlled release drug delivery system of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition.

An ideal drug delivery system should deliver the drug at the rate dictated by the needs of the body over the period of treatment i.e. it should provide the desired therapeutic concentration of drug in the plasma and maintain it constant for the entire duration of treatment. Controlled release dosage forms continue to draw attention in the search for improved compliance and decrease in the incidence of adverse drug reactions. A sustained release system includes any delivery system that achieves slow release of the drug over an extended period of time. Figure gives the co-relation of immediate, sustained and control release formulations.

In recent years, in association with progress and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop sustained release dosage forms for many drugs. The primary objective of this system is to ensure safety and to improve efficacy of the drugs as well as patient compliance. Pharmacokinetic theory suggests that the ultimate method for reducing the plasma maximum concentration (C_{max}) to plasma minimum concentration (C_{min}) ratio is to have zero-order absorption. Once steady state is achieved under these conditions, drug concentration in plasma is constant as long as absorption persists.

It is necessary to achieve and maintain the concentration of administered drug within the therapeutically effective range. Sustained release products aim in releasing the drug continuously at a predetermined rate and time in order to increase the patient compliance.

Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release.

- ✓ Dissolution-controlled release
- ✓ Diffusion-controlled release
- ✓ Ion exchange resins
- ✓ Osmotic controlled release
- ✓ Gastroretentive system

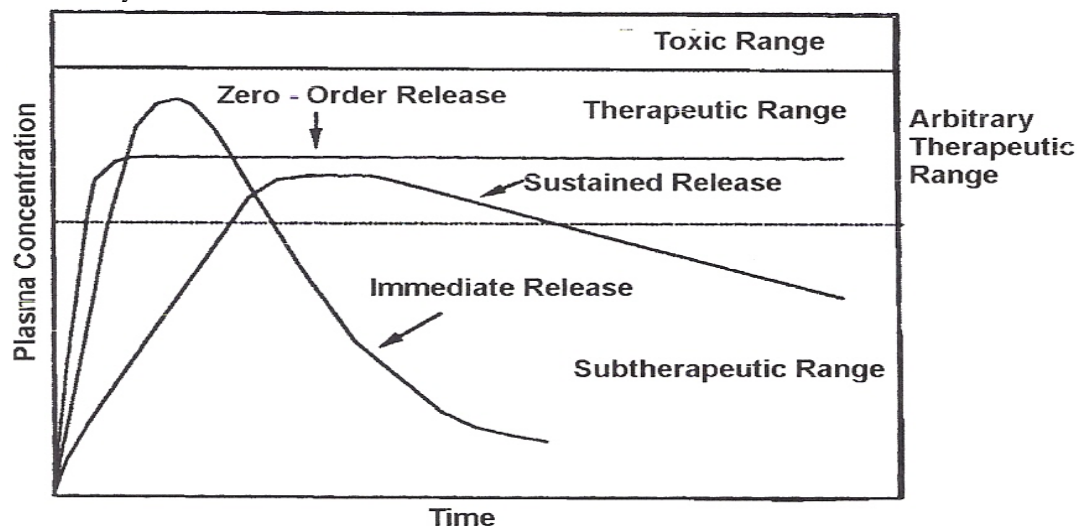


Figure No 1.9.1. Plasma drug concentration profiles for conventional formulation, a zero order controlled release formulation and a sustained release formulation.

The United States Pharmacopoeia (USP) defines the modified-release dosage form as “the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments or promptly dissolving dosage forms”. One class of modified-release dosage form is an extended-release dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or significant increase in patient or therapeutic performance when compared with that presented as a conventional dosage form. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.

In the case of orally administered dosage forms, this period is measured in h and critically depends on the residence time of the dosage form in the gastrointestinal tractz

1.9.2 Advantages and limitations of a controlled release dosage form^{7,8}

- **Clinical advantages**
- Reduction in frequency of drug administration.
- Improved patient compliance.
- Administration of drug is more convenient.
- Reduction in drug level fluctuation in blood.
- Reduction in total drug usage when compared with conventional therapy.
- Reduction in drug accumulation with chronic therapy.
- Reduction in drug toxicity (local/systemic).
- Improvement in bioavailability of some drugs because of spatial control.
- Economical to the health care providers and the patient.
- Reduction in the blood level oscillation characteristic of multiple dosing of conventional dosage forms.

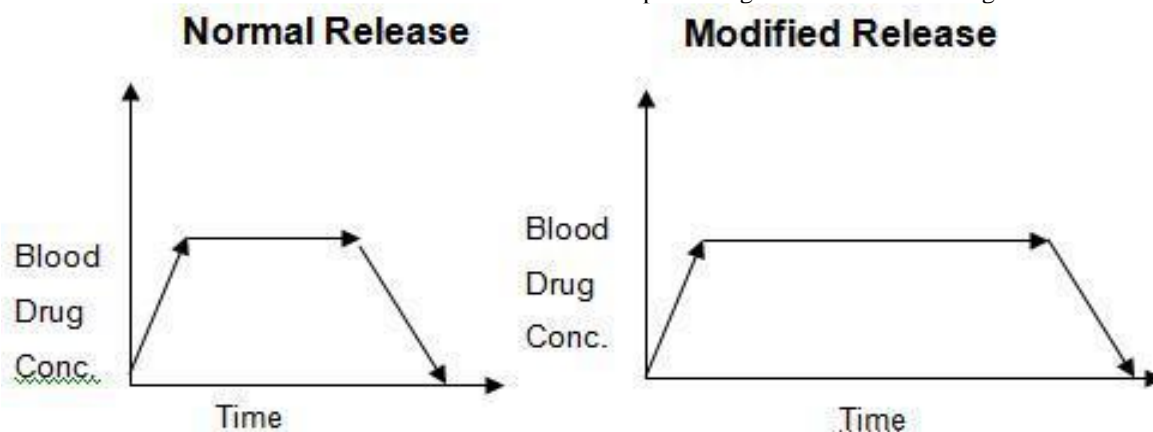


Figure No:1.9.2. Controlled release dosage form

- **Commercial/industrial advantages**
- Illustration of innovative/technological leadership.
- Product life-cycle extension.
- Product differentiation.
- Market expansion.
- Patent extension.
- **Potential limitations**
- Delay in onset of drug action.
- Possibility of dose dumping in the case of a poor formulation strategy.
- Increased potential for first pass metabolism.
- Greater dependence on GI residence time of dosage form.
- Possibility of less accurate dose adjustment in some cases.
- Cost per unit dose is higher when compared with conventional doses.
- Flexibility in adjustment of dosage regimen is limited.

1.9.3 Problems with Existing Oral Dosage Form⁹:

- Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an oesophagus may cause gastrointestinal ulceration.
- Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.
- Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult.
- Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications. Cost of products is main factor as parenteral formulations are most costly and discomfort.

1.10 Introduction to Diabetes

1.10.1 Introduction

Diabetes mellitus, often referred to simply as diabetes, is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the

beta cells of the pancreas. Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action.

Diabetes develops due to a diminished production of insulin (in type 1) or resistance to its effects (in type 2 and gestational). Both lead to hyperglycemia, which largely causes acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. Monogenic forms.

All forms of diabetes are treatable since insulin became medically available in 1921, but there is no cure. The injections by a syringe, insulin pump, or insulin pen deliver insulin, which is a basic treatment of type 1 diabetes. Type 2 is managed with a combination of dietary treatment, exercise, medications and insulin supplementation.

Diabetes and its treatments can cause many complications. Acute complications (hypoglycemia, ketoacidosis, or nonketotic hyperosmolar coma) may occur if the disease is not adequately controlled. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage (which can lead to blindness), nerve damage, and microvascular damage, which may cause erectile dysfunction and poor wound healing. Poor healing of wounds, particularly of the feet, can lead to gangrene, and the danger of amputation. Adequate treatment of diabetes, as well as increased emphasis on blood pressure control and lifestyle factors (such as not smoking and maintaining a healthy body weight), may improve the risk profile of most of the chronic complications. In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly and the leading cause of nontraumatic amputation in adults, and diabetes nephropathy is the main illness requiring renal dialysis in the United States.

1.10.2 Type of diabetes

The term diabetes, without qualification, usually refers to diabetes mellitus, which is associated with excessive sweet urine (known as "glycosuria") but there are several rarer conditions also named diabetes. The most common of these is diabetes insipidus in which the urine is not sweet (insipidus meaning "without taste" in Latin); it can be caused by either kidney (nephrogenic DI) or pituitary gland (central DI) damage.

The term "type 1 diabetes" has universally replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin-dependent diabetes (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as, among others, gestational diabetes, insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes). There is also maturity onset diabetes of the young (MODY) which is a group of several single gene (monogenic) disorders with strong family histories that present as type 2 diabetes before 30 years of age.

1.10.3 Type 1 diabetes mellitus

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to a deficiency of insulin. This type of diabetes can be further classified as immune mediated or idiopathic. The majority of type 1 diabetes is of the immune mediated variety, where beta cell loss is a T-cell mediated autoimmune attack. There is no known preventive measure which can be taken against type 1 diabetes; it is about 10% of diabetes mellitus cases in North America and Europe (though this varies by geographical location), and is a higher percentage in some other areas. Most affected persons are otherwise healthy and of a healthy weight when the onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

The principal treatment of type 1 diabetes, even in its earliest stages, is the delivery of artificial insulin via injection combined with careful monitoring of blood glucose levels using blood testing monitors. Without insulin, diabetes ketoacidosis often develops which may result in coma or death. Treatment emphasis is now also placed on lifestyle adjustments (diet and exercise) though these cannot reverse the progress of the disease. Apart from the common subcutaneous injections, it is also possible to deliver insulin by a pump, which allows continuous infusion of insulin 24 hours a day at preset levels, and the ability to program doses (a bolus) of insulin as needed at meal times. An inhaled form of insulin was approved by the FDA in January 2006, although it was discontinued for business reasons in October 2007. Non-insulin treatments, such as monoclonal antibodies and stem-cell based therapies, are effective in animal models but have not yet completed clinical trials in humans.

Type 1 treatment must be continued indefinitely in essentially all cases. Treatment need not significantly impair normal activities, if sufficient patient training, awareness, appropriate care, discipline in testing and dosage of insulin is taken. However, treatment is burdensome for patients; insulin is replaced in a non-physiological manner, and this approach is therefore far from ideal. The average glucose level for the type 1 patient should be as close to normal (80–120 mg/dl, 4–6 mol/l) as is safely possible. Some physicians suggest up to 140–150 mg/dl (7–7.5 mol/l) for those having trouble with lower values, such as frequent hypoglycemic events. Values above 400 mg/dl (20 mmol/l) are sometimes accompanied by discomfort and frequent urination leading to dehydration. Values above 600 mg/dl (30 mol/l) usually require medical treatment and may lead to ketoacidosis, although they are not immediately life-threatening. However, low levels of blood glucose, called hypoglycemia, may lead to seizures or episodes of unconsciousness and must be treated immediately, via emergency high-glucose gel placed in the patient's mouth or an injection of glucagon.

1.10.4 Type 2 diabetes mellitus

Type 2 diabetes mellitus is characterized differently and is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion which in some cases becomes absolute. The defective responsiveness of body tissues to insulin almost certainly involves the insulin receptor in cell membranes. However, the specific defects are not known. Diabetes mellitus, due to a known specific defect, are classified separately.

In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin

sensitivity or reduce glucose production by the liver. As the disease progresses, the impairment of insulin secretion worsens, and therapeutic replacement of insulin often becomes necessary.

There are numerous theories as to the exact cause of and mechanism in type 2 diabetes. Central obesity (fat concentrated around the waist in relation to abdominal organs, but not subcutaneous fat) is known to predispose individuals to insulin resistance. Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines that may possibly impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes. Other factors include aging (about 20% of elderly patients in North America have diabetes) and family history (type 2 is much more common in those with close relatives who have had it). In the last decade, type 2 diabetes has increasingly begun to affect children and adolescents, likely in connection with the increased prevalence of childhood obesity seen in recent decades in some places. Environmental exposures may contribute to recent increases in the rate of type 2 diabetes. A positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of polycarbonate plastic, and the incidence of type 2 diabetes.

Type 2 diabetes may go unnoticed for years because visible symptoms are typically mild, non-existent or sporadic, and usually there are no ketoacidotic episodes. However, severe long-term complications can result from unnoticed type 2 diabetes, including renal failure due to diabetes nephropathy, vascular disease (including coronary artery disease), vision damage due to diabetes retinopathy, loss of sensation or pain due to diabetes neuropathy, liver damage from non-alcoholic steatohepatitis and heart failure from diabetes cardiomyopathy.

Type 2 diabetes is usually first treated by increasing physical activity, decreasing carbohydrate intake, and loss of weight. These can restore insulin sensitivity even when the weight loss is modest, for example, around 5 kg (10 to 15 lb), most especially when it is in abdominal fat deposits. It is sometimes possible to achieve long-term, satisfactory glucose control with these measures alone. However, the underlying tendency to insulin resistance is not lost, and so attention to diet, exercise, and weight loss must continue. The next usual step, if necessary, is treatment with oral antidiabetes drugs. Insulin production is initially only moderately impaired in type 2 diabetes, so oral medication (often used in various combinations) can be used to improve insulin production (e.g., sulfonylureas), to regulate inappropriate release of glucose by the liver and attenuate insulin resistance to some extent (e.g., metformin), and to substantially attenuate insulin resistance (e.g., thiazolidinediones). According to one study, overweight patients treated with metformin compared with diet alone, had relative risk reductions of 32% for any diabetes endpoint, 42% for diabetes related death and 36% for all causes of mortality and stroke. Oral medication may eventually fail due to further impairment of beta cell insulin secretion. At this point, insulin therapy is necessary to maintain normal or near normal glucose levels.

1.10.5 Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all 33 pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

A 2008 study completed in the U.S. found that more American women are entering pregnancy with preexisting diabetes. In fact, the rate of diabetes in expectant mothers has more than doubled in the past 6 years. This is particularly problematic as diabetes raises the risk of complications during pregnancy, as well as increasing the potential that the children of diabetic mothers will also become diabetics in the future.

Most cases of diabetes mellitus fall into the two broad etiologic categories of type 1 or type 2 diabetes. However, many types of diabetes mellitus have known specific causes, and thus fall into separate categories as diabetes due to a specific cause. As more research is being done into diabetes, many patients who were previously diagnosed as type 1 or type 2 diabetes will be reclassified as diabetics due to their known specific cause.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. If diabetic mothers will also become diabetics in the future.

1.10.6 Antidiabetes Drug classification

1.10.6.1 Biguanides:

Metformin, Phenoformin.

1.10.6.2: Sulfonylureas:

a] First Generation: Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamide

b] Second Generation: Glyburide, Glipizide, Glyburide, Glimepiride, Gliclazide

1.10.6.3 Glitazenes [Thiazolidinediones]:

Rosiglinide, Pioglitazone, Troglitazone

1.10.6.4 Metaglinides:

Repaglinide, Nateglinide

1.10.6.5 α –Glucosidase inhibitors :

Acarbose, Miglitol

1.11 Adverse effect of Antidiabetic drugs:-

Gastrointestinal intolerance occurs quite frequently in the form of abdominal pain, flatulence, and diarrhea. Most of these effects are transient and subside once the dose is reduced or when administered with meals. However, as much as 5% of patients do not tolerate even the lowest dose]. About 10–30% of patients who are prescribed metformin have evidence of reduced vitamin B12 absorption due to calcium-dependent membrane antagonism, an effect that can be reversed with supplemental calcium.

This vitamin B12 deficiency is rarely associated with megaloblastic anemia. A multicentric study reported a mean decrease of 19% and 5% in vitamin B12 and folate concentration, respectively . Vitamin B12 deficiency has been related with dose and duration of metformin use and occurs more frequently among patients that use it for more than 3 - years and in higher doses . Other adverse reactions are sporadic.

1.12 Antidiabetic drugside effect²⁷:-

Antidiabetic drugs are associated with several side effects.

Common side effects are:-

- [Nausea](#),
- Vomiting,
- Diarrhea,
- Constipation,
- Decrease
- Dap petite,
- Rashes,
- Dizziness,
- Headache,
- Drowsiness,
- Ulcer.

2. NEED OF WORK

Per oral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release. Gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time.

The stomach is divided into 3 anatomic regions: funds, body, and ant rum (pylorus). The separation between stomach and duodenum is the pylorus. The part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The pattern of motility is however distinct for the two states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2–3 h. This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle. Food effects and the complex motility of the stomach play a major role in gastric retention behavior. Several approaches of non effervescent and effervescent formulation technologies have been used and patented in order to increase gastric residence time of the GRDF.

The Inlay tablet drug delivery system is preferred for the following reasons to co-administer,

- To minimize physical and chemical incompatibilities, for better drug release,
- SR and SR in the same tablet, for chronic condition requiring repeated dosing.
- To avoid drug layer separation of Metformin[SR] and Glimepiride[SR]
- To reduced cross contamination in between SR & SR layer.
- To achieve sequential released of drug layer in GIT.
- To achieve released of multiple API's in one dose.
- To maintained plasma level of drug constant & within therapeutic window.

3. Aim and Objectives

3.1 Aim:-

The aim of the present study is formulation evaluation and optimization of inlay tablet dosage form of Metformin and Glimepiride as sustained release.

3.2 Objective:-

- To formulate and evaluate Inlay Tablet of drug with the intention of obtaining better therapeutic efficiency by controlling drug release, thereby improving patient compliance and increasing bioavailability with decreased dosing and fewer side effects.
- To study and evaluate Inlay tablet formulation.

➤ To study release kinetics of Inlay Tablet.

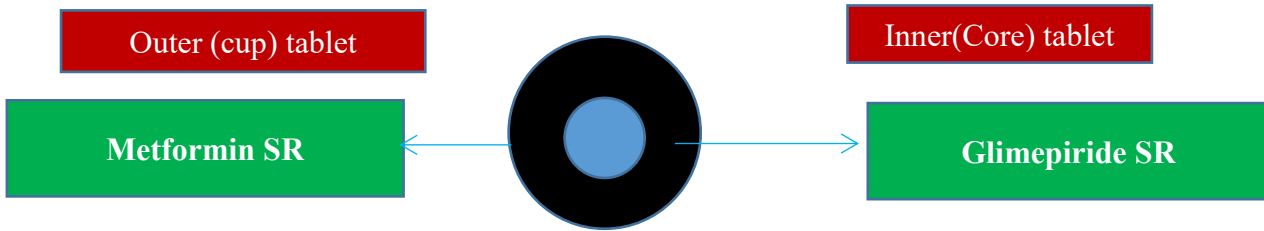
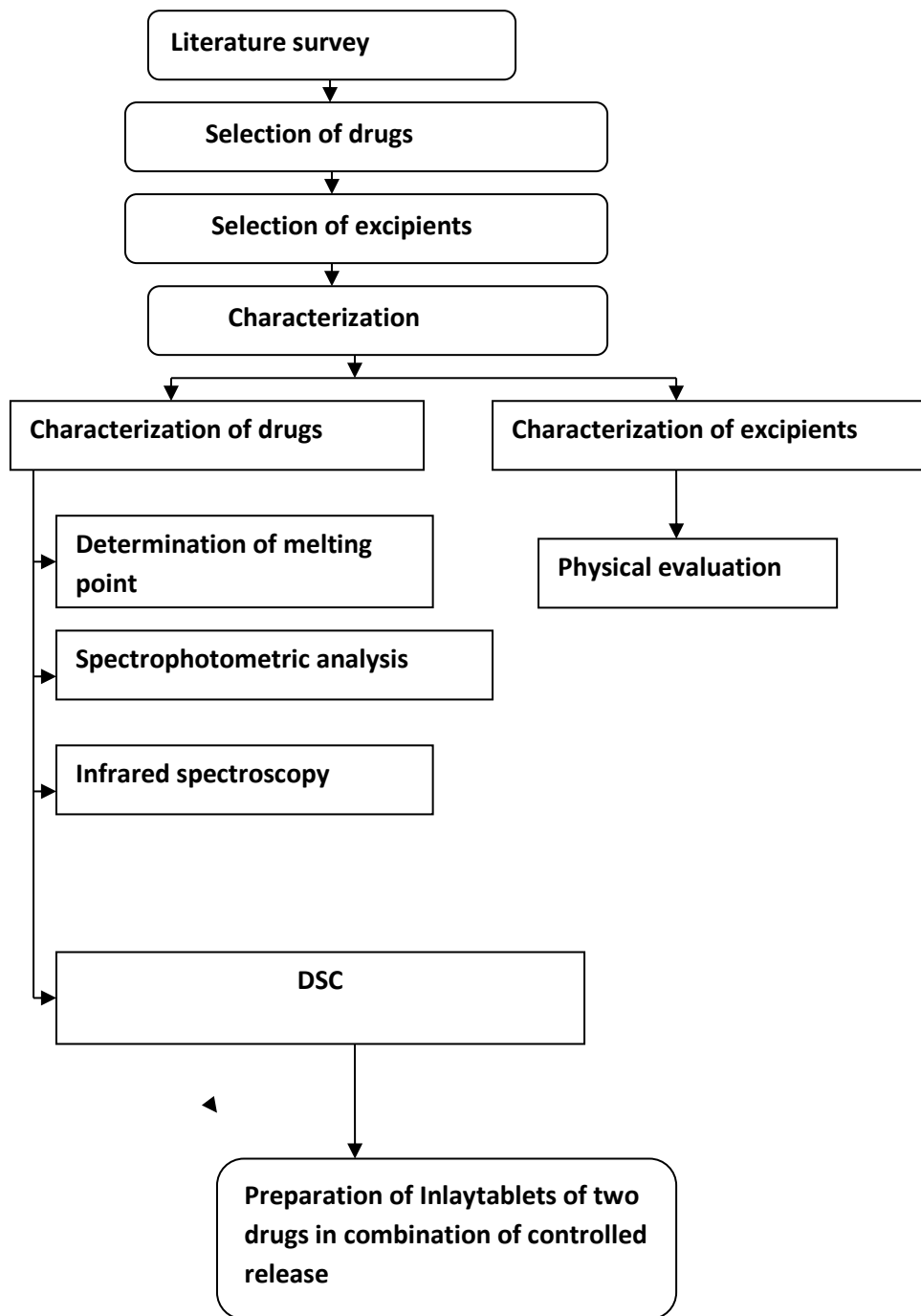
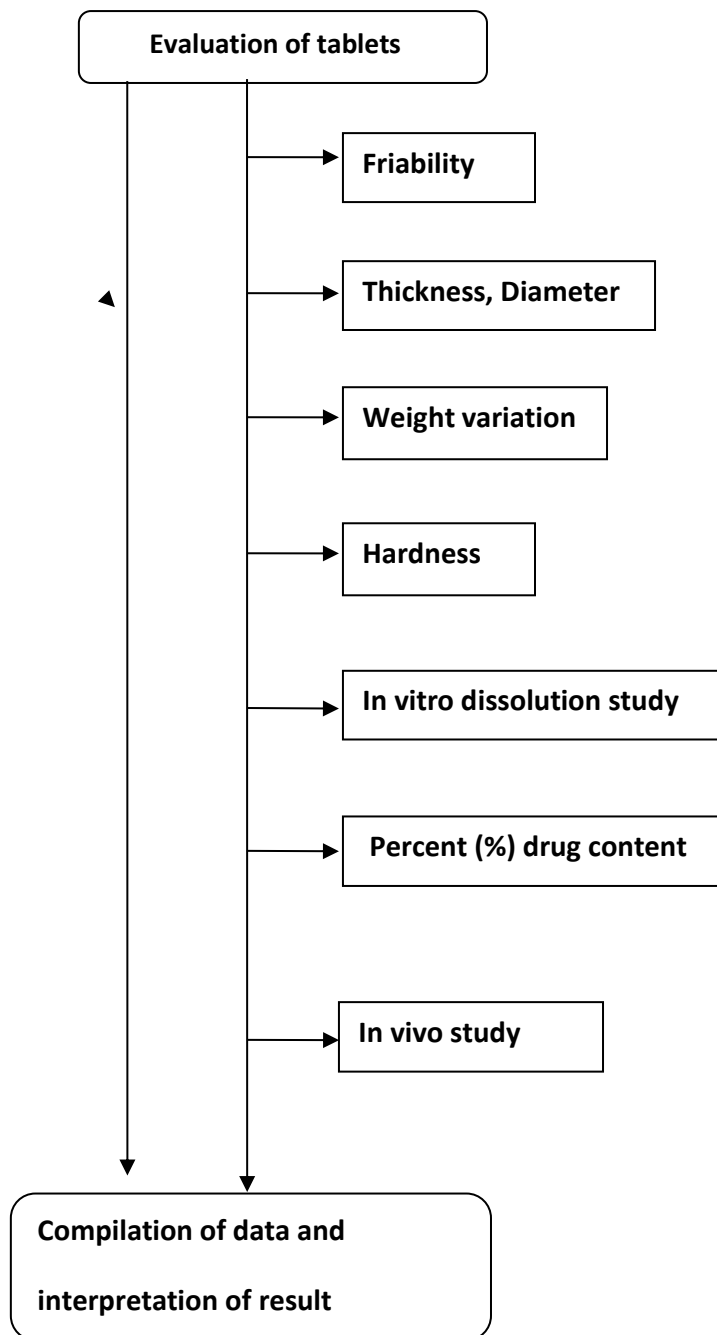


Figure No: 3.1.1 Inlay (core in cup) Tablet Dosage form(Front view)



4. PLAN OF WORK-



5. Literature survey

Following are some reviews covering aspects of as Inlay Tablet dosage form.

5.1 Review of Literature Related to Inlay Tablet dosage form:

5.1.1 Rajalakshmi R. et al International Journal of Advanced Pharmaceutics, (2011)¹:-Inlay tablet is the dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release with the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media. Dosage frequency of highly water soluble drugs can be reduced providing same efficacy. Thus any combinations drug combinations can be used with no interactions. Main problems of formulation of drugs like frequent dosing, interactions, burst effect can be reduced.

5.1.2 Patel Pratik.et al.IJPDT, (2013)²:- Manufacturing problems that occur during formulation of compression coated and inlay tablet can be overcome by OSDRC technology. OSDRC is the one step dry coated technology where variety of dosage forms can be formulated precisely, with high quality and uniqueness in single steps those cannot possible with existing tableting technology so, it opens new era of tableting technology and manufacturing of novel solid dosage form can be formulated at low cost, with simple one step operation by just simply changing the double punches assembly.

5.1.3 DronModi et al BBB(2013)³:-The compression-coated tablet process provides a means of compression coating by simple modifications to a three layer press. There are many advantages of this process over traditional compression coating. Separate formation of a core is not required and therefore no transfer mechanism is required for the core. Similarly, centering of the core is not a problem in this process, thereby leading to better reproducibility of release profiles in controlled-release applications. Inlay tablet is the dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release with the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media.

5.2 Review of Literature Related to Inlay Tablet in Drug combination

5.2.1 S. Brito Raj et al Journal of Pharmacy Research (2011)¹¹:-Inlay tablet is a novel technology which overcomes the difficulties that faced in other compression coated tablets. The formulation has achieved the objective of controlled drug delivery with prolonged drug release, cost effective, low dose and frequency of administration and hence improved patient compliance. Thus it may be concluded that the once daily Inlay tablet of Atorvastatin calcium with sustained release Metoprolol tartrate can be a best alternate to conventional dosage forms with more frequency of administration. The Inlay tablet can be administered to patients with Hypertension and Dyslipidemia, Myocardial infarction, Diabetic dyslipidemia and Hypertension.

5.2.2 Audinarayana et al.Int J PharmSci,(2011)¹²:- The formulation F4 has achieved the objective of sustained drug delivery with prolonged release, cost effective, decrease dose and frequency of administration, and hence improved patient compliance. Thus it may be concluded that the once daily Inlay tablet of Salbutamol sulphate with sustained release of Isoniazid can be administered to Tuberculosis cum Asthma.

5.2.3 A.R Mullaicharam et al. International Journal of Pharma and Bio Sciences (2010)¹¹:- The objective of the present study was to develop once-daily sustained release matrix tablets of Metoprolol Tartrate with inlay hydrochlorothiazide tablet as an immediate release formulation. The inlay tablets were prepared by wet granulation method using hydroxy propyl methylcellulose in various percentages. The drug-excipient incompatibility studies were performed by Differential Scanning Calorimetry(DSC). The granules showed satisfactory flow properties and compressibility. Five trial batches were prepared using various excipients. The trial batch M4(35% hydroxy propyl methyl cellulose) could extend the release of Metoprolol Tartrate for 24h and that of hydrochlorothiazide for 2h, which matched with the USP drug profile. The in vitro and the in vivo release studies in rabbit were performed. The mechanism of drug release was diffusion coupled with erosion.

5.3 Review of Literature Related to Metformin and Glimpiride:

5.3.1 Prabhakar Shirse et al International Journal of Pharma and Bio Sciences¹³

The aim of present study is to formulate and evaluate the bilayered tablets containing immediate release layer of HP-β-Cycloextrin inclusion complexed Glimpiride to produce immediate therapeutic effect and sustained release layer containing Metformin Hcl by using HPMC as release retardant. Glimpiride act by stimulating the release of insulin from functioning pancreatic beta cells. Metformin hydrochloride helps to suppress appetite and diminishes hepatic glucose excretion, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It doesn't stimulate insulin release and the combination of these two drugs is more effective than single drug therapy to treat NIDDM (Non insulin dependent Diabetes mellitus). The reason for Bilayer tablet formulation is to separate physically or chemically incompatible ingredients and to produce repeat action or prolonged action tablet. Total seven trial batches have been manufactured to optimize and develop a robust and stable formulation, both wet & dry granulation processes were used for formulation. The compressed tablets were evaluated for physico-chemical properties. The stability studies of the products also comply with ICH guidelines. FTIR studies clearly indicate that there is no drug polymer interaction. This formulation also exhibited the best fitted formulation into zero order kinetics and non-Fickian transport of the drug from the tablets was confirmed. The present study concluded that bilayer tablets of Glimpiride & Metformin Hcl shall be a good method to improve bioavailability of drugs.

5.3.2 Sahu Manranjan et al IJREP:-The aim of present study is to formulate and evaluate the bilayered tablets containing immediate release layer of HP-β-Cycloextrin inclusion complexed Glimpiride to produce immediate therapeutic effect and sustained release layer containing Metformin Hcl by using HPMC as release retardant. Glimpiride act by stimulating the release of insulin from functioning pancreatic beta cells. Metformin hydrochloride helps to suppress appetite and diminishes hepatic glucose excretion, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It doesn't stimulate insulin release and the combination of these two drugs is more effective than single drug therapy to treat NIDDM (Non insulin dependent Diabetes mellitus). The reason for Bilayer tablet formulation is to separate physically or chemically incompatible ingredients and to produce repeat action or prolonged action tablet. Total seven trial batches have

been manufactured to optimize and develop a robust and stable formulation; both wet & dry drug from the tablets was confirmed. The present study concluded that bilayer tablets of Glimepiride & Metformin Hcl shall be a good method to improve bioavailability of drugs.

5.3.3 Malay R Patel International Journal of Pharmacy and Pharmaceutical Sciences:-The aim of present investigation was to design the concept of bilayered tablet containing Glimepiride as immediate release using sodium starch glycollate as super disintegrant and Metformin Hydrochloride as sustained release floating delivery system. The purpose of this investigation was to prepare a Gastroretentive bilayer drug delivery tablet. Floating layer of Metformin Hydrochloride was prepared employing different grades of gel forming agent and by various gas generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for 6-10 hours. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

5.4 Review of Literature Related to sustained release tablet:-

5.4.1 Sarika Pundir et al.(2013)³⁰:-Review on Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. There are several advantages of sustained release (matrix) drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, increase patient compliance by reducing frequency of dose.

5.4.2 Kalyani Chithalur et al.(2011)²⁹:- prepare twice daily sustained release matrix tablets of losartan potassium using Eudragit RLPO, RSPO and Ethyl cellulose individually and in combination of above polymers. Matrix tablets assessed for their physicochemical properties and invitro drug release studies. Eudragit in higher polymer proportion drug release was extending up to 12hrs.

6. Drugs profile:-^{17, 18, 19}

6.1 Metformin:-

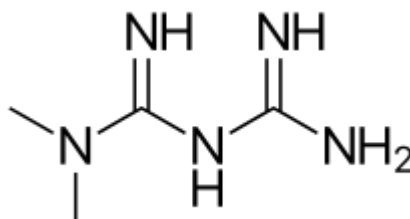


Figure no.6.1.1 structure of Metformin

6.1.1 Description:-Metformin is a biguanides antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin-mediated glucose uptake. Metformin may induce weight loss and is the drug of choice for obese NIDDM patients. When used alone, metformin does not cause hypoglycemia; however, it may potentiate the hypoglycemic effects of sulfonylureas and insulin. Lower doses should be used in the elderly and those with decreased renal functional. Metformin may also have a positive effect on lipid levels. In 2012, a combination tablet of linagliptin plus Metformin hydrochloride was marketed under the name Jentaduetto for use in patients when treatment with both linagliptin and Metformin is appropriate.

Appearance:-

- **Color:** - White or almost white powder.
- **Odor:** - Fishy odor.

6.1.2 Chemical name, Formula and Molecular weight:-

- **Chemical name:** -1,1-Dimethylbiguanide
- **Molecular Formula:** - $C_4H_{11}N_5$
- **Molecular Weight:** -129.16364 g/mol

6.1.3 Solubility: -

Solubility of Metformin in variety of solvents.

Sr.No.	Name of solvent	Solubility
1	Water	Freely soluble(50mg/ml)
2	Methanol	soluble(>24mg/ml)
3	Ethanol	soluble(35mg/ml)
4	Phosphate Buffer PH7.4	Slightly soluble(6mg/ml)

Table no.1 solubility of Metformin.

- **Storage:** - Store at room temperature and protect from light
- **Protein binding:** -minimal
- **Half life:** - 4-8.7 hour.

- **Melting point:** - 223°C-226°C
- **H₂O solubility:** - 1-4 mg/L (at 25 °C)
- **Shelf life:** - 4 years when stored at or below 30°C.

6.1.4 Pharmacology:-

It can lower blood glucose in several ways. It acts by countering insulin resistance, particularly in liver and skeletal muscle. It suppresses hepatic gluconeogenesis, increases peripheral insulin sensitivity in insulin sensitive tissues such as muscle and adipose tissue, and enhances peripheral glucose utilization. The protective effect on the cardiovascular system cannot be fully explained by its bloodglucose-lowering properties

6.1.5 Pharmacokinetics:-

Absorption and Bioavailability

The absolute bioavailability of a Metformin 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin HCl 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of Metformin HCl 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin HCl, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/ml. During controlled clinical trials of Metformin HCl, maximum Metformin plasma levels did not exceed 5 mg/mL, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

6.1.6. Category:-

Anti-diabetics agent,

6.1.7 Dossage:-

For the relief of osteoarthritis, the recommended dosage is 400-2500mg/day in divided doses (500mg bid or 1000mg bid)

6.1.8 Adverse effects:-

The adverse events most commonly associated with GLUCOPHAGE (MetforminHCl) are diarrhea, nausea, and upset stomach. Lactic acidosis is a rare, but serious side effect. Lactic acidosis is fatal in approximately 50% of cases.

6.1.9 Indications:-

Metformin is primarily suited for the treatment of subjects with non-insulin-dependent diabetes mellitus (type II diabetes). Compared to other antidiabetic agents, it has the advantages of lowering rather than increasing body weight, of not causing hypoglycemia, and of entailing a reduction of triglycerides and LDL-cholesterol levels. Metformin is therefore recommended in single drug therapy especially for obese subjects. In the majority of the treated subjects, a lowering of blood glucose levels by at least 25% is achieved (i.e. almost identical results as with sulfonylureas at the beginning of treatment).

6.1.10 Contraindications:-

Three particular contraindications to the use of metformin have been suggested. They include renal impairment with elevated serum creatine levels (*i.e.* more than 136 mol/l in men and 124 mol/l in women) or abnormal creatinine clearance, congestive heart failure requiring pharmacologic treatment and advanced age (more than 80 years of age).

Renal impairment represents a contraindication to metformin usage due to the increased risk of lactic acidosis (a form of metabolic acidosis due to the inadequate clearance of lactic acid from the blood). Although lactic acidosis linked to metformin is a rare condition, with an estimated prevalence of one to five cases per 100 000 population, it has a reported mortality of 30-50%

6.1.11 Warning and precautions:-

Warning: - Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypo perfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 pg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal

hypo perfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypo perfusion and hypoxemia are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients 280 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin hydrochloride tablets, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS). The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant Bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Metformin hydrochloride tablets should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mol/L in patients taking Metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.) Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

Precaution:-

General Monitoring of renal function- Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin. In patients with advanced age, metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those 280 years of age, renal function should be monitored regularly and, generally, metformin should not be titrated to the maximum dose (see WARNINGS and DOSAGE AND ADMINISTRATION). Before initiation of metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and metformin discontinued if evidence of renal impairment is present. Use of concomitant medications that may affect renal function or metformin disposition - Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see PRECAUTIONS: Drug Interactions), should be used with caution, Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous program, intravenous cholangiography, angiography, and computed tomography (CT) scans with contrast materials) - Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, metformin should be discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been reevaluated and found to be normal. Hypoxic states - Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued. Surgical procedures - Metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal. Alcohol intake - Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving metformin. Impaired hepatic function - Since impaired hepatic function has been associated with some cases of lactic acidosis, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Vitamin B₁₂ levels - A decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride tablets or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed.

6.1.12 Drug interaction:-

Drug interactions are often categorized as pharmacodynamic or pharmacokinetic in nature. A pharmacodynamic drug interaction is related to the drug's effect on the body. An example is the combination of alcohol with medications that cause sedation. A pharmacokinetic drug interaction is related to the body's effect on the drug. An example is an increase in the systemic concentration of a renally eliminated drug because of renal insufficiency. A pharmacokinetic drug interaction can be caused by an alteration in absorption, distribution, metabolism, or elimination of a drug.

Pharmacodynamic Interactions

Pharmacodynamic drug interactions can be either beneficial or detrimental to patients. A beneficial example is the additive blood pressure-lowering effect when an ACE inhibitor is added to a calcium channel blocker (CCB). Likewise, synergistic blood pressure lowering may be seen if a diuretic is added to an ACE inhibitor. The pharmacodynamic drug interaction can also be detrimental. When alcohol and a medication that causes sedation are combined, additive unwanted sedation may occur. Antagonistic effects may also be encountered, as with the combination of an acetyl-cholinesterase inhibitor for myasthenia gravis or Alzheimer's disease with amitriptyline for painful diabetic peripheral neuropathy. The acetyl-cholinesterase inhibitor increases acetylcholine levels, whereas amitriptyline has antagonistic anti-cholinergic effects.

Pharmacokinetic Interactions**Absorption interactions:**

Drug absorption is the movement of the drug from its site of administration into the bloodstream. Absorption interactions are changes in a drug's effects caused by food, drink, or medications taken concurrently. Classically, we think of the oral administration of a medication and absorption from the gastrointestinal system, but it applies to all routes of administration, including injection, inhalation, topical, buccal, sublingual, and others.

Drug-food interactions can affect the total amount of drug absorbed (bioavailability), but most often they only slow absorption. For example, the hypoglycemic effect of glipizide may be delayed slightly if taken with a meal versus 30–60 minutes before a meal, although hemoglobin A_{1c} (A1C) values are unaffected.^{9,10} Alteration of gastrointestinal motility, as is the case with exenatide, or pH may also affect absorption. In addition, components of food may interact. For example, vitamin K intake from green leafy vegetables interacts with warfarin. Similarly, several medications may complex or chelate with co-administered medications, significantly reducing their absorption.⁶ For example, levothyroxine absorption is reduced when co-administered with ferrous sulfate or antacids and should be moved either 1 hour earlier or at least 2 hours after administration of these drugs. It is best not to administer other medications with antacids because they can reduce the absorption of many medications.

Distribution interactions:

Distribution is the movement of the absorbed drug through the bloodstream and its transport throughout extracellular or intracellular compartments to the site of action. Many medications extensively bind to plasma proteins such as albumin in the blood-stream. When a drug is bound to these plasma proteins, it is not actively distributed to the site of action, and only the “free” drug is available to cause an effect. One drug can displace another from the binding sites on the plasma proteins if its binding is stronger. This increases the amount of “free” drug available to cause an effect.

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High-risk groups for drug interactions include neonates, infants, the elderly, and those with significant organ disease (i.e., renal or hepatic disease) warranting increased screening vigilance. Neonates, infants, and the elderly will often metabolize drugs slower than healthy adults, and lifestyle choices such as smoking (induces metabolism) and alcohol use (may induce or inhibit metabolism) can alter metabolism. Metabolism patterns can also be altered by genetically determined variations. For example, ~5–10% of Caucasians, but only 0–1% of Asians, have little CYP2D6 enzyme activity, making them “CYP2D6 poor metabolizers,” the consequences of this are dependent on the drug and alternative pathways available for metabolism.

Elimination interactions:

Drug elimination is the removal of a drug from the body. The major organs involved in elimination are the kidneys and liver, although other bodily processes, including saliva, sweat, or exhaled air, may be pathways for elimination. Elimination through the liver is primarily through bile. There are not many true drug-drug interactions through bile elimination, but drug-disease interactions, as described below, can be important when bile elimination is affected, as with severe biliary or liver disease. Renal drug-drug interactions are dependent on the pH of the urine and the pH of the drug or on competition for the same pathway of elimination. If the pH of the urine and the drug are the same, renal reabsorption of the drug will be increased. When two drugs compete for elimination through a single route, one drug may competitively inhibit the elimination of the other.⁸ Metformin and cimetidine, both cationic (positively charged) drugs, can compete for elimination through kidneys by renal tubular secretion, resulting in higher metformin concentrations in the plasma.

6.2 Drug profile of Glimepiride:-^{17, 18, 19}

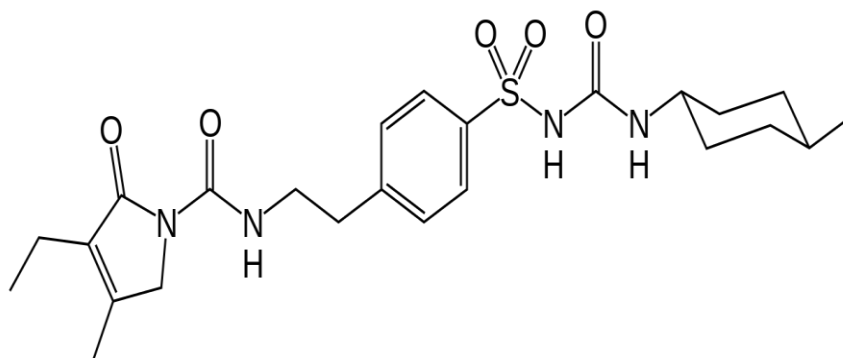


Figure no.6.2.1 structure of Glimepiride

Glimepiride is an oral [blood sugar](#)-lowering drug in a class of medicines for controlling [diabetes](#) called sulfonylureas. Glimepiride is related to other sulfonylurea's including [glyburide](#) (Diabeta, Glynase), [glipizide](#) ([Glucotrol](#), [Glucotrol XL](#)), tolbutamide, and [tolazamide](#). Glimepiride is used in [type 2 diabetes](#), the most common type of [diabetes](#) that is found in 90% of people with diabetes. In [type 2 diabetes](#), [insulin](#) usually is not necessary to control the blood [sugar](#). Instead, [diet](#) and oral medications often are sufficient. Intolerance to [sugar](#) that result in elevated blood sugar is caused by reduced insulin secretion by the pancreas and resistance to insulin's effects on the body's cells. Glimepiride lowers the sugar level in the blood by stimulating insulin to be secreted from the pancreas into the blood. Insulin causes sugar to leave the blood and enter cells throughout the body. Glimepiride was approved by the FDA in December 1995.

6.2.1 Description:-

- **Approved name:-**Glimepiride
- **Brand name:-**Adride-Grandix pharmaceutical.
- **Synonyms:-** Amaryl
- **Molecular Formula:-** C₂₄H₃₄N₄O₅S
- **Molecular Weight:-**490.617 gm/mol
- **Solubility:-**soluble in methanol, water, and ethanol.
- **Dose:-**1-2 mg
- **Melting point:-**212-215°c

6.2.2 Appearance:

- **Color:** - white.
- **Odor:** - Vaginal Odor.

6.2.3 Pharmacology:-

Glimepiride primarily lowers [blood glucose](#) by stimulating the release of insulin from [pancreatic](#) beta cells. Sulfonylurea bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

6.2.4 Pharmacokinetics

6.2.4.1 Absorption:-Studies with single oral doses of Glimepiride in healthy subjects and with multiple oral doses in patients with [type 2 diabetes](#) showed peak drug concentrations (C_{max}) 2 to 3 hours post-dose. When Glimepiride was given with meals, the mean C_{max} and AUC (area under the curve) were decreased by 8% and 9%, respectively.

Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of Glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of Glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics.

In healthy subjects, the intra and inter-individual variability's of Glimepiride pharmacokinetic parameters were 15-23% and 24-29%, respectively

➤ **Pharmacokinetic properties**

T_{max}:- 2-3 hours

t_{1/2} (half-life):-5 hours

Plasma protein binding:-99.5%

Bioavailability:-100%

Excretion: -90% in urine(metabolites)

~10% in faeces (unchanged)

6.2.4.2 Distribution

After [intravenous](#) dosing in healthy subjects, the volume of distribution (V_d) was 8.8 L (113 ml/kg), and the total body clearance (CL) was 47.8 ml/min. Protein binding was greater than 99.5%.

6.2.4.3 Metabolism

Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexylhydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of Glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic [enzymes](#). M2 is inactive.

In animals, M1 possesses about one-third of the pharmacological activity of Glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

6.2.4.4 Excretion

When ¹⁴C-glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the [urine](#) in 7 days. M1 and M2 accounted for 80-90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in [feces](#). M1 and M2 accounted for approximately 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant [biliary](#) excretion of Glimepiride or its M1 metabolite was observed.

6.2.5 Elderly:-No clinically relevant drug accumulation occurs. No dosage adjustment is required.

6.2.6 Hepatic impairment:-The maximum plasma concentration can increase by up to 50%. Caution should be exercised when treatment is initiated in patients with severe hepatic dysfunction.

6.2.7 Clinical Efficacy:-

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylurea's bind to the sulfonylurea receptor in the [pancreatic beta cell](#) plasma membrane, leading to closure of the [ATP-sensitive potassium](#) channel, thereby stimulating the release of insulin.

6.2.8 Adverse Effects:-

Side effects from taking Glimepiride include [gastrointestinal tract](#) (GI) disturbances, occasional allergic reactions, and rarely blood production disorders including thrombocytopenia, leucopenia, and hemolytic anemia. In the initial weeks of treatment, the risk of hypoglycemia may be increased. Alcohol consumption and exposure to sunlight should be restricted because they can worsen side effects.

6.2.9 Contra-Indications/Precautions:-

Contra-indications are known hypersensitivity to Glimepiride (or any other proton pump inhibitor) or any of the tablet ingredients, pregnancy and lactation. Precautions; exclude possibility of malignancy before starting sodium, severe hepatic dysfunction.

6.2.10 Drug Interactions:-

Aspirin: In a [randomized, double-blind](#), two-period, [crossover study](#), healthy subjects were given either placebo or aspirin 1 gram three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 1 mg dose of AMARYL was administered. The AMARYL doses were separated by a 14-day washout period. Co-administration of aspirin and AMARYL resulted in a 34% decrease in the mean glimepiride AUC and a 4% decrease in the mean Glimepiride C_{max}.

Cimetidine and Ranitidine: In a randomized, open-label, 3-way crossover study, healthy subjects received either a single 4 mg dose of AMARYL alone, AMARYL with ranitidine (150 mg twice daily for 4 days; AMARYL was administered on Day 3), or AMARYL with cimetidine (800 mg daily for 4 days; AMARYL was administered on Day 3). Co-administration of cimetidine or ranitidine with a single 4 mg oral dose of AMARYL did not significantly alter the absorption and disposition of Glimepiride.

Propranolol: In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or propranolol 40 mg three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 2 mg dose of AMARYL was administered. The AMARYL doses were separated by a 14-day washout period. Concomitant administration of propranolol and AMARYL significantly increased Glimepiride C_{max}, AUC, and T_{1/2} by 23%, 22%, and 15%, respectively, and decreased Glimepiride CL/f by 18%. The recovery of M1 and M2 from urine was not changed.

Warfarin: In an open-label, two-way, crossover study, healthy subjects received 4 mg of AMARYL daily for 10 days. Single 25 mg doses of warfarin were administered 6 days before starting AMARYL and on Day 4 of AMARYL administration. The concomitant administration of AMARYL did not alter the pharmacokinetics of R- and S-warfarin enantiomers. No changes were observed in warfarin plasma protein binding. AMARYL resulted in a statistically significant decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the [prothrombin time](#) (PT) curve and maximum PT values during AMARYL treatment were 3.3% and 9.9%, respectively, and are unlikely to be clinically relevant.

7. Excipients Profile:-

7.1 Hydroxy Propyl Methyl Cellulose (HPMC)²⁰:-

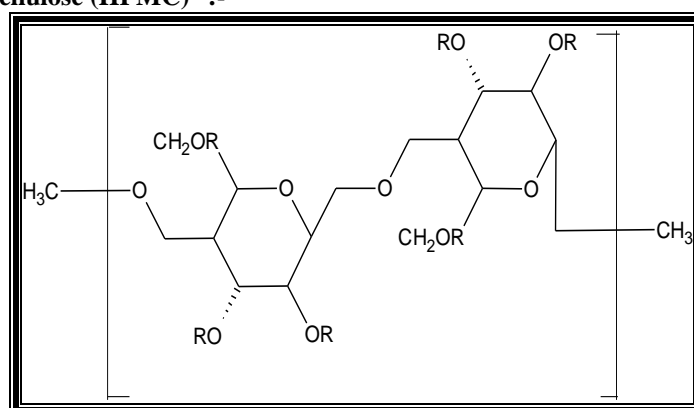


Figure no.7.1.1 structure of HPMC

R=H, CH₃ or CH₃CH(OH)CH₂

7.1.1 Chemical Name: Cellulose hydroxyl propyl methyl ether.

Non proprietary names:-

- BP: Hypromellose
- JP: Hydroxypropylmethylcellulose
- PhEur: Hypromellosem
- USP: Hypromellose

Synonym:-Hydroxypropyl methylcellulose (HPMC), Methylcellulose propylene glycol ether;Methocel, Methyl hydroxyl propylcellulose;

Description:-Hypromellose is an odorless and tasteless white or creamy white fibrous or granular powder.

7.1.2 Physical properties

- **Solubility:-**Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether.
- **pH:** - A 1% w/w solution has a pH of 5.5-8.0.
- **Melting Point:** - Browns at 190–200°C, Glass transition temperature is 170–180°C.
- **Acidity/alkalinity:-**pH = 5.5–8.0 for a 1% w/w aqueous solution.
- **Bulk Density:-** 0.341 gm/cm³
- **Tapped Density:-** 0.557 gm/cm³
- **True Density:-** 1.326 g/cm³
- **Gel Formation:-** Undergoes a reversible transformation from solution to gel upon heating and cooling respectively.
- **Storage:-**Stored in well closed containers.

7.1.3 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating and as a matrix polymer in extended-release tablet formulations. Concentrations between 2% w/w and 5% w/w may be used as a binder in either wet- or dry-granulation process. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used as a suspending and thickening agent in topical formulations. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

7.1.4 Viscosity:-

Methocelproduct USP 28	Nominal viscosity (mPas)
Methocel K100 Premium HV	100
Methocel K4M Premium	4000

7.1.5 Functional Category

Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Incompatibilities:-Hypromellose is incompatible with some oxidizing agents.

7.4 Magnesiumstearate²⁰:-

7.4.1 Nonproprietary Names

- BP: Magnesium stearate
- JP: Magnesium stearate
- PhEur: Magnesiistearas
- SPNF: Magnesium stearate

Synonyms:-Magnesium octadecanoate; magnesium salt.

Chemical Name:-Octadecanoic acid magnesium salt.

Functional Category:-Tablet and capsule lubricant.

7.4.2 Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It 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 creams.

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

7.4.3 Typical Properties

- **Crystalline forms:-**High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
- **Density (bulk):-** 0.159 g/cm³
- **Density (tapped):-**0.286 g/cm³
- **Density (true):-**1.092 g/cm³
- **Flowability:-** poorly flowing, cohesive powder.
- **Melting range:-** 117–150°C.
- **Solubility:-**practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

7.4.4 Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool and dry place.

7.4.5 Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloid salts.

7.5 Talc²⁰

7.5.1 Nonproprietary Names

- BP: Purified talc
- JP: Talc
- PhEur: Talcum
- USP: Talc

Synonyms:-

Hydrous magnesium calcium silicate, hydrous magnesium silicate, magnesium hydrogen metasilicate, powdered talc, purified French chalk.

Chemical Name: - Talc.

Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Functional Category

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

7.5.2 Applications in Pharmaceutical Formulation

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.

Use Concentration (%):-

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluents	5.0–30.0

It is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended-release pellets and as an adsorbant. In topical preparations, talc is used as a dusting powder. It should not be used to dust surgical gloves. Talc is additionally used to clarify liquids and is also used in cosmetics and food products mainly for its lubricant properties.

Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

7.5.3 Typical Properties

- **Acidity/alkalinity:** - pH = 7–10 for a 20% w/v aqueous dispersion.
- **Moisture content:** - Talc absorbs insignificant amounts of water at 25°C and relative humidifies up to about 90%.
- **Solubility:** - practically insoluble in dilute acid and alkali, organic solvent, and water.

Stability and Storage Conditions: - Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: - Incompatible with quaternary ammonium compounds.

7.6 Lactose²⁰

7.6.1 Nonproprietary Names

- BP: Lactose monohydrate
- PhEur: Lactosummonohydricum
- JP: Lactose
- SPNF: Lactose monohydrate

Functional Category: - Binding agent, diluent for dry-powder inhalers, tablet binder, tablet and capsule diluent.

Description: - Lactose occurs as white to off-white crystalline powder. Lactose is odorless and slightly sweet-tasting. This form of lactose is allowed to dry out and the moisture content falls below the usual 3% level. Spray-dried lactose is produced by spray drying the slurry containing lactose crystals. The final product contains mixture of crystals of lactose monohydrates. The former contributes fluidity and the latter gives the compressibility to the product. It has excellent flow properties and binding properties. It deforms plastically compared to the same sized α -Lactose monohydrate particles. Amorphous portion of the spray dried lactose is responsible for the better binding and plastic deformation. Compressibility is affected if it is allowed to dry below a level of 3% w/w moisture. A Millard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown or yellow-brown-colored products.

7.6.2 Applications in Pharmaceutical Formulation

Lactose is widely used as a filler or diluents in tablets, capsules, and infant feed formulas. Applications of lactose include as a carrier/diluents for inhalation products and in lyophilized products. It is also used in combination with sucrose (approximately 1:3) to prepare sugar coating solutions. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.

7.6.3 Storage Conditions:-Lactose should be stored in a well-closed container in a cool, dry place.

7.7 Eudragit RLPO20

EUDRAGIT® RL PO is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable.

Physical properties: It is a solid substance in form of white powder with a faint amine-like odor.

7.7.1 Chemical structure:

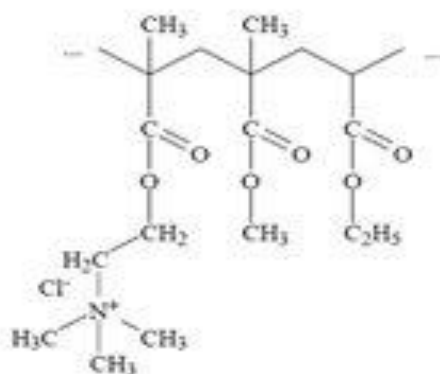


Figure no.7.1.2 structure of Eudragit RLPO

7.7.2 Product Form: Powder

7.7.3 Targeted Drug Release Area: Time controlled release, pH independent

7.7.4 Dissolution:

- Insoluble
- High permeability
- pH independent swelling

7.7.5 Characteristics:

- Customized release profile by combination of RL and RS grades in different ratios
- Suitable for matrix structures.

7.7.6 CAS number: 33434 – 24 – 1

7.7.7 Chemical/IUPAC name: Poly (ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2

7.7.8 INCI name: Acrylates / Ammonium Methacrylate Copolymer

7.7.8 Monographs:

Ph. Eur.: Ammonio Methacrylate Copolymer, Type A

USP/NF: Ammonio Methacrylate Copolymer, Type A - NF

JPE: Aminoalkyl Methacrylate Copolymer RS

7.7.9 GMP standard: The Joint IPEC – PQG Good Manufacturing Practice

Guide for Bulk Pharmaceutical Excipients 2006 and

USP-NF General Chapter <1078>

Weight average molar mass: approx. 32,000 g/mol

Alkali Value: 28, 1 mg KOH/ g polymer

Glass Transition Temperature (T_g): 63°C (+/- 5°C)

8. Materials and Equipments

Drug:-Metformin

Manufactured By: Mylan Laboratories Limited, Aurangabad

Drug: -Glimepiride

Manufactured By: AMRI India PvtLtd,Aurangabad

That were used without further purification and considered as standard drug.

Table No 2:-List of Selected Excipients and Drug.

Sr. No.	Drugs and Excipients	Supplied by
1	Metformin.	Mylan Laboratories Limited, Aurangabad.
2	Glimepiride.	AMRI India PvtLtd,Aurangabad.
3	HPMC K-4M*	Colorcon Asia Pvt.Ltd.,Goa.
4	HPMC K-15M*	Colorcon Asia Pvt.Ltd.,Goa.
5	HPMC K100	Colorcon Asia Pvt.Ltd.,Goa.
6	Eudragit RLPO 100*	Colorcon Asia Pvt.Ltd.,Goa.
7	Lactose. (LR)	Signet Chemicals Corporation, Mumbai.
8	Magnesium stearate (LR)	S.D.Finechemicals,Mumbai.
9	Talc (LR)	S.D.Finechemicals,Mumbai.

LR-Laboratory Reagent

* All the other solvents and reagents used for the study were of Analytical Reagent (AR) grade.

Table No 3. List of Equipments and Instruments used.

Equipments/Instruments	Name of Manufacturer	Model No.
Electronic analytical balance	Schimadzu.	AY 220
Labpresssingal rotatory CompressionMachine.	Labpress Compression Machine.	-
Dissolution Test apparatus	Electrolab TDT	Microprocessor Based
Hardness tester	Monsanto Hardness Tester	-
Bulk density Apparatus(USP)	Popular Service	Microprocessor Based
Friability test apparatus	Roche	-
UV Visible spectrophotometer	Jasco	V630
Digital pH meter	EUTECH Instruments	Eco tester pH1
FTIR	Schimadzu Model-8400S	-

Stability Chamber	CHS-6 Remi India	–
Melting Point Apparatus	Veego	
Hot Air Oven	Labin Instrument.	–

9 Experimental

9.1 Characterization of drug:-

The characterization of drugs were carried out by conducting various physicochemical tests including

- Melting Point Determination.
- Spectrophotometric characterization using :-
 - UV-Visible Spectrophotometry
- Recording thermal behavior by –
 - Differential Scanning Calorimetry (DSC).

9.2 Physical Tests

➤ Colour, Appearance and odour

The sample was observed visually.

- **Determination of melting point:** - Melting point of drugs was determined using glass capillary method. The programmable melting point apparatus (Make –Veego) was used. Precautions were taken to maintain the uniform heating of silicon bath, in which the capillary containing drug was placed.

9.3 Spectral analysis

9.3.1 Spectral analysis of Metformin.

- **Determination of UV Spectrum in Phosphate buffer PH 6.8:-** The stock solution **Metformin** (100 µg/ml) was prepared by dissolving it in Phosphate Buffer PH 6.8. A dilution of 10µg/ml was kept in cuvette of path length 10mm. The UV spectrum was recorded using double beam UV-VIS spectrophotometer in the wavelength range 200 nm - 400nm with Phosphate Buffer as blank.

9.3.2 Spectral analysis of Glimepiride.

- **Determination of UV spectrum in Phosphate buffer PH 6.8 :-** The stock solution of **Glimepiride** (100 µg/ml) was prepared by dissolving 10 mg of drug in 0.1N phosphate buffer PH 6.8 and final volume was made to 100 ml. A dilution of 10µg/ml was kept in cuvette of path length 10mm. The UV Spectrum was recorded using double beam UV-VIS spectrophotometer in the wavelength range 200 nm - 400nm with Phosphate Buffer PH 6.8 as blank.

9.3.3 Preparation of standard curve of Metformin.

- **Preparation of Standard Curve in Phosphate Buffer PH 6.8 :-** A stock solution of Metformin (100 µg/ml) was prepared by dissolving 10mg of drug in Phosphate buffer PH 6.8 and final volume was made to 100 ml. The solutions in concentration range of 5-25 µg/ml were prepared by appropriate dilutions of stock solution. The UV absorbance of these solutions was determined spectrophotometrically at λ_{max} 240 nm.

9.3.4 Preparation of standard curve of Glimepiride.

- **Preparation of Standard Curve in Phosphate Buffer PH 6.8:-** A stock solution of Glimepiride (100 µg/ml) was prepared by dissolving 10 mg of drug in Phosphate Buffer and final volume was made to 100 ml. The solutions in concentration range of 5-25 µg/ml were prepared by appropriate dilutions of stock solution. The UV absorbance of these solutions was determined spectrophotometrically at λ_{max} 225 nm.

9.4 Overlain Spectra:-

The 10 µg/ml solutions of Metformin and Glimepiride were prepared separately in Phosphate Buffer PH 6.8. The 10 µg/ml solution was kept in spectrophotometer and spectrum was recorded in spectrum mode. The overlain spectrum of 10 µg/ml solution of Glimepiride over Metformin spectrum was recorded. The absorbance of Metformin at 240 nm and Glimepiride at 225 nm was also recorded.

9.5 Infrared spectrum:-

The infrared spectrums of Metformin, Glimepiride were recorded by Potassium bromide dispersion technique using FTIR with diffuse reflectance attachment (FTIR - 8400s). The 1-2 mg of drug sample was kept and IR spectrum was recorded.

9.6 Differential Scanning Calorimetry:-

Differential scanning calorimetry (DSC) is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference are measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.

9.7 Formulation development

Selection of Drugs: - Metformin (400mg) and Glimepiride(1mg) in combination was selected for the formulation of Inlay Tablet.

Selection of Polymers: - The Methocel polymers were selected for controlled release formulations. These polymers form highly viscous gel in contact with fluids that controls drug release from formulation. They are nonionic in nature. The different viscosity

grades of Methocel were chosen for formulations of Inlay Tablet such as Methocel K4M and Methocel K100. Eudragit RLPO also used for controlled release formulation.

Selection of Excipients: - Apart from drug and polymer certain excipients such as diluents and lubricants are used in tablet formulations. Therefore, lactose as diluent,

Talc as Guidant and Magnesium stearate as lubricants were selected.

9.8 Formulation composition:-

Table no 4. Formulation composition of outer layer (cup) tablet of Metformin (SR) tablet:-

Sr.No.	Ingredients	O-1	O-2	O-3	O-4	O-5	O-6
1	Metformin	400	400	400	400	400	400
2	HPMC K100	5	5	5	10	10	10
3	HPMC K4M	5	7.5	10	5	7.5	10
4	Lactose	87	84.5	82	82	79.5	77
5	Magnesium Stearate	2	2	2	2	22	2
6	Talc	1	1	1	1	1	1

➤ Quantity in mg/Tab

Table no 5. Formulation composition of inner layer (core) tablet of Glimpiride (SR) tablet:-

Sr.No.	Ingredients	I-1	I-2	I-3	I-4	I-5	I-6
1	Glimpiride	1	1	1	1	1	1
2	Eudragit RLPO	5	5	5	7.5	7.5	7.5
3	HPMC K4M	5	7.5	10	5	7.5	10
4	Lactose	86	83.5	81	83.5	81	78.5
	Color	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
5	Magnesium Stearate	2	2	2	2	2	2
6	Talc	1	1	1	1	1	1

➤ Quantity in mg/Tab

9.9 The preparation of granules:- Two different types of powder blends were prepared.

9.9.1 Preparation of granules of Metformin (SR) (by wet granulation):-

All the polymers and drugs were passed through stainless steel sieve (mesh no 100) to break the lumps and aggregates. Drugs and Methocel (K100M, K4M) were accurately weighed and blended thoroughly using glass mortar and pestle manually with isopropyl alcohol in geometric proportion. Lactose was added to the above blend. The powder blends were passed through sieve (mesh no.12) then dried at room temperature for 15 minutes, Talc and magnesium stearate were added in to granules and evaluated for the properties such as loose bulk density, tapped bulk density, compressibility index and angle of repose.

9.9.2 Preparation of Glimpiride (SR) (by direct compression method):

The formula included variable amounts of Polymer (HPMC K4M, Eudragit RLPO) and other excipients are shown in Table Glimpiride drug per tablet were taken and then mixed with directly compressible diluents in a plastic container. Magnesium stearate and Talc was passing through sieve no. 100, mixed and blended with the initial mixture in the plastic container followed by compression of the blend. Compression was performed on an 8 station Lab press tablet compression machine.

9.10 Compression of granules into tablets:-

Granules were prepared and compressed on Lab press single rotator 8 station compression machines in two steps.

Step1: Preparation of core tablet: Firstly Glimpiride(SR) prepared granulates are compressed on Lab press single rotator 8 station compression machine by using 5mm punch and dies.

Step 2: Preparation of Inlay Tablet: Metformin (SR) prepared granules are filling in dies (10mm) cavity. Above prepared Core tablet is placed on it by surrounding Metformin granules with upper surface of core tablet are exposed. Finally compressed on Lab press single rotator 8 station compression machines by using 10mm punches.

9.11 Evaluation of precompression parameters^{21, 22, 23, and 24}:-

9.11.1 Angle of repose ²¹

The angle of repose, which signifies the flow properties of powder blends, was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of powder. The powders were allowed to flow through the funnel freely onto a clean surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:-

$$\tan \theta = h/r$$

k Where h is the height of powder cone and r is the radius of the powder cone.

Relationship between angle of repose (θ) and flow ability.

Angle of repose (θ)	Flow ability
< 20	Excellent
20-30	Good
30-34	Passable
> 40	Very poor

Table no 6. Relationship between angle of repose (θ) and flow ability

9.11.2 Bulk density²²

Both loose bulk density (LBD) and tapped bulk density (TBD) of powder blends were determined. A weighed amount of powder from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. It was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 to 3 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulae.

LBD = Weight of the powder/Volume of the packing

TBD = Weight of the powder/Tapped volume of the packing

9.11.3 Carr's Compressibility Index²³

An important measure that can be obtained from bulk density determinations is the percent compressibility C, which is defined as follows

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

9.11.4 Hausner ratio²⁴

Hausner ratio = Tapped density/Bulk density

Relationship between % compressibility and flow ability is as follows:

% Compressibility	Flow ability	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
≥ 40	Very very poor	≥ 1.6

Table no 7. Hausner ratio

9.12 Evaluation of post compression parameter of Inlay tablets:-

- 1) Appearance.
- 2) Thickness.
- 3) Hardness.
- 4) Weight variation test.
- 5) Drug Content.
- 6) In vitro drug release kinetics.
- 7) Friability test

9.12.1 Appearance:-Shape and color of tablets:-Uncoated tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light

9.12.2 Thickness²³:- The thickness of the tablet was determined using a Vernier Calliper. Three tablets from each type of formulations were used and average values were calculated.

9.12.3 Tablet Hardness²³:- The resistance of tablets to breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 3 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm². Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm².

9.12.4 Weight variation test²³:- For weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Specifications as per Indian Pharmacopoeia

Sr.No.	Average weight of tablet	% Deviation
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

9.12.6 Drug Content

9.12.6.1 Drug Content of Metformin¹⁴:- From each batch 2 tablets each containing 500 mg of Metformin were weighed and taken for the test. Tablets were triturated in mortar and quantity of powder equivalent to 10 mg Metformin was transferred to 100 ml volumetric flask. Sufficient quantity of Methanol was added with shaking and volume was made upto the mark and filtered through whatman filter paper no.41. Further dilutions were made in triplicate and the absorbance was recorded at 240nm against Methanol as a blank.

9.12.6.2 Drug Content of Glimepiride¹⁴:- From each batch 2 tablets were weighed each containing 1mg of Glimepiride was taken. Tablets were triturated in mortar and quantity of powder equivalent to 10 mg of Glimepiride was transferred to 100 ml volumetric flask. Sufficient quantity of dist. water was added with shaking and volume was made upto the mark and filtered through whatman filter paper no.41. Further dilutions were made in triplicate and the absorbance was recorded at 225 nm against dist. Water as a blank.

9.13 Dissolution studies²⁵**➤ In vitro dissolution of Metformin and Glimepiride tablets:-**

The study was carried out using dissolution apparatus USP Type II (Paddle)

Dissolution medium: 0.1 N HCl in 2Hr. After Phosphate Buffer PH 6.8.

Speed of paddle: 50 rpm.

Temperature of medium: $37 \pm 0.5^{\circ}\text{C}$

The release rate of Metformin and Glimepiride Inlay tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl in 2Hr. After 2Hr. using phosphate buffer PH6.8, at $37 \pm 0.5^{\circ}\text{C}$ and speed of 50 rpm. Aliquot (5 ml) of the solution was collected from the dissolution apparatus hourly for 12 hours and were replaced with fresh dissolution medium. The aliquots were filtered through whatman filter paper no. 41. Absorbance of these solutions was recorded at 240nm (Metformin) and 225nm (Glimepiride) in photometric mode for single drug and in multicomponent mode analysis for combined drugs. Aliquots were withdrawn at one hour interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Drug content in dissolution sample was determined by software (PCP disso v3) version.

9.14 Differential Scanning Calorimeter of optimized formulation:-

The differential calorimetric scanning of optimized formulation was carried out using Differential Scanning Calorimeter

9.15 Stability study²⁶:

ICH recommends carrying out stress testing on the drug substance to establish its inherent stability characteristic and to support the suitability of the proposed analytical procedure. It is also required that analytical methods should be validated to demonstrate that impurities unique to the new drug substance do not interfere with or are separated from specified and unspecified degradation products in the drug product. The drug should be subjected to forced degradation and assayed to detect the presence of degradants. This data is then useful while carrying out the assay of stability batch drug products to identify the degradation if any.

Stability study at room temperature is the surest method of determining the actual shelf life of product. Unfortunately it is difficult to make an accurate expiration date prediction until 2-3 years of data are generated, which will require long shelf life studies to be carried out at actual shelf life conditions. Hence accelerated stability studies are carried out at elevated temperatures will help to determine shelf life within a lesser period of time.

ICH Q1A (R2) stability guidelines

Stability study storage conditions-General case Study	Storage condition	Minimum time period covered by data at submission
Long term	$25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$	30 day
Intermediate	$30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$	60 day
Accelerated	$40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$	90 day

Preparation of stability study batch

Tablets obtained from optimized batch i.e. **O-6** and **I-6** was subjected to the stability testing. The tablets were packed in 40 cc high density polyethylene bottle (HDPE) and exposed to 40°C/75% RH in stability chambers (Neutr onics) for three months. During the stability storage period the tablets were evaluated for Physical characteristics, in vitro drug release and drug content (UV assay) at the end of 30 days, 60 days and 90 days of storage period.

The tablets were evaluated for various parameters like physical appearance, weight variation, % Drug content and in vitro dissolution study.

10. RESULT AND DISCUSSION:-

10.1.1. Identification of pure drug Metformin:

The IR spectrum of pure drug was found to be similar to the standard spectrum of Metformin. The spectrum of the Metformin shows the following functional groups at their frequencies.

- IR spectra of Metformin API:-**

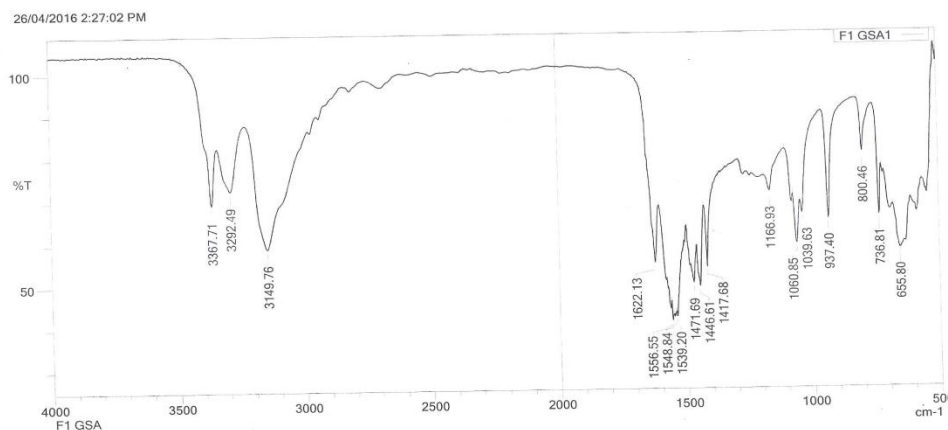


Figure no. 10.1.1.1: IR spectra Metformin API

- IR spectra of Metformin + Excipients:-**

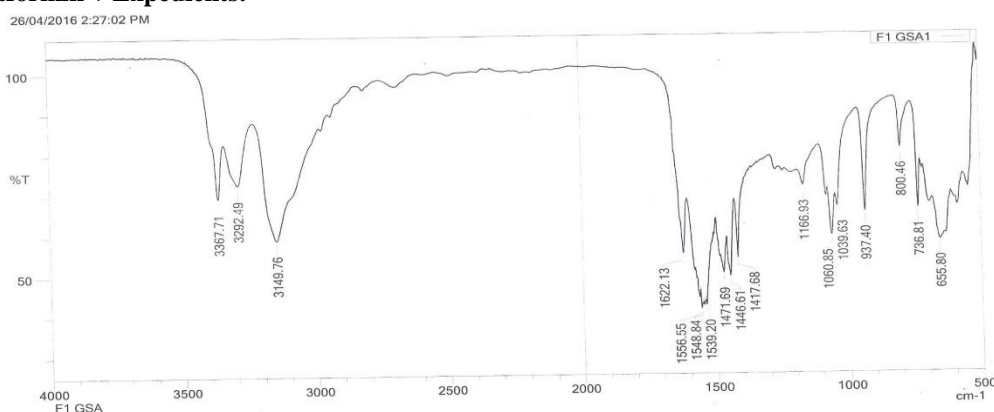


Figure no.10.1.1.2 IR spectra of Metformin+ Excipients

FTIR spectrum of Metformin +excipients. It indicate the absence of any interaction between drug and excipients used in the preparation, as there was no considerable change in characteristic bands for functions such as N-H,C=N,N-CH₃,C-N .

Functional Group	Wave number (cm ⁻¹)	
	API	API+Excipients
C-N.	1060cm ⁻¹	1039 cm ⁻¹
C=N	1446 cm ⁻¹	1060 cm ⁻¹
N-CH ₃ .	1622 cm ⁻¹	1471 cm ⁻¹
N-H	3149 cm ⁻¹	1548 cm ⁻¹
N-H stretch	3292 cm ⁻¹	3149 cm ⁻¹

Table no:8 IR interpretation of Metformin

10.1.2. Identification of pure drug of Glimepiride:

The IR spectrum of pure drug was found to be similar to the standard spectrum of Glimepiride. The spectrum of the Glimepiride shows the following functional groups at their frequencies.

- IR spectra of Glimepiride API:-**

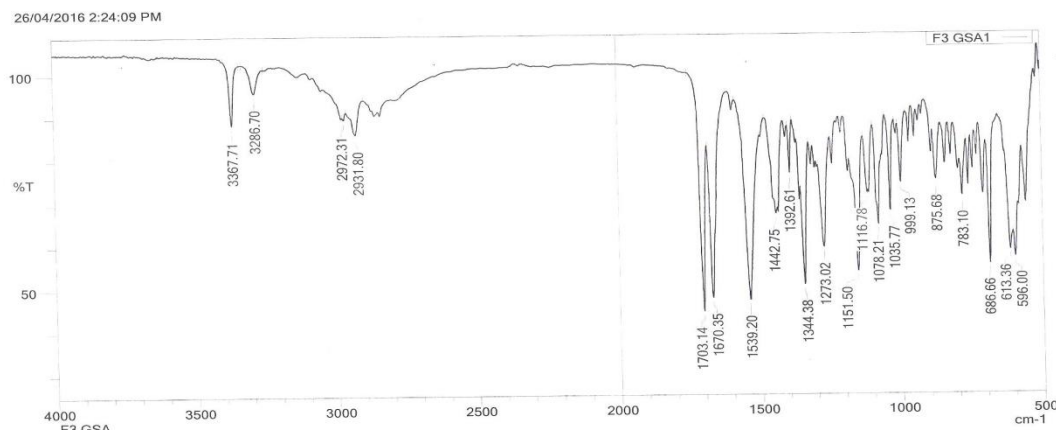


Figure no.10.1.2.1 IR spectra of Glimepiride API

- IR spectra of Glimepiride+Excipients**

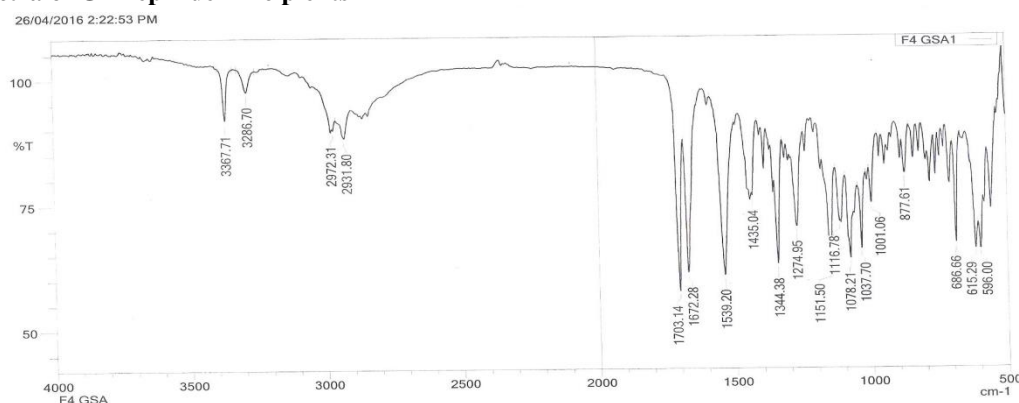


Figure no.10.1.2.2 IR spectra of Glimepiride + Excipients

FTIR spectrum of glimepiride and glimepiride+excipients. It indicates the absence of any interaction between drug and excipients used in the preparation, as there was no considerable change in characteristic bands for functions such as S=O, -CH, C=C, C=N, aromatic groups.

Functional Group	Wave number (cm ⁻¹)	
	API	API+ Excipients
S=O	1035	11001.70
C=C	1539	1078
C-H bend	1703	1151
N-H	2931	1344
C=O	3367	2931

Table no: 9 IR interpretation of Glimepiride

10.1.3. Solubility study of Glimepiride:

Sr.No.	Name of solvent	Solubility
1	Water	Freely soluble(50mg/ml)
2	Methanol	soluble(>24mg/ml)
3	Ethanol	soluble(35mg/ml)
4	PhosphaetBuffer PH 6.8	Slightly soluble(6mg/ml)

Table No.10. Solubility study of Metformin

10.1.4. Solubility study of Glimepiride:

Glimepiride is soluble in methanol, chloroform, water, ethyl acetate.

10.1.5. Melting point determination of Metformin:

The melting point of Metformin was found to be in the range of 224°C to value as reported in literature, thus indicating purity of the drug sample. Any impurity, if present, will cause variation in the melting point of a given drug substance.

10.1.6. Melting point determination of Glimepiride:

The melting point of Glimepiride was found to be in the range of 213°C to value as reported in literature, thus indicating purity of the drug sample. Any impurity, if present, will cause variation in the melting point of a given drug substance.

10.1.7. Differential scanning calorimetry of Metformin:

Differential Scanning Calorimetry (DSC) is a thermo analytical technique used for analyzing thermal transitions involving thermal energy with a great sensitivity. DSC of API is compared with DSC of API + excipients.

• **DSC of Metformin API:-**

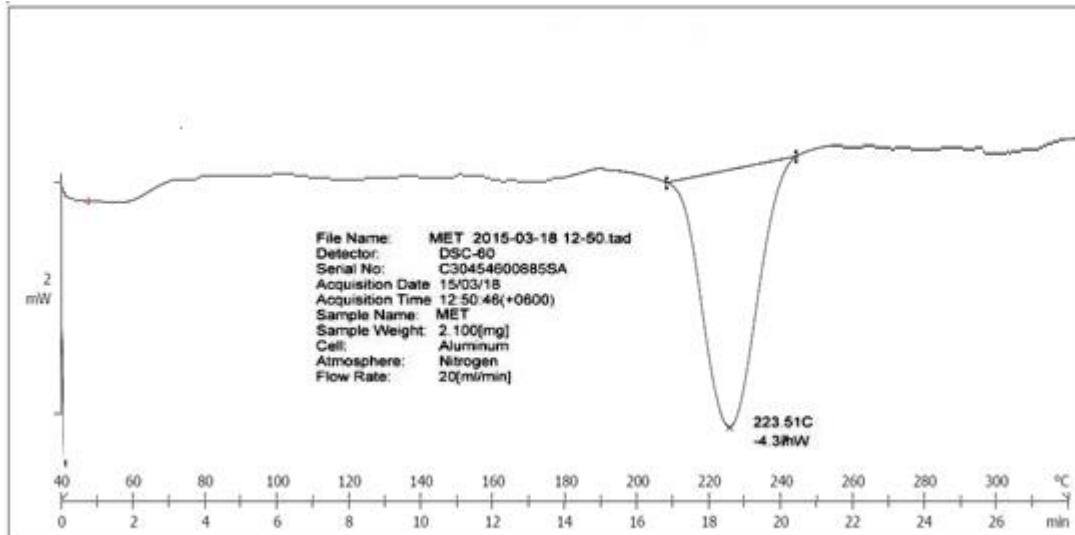


Figure no. 10.1.7.1 DSC Metformin API

• **DSC of Metformin+ Excipients:-**

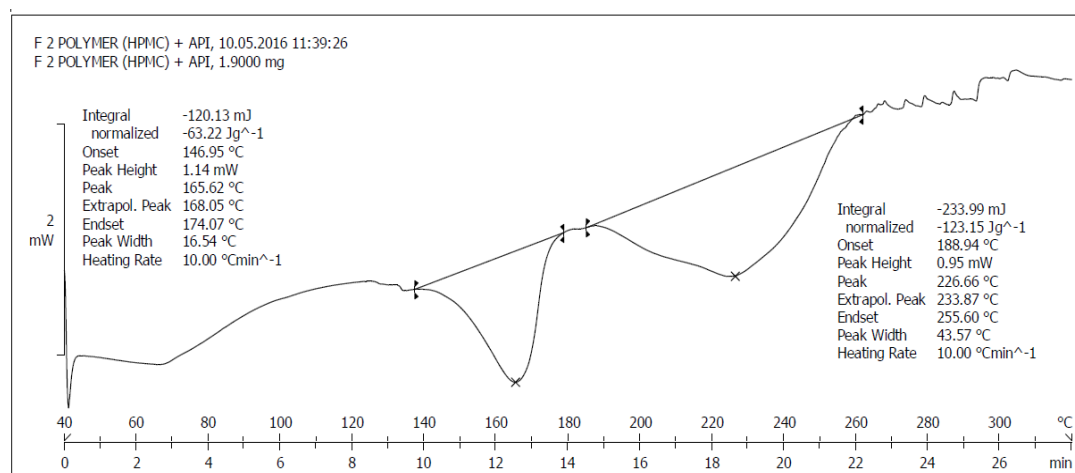


Figure no. 10.1.7.2 DSC of Metformin+ Excipients

The DSC thermogram shows the endothermic peak of API at 140°C and 224°C of Metformin+ excipients and formulation respectively indicated the melting point which was reported in literature. There was no sharp change in melting point of drug. Thus there was no significant interaction between the drug, and polymer. (Figure No 10.1.7.1 and 10.1.7.2)

10.1.8. Differential scanning calorimetry of Glimepiride:

Differential Scanning Calorimetry (DSC) is a thermo analytical technique used for analyzing thermal transitions involving thermal energy with a great sensitivity. DSC of API is compared with DSC of API + excipients.

• **DSC of Glimepiride API:-**

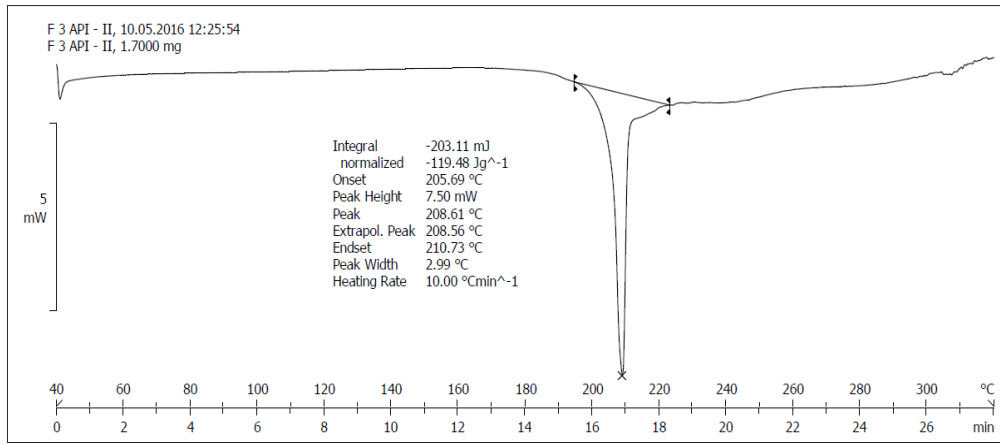


Figure no. 10.1.8.1 DSC of Glimepiride API

DSC of Glimepiride + Excipients:-

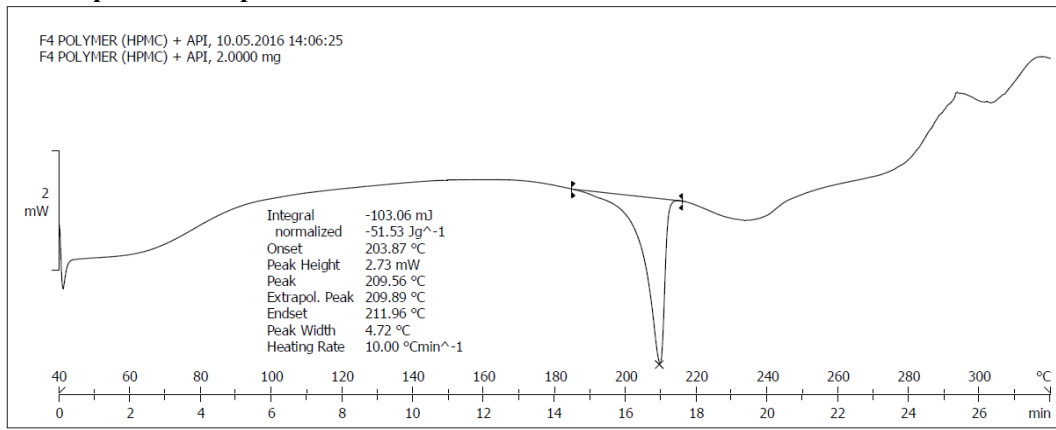


Figure no. 10.1.8.2 DSC of Glimepiride + Excipients

The DSC thermo gram shows the exothermic peak of API at 147°C and 213°C of Glimepiride + excipients and formulation respectively indicated the melting point which was reported in literature. There was no sharp change in melting point of drug. Thus there was no significant interaction between the drug, and polymer. (Figure No. 10.1.8.1 and 10.1.8.2)

10.1.9. Compatibility studies:-

From the spectra of pure drug and the combination of drug with excipients, it was observed that the entire characteristic peaks of were present in the combination spectrum, thus indicating compatibility of the drug and excipients. On the basis of IR spectra and DCS study of the pure drug and in combination with the excipients are shown the compatibility.

10.1.10 Ultraviolet Absorbance spectrum:-

I) Standard Calibration Of Metformin

i) Scanning of Metformin:-

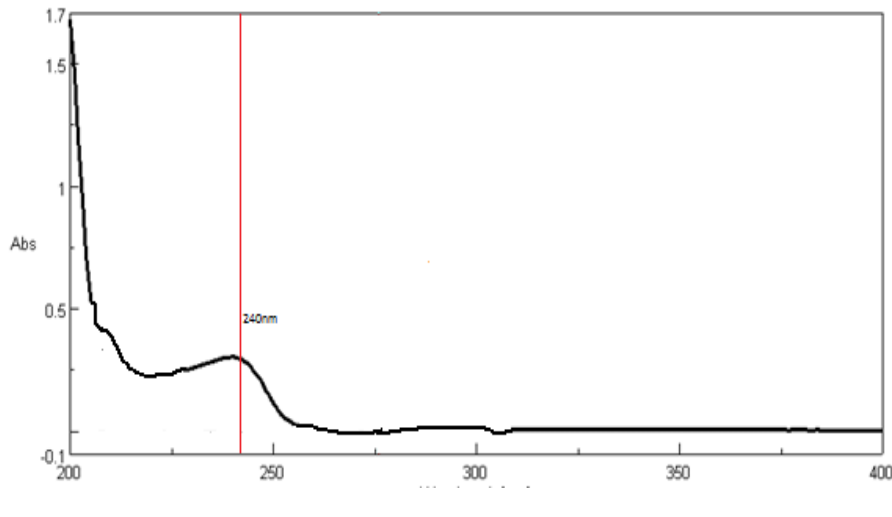
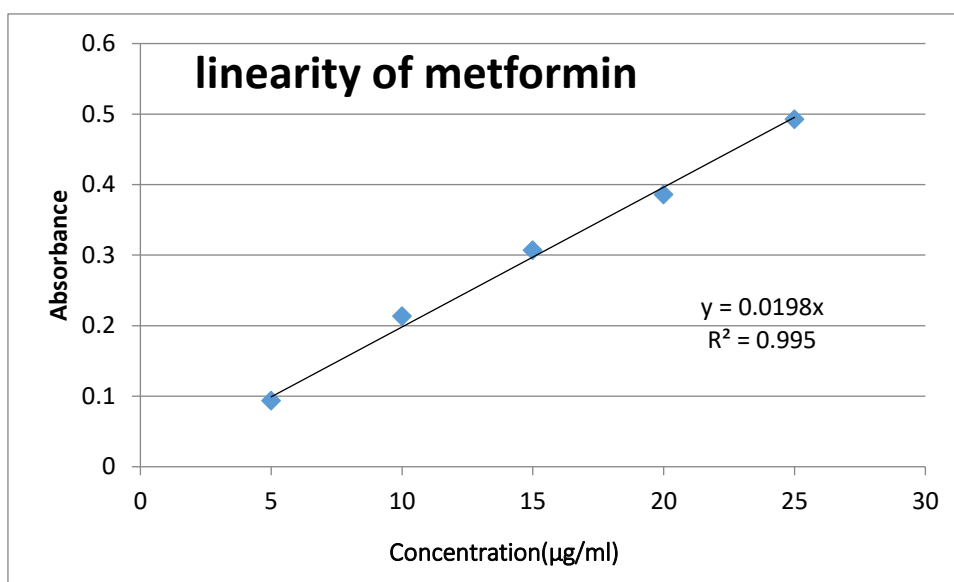


Figure No.10.1.10.1:- UV absorption spectrum of Metformin

Phosphate buffer PH6.8**ii) Absorbencies obtained for various concentrations of Metforminin Phosphate buffer PH6.8**

Sr.No	Conc. (µg/ml)	Absorbance at 240nm
1	0	0
2	5	0.0939
3	10	0.2135
4	15	0.3070
5	20	0.3860
6	25	0.4927

Table no:11 Absorbance obtained of various conc.(Met)**Table No.10.1.10.1:-Absorbencies obtained for various concentrations of MetforminPhosphate buffer PH6.8****Figure No.10.1.10.2:- Standard curve for Metformin PH6.8**

UV absorption spectrum of Metforminphosphate buffer PH6.8 showed λ max at 240nm (Figure No.10.1.10.1). Absorbance obtained for various concentrations of Metforminin phosphate buffer PH6.8 are given in (Table No.10.1.10.1) The graph of absorbance vs. concentration for Metformin was found to be linear in the concentration range of 5 – 25 mcg/ml (Figure No.10.1.10.2). The drug obeys Beer - Lambert's law in the range of 5 – 25 mcg/ml.

Solvent	Phosphate Buffer
λ max	240
R^2	0.995
Equation (Y= mx +c)	Y=0.019x

Table No.12:-Linear regression analysis parameters for standard curves of Metformin.**II) Standard Calibration of Glimepiride****i) Scanning of Glimepiride:-**

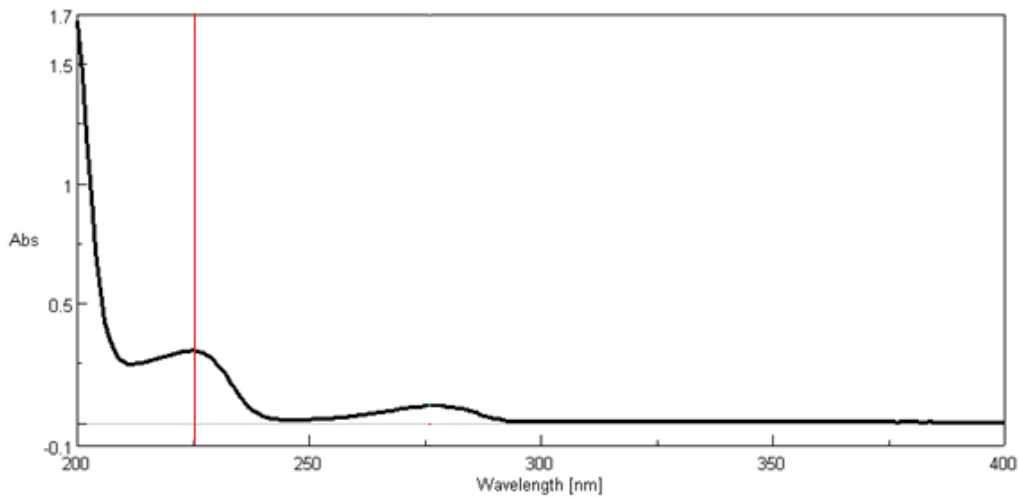


Figure No.10.1.10.3:- UV absorption spectrum of Glimepiride in phosphate buffer pH6.8.

ii) Absorbance's obtained for various concentrations of Glimepiride in Phosphate buffer pH6.8

Sr.No.	Conc.(µg/ml)	Absorbance at 225nm
1	0	0
2	5	0.2526
3	10	0.466
4	15	0.7034
5	20	0.9755
6	25	1.184

Table No.13:- Absorbance's obtained at various concentrations of (Glime)

• Glimepiride in Phosphate buffer pH6.8

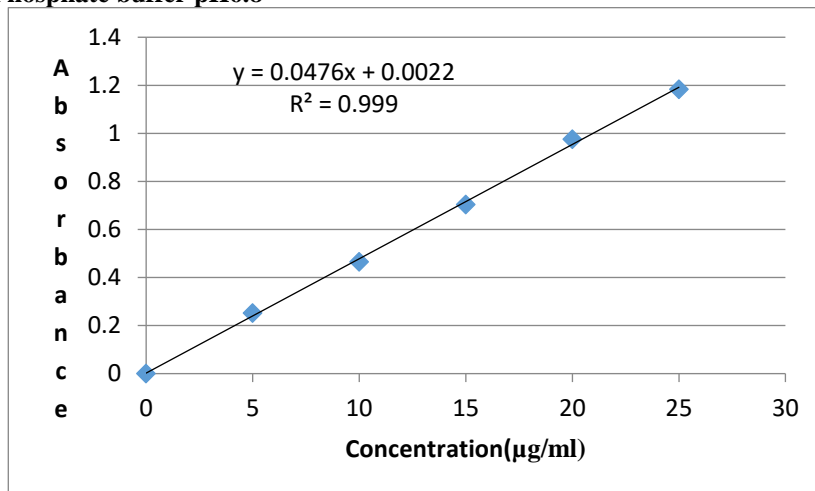


Figure No.10.1.10.4:- Standard curve of odium in Phosphate Buffer 6.8.

UV absorption spectrum of Glimepiride in phosphate buffer PH6.8 showed λ max at 225nm (Figure No.18). Absorbance's obtained at various concentrations of Glimepiride in phosphate buffer PH6.8 are given in Table No.9. The graph of absorbance vs. concentration for cinnarizine was found to be linear in the concentration range of 5 – 25 mcg/ml (Figure No.19). The drug obeys beer - lambert's law in the range of 5 – 25 mcg/ml.

Solvent	Phosphate Buffer
λ max	225
R^2	0.999
Equation (Y= mx +c)	Y=0.047x

Table No.14:-Linear regression analysis parameters for standard curves of Glimepiride.

10.2 Formulation and Development:

10.2.1 Evaluation of Precompression parametersof Metformin:-

Table No.15:- Evaluation of granules of formulation containing different amount of HPMC K4M and K100.

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Index (%)	Angle Of Repose (°)
O-1	0.65±0.07	0.76±0.05	1.16±0.09	15.54±0.06	24.22±0.51
O-2	0.66±0.05	0.75±0.03	1.13±0.06	15.43±0.05	25.15±0.43
O-3	0.62±0.03	0.70±0.06	1.12±0.03	17.4±0.02	28.45±0.61
O-4	0.61±0.04	0.75±0.02	1.19±0.07	16.55±0.06	27.57±0.55
O-5	0.65±0.03	0.78±0.03	1.12±0.03	17.21±0.04	24.15±0.32
O-6	0.62±0.02	0.72±0.07	1.16±0.05	11.59±0.06	25.03±0.65

The values of bulk density and tapped density were found in the range from 0.61 to 0.66 g/ml and from 0.72 to 0.78 g/ml respectively. The Carr's Compressibility indices were in the range of 11.59 to 17.4% and angle of repose was in the range of 24.22 to 28.45 °. This indicates that formulations have good flow property

10.2.2 Evaluation of Precompression parameters of Glimepiride:-

Table No.16:- Evaluation of Granules of formulations containing different amounts of Eudragit RLPO and HPMC K4M

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Index	Angle Of Repose
I-1	0.55±0.03	0.82±0.04	1.09±0.09	8.53±0.06	28.12±0.45
I-2	0.53±0.01	0.80±0.01	1.09±0.06	8.75±0.03	27.02±0.41
I-3	0.50±0.04	0.77±0.01	1.10±0.03	9.09±0.04	29.9±0.58
I-4	0.57±0.01	0.83±0.02	1.11±0.07	7.22±0.05	27.8±0.55
I-5	0.55±0.03	0.74±0.09	1.13±0.03	12.16±0.04	26.12±0.36
I-6	0.57±0.05	0.81±0.02	1.09±0.05	8.90±0.06	29.12±0.58

The values of bulk density and tapped density were found in the range from 0.50 to 0.57 g/ml and from 0.74 to 0.83 g/ml respectively. The Carr's Compressibility indices were in the range of 7.22 to 9.09% and angle of repose was in the range of 26.12 to 29.9 °. This indicates that formulations have good flow property

10.2.3 Evaluation Parameters for Post-compression parameters of Metformin (cup) and Glimepiride (core) Inlay Tablet:-

All the tablet formulations were subjected for evaluation according to various official specifications and other parameters. Shape, thickness, hardness, friability, weight variation, drug content, in vitro dissolution studies, model fitting of release profile and stability studies were carried out.

I. Shape and color of tablets:

Randomly picked tablets from each formulation batch examined under lens for shape and color in presence of light. All tablets of all the batches showed circular in shape. Brownish in color in middle core tablet and surrounded by white in color cup tablet.

II. Uniformity of thickness:

The thickness of the tablets was measured by using vernier caliper by picking the tablets randomly. The mean values are shown in Table 10.2.3.1. The values are almost uniform in all formulations. Thickness was found in the range of 5.01 mm to 5.3 mm respectively.

III. Hardness test:

Table No. 10.2.3.1 shows results obtained for all the formulation of hardness. Hardness test was performed by Monsanto hardness tester. Hardness was found to be within 6 kg/cm², as these tablets are sustained released. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness.

IV. Friability test:

The study results are tabulated in Table No. 10.2.3.1, was found well within the approved range (<1%) in all the formulations. Formulation D1 to D4 possesses good mechanical strength.

V. Weight variation test:

The percentage weight variation for all the formulation is tabulated in Table No10.2.3.1. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeias limits of not more than 7.5%. It was found to be from 499±5to 504±5mg. The weight of all the tablets was found to be uniform.

VI. % Drug content uniformity:

The content uniformity was performed for all the fore formulations and results are shown in Table No 10.2.3.1. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 97.2% to 99.25% of Glimepiride. The results indicated that in all the formulations the drug content was small changes in between fore formulations. The cumulative percentage drug released by each tablet in the in vitro release studies were based on the mean content of the drug present in the respective tablet.

Batch	Wt. Variation(mg)	Hardness (kg/cm ²)	Friability (%)	Thickness (mm)	%Drug Content Met.	%drug Content Glime.
O-1 & I-1	602±5	6.6	0.34	5.01	99.07	98.01
O-2 & I-2	599±5	6.8	0.57	5.2	99.01	97.2
O-3 & I-3	604±5	6.2	0.47	5.1	99	98.15
O-4 & I-4	600±5	6	0.29	5.3	98.01	99.25
O-5 & I-5	602±5	6.4	0.30	5.1	99.12	98.35
O-6 & I-6	601±5	6.2	0.28	5.2	98.17	97.50

Table17 Evaluation Parameters for Post-compression parameters of (cup) and Glimepiride (core) Inlay Tablet:

10.3 In vitro dissolution studies of Metformin SR (cup) and Glimepiride SR (core) Inlay tablet:

All the fore formulations were subjected for the in vitro dissolution studies using tablet dissolution tester USP II. The samples were withdrawn at different time intervals and analyzed at 240nm and 225nm for Metformin and Glimepiride respectively. Cumulative drug release and cumulative % drug retained were calculated on the basis of mean amount of Metformin and Glimepiride in tablet.

10.3.1 In vitro dissolution studies of MetforminSR tablet:

The results obtained in the in vitro drug release for the formulations O-1 to O-6 are tabulated in Table 10.3.1.1 to figure no.10.3.1.1.

Here in all batch of O-1 to O-6 the dissolution rate was found to variable with different concentration of polymer. It's showed in Table 10.3.1.1 to Table 10.3.1.2 this was increase time of drug release values for tablet formulation containing higher proportions of sustained released polymer i.e. HPMC K4M, K100 in MetforminSR (cup) tablet. In all formulation the drug release was nearer to 100% within 12 Hrs. O-6 prepared by wet granulation compression method for preparation of MetforminSR (cup) tablet showed good drug release (97.5%) than other formulation.

Time in Hr.	% Drug release					
	O-1	O-2	O-3	O-4	O-5	O-6
1	10.683	15.933	7.965	10.629	15.413	5.23
2	21.347	22.237	13.046	17.262	21.979	18.69
3	26.52	32.447	20.849	23.412	33.84	24.75
4	36.442	38.346	27.474	30.26	39.81	30.83
5	48.639	44.257	31.806	39.988	47.836	38.32
6	54.649	48.244	38.587	47.688	55.459	46.10
7	62.456	52.227	43.689	51.832	63.581	54.63
8	76.251	56.363	44.718	56.839	71.488	61.48
9	80.258	60.265	50.563	63.566	81.129	73.58
10	86.325	64.512	56.733	67.822	94.891	84.36

11	90.324	66.859	71.264	76.747		90.89
12	96.236	70.212	78.741	81.42		97.51

*n=3 Table No.18. In-vitro % drug release of all formulation of Metformin

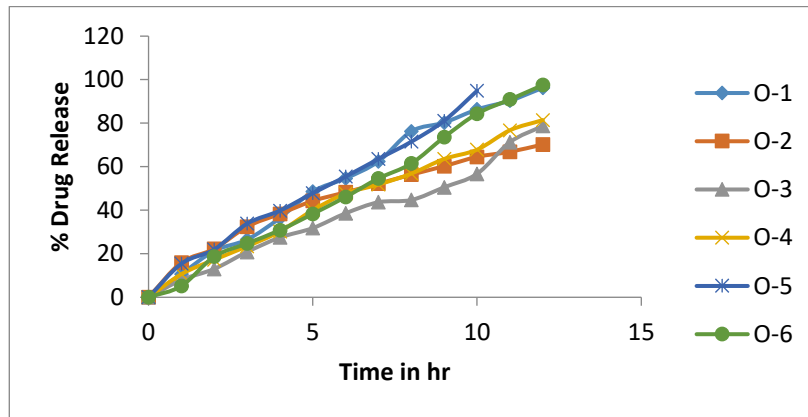


Figure No.10.3.1.1. In-vitro % drug release of formulations

• **Release kinetics and mechanism:**

To know the release mechanism and kinetics of Metformin optimized formulations (O-6) were attempted to fit into mathematical models and, R2 values for zero order, first order, matrix Korsmeyer- Peppas and Hixon- Crowel models were represented in table no.10.3.1.2

• **Model Fitting (Average)-**

Model name	R	K
Zero order	0.9977	8.1143
1st order	0.8450	-0.1956
Matrix	0.9202	22.9226
Peppas	0.9954	8.6586
Hix.Crow.	0.9303	-0.0451

Table No.19 In-vitro Drug Release Kinetics of O-6 formulation

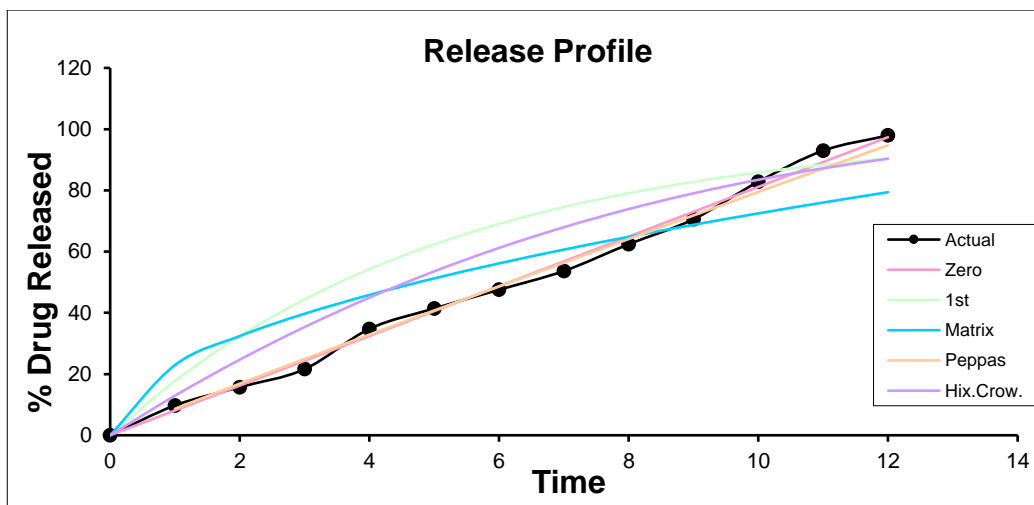


Figure no.10.3.1.2. In-vitro Drug Release Kinetics of O-6 formulation

10.3.2. In vitro dissolution studies of Glimepiride SR (core) tablet:

All the fore formulations were subjected for the in vitro dissolution studies using tablet dissolution tester USP II. The samples were withdrawn at different time intervals and analyzed at 225 nm. Cumulative drug release and cumulative % drug retained were calculated on the basis of mean amount of Glimepiride present in the respective tablet. The results obtained in the in vitro drug

release for the formulations I-1 to I-6 are tabulated in Table 10.3.2.1 and figure no.10.3.2.1.

Formulation I-1 to I-6 prepared by direct compression method was found to be drug release in the range of 89.43% to 99.77%. Here in all batch of I-1 to I-6 the dissolution rate was found to increase linearly with increasing concentration of polymer. It's showed in Table 10.3.2.1. This was decrease time of drug release values for tablet formulation containing higher concentration sustain release polymer i.e. Eudragit RLPO, HPMC K4M. In all formulation the drug release was nearer to 100% within 12Hr. I-6 prepared by direct compression method showed good drug release (97.707%) than other formulation.

Time in Hr.	% Drug release					
	I-1	I-2	I-3	I-4	I-5	I-6
1	38.69	35.26	15.89	12.54	10.02	4.680
2	50.37	48.12	31.56	24.33	20.23	18.283
3	75.37	67.42	42.76	37.26	31.44	25.839
4	99.86	76.33	59.08	43.89	42.59	34.321
5		82.65	64.96	57.23	56.39	39.396
6		93.46	70.53	67.02	62.47	46.040
7			76.38	78.92	69.87	54.456
8			81.23	88.57	76.51	62.862
9			89.33	96.25	81.36	72.763
10			93.45		87.43	84.764
11					92.61	89.959
12						97.707

Table No. 20. Invitro% drug release of all formulation of Glimepiride SR (core) tablet.

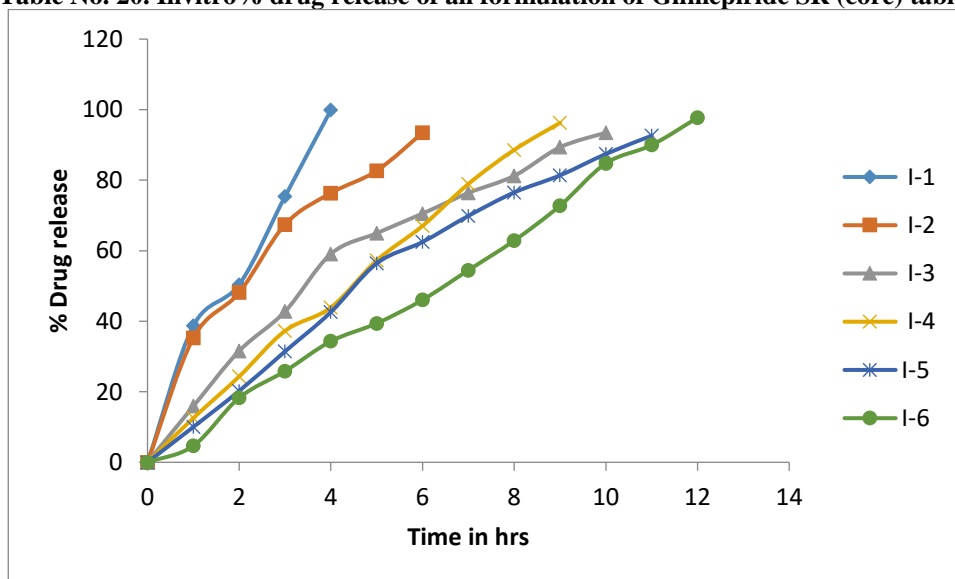


Figure No.10.3.2.1. Invitro% drug release of all formulation of Glimepiride tablet.

• **Release kinetics and mechanism:**

To know the release mechanism and kinetics of Glimepiride optimized formulations (I-6) were attempted to fit into mathematical models and, R2 values for zero order, first order, matrix Korsmeyer- Peppas and Hixon-Crowel models were represented in table no.10.3.2.2.

Model Fitting (Average)-

Model Name	R	k
Zero order	0.9978	8.1198
1st order	0.8569	-0.1905

Matrix	0.9221	22.9466
Peppas	0.9859	6.4118
Hix.Crow.	0.9387	-0.0446

Table No.21.In-vitro Drug Release Kinetics of I-6 formulation

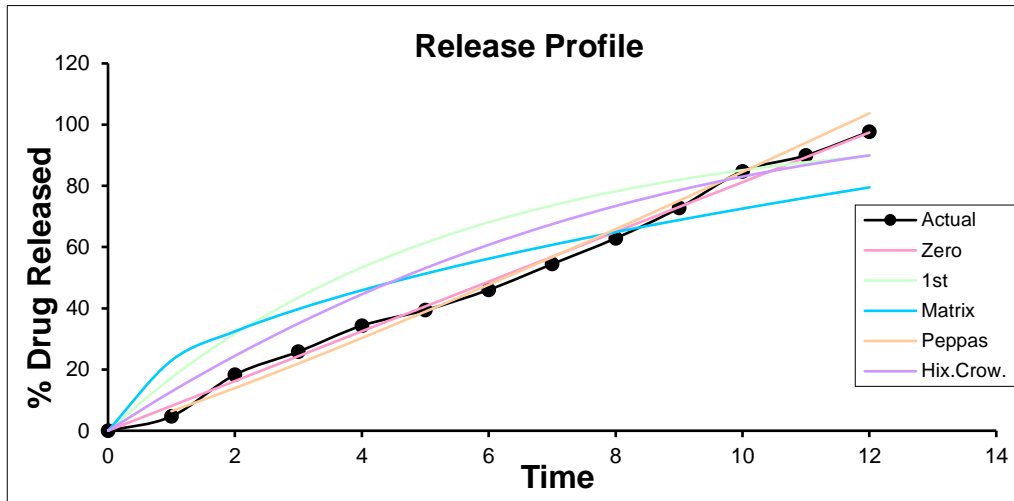


Figure no.10.3.2.2In-vitro Drug Release Kinetics of I-6 formulation

10.4 FTIR Of Optimize Batchof Inlay Tablet:-

The peaks present in IR spectra of Inlay tablet formulation are clearly seen in the IR spectra of API with minor shifts. It indicates that there was no interaction between the drug and polymer.

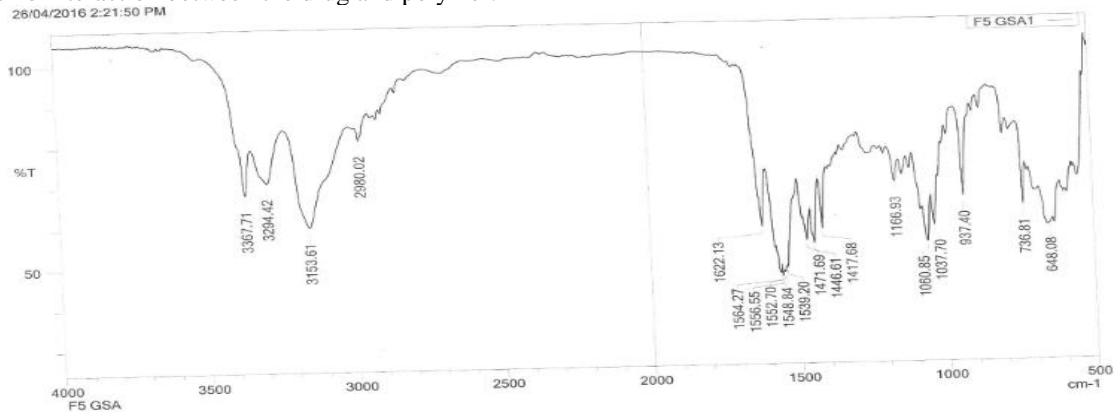


Fig.No.10.3.2.3 FTIR spectra of Inlay Tablet.

10.5 DSC of Optimized Batch of Inlay Tablet

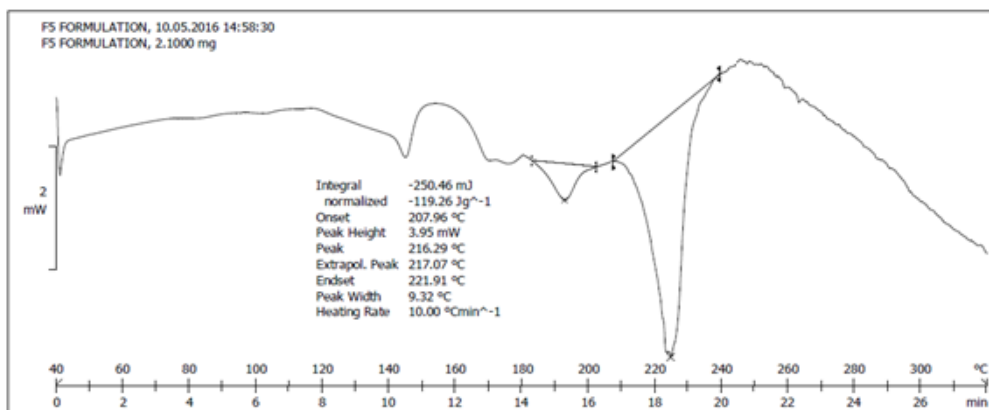


Fig No 10.3.2.4: DSC data of optimized batch

10.6 Stability Study:-

Table No.22:- Stability study data of optimized batch.

Physical Parameter		Observations			
		0day	30 th day	60 th day	90 th day
Percent Drug content	Metformin	97.51%	97.39%	97.34%	97.31%
	Glimepiride	97.707%	98.30%	98.27%	98.23%

SUMMARY AND CONCLUSION

Sustained release drug delivery system has a center stage in the area of pharmaceutical R and D business. Such system offer temporal and or spatial control over the release of drug .Oral control drug delivery system represented the most popular form of controlled drug delivery system for the obvious advantage of oral route of drug of drug administration such system release the drug with constant or variable release rate.

For the control of diabetes mellitus, type 2 third generation sulfonylurea drug is useful like Glimepiride. A drug substance like Glimepiride has several advantages when compared to other sulfonylurea. Therefore, drug commonly used in the treatment of Antidiabetes of differ in their efficacy depending on primary cause of dysmenorrheal, both drug have acidic environment. Half-life of Metformin 4-8 hrs. Hence to improve patient compliance and minimize the frequency of dosage administration it was decided to formulate the sustain release tablet. Glimepiride half-life is also 5hr with a small quantity of does and Glimepiride in biological classification class 2 drug i.e. highly soluble with low so avoiding burst effect coating with cup in which active ingredient in Metformin SR inlay tablet.

- Inner (core) tablet were prepared containing various concentration (15%-30%) of Eudragit.
- Eudragit RLPO Polymer and (15%-35%) of HPMC K4M polymer. The prepared granules were evaluated for angle of repose, bulk density tapped density for sustain releasetablet
- Outer(cup)tablet were prepared containing various concentration (5%-10%) of HPMC K4M. The prepared granule were evaluated for angle of repose for sustain release tablet
- The prepared inlay tablets were evaluated for weight variation, thickness, hardness, density, percentage of drug content, dissolution study.
- Drug release study was done in 900ml of dissolution medium (0.1N HCL) AT $37 \pm 0.5^{\circ}\text{C}$ at a rotation speed of 50 rpm.

Conclusion:

From the finding various physical, chemical, in vitro and can be concluded that.

- All the formulation showed satisfactory result of powder blends and physical properties of tablet.
- Differential Scanning calorimetric data and IR spectral analysis result indicated that there was no probable interaction between drug and excipients.
- The optimized batch Glimepiride (I-6) Eudragit RLPO in a concentration (7.5%) and HPMC k4M in a concentration (10%) of optimized of sustain release polymer for tablet and release was sustained to 12hrs mean reduces the dosing frequency
- The optimized batch of Metformin (O-6) HPMC K4M in concentration of (2%) and HPMCK100 in concentration of (2%) was optimized sustain release polymer for tablet and release was sustain to 12hrs. Means reduces dosing frequency.
- Metformin SR (cup) and Glimepiride SR (core) combination were successfully prepared and evaluated in Inlay tablet formulation.
- On the basis of stability study the optimised formulation was stable.

12. Future Scope

- To perform in-vivo study of optimize formulation.
- Development of Inlay tablets with other Antidiabetes with Metformin or other category of drug.
- Other rate retarding polymer can also be used in dual release layer dosage form.
- Other polymer like (HPMC K15, Eudragit, and Carbopol Aqua sf-1) can be used for design of Formulation.

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