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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF METFORMIN

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ABSTRACT

Among all dosage forms tablet is the most popular dosage form existing today because of its convenience of self administration, compactness and easy manufacturing; sometimes immediate onset of action is required than conventional therapy in many cases. So that to overcome these drawbacks, immediate release dosage form has emerged as alternative oral dosage forms. Immediate drug release dosage forms disintegrate rapidly after administration with enhanced rate of dissolution. The basic approach used in development tablets is the use of superdisintegrants like Cross linked Polyvinylpyrrolidone or crospovidone (Polyplasdone), Sodium starch glycolate (Primogel, Explotab), carboxymethylcellulose (Croscarmellose) etc. These superdisintegrants provide instantaneous disintegration of tablet after administration in stomach. In this field immediate release liquid dosage forms and parenteral dosage form have also been introduced for treating patients. In liquid dosage form can be suspensions with typical dispersion agents like hydroxypropyl methylcellulose, AOT (dioctylsulfosuccinate) etc. The development of immediate release therapy also provides an opportunity for a line extension in the marketplace, a wide range of drugs e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines and other drugs can be considered candidates for this dosage form. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen.

KEYWORDS: Immediate release, polymers, superdisintegrant.

1.1 Solid Oral Dosage Form

Oral route is the most common way of administering drugs, and Among the all solid dosages forms, the oral solid dosage form is most common type of solid dosages form, which defined as unit dosage forms of solid medicament prepared by compaction. Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance, and are solid, flat or biconvex discs shape prepared by compressing a drug or a mixture of drugs with or without suitable excipients. Tablets may be swallowed whole orbeing 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 pesseries may also be presented in form of tablet the intended mode of administration. Solid oral dosage form drug delivery systems can range from relatively simple immediate-release formulations to complex extended or modified-release dosage forms. According to the new modern medicine the pharmaceutical industry researching on tablets for long duration efficacy and effectiveness through the New Drug Delivery System (NDDS).

The general design criteria for tablets are given as follows

- Optimal drug dissolution hence, availability from the dosage form for absorption consistent with intended use (i.e., immediate or extended release).
- Accuracy and uniformity of drug content.
- Stability, including the stability of the drug substance, the overall tablet formulation, disintegration, and the rate and extent of drug dissolution from the tablet for an extended period.
- Patient acceptability. As much as possible the finished product should have an attractive appearance, including colour, size, taste, etc., as applicable, in order to maximize patient acceptability and encourage compliance with the prescribed dosing regimen.
- Manufacturability. The formulation design should allow for the efficient, cost- effective, practical production of the required batches.
- NDDS are advanced day by day with various ongoing research and current research development have provide more appropriate tablets oral dosage form.

1.2 Advantages of tablets as dosage form

- The oral route is the most conventional route that represents a convenient and safe way of drug administration.
- Compared to liquid dosage forms tablets have general advantages in terms of the

chemical and physical stability of the dosage form.

- The preparation procedure enables accurate unit dosing of the drug.
- Tablets are convenient to handle and can be prepared in a versatile way concerning their use and the delivery of the drug.
- Large-scale manufacturing is feasible in comparison to other dosage forms. Therefore, an economy can be achieved.
- Accuracy of the dose is maintained since the tablet is a solid unit dosage form.
- The Longer expiry period and minimum microbial spillage owing to lower moisture content.
- As the 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.
- Product identification is easy and markings were done with the help of groovedpunches and printing with edible ink.
- In composition to parenteral dosage form, a doctor or a nurse is not required for administration. i.e. self-administration is simply done.
- By the use of NDDS, we can enhance thermodynamic & thermokinetic, and bioavailability that results from the best therapeutic medicinal agent.

Disadvantages

- It is difficult to convert a high- dose poorly compressible API into a tablet ofsuitable size for human use.
- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
- Slow onset of action as compared to parenteral, liquid orals, and capsules.
- The amount of liquid drugs (e.g. Vitamin E) that can be trapped intoa tablet is very less.
- Difficult to swallow for kids, terminally ill, and geriatric patients.
- Patients undergoing radiotherapy cannot swallow the tablet.

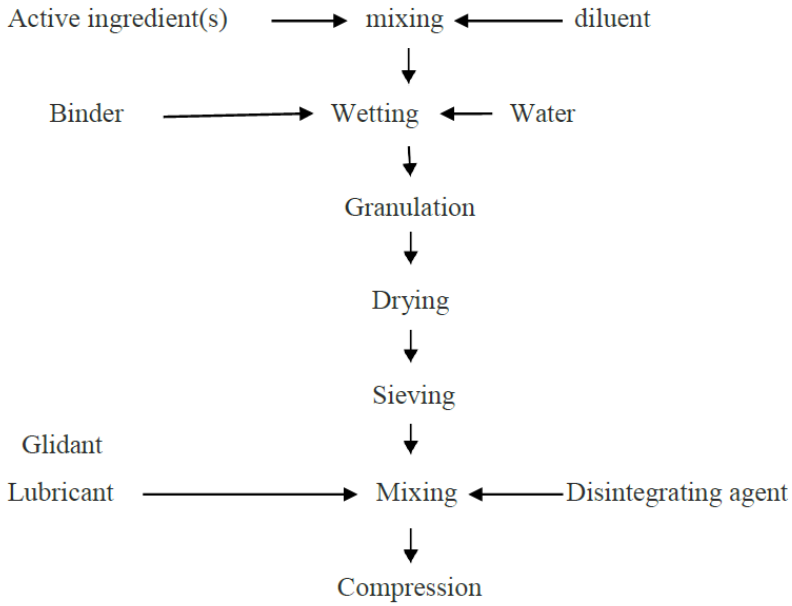
1.3 Tablet manufacturing

Tablets are compressed powders and their manufacturing is a complex, multi-step process according to the Indian Pharmacopoeia. The ultimate aim of these compressed solids is to easily disperse in gastrointestinal fluid, aid incomplete absorption of API, and, at the same time, offer stability to the formulation.

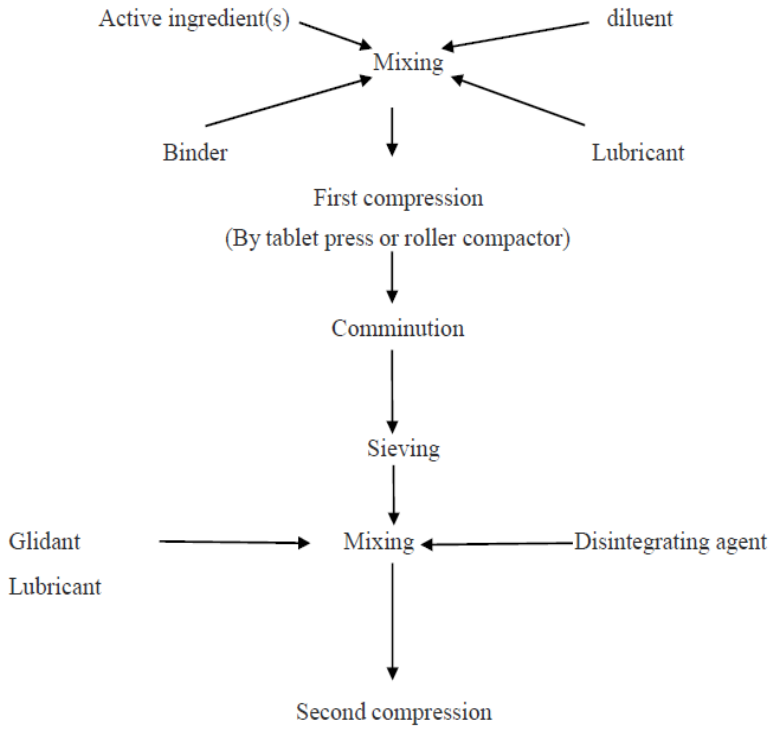
The tablet manufacturing process can be broadly classified as

- Granulation
  - Wet granulation
  - Dry granulation
- Direct compression.

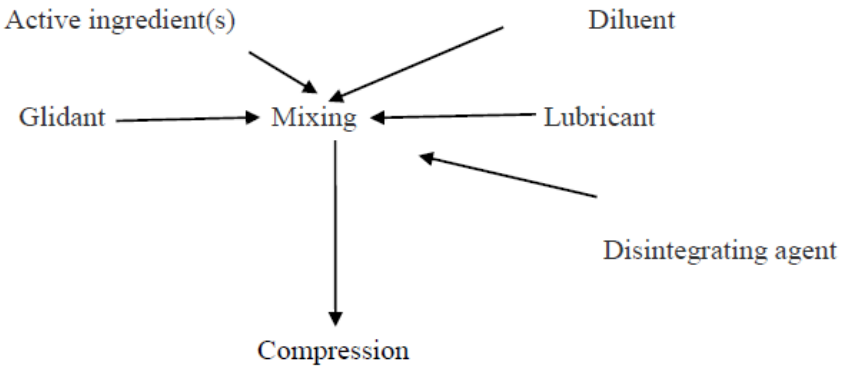
1.2.1 Wet granulation



1.2.2 Dry granulation



1.2.3 Direct compression



1.3. Types of Tablet

1.3.1 Orally Ingested Tablet

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. The exception is a chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. This is the most accepted dosages form by the Doctor and patient.

1.3.1.1 Compressed tablet or standard compressed tablet

These are the standard uncoated tablets made by direct compression or wet granulation or dry granulation or double compaction. They are used for local action in the gastrointestinal tract or systemic action. When the tablet exerts local action, they are formulated as more water- insoluble using selecting slow dissolving excipients and thus provides local action for the long period of effectiveness. e.g. Antacids and adsorbents. Drugs that produce systemic action have some aqueous solubility and are designed to disintegrate and dissolve quickly so that the drug can be quickly absorbed and manufacture systemic action. Generally, an API exhibits bioavailability depending upon Biopharmaceutical Class, which is based on water solubility and gastrointestinal membrane permeability criteria. But, it can be changed by appropriate selection of excipients and processing technology.

1.3.1.2 Multiple compressed tablets

The tablets in this category are prepared for two reasons: to separate physically or chemically incompatible ingredients and to produce repeat action/ prolonged action tablets. The tablet manufacturing machine is generally run at a relatively slower speed than standard compression tablets.

There are three categories under this class

- Layered tablets – two to three-component systems.
- Compression coated tablets – tablet within a tablet.
- Inlay tablet – coat partially surrounding the core.

The layered tablet is preferred over compression coated tablet as the surface contact is less and the production is simple and more rapid.

1.3.1.3 Multilayered tablets

When two or more active pharmaceutical ingredients are needed administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate a multilayered tablet. It consists of several different granulations are compressed to form a single tablet composed of two or more layers and usually, each layer is of a different color to produce a distinctive-looking tablet. Each layer is fed from a separate feed frame with individual weight control. Dust extraction is essential during compression to avoid contamination. Therefore, each layer undergoes light compression as each component is laid down. This avoids granules intermixing if the machine vibrates.

For example, admixture containing Phenylephedrin HCL and Ascorbic Acid with Paracetamol.

Paracetamol + phenyl ephedrine Hydrochloride → one layer Paracetamol + ascorbic acid → another layer.

1.3.1.4 Compression coated tablets

This type of tablet has two parts, the internal core, and the surrounding coat. The core is a small porous tablet and prepared on one turret. For preparing the final tablet, a bigger die cavity in another turret is used in which first the coating material is filled to half and then the core tablet is mechanically transferred, again the remaining gap is filled with coating material and finally compression force is applied. This tablet readily lends itself into a repeat action tablet as the outer layer provides the initial dose while the inner core releases the drug later on. But, when the core quickly releases the drug, an entirely different blood level is achieved with the risk of overdose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer will not release the drug in the stomach while the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while

manufacturing and dawdling the manufacturing process. Sometimes, the inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.

1.3.1.5 Inlay tablets

A type of layered tablet in which the core tablet is completely surrounded by coating, the top surface is completely exposed. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet. It has some advantages over compression coated 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 topcoating.

1.3.1.6 Delayed action tablets

An Enteric-coated tablet is such an example of delayed action tablet. This formulation is preferred when,

- The API irritates gastric mucosa e.g. Aspirin or strong electrolytes.
- Drugs that produce nausea and vomiting.
- API is sensitive to low pH e.g. Erythromycin
- When it's necessary to release the drug undiluted. e.g. Intestinal antibacterial, antiseptic agents, intestinal vermifuge etc.

The commonly used coating agents are Cellulose acetate phthalate, Hydroxy methyl propyl phthalate, polyvinyl acetate phthalate, Eudragit®, etc. This dosage form isintended to hydrate and begin to dissolve in duodenum (pH 4 to 6) or in small intestine where pH increases to 7 to 8. The presence of esterase or bile salts like surface-active agents plays a role in drug release.

1.3.1.7 Targeted tablets

When we need to release the API at a specific site in the elementary track, targeted drug delivery is a preferred option. Depending upon the composition and release mechanism of a tablet, the drug is delivered to a particular region. Under this category we have two types of tablets:

1.3.1.7.1 Gastro retentive tablet

This dosage form is to have opted when API release is desired in the stomach (Antacids, APIs used against H. pylori infection) or site of absorption is either stomach or upper part of the small intestine.

To retain the drug for a longer time period in the stomach, The following approaches to be used:

I) Low density tablet (effervescent or non effervescent)

ii) Tablets can expand in gastric environment (swelling or by unfolding) and thus increasing the size so that it cannot cross the pyloric sphincter.

iii) Using mucoadhesive polymers that stick to the mucosa of the stomach and provide slow drug release. Supine position is to be avoided and also a high level of fluid is necessary or if the swelling formulation leaves the stomach before it swells it's ineffective. Drugs like Diazepam, Levodopa, Benserazide, and Ciprofloxacin are successfully marketed in this formulation.

1.3.1.7.2 Colonic tablets

When the aim is to deliver the drug into colon without dilution in other regions of the gastrointestinal tract or the drug has poor absorption in the stomach or small intestine, colonic drug delivery is an answer of choice. The pH in this region varies from 6.4 - 7 and presence of microbial flora plays an important role in drug release, especially in this region. Various mechanisms are adopted for drug release in this area are coating with pH-sensitive polymer e.g. Eudragit®S100 Eudragit® L100, biodegradable polymers which are sensitive to colonic bacteria, bioadhesive polymers which selectively sticks to colonic mucosa e.g. polycarbophil or polyetylene, redox-sensitive polymers that respond to redox potential in the colon which expresses the total metabolic and bacterial action.

1.3.1.8 Repeat- Action tablet

The mode of operation of repeat- action tablet and its limitation is based on uncontrolled and unpredictable gastric emptying. In addition to multiple compressed tablets being used for this effect, sugar-coated tablets are also be employed. The core tablet is usually coated with shellac or an enteric polymer that will not release its drug load in stomach. The second dose of drug is then added in the sugar coating either in solution in the sugar syrup as a part of the dusting powder added for rapid coat buildup. More uniform drug addition occur if the drug in the solution or fine suspension in sugar solution, especially if an automated- spray sugar-

coating operation is employed.

1.3.1.9 Chewable tablets

For the patients who have difficulty swallowing tablets whole for children who have not yet learned to swallow a tablet, a chewable tablet serves as an attractive alternative. The added advantage of medication that can be taken at any time or when water is not available. Mannitol is widely used as a base due to low hygroscopy and more importantly, it gives pleasant, cooling sensation. Antacid tablets are invariably prepared as chewable to obtain quick ingestion relief as well as the antacid dose is too large to swallow the activity is related to particle size. Another example is the multivitamin tablet which a patient can take as a daily dose.

1.3.1.10 Dispersible tablet

These tablets disintegrate either rapidly in water, to form a stable suspension or disperse instantaneously in the mouth to be swallowed without the aid of water. So, it's preferred for pediatric patients who cannot swallow a solid dosage form and the API is unstable if formulated in liquid formulation. And helpful for patients having prolonged illnesses who are prone to nauseatic sensations if they have to swallow a tablet. The added advantage of this formulation is faster onset of action as compared to standard compressed tablet. The properties of the water-dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity after dispersion and necessary to investigate during manufacturing which decides the product performance. The common examples of API formulated in this dosage form are analgesics e.g. Aspirin, ibuprofen, etc.

1.3.2 Tablets used in the oral cavity

The tablets under this group are aimed to release API in the oral cavity to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of the oral cavity.

1.3.2.1 Lozenges and troches

The tablet is a flat-faced about 18mm in diameter and meant to suck and dissolves in the mouth. The compressed tablet is called troches and the tablets produced by fusion or candy molding process are called lozenges. Flavors and sweeteners are added to make tablets palatable. The tablet generally contains sucrose or lactose and gelatin solution to impart

smooth taste. Lozenges for local action in mouth/throat are antiseptics, antibiotics, demulcents, antitussive agents or astringents. To produce systemic action: multivitamin tablet.

1.3.2.2 Sublingual tablets

They are to be placed under the tongue and produce an immediate systemic effect by enabling the drug absorbed directly through the mucosal lining of the mouth beneath the tongue. The drug absorbed from stomach goes to mesenteric circulation which connects to the stomach via the portal vein. Thus, absorption through the oral cavity avoids first-pass metabolism. The tablets are usually small, and flat, compressed lightly to keep them soft. The tablet must dissolve quickly allowing the API to be absorbed quickly. It's designed to dissolve in a small quantity of saliva. After the tablet is placed in the mouth below the tongue, the patient should avoid eating, drinking, smoking and possibly talking to keep the tablet in place. Swallowing of saliva should also be avoided since the saliva may contain dissolved drug. Bland excipients are used to avoid salivary stimulation. Due to inconvenience in administration, this dosage form is prepared only for those API(s) for which the only satisfaction non-parenteral method in this route. For example, Glyceryl trinitrate (vasodilator) and Isoprinosine sulphate (bronchodilator).

1.3.2.3 Buccal tablets

Completeness of drug absorption is desired but fast drug absorption is not intended. The tablets are designed not to disintegrate. They are flat elliptical or capsule shaped tablets and it can be easily held between gum and cheek. It's placed near the opening of the parotid duct to provide the medium to dissolve the tablet. Since these tablets are kept for 30 - 60 minutes in oral cavity, care should be taken to see that all the ingredients are finely divided to avoid gritty or irritating sensation. This tablet is most often used when replacement hormonal therapy is to be administered. Antifungal drugs are preferred to be administered by this route. e.g. Miconazole–under preclinical trial – still not in market.

1.3.2.4 Dental cones

These tablets are designed to be loosely packed in the empty socket remaining following a tooth extraction. The main purpose behind the use of this tablet is either to prevent the multiplication of bacteria in the socket by employing a slow-releasing antibacterial compound or to reduce bleeding by an astringent or coagulant- containing tablet. It is formulated to dissolve or erode slowly in presence of a small volume of serum or fluid over a

20-40 minutes period.

1.3.3 Tablets administered by other routes

These tablets are administered by another route except for the oral cavity and drugs are avoided from passing through gastrointestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into the systemic circulation from the site of application.

1.3.3.1 Vaginal tablets

This tablet undergoes slow dissolution and drug release in the vaginal cavity of women. The shape is pear-shaped to facilitate retention in the vagina. The tablet should be made compatible with plastic tube inserters which are designed to place the tablets in the upper region of vaginal tract. These tablets generally release antibacterial, antiseptics or astringents to treat the vaginal infections or release steroids for systemic absorption.

1.3.3.2 Implants

These tablets are inserted into subcutaneous tissue by surgical procedures where they are very slowly absorbed over a period of a month or a year. A special injector with a hollow needle and plunger is used to administer the rod-shaped tablet for other shapes surgery is required. The tablets may be pellet, cylindrical or rosette shaped with diameter not more than 8mm. They are sterile formulation without excipients and made hard with large particle sizes to achieve gradual drug release. The tablets are produced by a sterile single punch hand operated machine in which the die cavity is filled with hand since the material does not normally flow well. Mainly these tablets are prepared to deliver growth hormones to food-producing animals and ear is the preferred site for administration of the drug.

1.3.4. Tablets used to prepare solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parenteral application for topical use depending upon type of medicament used.

1.3.4.1 Effervescent tablets

The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus the onset of action is prolonged. This can be overcome by administrating the drug in liquid form but, many APIs have a limited level of

stability in liquid form. So, effervescent tablets act as an alternative dosage form. The tablet is added to a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO2 in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water.

1.3.4.2 Hypodermic tablets

These tablets contain one or more readily water-soluble ingredients and are intended to be added in water for injection of sterile water to form a clear solution that is to be injected parenterally. They were widely used by the rural physician due to its portability. One bottle of sterile water was carried by the doctor to prepare many types of injectables. It can be used for medicaments whose stability in water is very poor.[7]

1.4 Immediate Release

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug is neither appreciably nor intentionally, retarded by galenic manipulations. In the present case. It may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and absorption. Thus, the term excludes formulations that are adapted to provide for "modified, "controlled, "sustained, "prolonged, "extended" or "delayed" release of drug**.**

In this context, the term "release" includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues, and/or into a systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1to3, especially at, or about, pH=1.

Tablets for immediate release often consist of filler, a binder, lubricants and disintegrants (Fukami et al., 2006). In many cases, the disintegration time of solid dosageforms is too long to provide an appropriate therapeutic effect. To improve the disintegration time, so-called disintegrants are used. The most accepted mechanisms of their action are wicking, swelling and deformation recovery and particle repulsion. Together, these phenomena create a disintegrating force within the matrix (Zhao and Augsburger, 2005b). In the past, non-modified disintegrants were used to accelerate disintegration, that is, alginates, starches, ambrette resins, cellulosic materials, pectineus and others. Today, a fast working super

disintegrant is chemically modified, typically by crosslinking the organic chains of a polymeric molecules. Three classes of super disintegrants are commonly used: modified cellulose (croscarmellose sodium - Ac-Di-Sol, Vivasol), crosslinked polyvinyl-pyrrolidone (Polyplasdone XL-10) and modified starch (Sodium Starch Glycolate – Primojel, Explotab).

1.4.1 Desired Criteria for Immediate Release Drug Delivery System

Immediate-release dosage form should, in the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

1. In the case of liquid dosage form, it should be compatible with taste- masking.
2. Be portable without fragility concerns.
3. Have a pleasing mouthfeel.
4. It should not leave minimal or no residue in the mouth after oral administration.
5. Exhibit low sensitivity to environmental conditions as humidity and temperature.
6. Be manufactured using conventional processing and packaging equipment at a low cost.
7. Rapid dissolution and absorption of the drug, which may produce rapid onset of action.[49]

1.4.2 Advantages of Immediate Release Drug Delivery System

An immediate release pharmaceutical preparation offers many advantages

- Improved compliance.
- Improved stability.
- Suitable for controlled/sustained release active agent.
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solidpreparation.
- Adaptable and amenable to existing processing and packaging machinery.
- Cost- effective

1.4.3 Conventional Technique Used In the Preparation of Immediate Release Tablets

- Tablet molding technique
- Direct compression technique
- Wet granulation technique
- Mass extrusion technique

1.4.3.1 Tablet Molding

In this technology, water-soluble ingredients are used so that tablets disintegrate and dissolve

rapidly. The powder blend is moistened with a hydroalcoholic solvent and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor taste-masking characteristics. Using binding agents such as sucrose, acacia & polyvinyl pyrrolidone can increase the mechanical strength of the tablet. To overcome poor taste-masking characteristic Van Scoik incorporated drug-containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol. Active ingredient into a lactose-based tablet triturate form.

1.4.3.2 Direct Compression Method

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets ofacceptable quality. A type of disintegrant and its proportion are of prime importance. Theother factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness, and water absorption capacity. All these factors determine disintegration. The disintegrant addition technology is cost-effective and easy to implement at the industrial level.

1.4.3.3 Wet Granulation Method

Wet granulation is the process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs that are degraded by hydrolysis.

1.4.3.3.1 Procedure

Step 1: The active ingredient and excipients are weighed and mixed.

Step 2: The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, and cellulose derivatives such as methyl cellulose, gelatin, and povidone.

Step 3: Screening the damp mass through a mesh to form pellets or granules.

Step 4: Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.

Step 5: After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process.

1.4.3.4 Mass-extrusion

This technology involves softening the active blend using the solvent mixtureof water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using a heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

What Is Diabeties?

Diabetes is a disease that occurs when your blood glucose level, also called blood sugar, is too high. Blood glucose is the source of energy and comes from the food you that we eat. Insulin, a hormone made by the pancreas, helps to regulate glucose level from food & get into your cells to be used for energy.

Over time, having too much glucose in your blood can cause health problems. Although diabetes has no cure, you can take steps to manage your diabetes and stay healthy.

Sometimes people call diabetes “a touch of sugar” or “borderline diabetes.” These terms suggest that someone doesn’t really have diabetes or has a less serious case, but every case of diabetes is serious.

What are the different types of diabetes?

The most common types of diabetes are type 1, type 2, and gestational diabetes.

Type 1 diabetes

If you have type 1 diabetes, your body does not make insulin and thus the pancreas not functioning according to the body requirements. Your immune system attacks and destroys the cells in your pancreas that make insulin. Type 1 diabetes is usually diagnosed in children and young adults, although it can appear at any age. People with type 1 diabetes need to take insulin every day to stay alive.

Type 2 diabetes

If you have type 2 diabetes, your body does not make or use insulin well. You can develop type 2 diabetes at any age, even during childhood. However, this type of diabetes occurs most often in middle-aged and older people. Type 2 is the most common type of diabetes.

Gestational diabetes

Gestational diabetes develops in some women when they are pregnant. Most of the time, this type of diabetes goes away after the baby is born. However, if you've had Gestational diabetes, you have a greater chance of developing type 2 diabetes later in life. Sometimes diabetes diagnosed during pregnancy is actually type 2 diabetes.

Other types of diabetes

Less common types include monogenic diabetes, which is an inherited form of diabetes, and cystic fibrosis-related diabetes.

How common is diabetes?

As of 2015, 30.3 million people in the United States, or 9.4 percent of the population, had diabetes. More than 1 in 4 of them didn't know they had the disease. Diabetes affects 1 in 4 people over the age of 65. About 90-95 percent of cases in adults are type 2 diabetes.[1]

Who is more likely to develop type 2 diabetes?

You are more likely to develop type 2 diabetes if you are age 45 or older, have a family history of diabetes, or are overweight. Physical inactivity, race, and certain health problems such as high blood pressure also affect your chance of developing type 2 diabetes. You are also more likely to develop type 2 diabetes if you have pre-diabetes or had gestational diabetes when you were pregnant. Learn more about risk factors for type 2 diabetes.

What health problems can people with diabetes develop? Over time, high blood glucose leads to problems such as

- Heart Disease
- Stroke
- Kidney Disease
- Eye Problems
- Dental Disease
- Nerve Damage
- Foot Problems

DRUG PROFILE

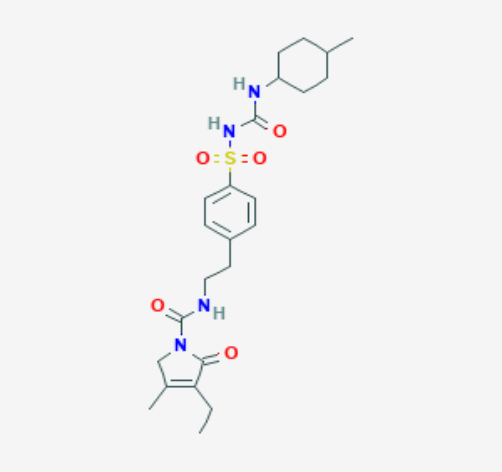
3.1 METFORMIN

Description

Metformin is a third generation sulphonyl urea derivative which is commonly applicable for the treatment of non insulin dependent Type 2 diabetes mellitus. It is a very potent sulphonyl urea with long duration of action, compare to other generations of sulfonylureacompounds. It is an oral hypoglycemic agent that increases release of insulin by blockage of ATP sensitive K^+ channel resulting in membrane depolarization and Ca^{++} influx.

1.4.2-Chemical Formula: C24H34N4O5S

1.4.3-Chemical structure



IUPACName: 4-ethyl-3-methyl-N-[2-[4-[(4methylcyclohexyl) carbamoylsulfamoyl]phenyl]ethyl]-5-oxo-2H-pyrrole-1-carboxamide

Average Molecular weight: 490.62

Melting Point: 207 °C

Solubility: Water insoluble, soluble in dimethylformamide, sparingly soluble in dichloromethane, slightly soluble in methanol.

LogP: 3.5

Physical Description: Solid.

Phamacology

Indication: For concomitant use with insulin for the treatment of noninsulin-dependent (type 2) diabetes mellitus.

Associated Conditions: Type 2 Diabetes Mellitus.

Pharmacodynamics: Metformin is like glyburide and glipizide, which is a "second-generation" sulfonylurea agent. Metformin is used with diet to lesser blood glucose by growing the secretion of insulin from pancreas and enhancing the sensitivity of peripheral tissues to insulin.

Mechanism of action: The mechanism of action of metformin in dropping blood glucose appears to be dependent on exciting the release of insulin from functioning pancreatic beta cells, and enhancing sensitivity of peripheral tissues to insulin. Metformin likely binds to ATP-sensitive potassium channel receptors on the pancreatic cell apparent, and to reducing potassium conductance and which are causing depolarization of the membrane. Membrane depolarization which is to stimulates calcium ion influx over voltage-sensitive calcium channels. This to enhance in intracellular calcium ion concentration prompt the secretion of insulin.

Absorption: Completely (100%) absorbed following oral administration

Volume of distribution

- 21.8 ± 13.9 L [Volunteers]
- 19.8 ± 12.7 L [Patients with Type 2 diabetes, SingleDose]
- 37.1 ± 18.2 L [Patients with Type 2 diabetes, MultipleDose]

Protein binding: Over 99.5% bound to plasma protein.

Metabolism: Hepatic. Following either an intravenous or oral dose, the drug metformin which is fully metabolized by oxidative biotransformation to a main metabolite, cyclohexyl

hydroxymethyl derivative (M1), via the hepatic cytochrome P450 II C9 subsystem. M1 is further metabolized to the carboxyl derivative (M2) by one or several cytosolic enzymes. M1, but not M2, possessed approximately one third of the pharmacologic activity of its parent in an animal model. However, whether the glucose- lowering effect of M1 is clinically significant is not clear.

Excretion: Urine (~60%), feces (~40%)

Bioavailability: 100%

Half- life: Approximately 5 hours following single dose.

Clearance

- 52.1 +/- 16.0 ml/min [Normal subjects with single oral dose]
- 48.5 +/- 29.3 ml/min [Patients with Type 2 diabetes, with single oraldose]
- 52.7 +/- 40.3 ml/min [Patients with Type 2 diabetes, with multipleoral dose]
- 47.8 ml/min [healthy after intravenous (IV) dosing]

Toxicity: Severe hypoglycemic reactions with coma, seizure, or other neurological impairment are associated with metformin.

Affected organisms: Humans and other mammals.

Production Methods

Alkali cellulose is prepared by steeping cellulose, obtained from wood pulp or cotton fibers, in sodium hydroxide solution. The alkali cellulose is then reacted with sodium monochloroacetate to obtain carboxymethylcellulose sodium. After the substitution reaction is completed and all of the sodium hydroxide has been used, the excess sodium monochloroacetate slowly hydrolyzes to glycolic acid. The glycolic acid changes a few of the sodium carboxymethyl groups to the free acid and catalyzes the formation of crosslinks to produce croscarmellose sodium. The croscarmellose sodium is then extracted with aqueous alcohol and any remaining sodium chloride or sodium glycolate is removed. After purification, croscarmellose sodium of purity greater than 99.5% is obtained. The croscarmellose sodium may be milled to break the polymer fibers into shorter lengths and hence improve its flow properties.

Procedure

1. Prepared Drug and Excipients mixture (1:1 mixture)
2. The Drugs and Excipients individually and in combination were subjected for accelerated and long term and freeze study conditions along with control samples and study at fixed intervals of initial, 15 days and 30 days.
3. The recommended drug-excipients ratios for solid dosage forms are tabulated below (Shown in table no. 4.6)
4. After exposure of samples to the study conditions, the following parameters were analyzed.

5.1 FORMULATION CHART OF IMMEDIATE RELEASE TABLET OF METFORMIN (10 MG)

Table No. 5.1 Formula of Metformin tablet.

S.NO.	INGREDIENTS(mg)	F1 (mg/tab.)	F2 (mg/tab.)	F3 (mg/tab.)
1	Metformin	10	10	10
2	Lactose monohydrate	30.80	30.80	30.80
3	Dibasic calcium phosphate	53.50	58.25	60.44
4	Corn starch(maize)	57.25	55.00	55.50
5	Corn starch(maize)	7.95	6.95	4.95
6	Purified Water	q.s.	q.s.	q.s.
7	Sodium starch glycolate	3.00	4.00	5.00
8	Magnesium stearate	5.00	2.50	1.70
9	Total Tablet Weight(mg)	165.00	165.00	165.00

Note- In the above formulation chart corn starch used two times as a binder and as a disintegrant in different ratios.

5.2 METHOD OF PREPARATION

5.2.1.1 Dispensing

Carried out the dispensing of active pharmaceutical ingredient and excipient in separate dispensing booth. Wore personal protective gloves when required during all stages of dispensing.

5.2.1.2 Sifting

All ingredient used in the formulation were sifted through Metformin 30#, Lactose monohydrate 30#, Dibasic calcium phosphate 30#, Corn starch 80#, Sodium starch glycolate 40#, and Magnesium stearate 60#.Vibro sifter was used for sifting the material. Load the Metformin, Lactose monohydrate, Dibasic calcium phosphate, and Corn starch(maize) in conta blender to dry mixing for 5 min.

5.2.1.4 Binder Preparation

Took 20 ml purified water in beaker then added maize starch in it. After that took 30 ml of purified water in beaker and boil it. Then added slowly starch solution in it and made translucent slurry.

5.2.1.5 Granulation

1) Loaded the sifted material (Active and Diluents) in Rapid Mixer Granulator and mixed for 10 min. at slow speed of Impeller and Chopper in off position. Added binder to premixed material in RMG slowly and mixed continuously for 3 minutes at slow Speed and Chopper in OFF position.
2) Stopped the RMG and rack the material. Closed the mixer lid and continue granulation further for about 2 min. at slow speed of Impeller and Chopper or till required Ampere load of Impeller achieved. Record Impeller and Chopper Ampere load.
3) Then prepared wet mass of granules.

5.2.1.6 Drying

Loaded the FBD bowl containing wet mass in FBD and started the FBD as per set recipe. Dried the granules in FBD at inlet temperature upto 70±2°C or LOD reached within 2.0 % to 3.0 % w/w on Infrared Moisture Balance at 105°c. Checked the inlet and outlet temperature (if required) after every 15 minutes. After completion of drying, removed the FBD bowl from FBD. Collect the random sample of dried granules and checked the LOD on moisture balance.

5.2.1.7 Sizing of Dried Granules

Sifted the dried granules through 16 # using Vibrosifter.

5.2.1.8 Lubrication

Loaded the sifted dried granules and Disintegrant, in conta blender to mix for 10 min. Then added lubricant magnesium stearate and mixed for 3 min. at 10 rpm.

5.2.1.9 Compression

5.2.1.9.1 Machine Setting

Upper Punch – 7.00 mm round shape, plain both side, standard concave Punches. Lower Punch – 7.00 mm round shape, plain both side, standard concave plain Punches. Dies - Suitable for above punches.

5.2.1.9.2 Compression

Compressed the lubricated materials in 12 station compression machine, Using U/L Punch, with 7.00 mm round shape, plain both side, standard concave, punches.

5.2.1.10 Coating Process of tablet

1. Took IPA (iso propyl alchol) and water according to specification and mixed them, then added hypromellose and shaked for 30 min.
2. Then added ethyl cellulose and mix for 10 min.
3. After that added diethyl phthalate, talc and white opaspray k-1-7000-s and shaked for30 min.

5.3. PRE-COMPRESSION CHARACTERIZATION

5.3.1. Bulk density

Weighed quantity of powder (W) was taken in a graduated measuring cylinder and volume (V_0) was measured.

Bulk Density calculated as:

Bulk Density = Weight of powder/ Volume of powder (W/V_0 g/ml)..... eq. 5.1

5.3.2 Tapped density

Weighed quantity of powder was taken in a graduated cylinder and the volume was measured (V_0). The graduated cylinder was fixed in the tapped Densitometer and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tapping was less than 2%. The final reading was denoated by (V_F); the volume of blend was used to calculate the Tapped density, Hausner's ratio, and Carr's index.

Taped Density calculated as:

Tapped density = Weight of powder/ Final Volume of powder (W/V g/ml)……eq. 5.2

5.3.3 Hausner's ratio

Hausner Ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density.

Hausner ratio calculated as:

Hausner Ratio = Tapped density/ Bulk density ($H.R = V_F/V_0$).....eq. 5.3

Where, V_F = Final volume, V_0 = Initial volume.

5.3.4 Carr's index

Carr's index is also known as the compressibility index. It is directly related to the relative flow rate, cohesiveness and particle size. It is simple method ofpredicting powder flow.

Carr's Index calculated as:

Carr's Index = (Tapped Density – Bulk Density)/ Tapped Density x 100……..eq. 5.4

5.3.5 Angle of repose

Angle of repose is defined as the maximum angle possible between thesurface of pile of powder and the horizontal plane. The angle of repose calculated as:

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

(Where, h=height of pile, r = radius of pile)…….eq. 5.5

Particle size analysis

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution and chemical reactivity are directly affected by size, shape and surface morphology of the drug particles.

The particle size analysis of Metformin involves the mechanical shaking of sample through a series of successively smaller sieves.

Apparatus used for particle size analysis is Mechanical Shaker with vibratory motion.

Table No. 5.3: Bulk characterization of granule.

S.No.	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose(°)
F1	0.676±0.12	0.789±0.05	12.768±1.0%	1.163±0.05	32.24°±0.08
F2	0.649±0.06	0.781±0.08	16.883±2.0%	1.203±0.03	32.00°±0.06
F3	0.612±0.08	0.769±0.06	20.408±3.0%	1.256±0.06	29.19°±0.05

Where n=3 (S.D. + Mean)

Table No. 5.4: Particle size analysis of granule.

S. No.	Sieve No.				
	20#	40#	60#	80#	100#
F1	**18.16%**	**7. 32%**	**11.325%**	**4.78%**	**38.642%**
F2	**16.29 %**	**6.425%**	**13.268%**	**6.42%**	**41.66%**
F3	**17 %**	**5.36%**	**14.48%**	**7.36%**	**50.32%**

5.4 POST- COMPRESSION CHARACTERIZATION

Weight

Weight of formulated immediate release tablet was determined by weighing balance (Mettler Toledo).

5.4.1 Thickness

Thickness of tablets was measured by Varnier Caliper (Mitutoyo Corporation, Japan) and average was calculated.

5.4.2 Hardness

The hardness of the tablets from each batch was measured by using hardness tester (Dr. Schluniger).

5.4.3 Tablet friability

The friability of the tablets was measured in a Roche friabilator (Electrolab). Tablets of a known weight (W_0) or a sample of 20 tablets are de dusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

Determination was made in triplicate.

F = (W initial) - (W final)/ (W initial) × 100Where W initial = Initial weight of tablets.

W final = Final weight of tablets

5.4.4 Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The disintegration test was performed using tablet disintegration test apparatus (Electrolab, India) using distilled water without disk at room temperature (37±2°C).

5.4.5 Weight variation test

Twenty tablets were selected randomly and weighed individually. Average weight of tablets were calculated and compared with that of the individual tablets. Weight not more than two of the individual weight deviate from the average weight by more than the percentage shown in table.

5.4.6 Content Uniformity

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. The content uniformity test is mandatory for tablets whose average weight is below 50 mg. This test is performed by preparing standard solution of pure drug and sample solution solution of prepared formulation.

Standard solution: Weighed accurately about 50 mg of standard Metformin, dissolved and diluted to 100ml with 0.1 N HCl. Diluted 3 ml of this solution to 100 ml with 0.1 NHCl.

Sample solution: One tablet of Metformin 10mg transferred in to a 100ml volumetric flask and added 80 ml of 0.1 N HCl, placed in an ultrasonic bath for 10 minutes until total disintegration of powder makes up with HCl 0.1 N, shaked and filtered. Diluted the 5 ml of this solution to 25 ml with 0.1N HCl.

Procedure

Determined the absorbance of standard and sample solution at 303nm and took 0.1 N HCl as a blank. Then calculated the content of Metformin in the sample with the data obtained.

Table No. 5.5 Post-Compression Characterization.

PARAMETER	FORMULATION		
	F1	F2	F3
Avg. Weight (Mg)	174±3.2	174±3.7	176±3.9
Thickness (mm)	3.66±0.4	3.85±0.7	3.65±0.9
Hardness (N)	151±10.1	147.4±8.2	149.36±8.5
Friability (%W/W)	0.424±0.02	0.567±0.04	0.437±0.03
Disintegration time (Minutes-Sec)	3.00±0.17	2.50±0.13	2.40±0.16
Weight Variation (%)	2.84±0.25	3.97±0.30	3.40±0.27
Content Uniformity (%)	99.18±0.37	100.08±0.35	105.32±0.29

Where n=3(S.D. +Mean)

RESULT AND DISCUSSION

In the above study of drug characterization different parameters of drug were carried out including identification, related substance(0.17%), heavy metal (less than20ppm), sulphated ash (0.04%), optical rotation(-0.05°to+0.05°), assay (99.51%), and melting point(177.2°C) by different method and the result was found to be acceptable.

Further this was characterized for drug solubility study in the different solvent including

water, acetone, alcohol, methylene chloride, and dilute mineral. Later after it was observed that metformin was soluble in Methylene chloride and dilute mineral, sparingly soluble in acetone, and insoluble in water and alcohol.

Particle size analysis of metformin was performed using vibratory sifter and the result was found to be within limit and had more fines that were determined to be 91.885%. Bulk characterization was carried out to observe the flow property of active drug that have great effect during formulation process. This includes bulk density (0.66gm/ml), tapped density (0.86gm/ml), Hausner's ratio (1.30), Carr's index (23.25%), and angle of repose (26°). The result of bulk characterization was found to be acceptable and had good flow property.

The drug- excipient interaction was carried out by preparing different ratios of drug and excipient, and it was determined on the different temperature and relative humidity condition to find out the interaction and related impurities, water content and appearance of the drug and excipient. It was observed that at different condition all parameter was within limit and found to be compatible.

Calibration curve of metformin was prepared. In this the absorbance of standard solution of metformin at 0-16 µg/ml were plotted as absorbance verses concentration which gave almost a straight line passing from the origin with regression- coefficient o.989.

So it followed Beer's and Lambert's law at the concentration range of 0-16 µg/ml.

In the above study of pre- compression characterization all parameters were determined and it was found that bulk density (0.612±0.08-0.676±0.12gm/cm^3), tapped density (0.7690.06±0.7890.05±gm/cm^3), Carr's index (12.768±1-20.408±3%),

Hausner's ratio (1.163±0.05-1.256±0.06) and angle of repose (29.19°±0.05- 32.24°±0.08), particle size analysis was also performed and found to be 20# (16.29- 18.16), 40#(5.36-7.32), 60#(11.325-14.48), 80#(4.78-7.36), 100#(38.642-50.32). Here all parameter were found to be within limit and suitable for the further process of formulation.

Post-compression characterization was performed and the parametersevaluated were average weight (174±3.2-176±3.9mg), thickness (3.65±0.9-3.85±0.7), hardness (147.4±8.2151±10.1N), friability(.424±.567±0.04%), disintegration(2.40±0.16-3.00±0.17min.) and weight variation (2.84±0.25-3.97±0.30%) the drug content ranged

from (99.18±0.37- 105.32±0.29%) and all these parameter were found to be within limitand formulation F3 gave best result as per the objective of this project.

In the present work *in- vitro* studies were performed and it was observed that in formulation F1 when used 3% superdisintigrant the drug release was to be found 72.36±0.3% after 15 min. and was below the limit. Further increasing the concentration of superdisintegrant in the formulation F2 by 4%, the release of drug was found to be 75.39±0.5% after 15 min. and 99.51±0.7% after 20 min. and this was also not satisfactorily. At last in the formulation F3, 5% of superdisintegrant was used and found to be 82.06±0.5% after 15 min. and 102.54±0.6% after 20 min. and this was denoted as the best and final formulation. After dissolution studies it was observed that on increasing the content of super disintigrant the release of drug was also increased. Since Metformin is acidic in nature and its absorption window is stomach, so it released the drug in the stomach. So the dissolution studies were performed using 0.1N HCl.

The accelerated stability studies were carried out on the optimized formulation i.e. F3. The formulation was stored 40 ± 2 ^{0}C, 75 ± 5% RH for 3 month to assess their long term stability. The results were indicating that, irrespective of the concentration of polymers, these formulations were remained stable for three months.

SUMMARY AND CONCLUSION

Immediate release tablet are those tablet which designed to disintegrate and release their medication with no special rate controlling features such as special coating or other technique.

Metformin is hypoglycemic drug used in the sort- term therapy of diabeties disease. The drug is bitter in taste and light sensitive. Because of its sort -term therapy the formulation was proposed to design an immediate release formulation. Before the preparation of the immediate release tablet, preformulation studies of the provided drug were carried out for the various parameters including identification, solubility, related impurities, and UV spectrum analysis.

The different parameters of drug performed were related substance (0.17%), heavy metal (less than20ppm), sulphated ash (0.04%), optical rotation (-0.05°to+0.05°), assay (99.51%), and melting point (177.2°C) by different method and the result was found to be acceptable.

The drug solubility studies in the different solvent were performed including water, acetone, alcohol, methylene chloride, and dilute mineral. Later after it was observed that metformin was soluble in methylene chloride and dilute mineral, sparingly soluble in acetone, and insoluble in water and alcohol.

Particle size analysis of metformin was performed using vibratory sifter and the result was found to be within limit and had more fines that were determined to be 91.885%. Bulk characterization observed were bulk density (0.66gm/ml), tapped density (0.86gm/ml), Hausner's ratio (1.30), Carr's index (23.25%), and angle of repose (26°). The result of bulk characterization was found to be acceptable and had good flow property.

The drug- excipient interaction was carried out by preparing different ratios of drug and excipient, and it was determined on the different temperature and relative humidity condition to find out the interaction and related impurities, water content and appearance of the drug and excipient. It was observed that at different condition all parameter was within limit and found to be compatible.

Calibration curve of metformin was prepared. In this the absorbance of standard solution of metformin at 0-16 µg/ml were plotted as absorbance verses concentration which gave almost a straight line passing from the origin with regression- coefficient o.989. So it followed Beer's and Lambert's law at the concentration range of 0-16 µg/ml.

The material and method were selected to prepare the formulation. Metformin is light sensitive drug, so there was created a condition to protect the drug from light.

In the present work the tablet was prepared by wet granulation method using the superdisintegrant in the ratio of 3%, 4%, 5%. There were three formulation prepared using material lactose monohydrate, dibasic calcium phosphate, corn starch (maize), sodium starch glycolate, magnesium stearate. The granules were prepared and subjected to pre-compression analysis. Pre-compression analysis were found to be bulk density (.612-.676 gm/ml), tapped density(.769-.789gm/ml), Carr's index(12.768-20.408%), hausner's ratio(1.163-1.256), angle of repose and size analysis(29.19-32.24). Later after tablet was compressed using 7.00 mm round shape, plain both side, standard concave Punches by 12 station compression machine (Rimek). The manufactured tablet were evaluated for post-compression parameters including average weight (174- 176mg),thickness (3.65- 3.85),

hardness (147.4-151N), disintegration time (2.40- 3.00min), friability(.424-.567%), weight variation (2.84-3.97%), Content uniformity (105.32%) and in- vitro drug release (96.12-102.54%). After observation we found that formulation F1 gave less release, so further trail was taken by changing the concentrationof binder and the final formulation F3 was found to be satisfactorily on increasing the concentration of superdisintegrant. Later after stability studies was also performed at the accelerated stage for 3 months and the result found to be there was no more change in thephysical and chemical properties and was acceptable.

At last the formulation was coated by film coating for the following reason-

1. To mask the taste.
2. To protect from light.
3. To avoid dust formation.
4. For brand differentiation and consumer recognition.

After preparing the formulation of metformin immediate release tablet, there were found the great effect of superdisintegrant on release of drug. The increased ratio of polymer increased the dissolution profile of drug and released the drug in less time.

According to the found result it was concluded that immediate release tablet of metformin prepared on the above ratio is the best formulation in the treatment of short term therapy of diabeties.

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