FORMULATION AND EVALUATION OF BILAYER TABLETS: GLIMEPIRIDE IN FLOATING DRUG DELIVERY AND METFORMIN IN SUSTAINED RELEASE

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Submitted by

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MAY - 2019

CERTIFICATES

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF BILAYER TABLETS: GLIMEPIRIDE IN FLOATING DRUG DELIVERY AND METFORMIN IN SUSTAINED RELEASE"** is a bonafide work submitted by **Reg. no. 261711104,** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment for **Master of Pharmacy** in **Pharmaceutics** and has been conducted under the guidance of **Dr. S. Subramanian, M. Pharm, Ph.D.,** Department of Pharmaceutics, PSG College of Pharmacy, Peelamedu, Coimbatore in the academic year of 2018-2019

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I do hereby declare that the dissertation work entitled **"FORMULATION AND EVALUATION OF BILAYER TABLETS: GLIMEPIRIDE IN FLOATING DRUG DELIVERY AND METFORMIN IN SUSTAINED RELEASE"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment for **Master of Pharmacy** in **Pharmaceutics** and has been conducted under the guidance of **Dr. S. Subramanian, M. Pharm, Ph.D.,** Department of Pharmaceutics, PSG College of Pharmacy, Peelamedu, Coimbatore in the academic year of 2018-2019.

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EVALUATION CERTIFICATE

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Above all we humbly submit our desertion work, into the hands of Almighty, who is the source of all wisdom and knowledge for the successful completion of our thesis.

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ABBREVIATIONS

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DM	- Diabetes Mellitus
IDDM	- Insulin Dependent Diabetes Mellitus
NIDDM	- Non Insulin Dependent Diabetes Mellitus
FFA	- Free Fatty Acid
GRDDS	- Gastro Retentive Drug Delivery System
GI	- Gastro Intestinal
FDDS	- Floating Drug Delivery System
AMPK	- Adenosine Mono phosphate activated Protein Kinase
PVP	- poly vinyl pyrolidone
FT-IR	- Fourier Transform Infrared Spectrophotometer
nm	- Nanometer
MCC	- microcrystalline cellulose

INTRODUCTION

1. INTRODUCTION

1.1. DIABETES MELLITUS [1]

Diabetes mellitus is the most common endocrine disorder. It is chronic condition, causes by hyperglycemia due to impaired insulin secretion. It is important to understand another related term metabolic syndrome called syndrome x or insulin resistance syndrome and it combines of metabolic abnormalities. It increases the risk of cardiovascular disease, also major feature of metabolic syndrome are central obesity, hypertriglycerideamia, low density lipoprotein, hyperglycemia and hypertension.

If hyperglycemic conduction increases there will be lose of glucose in urine, this condition called as glucosuria. Diabetes mellitus has three "polys", an excessive urine production is polyuria, an excessive thirst is polydipsia, and excessive eating is polyphagia.

Diabetes mellitus has two major types:

- Type-1 (Insulin dependent diabetes mellitus)
- Type-2(Non insulin dependent diabetes mellitus)

TYPE-1 DIABETES MELLITUS:

It is also called as Insulin dependent diabetes mellitus (IDDM). This type of patients is due to lack of insulin production. In earlier this conduction was called "juvenile onset diabetes". This conduction patient needs regular insulin to save their life. Type-1 DM patient are affected age below 30 years.

Type-1 (IDDM) is further divided into two types:

i. Type-1A
ii. Type-1B

Type-1A (immune mediated):

It is autoimmune disease of pancreatic β cells. It destroys the β cells and lead to insulin deficiency.

Type-1B (Idiopathic DM):

Idiopathic DM is viral infection such as echovirus can also damages the pancreatic β cells.

Type-1 DM includes the hyperglycemia with polyuria, polydipsia, polyphagia and ketoacidosis. These patients are not obese. Diabetic ketoacidosis is the end result of insulin deficiency. If insulin is not present to help the entry of glucose in skeletal muscles and body cells, the cells use fatty acid to produce ATP to provide energy. This accelerates fat breakdown generates acetyl COA. Due to DM this acetyl COA, cannot be removed by Krebs cycle. In absence of anaerobic carbohydrate conduction two acetyl COA molecules joint to form acetoacetic acid and β-hydroxy buturic acid, which is called ketone bodies and it, excretes in urine (ketonuria). This aceto acetate (ketone body) is converted in liver to acetone which is excreted through lungs and gives fruity odour breath. Diabetic ketoacidosis decreases glucose uptake in brain and blood pH decreases and leads to coma and death.

TYPE-2 DIABETES MELLITUS:

This is also called as non insulin dependent diabetes mellitus (NIDDM) or "maturity onset diabetes". Approximately 90-95%of diabetes population is affected by type-2 DM, it usually occurs in age above 40 due to obesity. For these patients diabetes occurs due to target cell become insensitive to insulin or insulin secretion will be less.

Type-2 DM is almost same as type -1 DM, but type-2 DM have chance to develop hyper osmolar coma instead of ketoacidosis, it is a condition of hyperglycemia and dehydration. This patient's needs insulin administration and I.V fluids.

In type-2 DM two complications may occurs micro vascular and macro vascular. In micro vascular retinopathy, nephropathy, neuropathy occurs and in macro vascular atherosclerosis and diabetic dyslipidemia (elevated triglyceride and low density lipoprotein). Diabetes neuropathy is related to axons. Diabetes nephropathy is accumulation of sorbitol. Sorbitol causes thickening of capillary endothelium, leads to narrowing of micro vascular and deficiency in tissue perfusion. Diabetes retinopathy is deposition of glucose in eye lens, and visible like cloudy. Brain is the last organ to be affected, because it utilizes blood glucose in absence of insulin.

1.2. GLIMEPIRIDE [2]:

Glimepiride act on sulphonylureas receptor. The receptor links to the ATP dependent K channel in the cell membrane of the islet beta cells. The receptor activates to close the K channel and cell membrane to depolarize. These occurs calcium influx into the cell. They are effective only in the presence of a functioning pancreas.

Sulphonylureas release insulin slowly and from prolonged period into the portal circulation where its primary action is on the liver, in contrast to inject insulin which enters the systemic circulation.

In liver muscles and adipose tissue increases the sensitivity to insulin, the hepatic output of glucose is decreases if muscle uptake is increased. The hepatic glucogen increases the storage. The action of all sulphonylureas is same, but they differ in pharmacokinetic properties.

Pharmacological action of Glimepiride lowers the sugar in selected diabetes and lowers the elevated free fatty acid (FFA), normalizes the metabolic state of diabetes and promotes weight gain.

1.2.1. ANATOMY OF STOMACH [3]:

The stomach is a ‘j’ shaped enlargement of the track directly inferior to the diaphragm in the epigastric, umbilical and left hypochondria region of the abdomen. The stomach connected with the esophagus to the duodenum. The stomach has four regions cardia, fundus, body and pylorus.

Cardia:

Cardia is the portion of stomach surrounded by cardio esophageal junction or cardiac orifice. The cardia is the first opening of stomach.

Fundus:

The fundus is the enlarged portion to the left and above the cardiac orifice.

Body:

The body or corpus is the central part of the stomach.

Pylorus:

Pylorus is the region of stomach connected with the duodenum. It has two parts, pyloric antrum, and pyloric sphincter. The pyloric antrum connects body of stomach and pyloric canal. The pyloric which communicates duodenum of small intestine via sphincter is called pyloric sphinter.

1.2.3. GASTRORETENTIVE DRUG DELIVERY SYSTEM [3]:

Gastro retentive drug delivery system (GRDDS) is site specific delivery to gastrointestinal track (GIT) by controlling the GI transit of orally administered dosage form. Such GRDDS possess the ability of retaining the dosage form in GIT particularly in the stomach for long period.

The transit times in GIT from mouth to anus various from one person to another. It also depends upon the physical properties of object ingested and physiochemical conduction of the alimentary canal. Several drugs are absorbed in upper part of the small intestine. Many drugs have poor bioavailability in the metabolic enzyme like cytochrome P450 present in the intestinal epithelium. An absorption window exists because of physiological, physiochemical and biochemical factor. The drug having sit specific absorption is difficult to design GRDDS, because drug releases in absorption window only, if the drug crosses the window there will be on absorption and drug will be wasted. So GRDDS can improve the delivery of drug to absorption window by continuously releasing for long period until it reaches absorption site.

GRDDS are using various concept to increase gastric retention time, the concepts are floating drug delivery system (FDDS), swelling and expanding system, Bioadhesive drug delivery system (BDDS) and high density system.

1.2.4. FLOATING DRUG DELIVERY SYSTEM (FDDS) [3]:

Floating system have a bulk density lowers that of gastric fluid and remains buoyant in stomach for long period of time. Floating system can be effervescent or non-effervescent in nature. In effervescent gas generating agent, for example, bicarbonate salt, acidic ingredients are used that produces carbon dioxide in presences of gastric fluid. Volatile organic solvents are introduced into the floating chamber to generate gas at physiological temperature. In non-effervescent system, usually highly swell able and gel forming excipients are used. Floating

system suffers has disadvantages that is effective in only fluid level in stomach is sufficiently high, otherwise the tablet will be stay in pylorus instead of floating.

Effervescent system:

Matrix type of system is prepared with help of swell able polymer such as methylcellulose and chitosan and various effervescent agents, for example sodium bicarbonate, tartaric acid, citric acid. Formulations when it comes in contact with the acidic gastric contents carbon dioxide liberates and gets entrapped in the swollen hydrocolloids, which gives floating to the dosage form. The effervescent system can make the tablet to float in stomach by floating chamber, which is filled by inert gas, vacuum or air. The gas in floating chamber can be either volatilization of organic solvent effervescent reaction between organic acid and bicarbonate salts.

Non-effervescent system:

Hydro dynamically balance system (HBS) contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers. These system has high level of one or sustained release (hydrocolloids) gastric fluid colloid gel barrier sustained release layer, immediate release layer more gel forming, highly swellable cellulose, type hydrocolloids, for example, hydroxy propyl cellulose, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose.

Polymers used:

- Hydroxy propyl methyl cellulose
- Sodium bicarbonate
- Carbopol
- Xanthum gum
- Gum agar
- Poly ethylene oxide
- Poly acrylates
- Poly vinyl acetate

1.3. METFORMIN HYDROCHLORIDE [2]:

Metformin action is not clear. It does not stimulate insulin secretion from pancreas. But presence of external or internal insulin is necessary for its action. Several mechanisms are involved in the anti-diabetic effect of Metformin.

Inhibits hepatic neoglucogenesis, it decreases hepatic and renal output. This is considered as major action. It may act on the enzyme Adenosine Monophosphate activated Protein Kinase (AMPK). Increases the peripheral glucose utilization by enhancing anaerobic glycolsis

It act as insulin sensitizer in the muscle and adipose tissue and reduce hyperinsulinemia. This action has minor role in delaying glucose absorption and reduce the appetite which may be helpful in obese subject.

Metformin does not lower the blood sugar in normal subject and it does not produce hypoglycemic in diabetes, it potent the hypoglycemic action of insulin and sulphonylureas. It does inhibit ketogenesis in the liver, but may develop ketoacidosis with minimum hyperglycemia and glycouria. Metformin decreases the glycogen content of liver. Metformin reduces lipid oxidation and free fatty acid production.

Weight loss is due to reduction in appetite. It main benefit is prevention of weight gain in contrast to sulphonylureas.

1.3.1. SUSTAINED RELEASE DRUG DELIVERY SYSTEM (SRDDS) [4]:

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.

The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug delivery. During the last 2-3 decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of

new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems.

Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled and prolonged release of drug from the complex for 8-12 hours in the GI tract.

SRDDS reduced the toxicity by slowing drug absorption, improved palatability, and availability of formulation in liquid and solid SRDDS, increased stability by protecting the drug from hydrolysis or other degradative changes in the gastrointestinal tract. Very early on, due consideration has to be given to their pharmacokinetics in order to obtain that specific release profile which guarantees optimum therapeutic efficiency.

Enclosing drugs in diffusion-controlled membranes is an important basic principle of controlled time release. Combining neutral, permeable polymers with anionic soluble types permits realization of various release mechanisms, while paying due regard to the physicochemical properties of the drug.

Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern. Localize drug action by spatial placement of a controlled release system usually rate controlled adjacent to or in the diseased tissue or organ.

Sustained release formulations describe the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period for 8-24 hours of time.

In oral form it is in hours, and in parenteral it is in days and months. Controlled release dosage form describes the rate or speed at which the drug is released is controlled. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design.

The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

Ideally a sustained release oral dosage form is designed to release rapidly some predetermined fraction of the total dose into GI tract.

This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then releases at a controlled rate.

The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required.

Ideally two main objectives exist for these systems:

Spatial delivery which is related to the control over the location of drug release; temporal drug delivery of the drug is delivered over an extended period of time during treatment (SR) and idealized zero-order controlled release (ZOCR) drug delivery systems.

Advantages:

- Improve patients compliance due to less frequent drug administration
- Reduces fluctuation in steady state drug level.
- Minimum consumption of drug
- Increases safety margin of potent drug
- Reduces healthcare cost
- Shorter treatment period
- Less frequency of dosing

Polymers used:

- Hydroxypropylmethylcellulose K100V
- Hydroxypropylmethylcellulose K4M
- Hydroxypropylmethylcellulose K15M
- Xanthium gum
- Poly vinyl pyrolidone K90D
- Guar gum
- Eudragit RSPO
- Carbopol

1.4. BILAYER TABLET:

Bilayer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bilayer tablets will be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bilayer tablet is suitable for sequences of two drugs in combination and also for sustained release of tablet in which one layer is for floating layer and second layer is sustained release. So the use of bilayer tablet is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drug where combination therapy is often used

Ideal characteristics of bilayer tablets:

- A bilayer tablet should have elegant identity which is free of defects such as chips, crack, discoloration and contamination, etc.
- It should have sufficient strength to withstand mechanical shock during its production packing, shipping and dispensing.
- It should have the chemical and physical stability to maintain its physical attributes over time
- The bilayer tablet must be able to release the medical agents in a predictable and reproducible manner
- It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Advantages:

- Weight monitoring / control for accurate and independent weight control of the individual layer
- Low compression force exerted on the first to avoid capping and separation of the two individual layers
- Independence from the machine stiffness
- Increasing dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed
- Maximum prevention of cross- contamination between the two layer
- Clear visual separation between the two layer and maximized yield

LITERATURE REVIEW

2. LITERATURE REVIEW

1. **Sahilhusen I Jethara *et al.*, (2014)** sustained release drug delivery system (SRDDS) is designed to drug release at a controlled rate by maintaining a constant drug delivery for specific period of time with minimum side effects. Now a day's focusing on development of SRDDS is increased. The major aim of SRDDS is to modify and to improve the drug performance by increasing duration of action, decreases the dose frequency, reduces side effect, decreasing the required dose administration and providing the short time by using small amount of drug by suitable route.

2. **Quazi Rubiya *et al.*, (2015)** floating tablet of glimepiride was developed to prolong the gastric residence time and increases drug bioavailability. Diabetes conduction influence the gastric empting time which affect absorption of drug. Glimepiride was chosen as model because it has incomplete absorption due to less gastric residence time. The tablet was prepared by using polymers such as HPMC K4M, K15M, and K100M. The gas generating system plays an important role in floating lag time and drug release. It was found that the best formulations have released floating lag time of 20 sec and 98.6% dug release in 12 hours.

3. **Pamu Sandhya *et al.*, (2015)** the attempt has been made to development gastro retentive floating controlled release tablet of glimepiride by selecting HPMC K4M and xanthium gums retarding polymer. The polymer are used in different ratio, all the formulations shows good flow properties such as angle of repose, bulk density, tapped density. The prepared tablet passes all the quality control evaluation parameter as per I.P limit.3^2 factorial design was applied for the optimization of formulations. It was observed that the combination ratio of HPMC K4M, Xanthum gum at 20:12 has compared to all combination of polymers.

4. **Zhenghong Wua *et al.*, (2015)** to prolong the residence time of dosage forms within gastrointestinal trace until all drug released at desired rate was one of the real challenges for oral controlled-release drug delivery system. We developed a fine floating tablet via compression coating of hydrophilic polymer (hydroxyl propyl cellulose) combined with effervescent agent (sodium bicarbonate) to achieve simultaneous control of release rate and location of ofloxacin. Sodium alginate was also added in the coating layer to regulate the drug release rate. The effects of the weight ratio of drug and the viscosity of HPC on

the release profile were investigated. The optimized formulations were found to immediately float within 30 s and remain lastingly buoyant over a period of 12 h in simulated gastric fluid (SGF, pH 1.2) without pepsin, indicating a satisfactory floating and zero-order drug release profile. These results demonstrated that those controlled-released floating tables would be a promising gastro-retentive delivery system for drugs acting in stomach.

5. **Rahim Bahri-Najafil *et al.,* (2017)** in the current study, floating dosage form containing acyclovir was developed to increase its oral bioavailability. Effervescent floating tablets containing 200 mg acyclovir were prepared by direct compression method with three different rate controlling polymers including Hydroxypropylmethylcellulose K4M, Carbopol 934, and Poly vinyl pyrrolidone. Optimized formulation showed good floating properties and in vitro drug release characteristics with mean dissolution time and dissolution efficacy of about 4.76 h and 54.33%, respectively. X-ray radiography exhibited that the tablet would reside in the stomach for about 5 ± 0.7 h. After oral administration of floating tablet containing 200 mg acyclovir, gastro retentive formulation were found to be 551 ± 141ng/mL, 2.75 ± 0.25 h and 3761 ± 909.6 ng/mL/h, respectively.

6. **Gharti KP *et al., (*2012)** the present study was carried out an objective of preparation and in vitro evaluation of floating tablet of Hydroxypropylmethylcellulose and polyethylene oxide using ranitidine hydrochloride as model drug. The floating tablet was based on effervescent approach using sodium bicarbonate a gas generating agent. The tablet as prepared by dry granulation method. The effect of sodium bicarbonate and stearic acid on drug release profile and floating properties are investigated. The results of in vitro dissolution study showed that the drug release profile could be sustained by increasing the concentration of HPM K15MCR and polyox WSR303 and concentration are 13.88% shows 91.2% drug release at the end of 24 hours. The changing of viscosity of grade of HPMC from K15MCR to K100MCR had no significance effect on drug release profile. Sodium bicarbonate and stearic acid in combination showed on significant effect on drug release

7. **Rajani Shakya *et al., (*2013)** this study aimed to develop hydrophilic matrix based controlled release gastro retentive drug delivery system of system of ofloxacin and conducting its in vitro in vivo evaluation. Effervescence floating gastro retentive drug delivery system of ofloxcin was prepared utilization box-behnker statistical design with 3

factors, 3 level and 15 experimental trials. In vivo studies were carried out for 12 healthy volunteers and pharmacokinetic parameter was compared with marketed tablet (zanocin OD). Optimized and marketed formulations were found to have similar in vitro release profile and are found to be bioequivalent. C_{max} and AUC values of optimized formulation were found to be significantly higher than of marketed product despite their bioequivalence.

8. **Anjali Sharma *et al.*, (2015)** the study was to develop optimized gastro retentive floating drug delivery system of Olmesartan Medoxomil and investigates the effect of hydrophilic retardant on release by using 3^2 full factorial designs. Floating tablet of Olmesartan Medoxomil was prepared by direct compression method using effervescent technique by employing two different grade of HPMC (HPMC K4M and HPMC K100M). Sodium bicarbonate was incorporated as gas generating agent. The concentration of HPMC K4M (X1) and concentration of HPMC (X2) were selected as independent variable. The floating lag time and total floating time and time taken to 80% drug release were selected as dependent variable. The results indicates that the concentration of X1and X2 affected the floating lag time, total floating time and time to reach 80%. Drug release properties were affected by concentration of HPMC K4M and HPMC K100M. The optimized formulation increases the concentration of X1 and X2 and sodium bicarbonate showed good physical properties with short lag time of 55 sec and 80% of drug release in 18 hours.

9. **Sonail B Deokate *et al.*, (2017)** the main work was to prepare sustained release matrix tablet of glimepiride by using various concentration of polymers. Glimepiride is poorly water soluble drug, so solubility is the main constrain for its oral bioavailability. Glimepiride exhibit very poor solubility at 37°C. In media PH > 7 solubility of drug is slightly increased. The rational of this study was to enhance the solubility of drug by adding β-CD and HP β-CD. The tablet Glimepiride was prepared by direct compression method. Different formulation was developed with varying concentration of polymer like polyvinyl alcohol, hydroxyl propyl methyl cellulose, K4 and K100 and carbopol 934. FTIR and DSC studies shown there was no interaction between drug and polymer. A result of the present study indicates the suitability of the above mentioned polymer in the preparation of glimepiride tablet.

10. **Prakash Thapa *et al.*, (2018)** to develop sustained release gastro retentive effervescent floating tablet a quality based experimental design approach was utilized during the

compression of a hydrophilic matrix loaded with a high amount of a highly soluble model drug metformin HCL. Effect of the amount of polyethylene oxide WSR 303, sodium bicarbonate, and the tablet compression force were used as independent variable. Polymer screening showed that PEO had the highest gel strength among the various tested polymer. Sodium bicarbonate has highest floating lag time. The design space was built in according with the drug release profile, tensile strength and floating lag time simulations. The release mechanism was best described by Korsemeyer peppas model. The current study provided a perspective on the systematic approach of gastro retentive loaded with highly water soluble drugs by applying quality by design concept.

11. **Pamu Sanduya *et al.*, (2014)** the main aim of study is to formulate metformin sustained release and glimepiride immediate release matrix tablet as a dosage form by different polymer such as HPMC, povidone, lactose monohydrate, ethyl cellulose, microcrystalline cellulose, and to study in vitro release pattern of the drug. In the study bi layer tablet the glimepiride prepared by direct compression method and metformin prepared by wet granulation technology. The prepared tablet were evaluated for various physicochemical parameter such as drug Excipient interaction by FTIR, flow properties, hardness, weight variation, friability, and in vitro dissolution studies optimized based on desired sustained release time 16 hours and acceptable floating properties. The FTIR studies revealed there is no drug excipients interaction. During formulation there should not be drug excipients interaction, drug-drug interaction. This formulation should provide zero order or near for immediate and Higuchi model for sustained release.

12. **Upadhyay Uma *et al.*, (2014)** the aim of the current study is to design a sustained release matrix tablet of metformin HCL to maintain plasma level of drug for prolong period of time. Metformin HCL is anti hyperglycemic agent in the treatment of type 2 non insulin dependent diabetic mellitus. Sustained release formulation of metformin HCL prolong drug absorption in the upper GI track and permits once daily dosing in patients with type 2 diabetes mellitus. This newer formulation may enhance patient compliance compare to conventional immediate release metformin HCL. Metformin present significant challenges due to its poor inherent compressibility, high dose and high water solubility. So matrix tablet of metformin is formulated by different combination of matrix forming polymers such as Hydroxypropylmethylcellulose and hydroxyl propyl cellulose by direct compression method. PVPK30 is used as a binder. Magnesium stearate and micro

crystalline are used as lubricant and filler respectively. Drug and polymer compatibility study is done by IR spectroscopy. The formulated powder mixture is evaluated for pre compression parameter such as bulk density, tapped density, to determine flow properties of mixture. The prepared tablets are subjected to post marketing parameter such as hardness, thickness, drug content. No physicochemical interaction is found in IR studies. If the formulation contains less polymer drug release will be earlier.

13. **Pratik Upadhyay *et al.*, (2014)** the present is intended to enhance gastric retention of sustained release tablet of valacycovir hydrochloride by combined approach of floating and swelling. The tablets are prepared by direct compression method. Polyox is selected as the swelling matrix agent. Sodium starch glycolate (SSG) is used as swelling enhancer and sodium bicarbonate is used as effervescent agent. 3^2 full factorial design is applied to systematically optimize the formulation. The concentration of polyox WSR (x_1) 303 and concentration of SSG (x_2) are selected as variables. The percentage drug release at 12 hrs floating lag time, total floating time, percentage swelling, in vitro drug release and in vivo floating study. Release rate decreases as the concentration of polyox increases. Regression analysis and numerical optimization are performed to identify the best formulation. Formulation F5 is found to be best formulation as polyox WSR 303 (15%) and SSG (10%). F5 follows zero order release mechanism.

14. **M. Kaleemuliah *et al.*, (2016)** currently the use of natural gums and mucilage is of increases improving importance in pharmaceutical formulation as valuable drug excipients. Natural plant based material are economic, free lated by employing hibiscus rosa-sinensis leaves mucilage as natural polymer and HPMC (K100M) as a synthetic polymer to sustained the drug release from matrix system. Direct compression method in term of physical appearance, weight variation, thickness, diameter, hardness, friability and in vitro drug release. The difference between synthetic and natural polymer was investigated concurrently. Matrix table develop from each formulation passed all standard physical evaluation test. The dissolution studies of formulated tablet s sustained release up to 24 hours compare to reference drug. The best formulation is selected base on the similarity study value and drug release. The natural polymer is increased the sustainability of drug release when compared to reference drug. The kinetic study follows non-fickian type diffusion mechanism.

15. **Kambham Venkateswarlu et al., (2016)** the objective of the study was to develop sustained release tablet of stavudine (SVD), an anti-retroviral drug and effect of retardants on drug release. The sustained release tablet was prepared by wet granulation method. The various batches were prepared by altering the process and formulation parameter in order to design ideal formulate for the treatment of infection with better patient compliance. The formulation is developed in tamarind gum, sodium alginate, and sodium carboxy methyl cellulose. The Compatibility of the drug with various excipients was studied by FTIR peak. The compressed tablets were evaluated and showed compliance with standard limits. The release of stavudine the formulation (F9) was sustained and thereby expected to provide patient compliance with reduced frequency of administration and side effects by avoiding the sudden burst release.

16. **Mandip Shergilla *et al.*, (2016**) the drug being administered has limited aqueous solubility it can result in poor bioavailability. Furthermore, the low pH of the stomach as well as enzymatic activity can result in drugs delivered via the oral route being rapidly metabolized and degraded. Here we demonstrate the development and characterization of sustained release solid dispersion oral tablets, containing the poorly water-soluble drug disulfiram (DSF). The tablets, which are manufactured from two different polymers (Kolliphor1 P 188 and P 237) specifically designed for the manufacture of solid dispersions and two different polymers (Kollidon1 SR and HPMC) specifically designed to provide sustained release, can enhance the solubility of DSF, sustain its release, while protecting it from degradation in simulated gastric fluid (SGF). The paper demonstrates that when using the hot melt method at 80 C the DSF loading capacity of the Kolliphor1 P 188 and P 237 polymers is approximately 43 and 46%. The release rate of DSF can be manipulated by both the loading and type of sustained release polymer used, with HPMC providing for a much faster release rate compared to Kollidon1 SR.

17. **Jin Sun *et al.*, (2014)** this study was to prepare azithromycin sustained-release products in order to allow for a high dose to be administered, it reduces gastrointestinal side-effects and increase the compliance of patients. Azithromycin sustained-release tablets with different release performance were successfully prepared by wet granulation. The release rate of F-I am affected by dissolution media with different pH, but not for F-II. Hixsone Crowellmodel was the best regression fitting model for F-I and F-II. Additionally, F-I and F-II both belonged to non-Fick diffusion. Compared with the reference, the C_{max} of F-I

and F-II were decreased, and the T_{max} were prolonged, in that case which meet the requirement of sustained-release tablets. The relative bioavailability of F-I and F-II were 79.12%and 64.09%.

18. **Anirbandeep Bose *et al.*, (2013)** The objective of this present investigation was to develop and formulate sustained release (SR) matrix tablets of Itopride HCl, by using different polymer combinations and fillers, to optimize by Central Composite Design response surface methodology for different drug release variables and to evaluate drug release pattern of the optimized product. Sustained release matrix tablets of various combinations were prepared with cellulose-based polymers: hydroxy propyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP) and lactose as fillers. Study of pre-compression and post-compression parameters facilitated the screening of a formulation by response surface methodology (Central Composite Design). The in vitro study revealed that combining of HPMC K100M (24.65 mg) with PVP (20 mg) and use of lactose as filler sustained the action more than 12 h. The developed sustained release matrix tablet of improved efficacy can perform therapeutically better than a conventional tablet.

19. **Hye Jin Kim *et al.*, (2014)** Sarpogrelate HCl (SGL) has been used clinically as an anti-platelet drug for the prevention of thrombus, proliferation of vascular smooth muscle cells and platelet aggregation. This study was to investigate the bioavailability of sustained-release solid dispersion (SRSD) formulation of SGL to sustain the drug release for up to 24 h. The SR-SD formulations with various drug-to polymer ratios were prepared by hot–melt coating method. Waxy material carriers such as Compritol 888 ATO and stearyl alcohol were added to SGL and different amounts of HPMC K 15 (HPMC) were mixed. Dissolution profile and bioavailability were compared to SGL powder. Compritol 888 ATO showed the controlling effect of the initial release rate of drug from the formulation and the controlling effect was increased for 24 h by addition of HPMC. As the amount of HPMC increased, the drug release rate from SR-SD decreased because HPMC formed gel layer in aqueous media. These data suggest that the SR-SD formulation effectively controls the drug release rate for 24 h, hoping to be useful for the development of once-a-day formulation of SGL.

20. **Jin Wook Tak *et al.*, (2016)** the study was to characterize and optimize loxoprofen immediate release (IR)/sustained release (SR) tablet utilizing a three-factor, three-level Box–Behnken design (BBD) combined with a desirability function. The independent factors included ratio of drug in the IR layer to total drug (X1), ratio of HPMC to drug in the SR layer (X2), and ratio of Eudragit RL PO to drug in the SR layer (X3). The dependent variables assessed were % drug released in distilled water at 30 min (Y1), % drug released in pH 1.2 at 2 h (Y2), and % drug released in pH 6.8 at 12 h (Y3). The responses were fitted to suitable models and statistical validation was performed using analysis of variance. The optimized loxoprofen IR/SR tablets were successfully prepared with the determined amounts of ingredients that showed close agreement in the predicted and experimental values of tablet characterization and drug dissolution profile.

AIM AND OBJECTIVE

3. AIM AND OBJECTIVE

3.1. AIM:

To formulate and evaluate bilayer tablet of Glimepiride in floating drug delivery and Metformin in sustained release.

3.2. OBJECTIVE:

- To prepare Glimepiride floating formulation
- To prepare Metformin sustained release formulation
- To prepare bilayer tablet of Glimepiride and Metformin
- To study the physicochemical parameters of bilayer tablet
- To study the release character of tablet by *Invitro* dissolution

PLAN OF WORK

4. PLAN OF WORK

PHASE I

PRE FORMULATION STUDY

1. Identification of drug

- Melting point
- solubility

2. FTIR study

- Drug
- 5 physical mixture of drug and polymer

3. Calibration curve

- UV Spectrophotometer

PHASE II

PREPARATION OF TABLE

- Preparation of Glimepiride floating formulation
- Preparation of Metformin sustained release formulation
- Combination of Metformin and Glimepiride bilayer tablet

PHASE III

PHYSICOCHEMICAL EVALUATION

- Hardness
- Weight variation
- Thickness
- Friability
- Disintegration

PHASE IV

- *In vitro* evaluation
- kinetics studies of drug release

METHODOLOGY

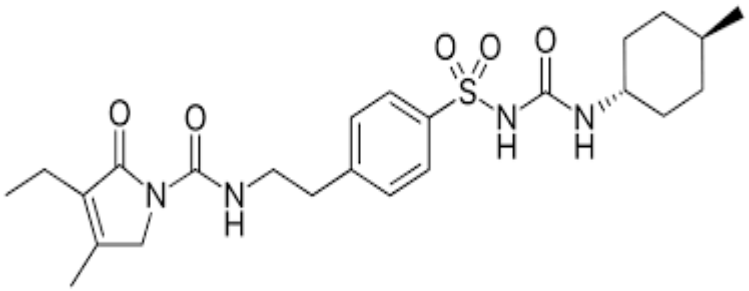
DRUG PROFILE

5. METHODOLOGY

5.1. DRUG PROFILE [5, 6, 7, 8]

5.1.1. GLIMERIRIDE:

Chemical structure:



Chemical formula:

$C_{24}H_{34}N_4O_5S$

Chemical name:

1-[[4-[2-(3-ethyl-4-methyl-2-oxo-3pyrrolidone-1-carboxamido) -ethyl] phenyl] sulphonyl]-3-trans-(4-methyl cyclohexyl) urea

Molecular weight:

490.6 g/mol

Category:

Anti diabetic (sulfonylurea)

Dose:

1 mg, 2 mg, 4mg

Dosage regimen:

1 mg to 8 mg

Bioavailability:

Completely 100% absorbed in oral administration

Solubility:

Completely soluble in dimethylformamide, sparingly soluble in dichloromethane, slightly soluble in methanol

Melting point:

Its starts to melt at 205°C and completely melt at 215°C

Indication:

To treat diabetes mellitus type 2 to increase insulin secretion and not to use in diabetes mellitus type1

Side effect:

Low blood sugar-shaking, anxiety, nervous, others-headache, nausea, dizziness

Toxicity:

Severe hypoglycemic reaction, seizure, neurological impairment

Metabolism:

Completely hepatic metabolism (1^{st}stage through CYP2C9)

Protein binding:

Over 99.5% bound to plasma protein

Volume of distribution:

21.8 ± 13.9 L (voluntaries)

19.8 ± 12.7 L (patients with diabetes type 2)

Elimination half time:

5-8 hours

Excretion:

In urine 60%

In fecse 40%

C_{max}:

103 ± 34ng/ml (single dose of 1 mg)

T_{max}:

2.4 ± 0.8 hours

Onset of action:

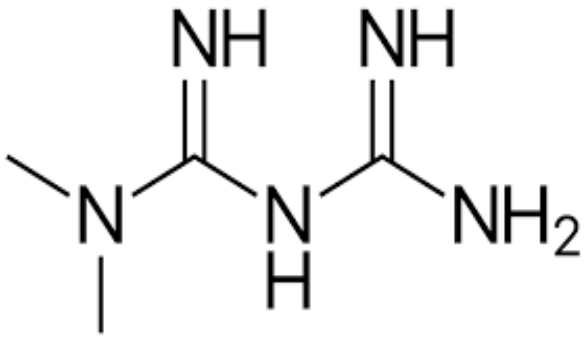
Within 3 hours

Duration of action:

Up to 24 hours

5.1.2. METFORMIN HYDROCHLORIDE [8, 9, 10]

Chemical structure:



Chemical name:

$C_4H_{11}N_5$

Chemical names:

1, 1 dimethylbiguanide

Molecular weight:

165.6 g/mol

Category:

Anti diabetic (biguanides)

Dose:

250 mg, 500 mg, 1000 mg

Dosage regimen:

250 mg to 3000 mg

Bioavailability:

50-60%

Solubility:

Freely soluble in water, partically insoluble in acetone, ether, chloroform, slightly soluble in ethanol

Melting point:

Its start to melt at 223°C and completely melt at 235°C

Indication:

To treat diabetes mellitus type 2, to enhance insulin mediated glucose uptake

Side effect:

Nausea, vomiting, gastric irritation diarrhea, constipation

Toxicity:

Lactic acidosis, decreases renal function if renal clearance is decreased

Metabolism:

Not metabolized

Protein binding:

Protein binding is negligible

Half life:

8-12 hours

Volume of distribution:

654 ± 358 L (single dose of 850 mg)

Elimination half life:

17.6 hours in blood

6.2 hours in plasma

Excretion:

Renal tubular secretion

C_{max}:

473 ± 145 ng/mol (single dose 500 mg)

T_{max}:

7.5 ± 1.2 hours

Duration of action:

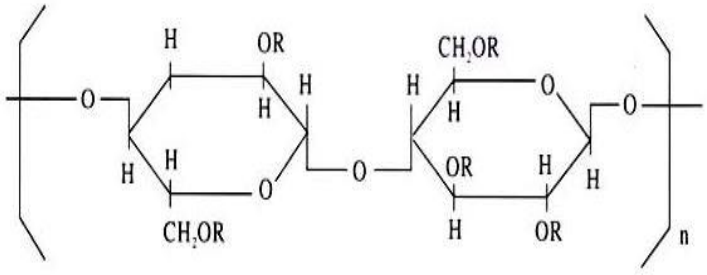
6-8 hours

EXCIPIENT PROFILE

5.2. EXCIPIENT PROFILE

5.2.1. HYDROXYPROPYLMETHYLCELLULOSE (K100M): [11]

Chemical structure:



Synonyms:

Hypromellose, methocel, metolose, methylcellulose propylene glycol, methyl hydroxylpropyl cellulose, HPMC, benecel MHPC

Chemical formula:

$C_{56}H_{108}O_{30}$

Molecular weight:

1261.41 g/mol

Category:

Semi synthetic polymer

Appearance:

Powder form

Color:

White or creamy white power

Density:

1.3 g / cm^3

Solubility:

Soluble in water, soluble in some organic solvent ethanol and methanol

Description:

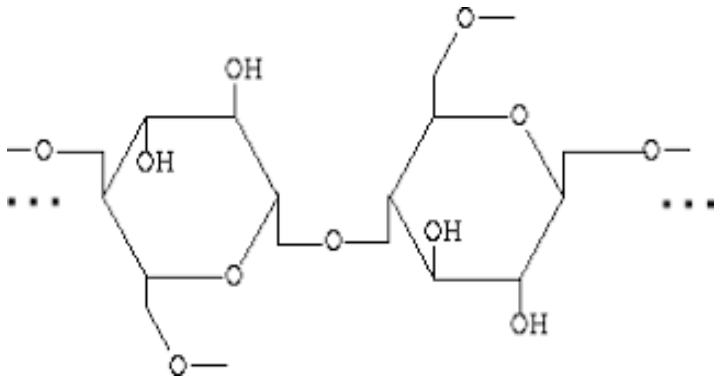
It is odorless and tasteless power used in sustained release tablet to control the release of drug.

Uses:

Water soluble polymer, lubricant, film former, thickener, binder, food additives

5.2.2. METHYL CELLULOSE: [15]

Chemical structure:



Synonyms:

Rhomellose, cellogel, methocel, nicel, cologel, MC

Chemical formula:

$C_{17}H_{32}O_{11}$

Molecular weight:

412.43 g/mol

Appearance:

Powder form

Color:

White powder or yellow white

Density:

1.31 g / cm^3

Melting point:

295 to 305 ° C

Solubility:

Soluble in water and glacial acetic acid, in soluble in alcohol, ether, chloroform and hot water

Description:

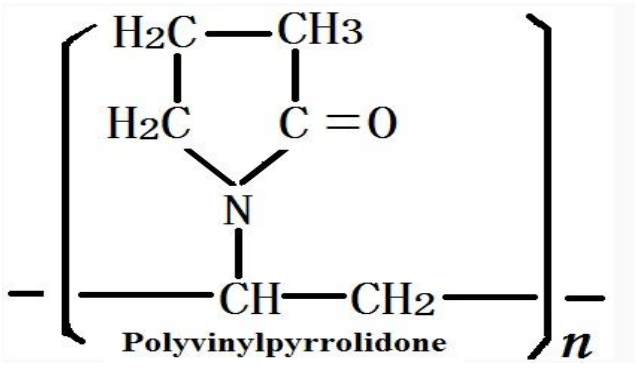
It is tasteless and odorless powder used in tablet as polymer and binder

Uses:

It is used in the food additives, growing crop, agriculture and pharmaceutical industry. It is used as thickener, emulsifier and film former

5.2.3. POLY VINYL PYRROLIDONE (K30): [14]

Chemical structure:



Synonyms:

Polyvidone, povidone

Chemical formula:

C_6H_9NO

Molecular weight:

2500 to 2900000 Daltons

Category:

Binder, lubricant

Appearance:

Powder form

Color:

White

Density:

1.2 g / cm^2

Solubility:

Soluble in water, organic solvents, insoluble in ether

Melting point:

150°C

Description:

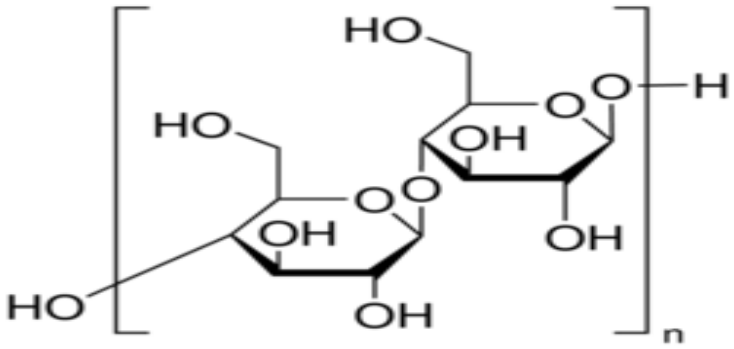
Poly vinyl pyrolidone is odorless, white powder used in tablet and capsules. PVP is water soluble polymer used to improve dissolution rate and bioavailability

Uses:

Poly vinyl pyrolidone is used binder, stabilizer, adhesive, and film forming agent. Poly vinyl pyrolidone is used in cosmetic product and food products.

5.2.4. MICROCRYSTALLINE CELLULOSE: [13]

Chemical structure:



Synonyms:

Avicel PH, cellulose gel, celphere, crystalline cellulose, pharmacel, tabulose, emcocel.

Chemical formula:

$C_{14}H_{26}O_{11}$

Molecular weight:

370.3 g/mol

Category:

Adsorbent, suspending agent, diluents

Appearance:

Power form

Color:

White

Density:

1.66 g/cm

Solubility:

Insoluble in water, ethanol, ether and slightly soluble in sodium hydroxide

Melting point:

260-270°C

Description:

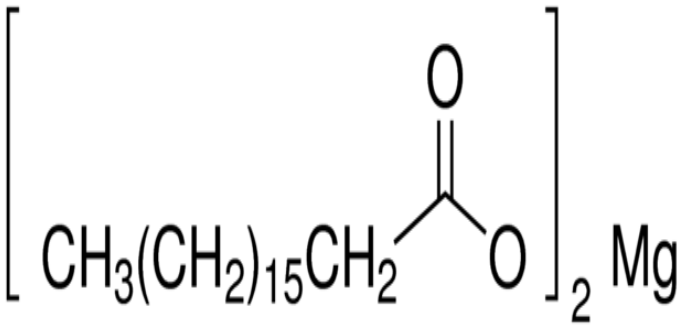
Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline power composed of porous particles. It is commercially available in different particles.

Uses:

Used in pharmaceutical formulation as binder, diluents and it is uses as lubricant and disintegrant, used in cosmetics and food products

5.2.5. MAGNESIUM STEARATE: [16]

Chemical structure:



Synonyms:

Stearic acid, octadecanoic acid, dibasic magnesium stearate, magnesium salt

Chemical formula:

$C_{36}H_{70}MgO_4$

Molecular weight:

591.25 g/mol

Appearance:

Fine Powder form

Color:

white

Density:

1.026 g / cm^3

Solubility:

Insoluble in water, slightly soluble in alcohol and ether, soluble in benzene

Melting point:

88°C

Description:

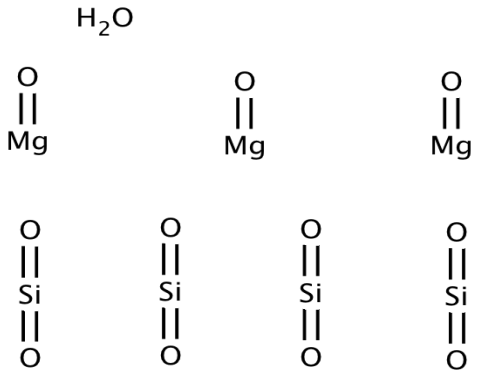
Magnesium stearate is a fine white powder that sticks to our skin and is greasy to touch. It's a simple salt made of two substances, a saturated fat called stearic acid and mineral magnesium

Uses:

Magnesium stearate is commonly used in food products, pharmaceuticals, and cosmetic products. It is used as lubricant prevents sticking in tablet and considered as free flowing agent in capsule

5.2.6. TALC: [17]

Chemical structure:



Synonyms:

Talcum powder

Chemical formula:

$H_2Mg_3O_{12}Si_4$

Molecular weight:

379.25 g/mol

Appearance:

Powder form

Color:

White

Density:

2.7 g/cm^3

Solubility:

Insoluble in water, cold acids, alcohol and slightly soluble in diluted mineral acids

Melting point:

900 to 1000°C

Description:

Talc is mineral made up of elements magnesium, silicone and oxygen. It absorbs moisture well, keeping skin dry and to prevent from rashes. It is widely used in cosmetic products like baby powder, facial powder

Uses:

It is mainly used in cosmetic products and act as lubricant and absorbent, it is used as filler in tablet and capsules.

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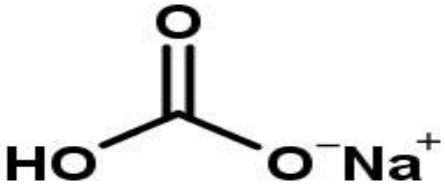
5.2.7. SODIUM BICARBONATE: [12]

Chemical structure:



Synonyms:

Baking soda, monosodium carbonate, effer soda, sodium acid carbonate, sodium hydrogen carbonate

Chemical formula:

$NaHCO_3$

Molecular weight:

84.01 g/mol

Category:

Alkalizing agent

Appearance:

Granules form

Color:

White granules

Density:

2.2 g/cm^3

Solubility:

Soluble in water and insoluble in ethanol

Melting point:

270°C

Description:

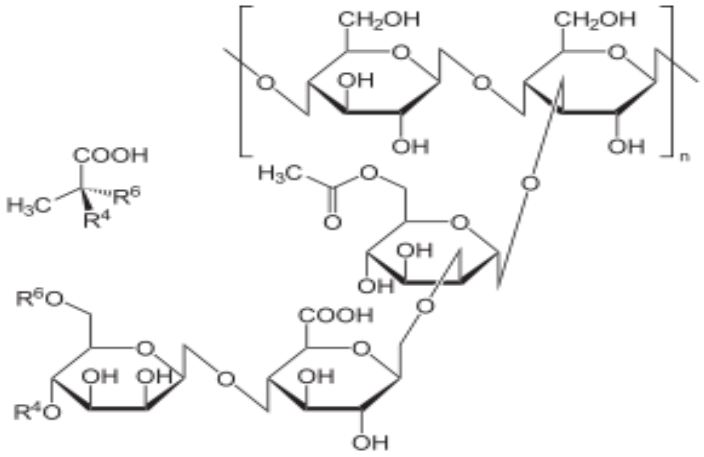
Sodium bicarbonate is odorless, white, crystalline power with saline, slightly alkaline in taste. The grades with different particles size, from a fine power to free flowing granules, are commercially available.

Uses:

Used in pharmaceutical formulations sources as carbon dioxide in effervescent tablet, and used to maintain the alkaline ph in pharmaceuticals preparation. Used in food products as baking soda, and to reduces gastric irritation in stomach.

5.2.8. XANTHAN GUM: [18]

Chemical structure:



Synonyms:

Corn sugar gum, Goma xantana, Gomme xanthana, polysaccharide bacterien, polysaccharide xanthana

Chemical formula:

$C_{36}H_{58}O_{29}P_2$

Molecular weight:

1016.77 g/mol

Appearance:

Powder form

Color:

White or Cream color

Density:

1.5 g / cm^3

Solubility:

Soluble in water and insoluble in organic solvents

Description:

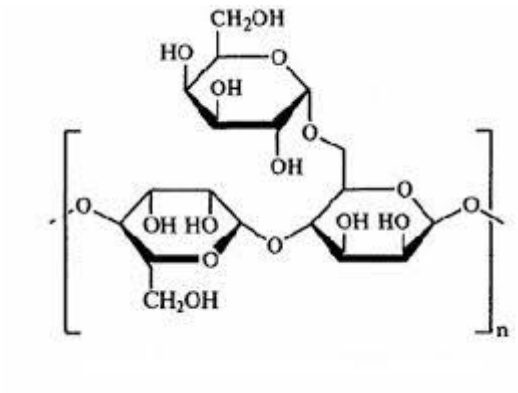
Xanthan gum is produced from simple sugar by fermentation process using bacteria xanthomonas campestris

Uses:

It is used as food additives, thickening agent, stabilizer, and natural polymer

5.2.9. GUAR GUM:

Chemical structure:



Synonyms:

Jaguar gum, guar flour, Indian guar plant, cyamopsis psoraliodes, dolichos psoraloides

Chemical formula:

$C_{10}H_{14}N_5Na_2O_{12}P_3$

Molecular weight:

535.14 g/mol

Appearance:

Powder form

Color:

Off white to yellowish-white

Density:

0.8-1.0 g/ml at 25°C

Solubility:

Soluble in water and insoluble in ethanol

Description:

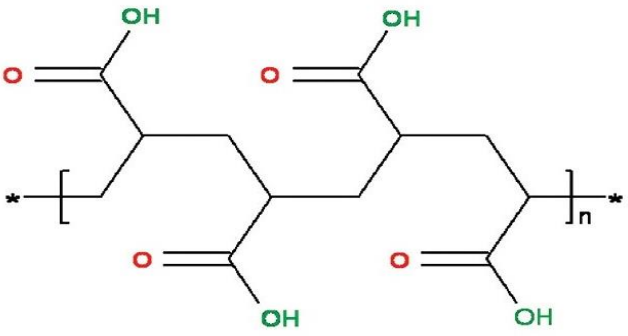
Guar gum is five to eight times thickening of starch. Water solutions are tasteless, odorless, and nontoxic and have a pale translucent gray color with neutral Ph. Water solutions converted to gel small amount of borax

Uses:

Guar gum is used as emulsifier, thickener, stabilizer in food and cosmetic product. It is used in textile, paper industry and also used as tablet binder

5.2.10. CARBOPOL 934:

Chemical structure:



Synonyms:

Acrylic acid, carbomer, polyacrylic acid, polyacrylate sodium, sodium acrylates

Chemical formula:

$C_3H_3NaO_2$

Molecular weight:

94.04 g/mol

Appearance:

Fine powder

Color:

White

Density:

1.1-1.4 g/cm^3

Solubility:

Soluble in water

Description:

Carbopol is available in different grades, which are widely used in manufacture of cosmetic like gel, cream lotions, detergents and air freshener.

Uses:

Carbopol is an emulsifier, stabilizer, suspending, thickening and gelling agent in many industries

.

CHEMICALS AND EQUIPMENTS

LIST OF CHEMICALS

Table No 1: List of chemicals

MATERIALS	SOURCES
Glimepiride	Gifted sample
Metformin	Gifted sample
Guar Gum	S D Fine Chem limited
Xanthan Gum	Himedia lab
Carbopol 394	Loba Chemie
Sodium bicarbonate	Kemphasol
Talc	Loba Chemie
Magnesium stearate	Himedia lab
Amaranth	Loba Chemie
Hydroxylpropyl methylcellulose K100M	Yarrow Chem.
Methyl cellulose	Loba Chemie
Poly vinyl pyrolidone K 30	Loba chemie
Micro crystalline cellulose	Loba Chemie

LIST OF EQUIPMENTS

Table No 2: List of equipments

EQUIPMENT	SUPPLIERS
Melting point equipment	Selec TC 303
Digital balance	ELB 300, Shimadzu, Philippines
UV Spectrometer	UV 1650, PC Shimadzu
FT-IR	JASCO 4100-FT/IR, FTIR8400 Shimadzu
Tablet punching machine	Rimek mimipress-I
Dissolution	Lab India DS 8000
Disintegration	Lab India DT 1000
Friability tester	Inweka
Hardness tester	Dolphine
PH meter	Systronics µph system 361

PREFORMULATION STUDY

5.3. PRE FORMULATION STUDY

5.3.1. IDENTIFICATION OF DRUG [21, 22]

Melting point:

Digital melting point apparatus is used to determine the melting point of Metformin and Glimepiride by capillary tube method. One end of capillary tube was sealed with gentle heat using burner and then a small quantity of pure drug Metformin and Glimepiride was filled into the sealed capillary tube. Then this capillary tube with pure drug was placed in the melting point apparatus. The temperature at which the drug gets melted is taken as melting point of the drug.

Solubility:

Glimepiride was dissolved in different solvents like methanol, dimethyl sulfoxide and water, to identify drug is freely soluble or sparingly soluble.

Metformin was dissolved in different solvents like water, ethanol and chloroform, to identify drug is freely soluble or sparingly soluble.

5.3.2. FOURIER TRANSFORM INFRARED SPECTROPHOTOMETER

FT-IR drug polymer compatibility study [23]:

Infrared spectra of the drug and its inclusion complexes were recorded by K Br pellet method using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide and then spectra of dried mixture of drug and inclusion complexes with potassium bromide were recorded. The samples were prepared as K Br pellets by compression at 6ton /nm^2. The wavelength range was selected between400-4000 cm^{-1}.

5.3.3. CALIBRATION CURVE OF DRUG

UV Spectrophotometer [23]

Determination of lambda max (Glimepiride):

10 mg of pure drug Glimepiride was dissolved in 10 ml of methanol 1mg/ml (stock solution A). 1 ml of stock solution A was diluted in 100 ml of distilled water 10µg/ml (stock

solution B). 1 ml of stock solution B is diluted in 10 ml standard flask, scanned in UV spectrophotometer 400-200 nm. The maximum absorption is taken as lambda max.

Standard curve:

10 mg of the drug was dissolved in 10 ml of methanol 1mg/ml (stock solution A). 1 ml of stock solution A was diluted in 100 ml of distilled water 10µg/ml (stock solution B). Serial dilution of stock solution B was done to get 1µg/ml -10µg/ml. These solutions were analysed in the UV Spectrophotometer at the 228 nm. The calibration curve was plotted in the concentration on the x-axis and the absorbance on the y-axis. The correlation coefficient was also calculated.

Determination of lambda max (Metformin):

10 mg of drug was dissolved in 100 ml of distilled water 100µg/ml (stock solution A). 10 ml of stock solution A was further diluted to 100 ml 10µg/ml (stock solution B). 1 ml of stock solution B was diluted to 10 ml in standard flask, and scanned in UV Spectrophotometer 400-200 nm. The maximum absorption is taken as lambda max.

Standard curve:

10 mg of drug was dissolved in 100 ml of distilled water 100µg/ml (stock solution A). 10 ml of stock solution A was further diluted to 100 ml 10µg/ml (stock solution B). Serial dilution of stock solution B was done to get 2µg/ml-20µg/ml. These solutions were analyzed in UV spectrophotometer at 232 nm. The calibration curve was plotted in the concentration on the x-axis and the absorbance on the y-axis. The correlation coefficient was also calculated.

Simultaneous estimation of Glimepiride and Metformin [24]:

10 mg of Glimepiride is dissolved in 10 ml of methanol, make up to 100 ml by using co solvent as water (solution 1) and 10 mg of metformin is dissolved in 100 ml of water (solution 2). 50 ml from solution 1 and 50 ml from solution 2 is mixed and this mixed solution is taken as solution 3. The solution 3 contains 100 µg / ml

Determination of lambda max:

2 ml of solution 1 and solution 2 is scanned separately under 200-400 nm in UV spectrophotometer. The both curve is overlapped to each other. The overlapped nm is takes as simultaneous nm

Simultaneous linearity:

From solution 3 serial dilutions is done by using water by to get 10 µg/ml -50 µg /ml. These diluted solutions are analysed in simultaneous nm in UV spectrophotometer by using water as blank. The linearity curve is plotted in the concentration on the x-axis and the absorbance on the y-axis. The correlation coefficient was also calculated with 95% confidence level plot.

5.4. PREPARATION OF BILAYER TABLET

5.4.1. PREPARATION OF GLIMEPIRIDE FLOATING TABLET [26, 26]:

The tablet contains 100 mg of Glimepiride is prepared by direct compression method by using polymer in different ratio. All ingredients were passed through sieve mesh no: 40 separately. Drug and polymer were mixed homogenously, and magnesium stearate and talc is added as lubricant and filler. All ingredients were mixed and weighted accurately and compressed in tablet punching machine (REMIK mini press 1) in low compression force.

Formulation table for Glimepiride floating layer:

Table No 3: Formulation table for Glimepiride floating tablet

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Glimepiride	2	2	2	2	2	2	2	2
Guar gum	15	15	25	25	15	15	25	25
Xanthan gum	15	25	15	25	15	25	15	25
Carbopol 934	15	15	15	15	25	25	25	25
Sodium bicarbonate	23	23	23	23	23	23	23	23
Talc	25	15	15	5	15	5	5	0
Magnesium stearate	5	5	5	5	5	5	5	5
Amaranth	qs	qs	qs	qs	qs	qs	qs	qs
Total	100	100	100	100	100	100	100	100

In formulation table all ingredients are mentioned in milligram (mg)

5.4.2. PREPARATION OF METFORMIN SUSTAINED LAYER TABLET [27]:

The tablet contains 350 mg of Metformin is prepared by direct compression method by using polymer in different ratio. All ingredient were passed through sieve mesh no: 40 separately. Drug and polymer were mixed homogenously, and magnesium stearate and microcrystalline cellulose is added as lubricant and filler. All ingredients were mixed and weighted accurately and compressed in tablet punching machine (REMIK mini press 1)

Formulation table for sustained release tablet:

Table No 4: Formulation table for Metformin sustained release tablet

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Metformin	250	250	250	250	250	250	250	250
HPMC K100 M	15	15	25	25	15	15	25	25
Methyl cellulose	15	25	15	25	15	25	15	25
PVP K 30	15	15	15	15	25	25	25	25
MCC	15	15	15	15	15	15	15	15
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	30	20	20	10	20	10	10	0
Total	350	350	350	350	350	350	350	350

In formulation table all ingredients are mentioned in milligram (mg)

HPMC - Hydroxyl Propyl Methyl Cellulose

PVP - Poly Vinyl Pyrolidone

MCC - Micro Crystalline Cellulose

5.4.3. FORMULATION OF BILAYER TABLET:

Table No 5: Preparation of bilayer tablet of Glimepiride and Metformin

FIRST LAYER	Glimepiride 2 mg with polymer ratio (Guar gum / xanthan gum / carbopol), excipients- talc, magnesium stearate, and sodium bicarbonate as effervescent, amaranth as colouring agent	Tablet 100 mg: Drug -2 mg Polymer - 15 / 25 mg $NaHCO_3$ -23 mg Talc -q s Mg. stearate-5 mg Amaranth -q s
SECOND LAYER	Metformin 250 mg with polymer ratio (HPMC / MC / PVP), excipients- MCC, magnesium stearate, talc	Tablet 350 mg: Drug -250 mg Polymer -15 /25 mg MCC -15 mg Mg. stearate-10 mg Talc -q s

5.5. PHYSIOCHEMICAL EVALUATION [28]

5.5.1. WEIGHT VARIATION TEST:

To study weight variation, 6 tablet of formulation were weight using an electronic balance and the test was performed according to the standard IP. The weight were calculated in the given formula

$$\% \text{ weight variation} = \frac{\text{Individual weigh - Average weight}}{\text{Average weight}} \times 100$$

5.5.2. THICKNESS:

Thickness of tablet is important for uniformity of tablet size. Six tablets were selected at random and thickness is measured by using vernier-calliper scale, which permits accurate measurement.

5.5.3. HARDNESS OF TABLET:

Hardness of tablet is the indication of its strength against resistance of tablet to capping, abrasion or breakage under conduction of storage, temperature and handling before usage. Hardness is the measure of force required to break the tablet a specific device. Hardness of six tablets is determined by Monsanto hardness tester. Hardness is measured in kg /cm^2.

5.5.4. FRIABILITY TEST:

Tablet friability is determined with Inweka friabilator. Accurately weight the tablet, and place the tablet in the drum. Rotate the drum 10 times, remove the tablet. The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 rpm. Thus at each turn the tablet roll or slide and fall onto the drum wall or onto each other. A maximum means loss from three samples of not more than 1% is considered acceptable for most products.

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

5.5.5 DISINTEGRATION TIME:

Disintegration test is done disintegration apparatus in six rack basket. The tablet is placed in basket in buffer medium (pH 1.2). Time is noted when tablet is completely dissolved in basket. This time is taken as disintegration time.

5.5.6. FLOATING LAG TIME AND FLOATING CAPACITY:

Time takes to reach the surface of water is floating lag time and period of time than constantly floats on the surface of medium is floating capacity. This procedure is done in dissolution vessel contains 0.1 N HCL as buffer medium (pH 1.2). Time is noted between, the tablet introduced into the buffer medium and time takes to reach the upper surface of tablet. This time is taken as floating lag time. Time that retains on surface on medium is taken as floating capacity.

5.6. *IN VITRO* EVALUATION [29]:

Drugs release studies were carried out in dissolution test apparatus using specified volume 900 ml of dissolution media maintained at 37°C ± 0.5°C. The tablet is directly placed in the medium and immediately operates the apparatus at specified rate. Within the time interval specified (1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr & 15hr) withdraw a specimen from zone midway between the surface of the dissolution medium and the top of the rotating paddle not less than 10 mm from the vessel wall and same volume of fresh medium is replaced each time. The samples are filtered and from the filtrate 1 ml is taken and diluted to 10 ml. These sample are analysed and further calculated is carried out to get drug release. Drug release are tested with zero order (cumulative % drug release VS time), first order (log % remained VS time). The invitro dissolution kinetic parameter, dissolution rate constant, correlation coefficient and dissolution efficiency were calculated.

Dissolution system:

Medium	: 0.1 N HCL (pH 1.2), phosphate buffer (pH 7.4)
Apparatus	: USP, type 2 paddle
RPM	: 50
Temperature	: 37 ± 0.5°C
Volume	: 900 ml
Sampling time interval	: 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr & 15hr

5.7. KINETICS STUDYS OF DRUG RELEASE [30, 31, 32]

The kinetics of drug release was a useful tool to demonstrate the behavior of drug release in vitro through mathematical model. Kinetics model helps to achieve more information about mechanism of drug release through fitting in kinetics model. The kinetics models are zero order, first order, Higuchi, Korsemeyer peppas plot. The equations are applied to describe the kinetics of drug release. The data obtained from *Invitro* drug release are used to calculate the correlation coefficient (r) value.

RESULTS AND DISCUSSION

6. RESULTS & DISCUSSION

6.1. PREFORMULATION STUDIES

6.1.1. IDENTIFIATION OF DRUG:

Melting point study:

Melting point of Glimepiride is found to be 215°C

Melting point of Metformin is found to be 235°C

Solubility study:

Solubility of glimepiride:

Dimethyl sulfoxide	- freely soluble (10 mg of drug in 1 ml of dimethyl sulfoxide)
Methanol	- slightly soluble (10 mg of drug in 10 ml of methanol)
Water	- In soluble

Solubility of metformin:

Water	- freely soluble (10 mg of drug in 1 ml of water)
Ethanol	- slightly soluble (10 mg of drug in 10 ml of ethanol)
Chloroform	- Insoluble

6.1.2. FOURIER TRANSFORM INFRARED SPECTROPHOTOMETER

Figure no 1: FT-IR of Glimepiride

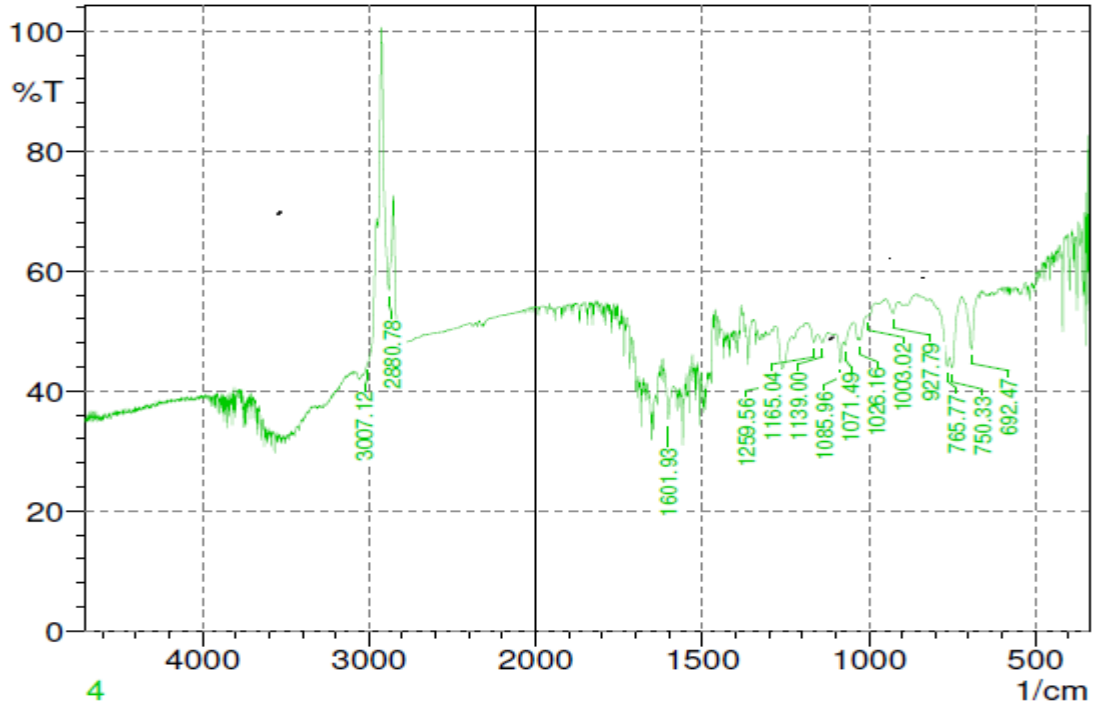


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Table No 6: FT-IR data of Glimepiride

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	1601	C=C stretching
2	1259	C-O stretching
3	3007	C-H starching

Figure No 2: FT-IR of Metformin

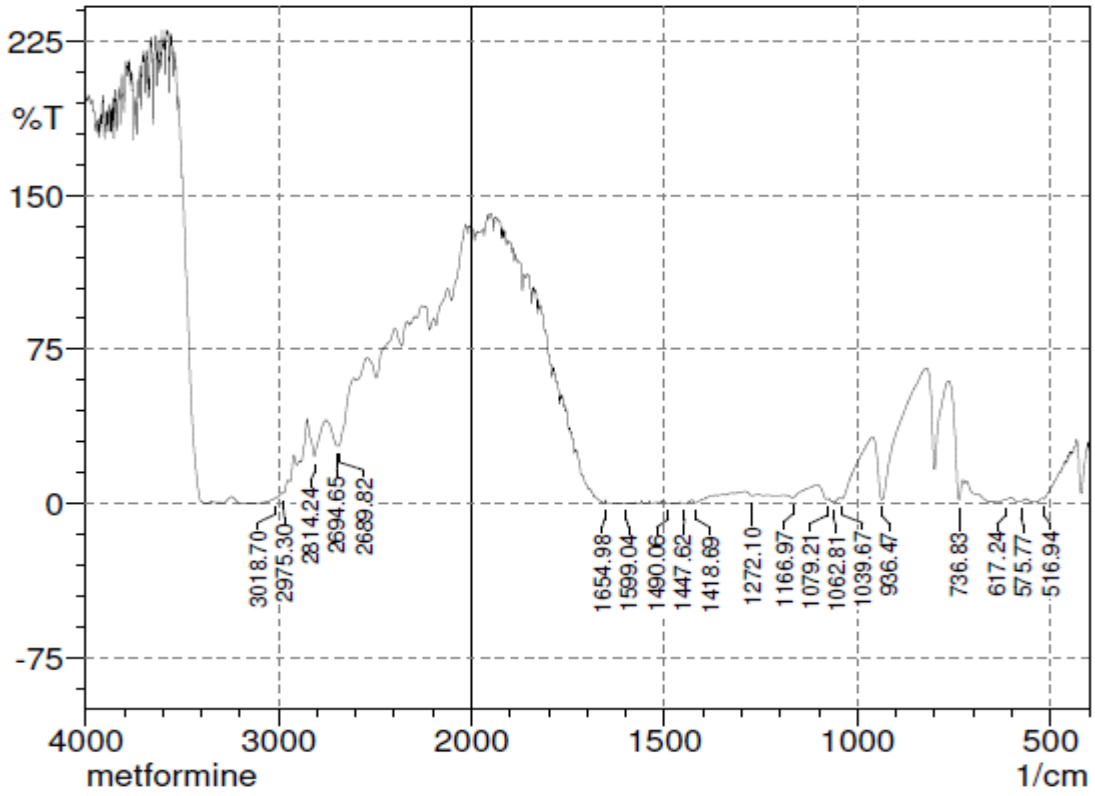

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Table No 7: FT-IR data of Metformin

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	2975	O-H stretching
2	2814	N-H stretching
3	3018	C-H stretching

Figure No 3: FT-IR of Guar gum

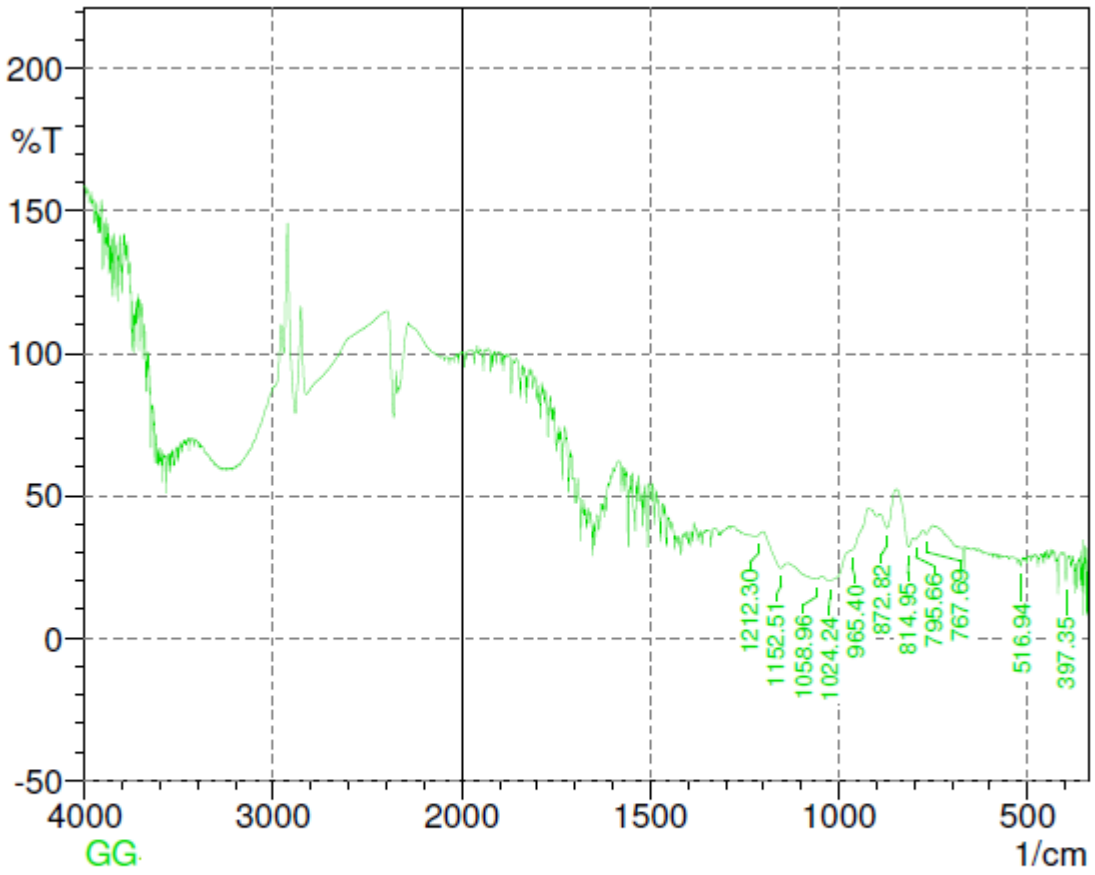

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Table No 8: FT-IR data of Guar gum

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	965	C=C bending
2	814	C-H bending
3	767	C-H bending

Figure No 4: FT-IR of Xanthan gum

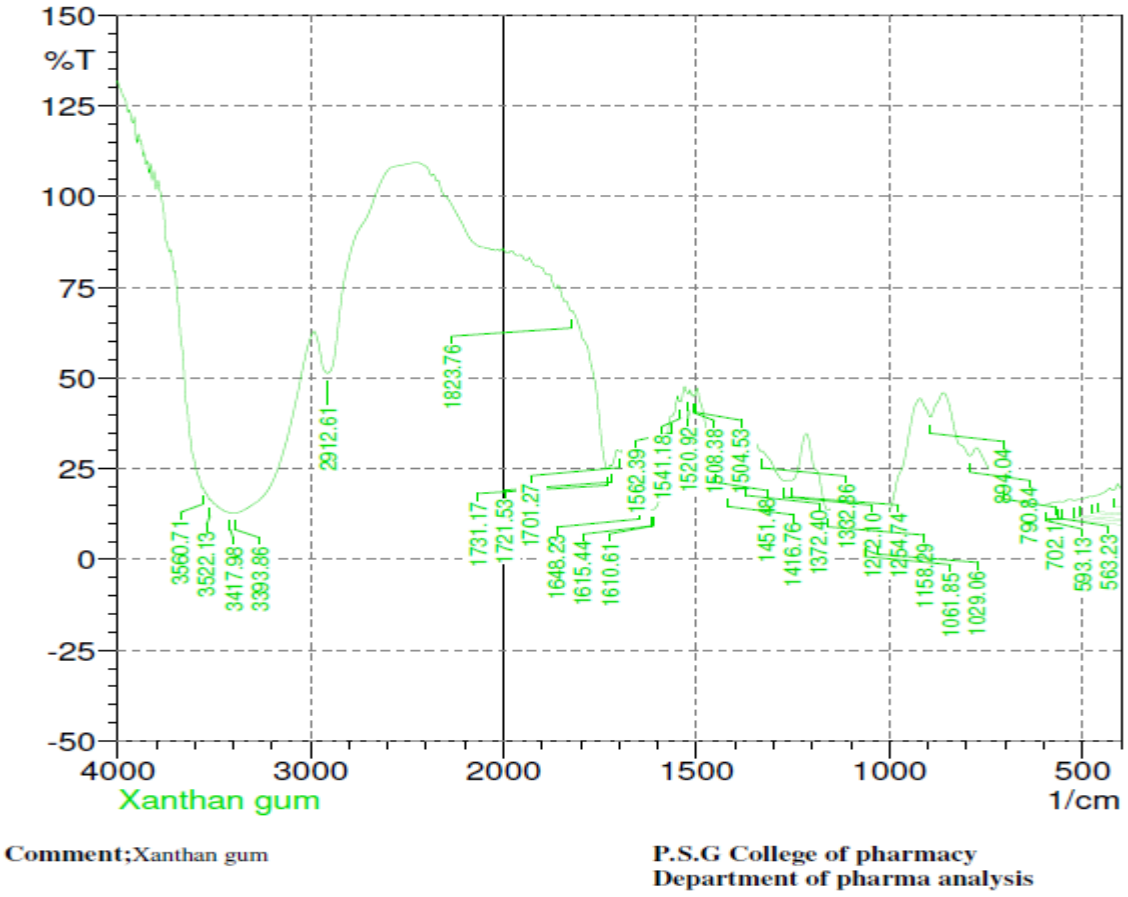

Table No 9: FT-IR data of Xanthan gum

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	1731	C=O stretching
2	2912	C-H stretching
3	3393	O-H stretching

Figure No 5: FT-IR of carbopol

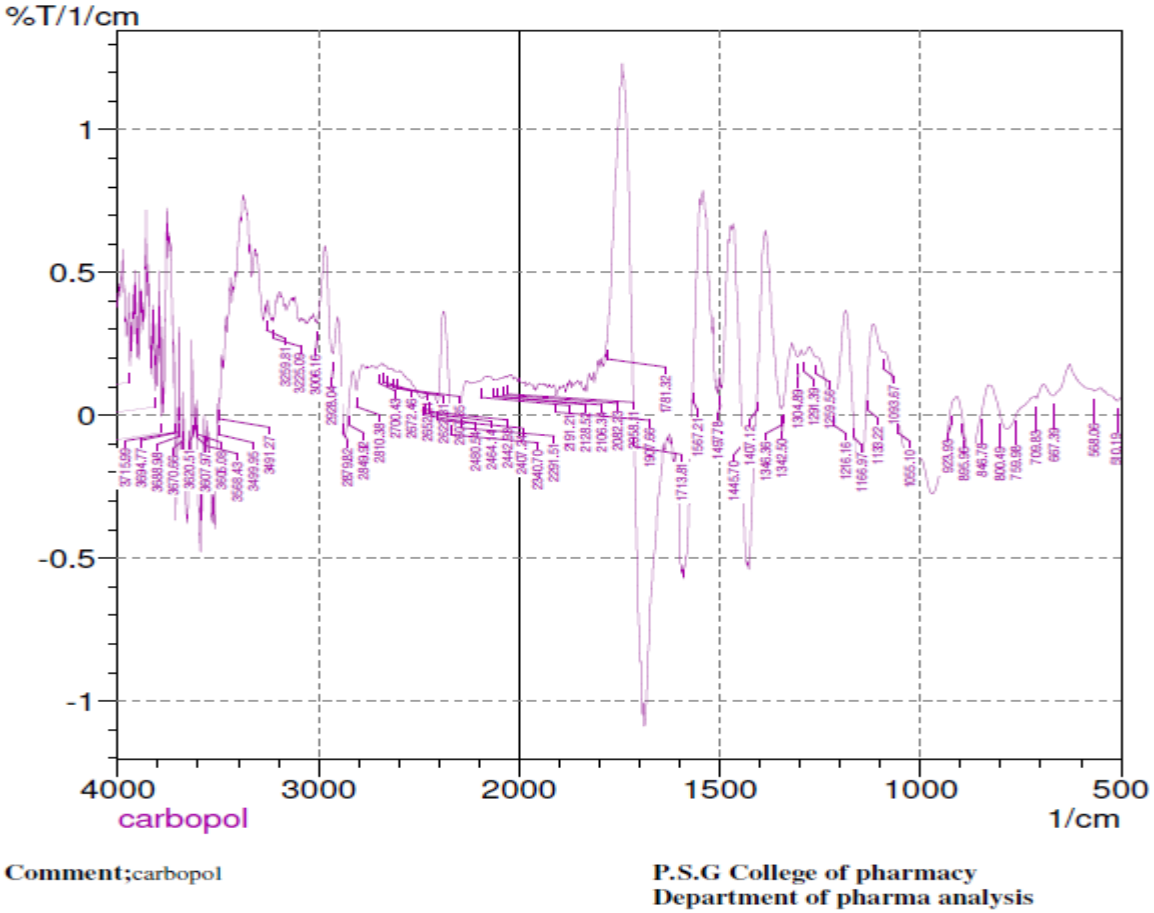

Table No 10: FT-IR data of Carbopol

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	2340	O=C=O stretching
2	800	C=C bending
3	1216	C-O stretching

Figure No 6: FT-IR of Sodium bicarbonate

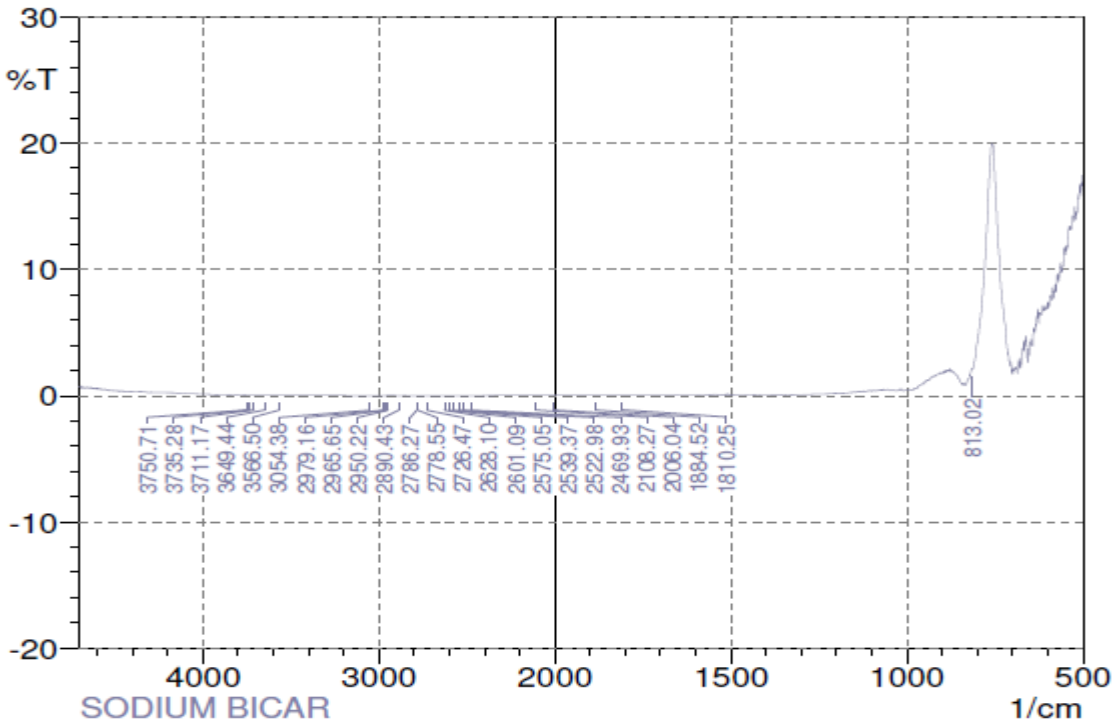

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Table No 11: FT-IR data of Sodium bicarbonate

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	813	C-H stretching
2	3649	O-H stretching
3	2979	C-H stretching

Figure No 7: FT-IR of Talc

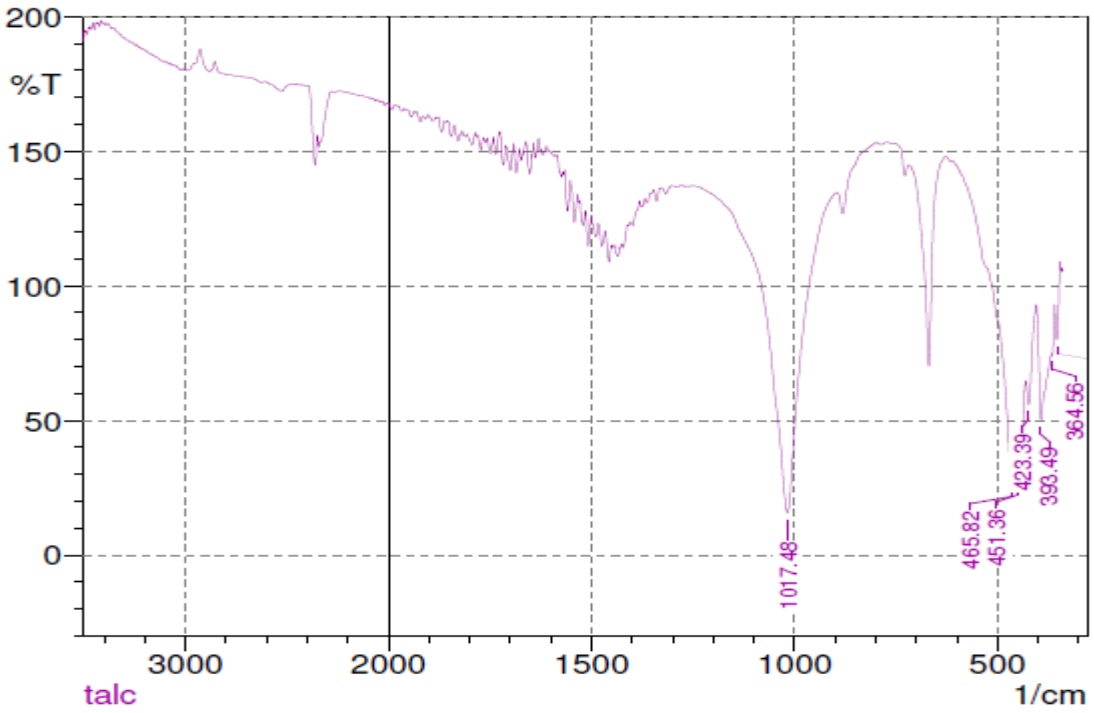

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Table No 12: FT-IR data of Talc

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	1017	S=O stretching
2	2447	N-H stretching

Figure No 8: FT-IR of Magnesium stearate

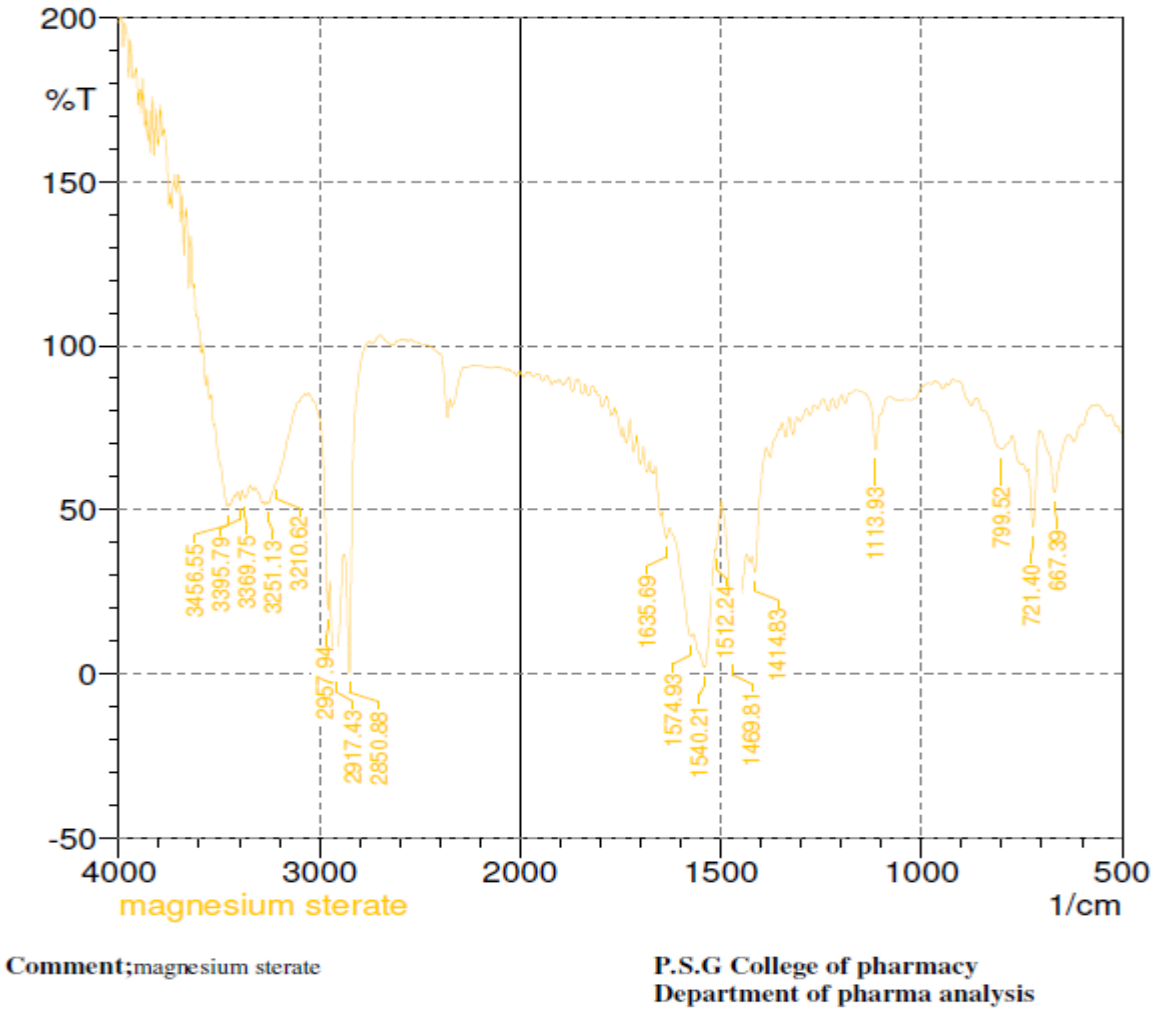

Table No 13: FT-IR data of Magnesium stearate

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	2917	C-H stretching
2	1469	C-H bending
3	3210	O-H stretching

Figure No 9: FT-IR of HPMC K100M

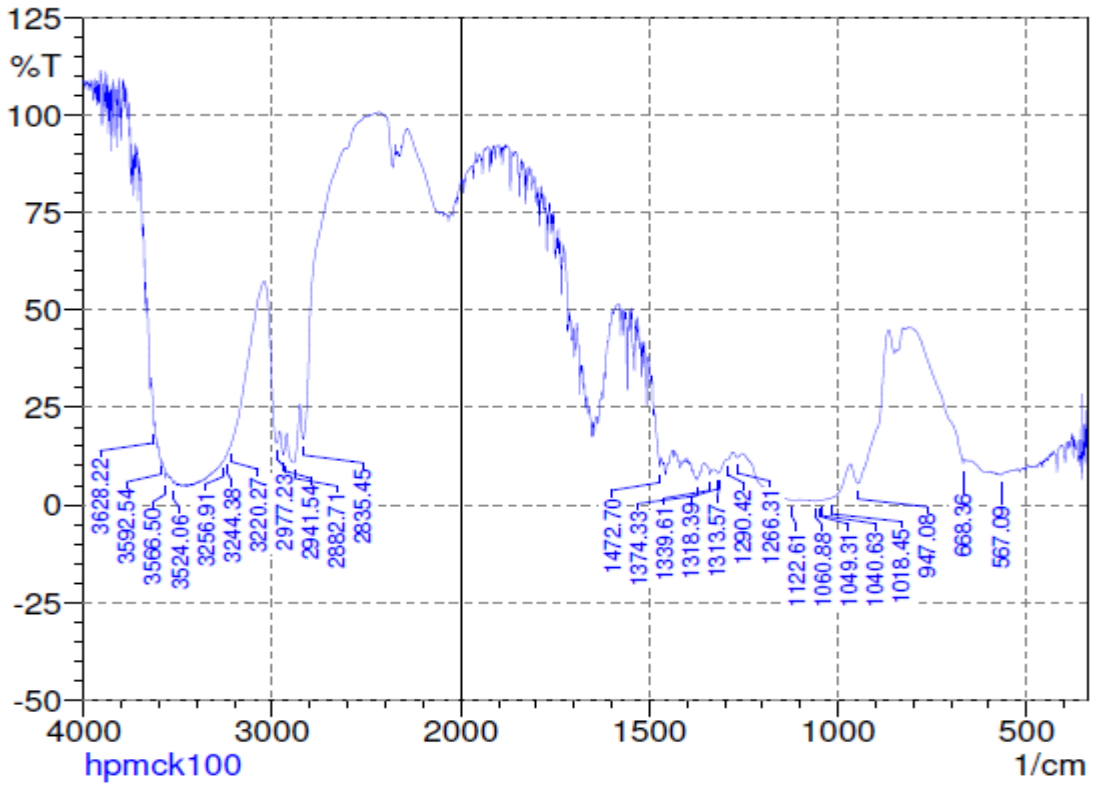

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Table No 14: FT-IR data of HPMC K100M

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	2977	C-H stretching
2	1122	C-O stretching
3	3220	O-H stretching

Figure No 10: FT-IR of Methyl cellulose

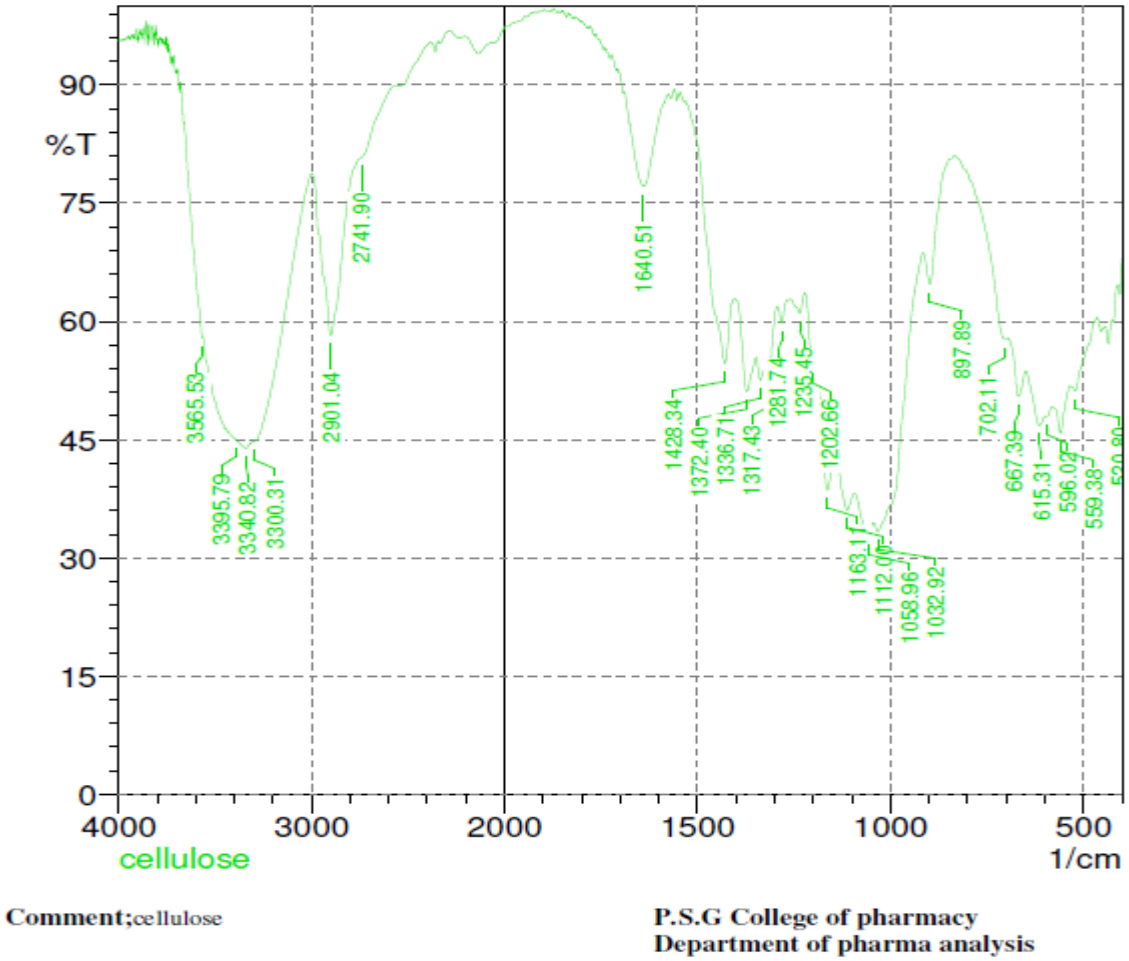

Table No 15: FT-IR data of Methyl cellulose

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	3300	N-H stretching
2	1032	C-O stretching
3	2901	C-H stretching

Figure No 11: FT-IR of PVP K30

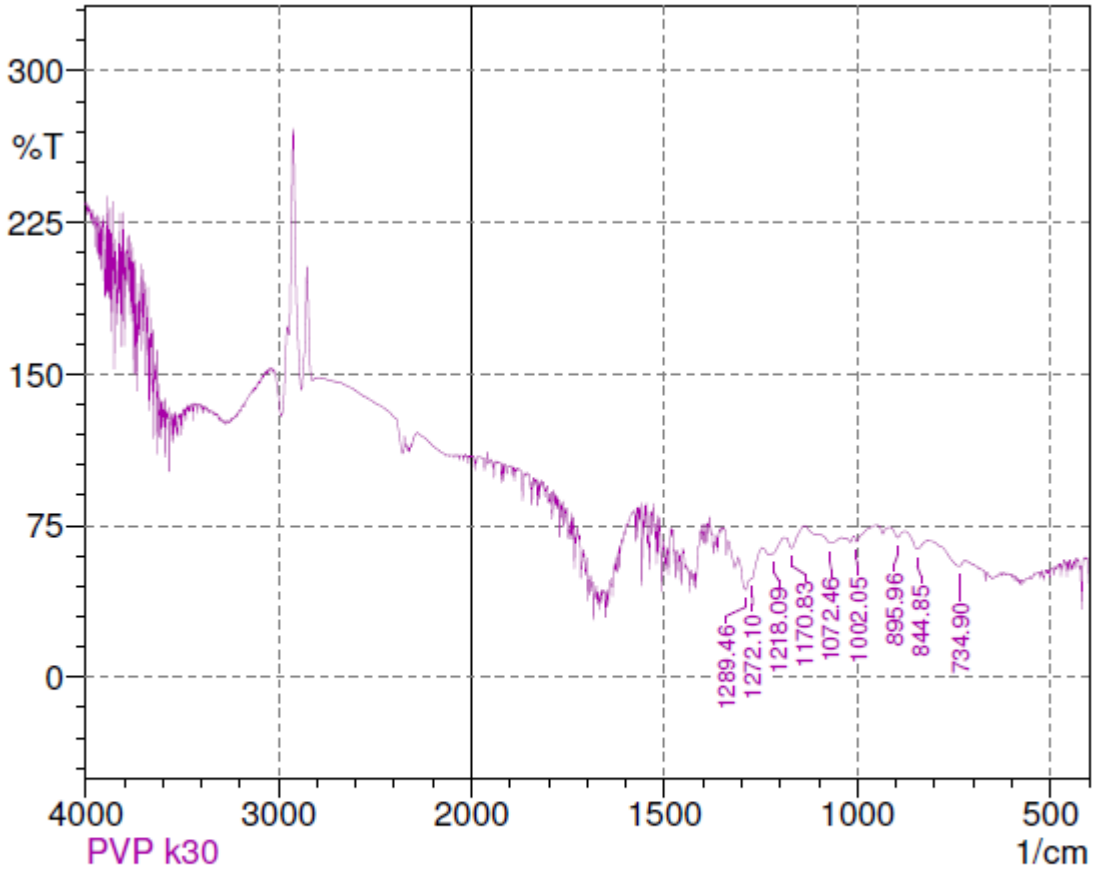

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Table No 16: FT-IR data of PVP K30

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	895	C-H bending
2	1170	C-O stretching
3	1289	C-N stretching

Figure No 12: FT-IR of microcrystalline cellulose

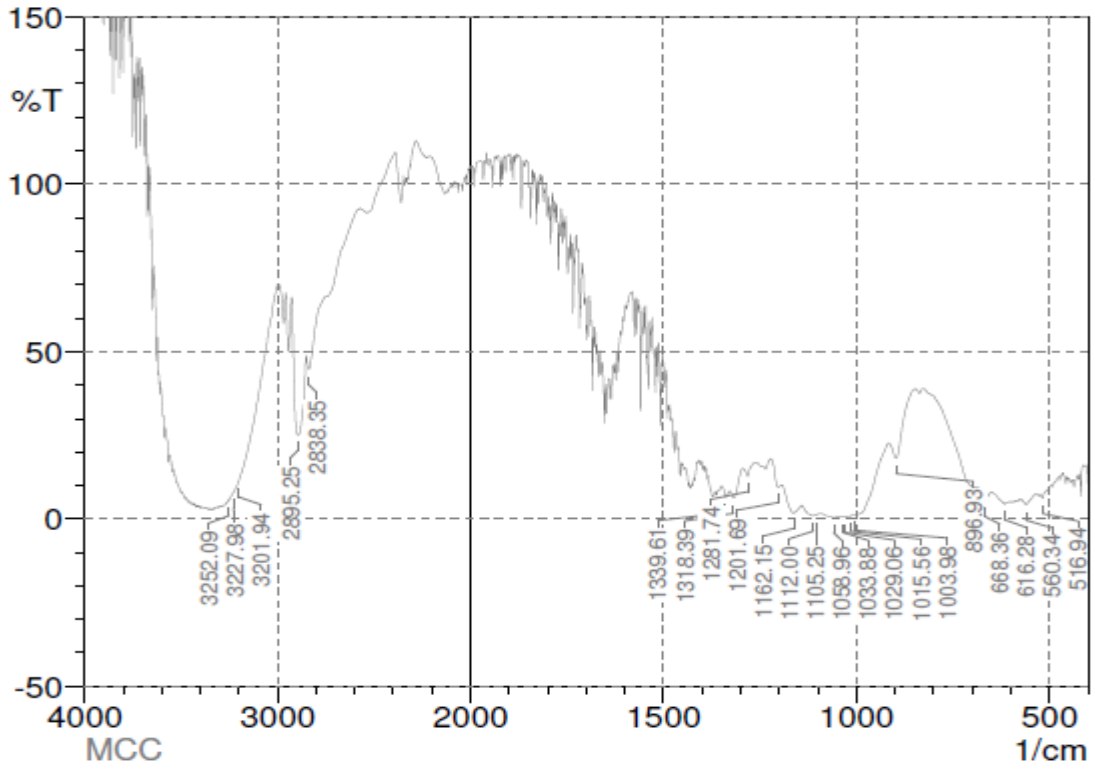

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Table No 17: FT-IR data of microcrystalline cellulose

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	3227	O-H stretching
2	1112	C-O stretching
3	896	C-H bending

Figure No 13: FT-IR of Glimepiride + Excipients

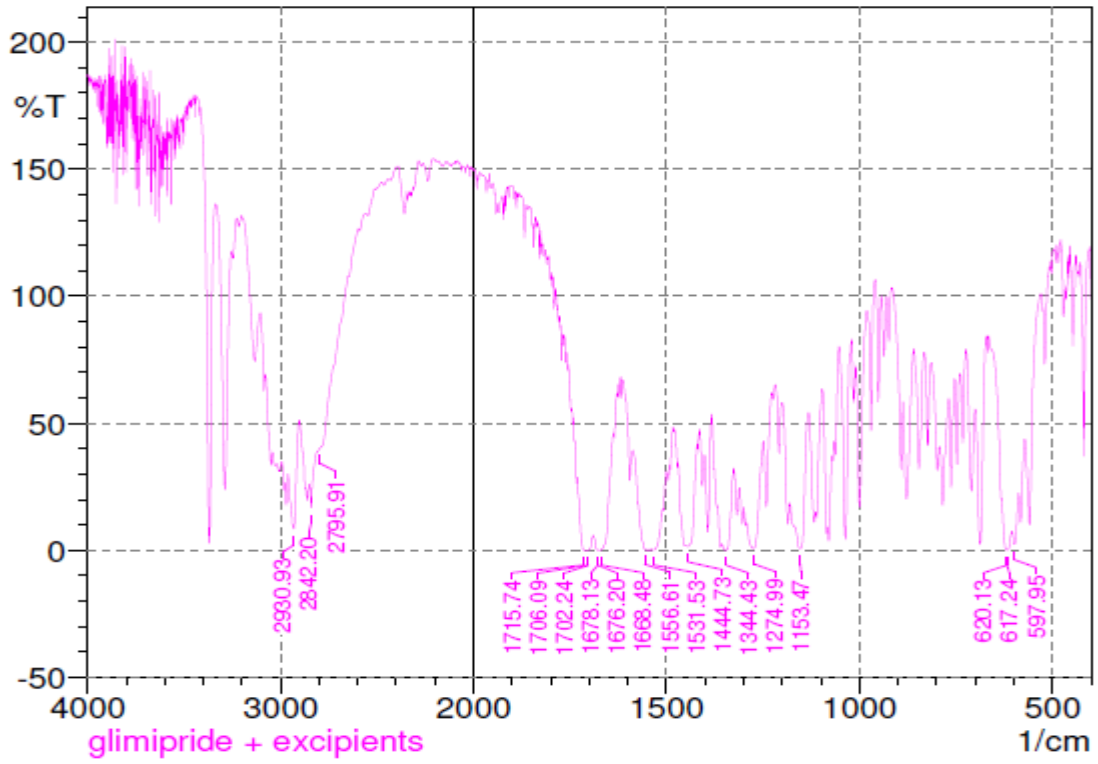

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Table No 18: FT-IR data of Glimepiride + Excipients

S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	2843	C-H stretching
2	1715	C=O stretching
3	1668	C=N stretching
4	1344	S=O stretching

Figure No 14: FT-IR of Metformin + Excipients

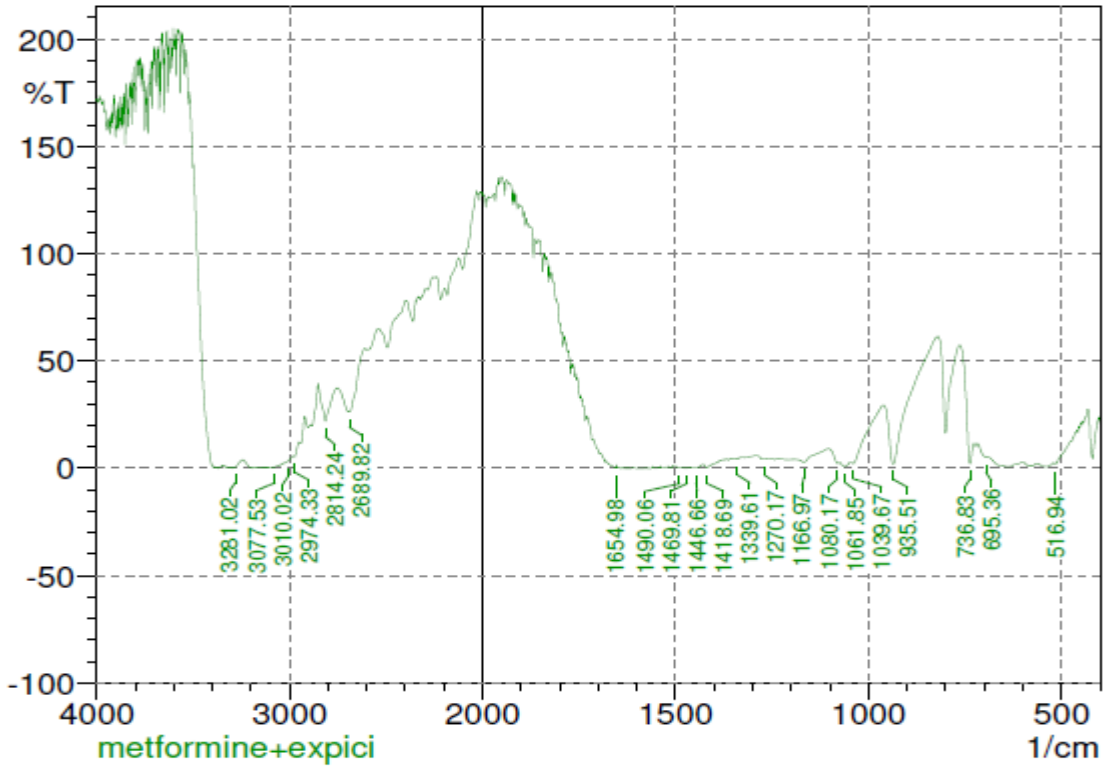

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Table No 19: FT-IR data of Metformin + Excipients

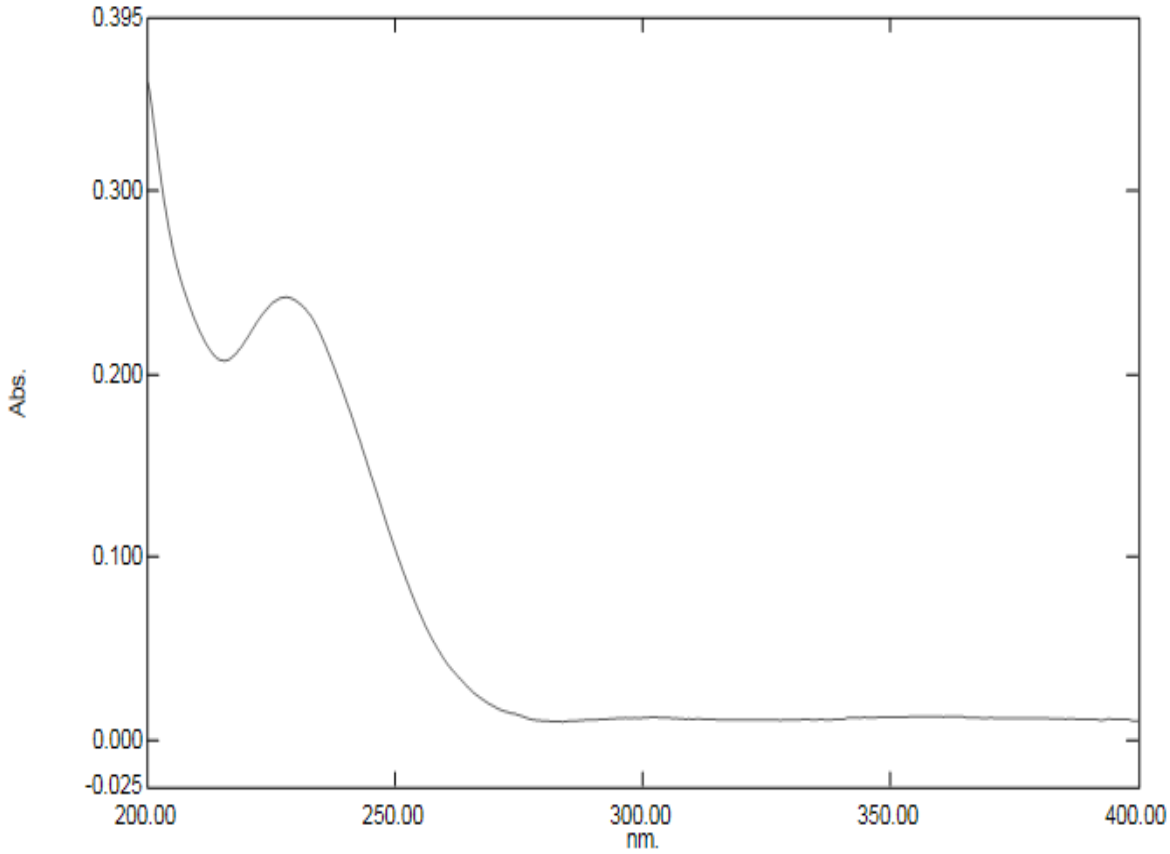
S.NO	WAVE NUMBER cm^{-1}	ASSIGNMENT
1	3281	O-H stretching
2	3077	C-H stretching
3	2814	N-H stretching
4	1654	C-H bending

6.1.3. CALIBRATION CURVE OF DRUG:

UV Spectrophotometer

Determination of lambda max (Glimepiride):

The diluted stock solution is scanned for maximum wavelength, and the maximum wavelength is observed at 228 nm, which is selected as maximum wavelength for further studies



No.	P/V	Wavelength	Abs.	Description
1		394.20	0.012	
2		228.00	0.242	
3		215.60	0.208	

Figure No 15: Determination of lambda max of Glimepiride

Calibration curve of Glimepiride:

Standard curve of Glimepiride was plotted by using UV Spectrophotometer and the absorbance was noted at 228 nm. A serious of concentration of solutions ranging from 1-5 µg / ml is prepared and the corresponding absorbance was noted. The values are shown in the table and regression value to be found in the graph.

Table No 20: Standard curve of Glimepiride

CONCENTRATION (mcg/ml)	ABSORBANCE (228 nm)
1	0.026
2	0.050
3	0.076
4	0.101
5	0.125

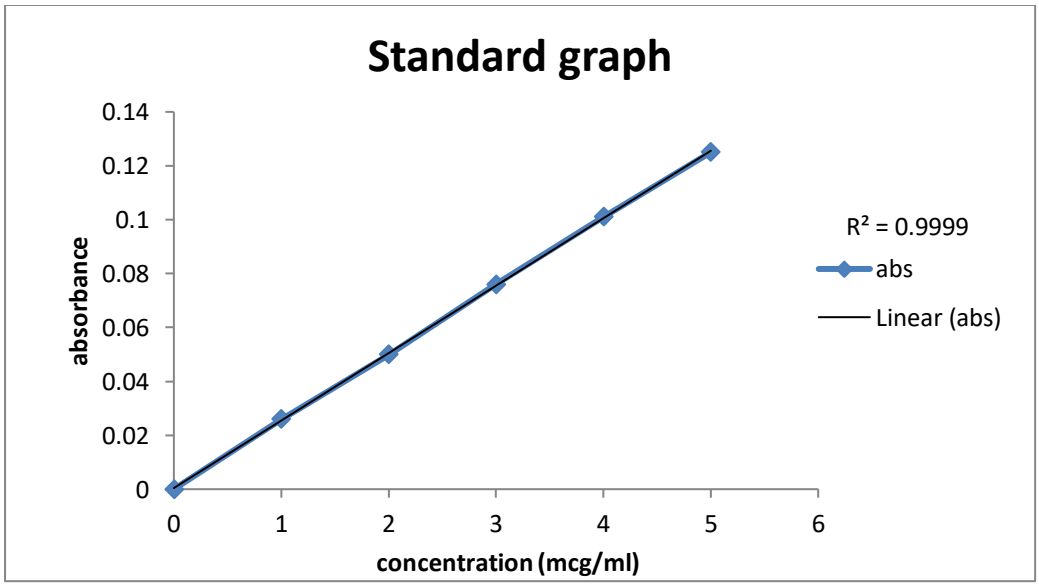
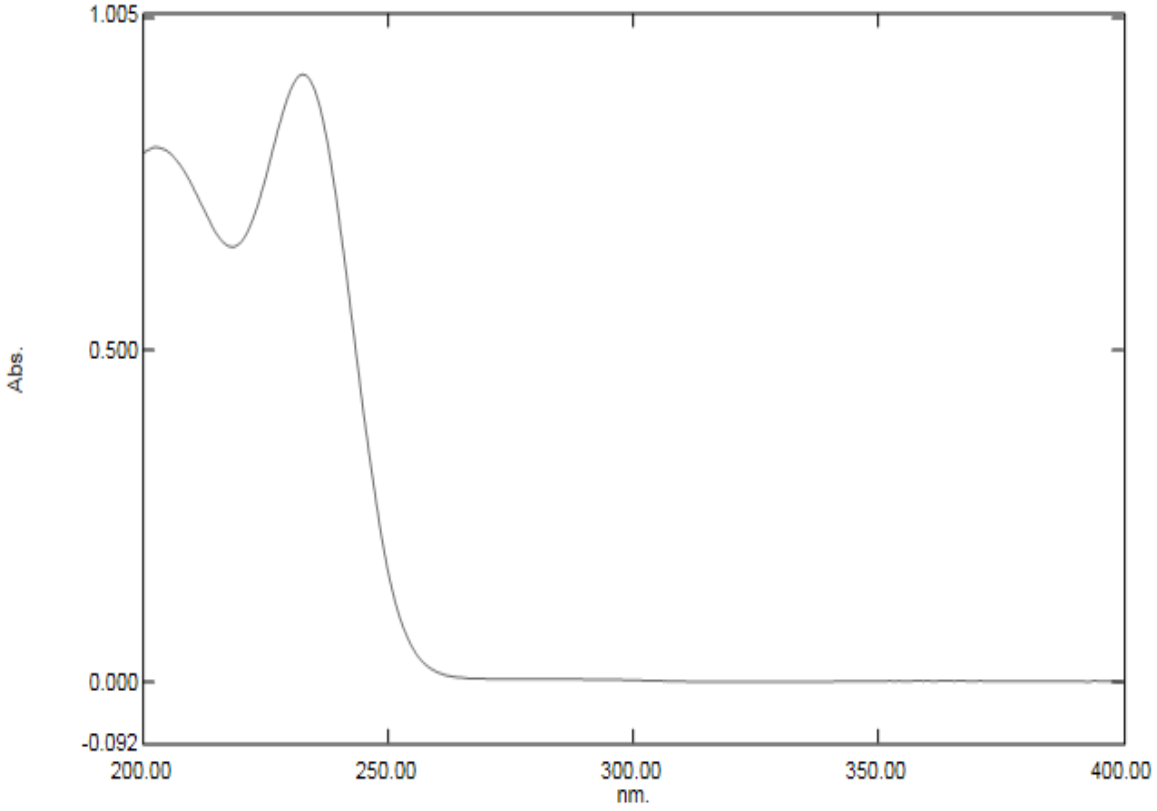


Figure No 16: Standard graph of Glimepiride

Determination of lambda max (Metformin):

The diluted stock solution is scanned for maximum wavelength, and the maximum wavelength is observed at 232 nm, which is selected as maximum wavelength for further studies.



No.	P/V	Wavelength	Abs.	Description
1	↑	394.20	0.001	
2	↑	232.60	0.914	
3	↑	202.60	0.804	
4	↓	273.00	0.003	
5	↓	218.20	0.654	

Figure No 17: Determination of lambda max of Metformin

Calibration curve of metformin:

Standard curve of Metformin was plotted by using UV spectrophotometer and the absorbance was noted at 232 nm. A serious of concentration of solutions ranging from 1-10 µg / ml is prepared and the corresponding absorbance was noted. The values are shown in the table and regression value to be found in the graph.

Table No 21: Standard curve of Metformin

CONCENTRATION (mcg/ml)	ABSORBANCE (232 nm)
0	0.00
2	0.079
4	0.150
6	0.224
8	0.303
10	0.371
12	0.457
14	0.536
16	0.615
18	0.705
20	0.803

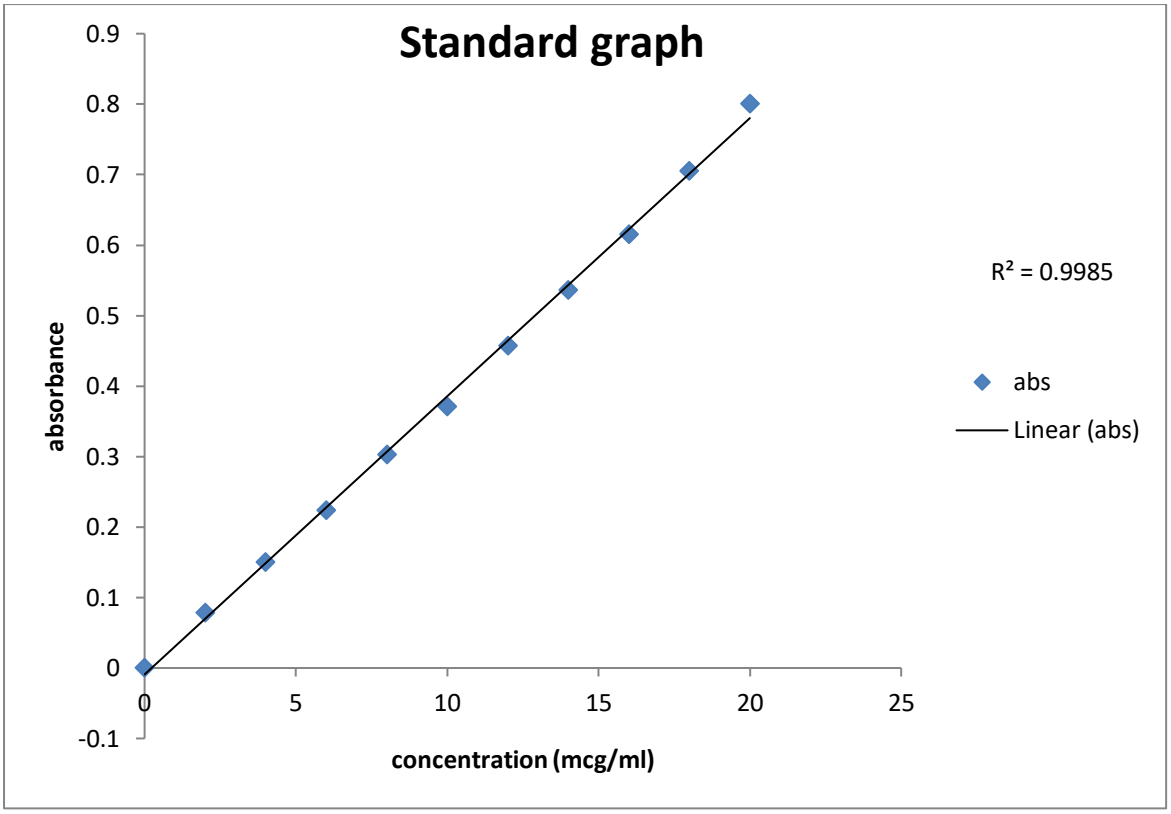


Figure No 18: Standard graph of Metformin

Simultaneous estimation of Glimepiride and Metformin:

Solution 1 and solution 2 are scanned separately between 200-400 nm. Both curves are overlapped and interacting point 252 nm is taken as isobestic point. This nm is taken for further studies

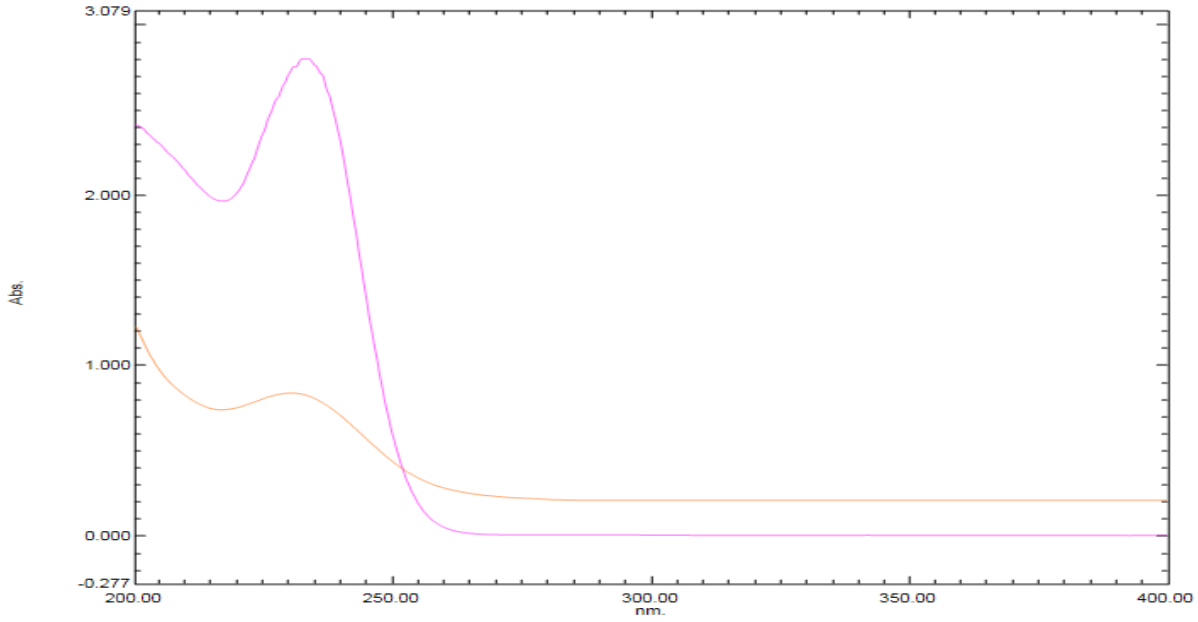


Figure No 19: Overlay spectrum of Glimepiride and Metformin

Simultaneous linearity:

Linearity of solution 3 was plotted by using UV spectrophotometer and the absorbance was noted at 252 nm. A serious of concentration of solutions ranging from 10-50 µg / ml is prepared and the corresponding absorbance was noted. The values are shown in the table and regression value to be found in the graph.

Table No 22: Simultaneous linearity of Glimepiride and Metformin

CONCENTRATION (mcg/ml)	ABSORBANCE (252)
0	0.000
10	0.097
20	0.185
30	0.263
40	0.342
50	0.434

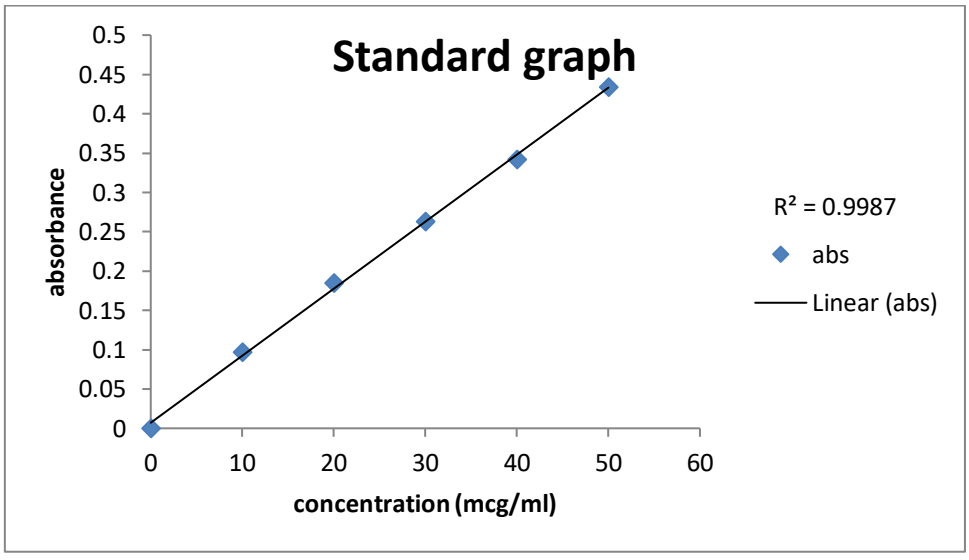


Figure No 20: Linearity graph of Glimepiride and Metformin

6.2. FORMULATION OF BILAYER TABLET:

Preparation of bilayer tablet of glimepiride floating layer and metformin sustained layer.

FIRST LAYER OF TABLET:

Pure drug Glimepiride 2 mg with polymer ratio (Guar gum-15/25), (xanthan gum-15/25), (carbopol-15/25), other excipients are sodium bicarbonate used as effervescence agent, talc and magnesium stearate is used as filler and lubricant, amaranth is used as colouring agent. Total weight of tablet will be 100 mg

SECOND LAYER OF TABLET:

Pure drug Metformin 250 mg with polymer ratio (HPMC K100M- 15/25), (methyl cellulose- 15/25), (PVP K30- 15/25), and other excipients are microcrystalline cellulose and magnesium stearate is used filler and lubricant. Total weight of tablet will be 350 mg.

Figure No 21: Bilayer tablet

6.3. PHYSIOCHEMICAL EVALUATION

6.3.1. WEIGHT VARIATION TEST:

Table No 23: Weight variation test

FORMULATION CODE	AVERAGE WEIGHT OF 6 TABLET (mg)
F1	436.6 ± 4.7
F2	434.8 ± 4.5
F3	431.6 ± 4.1
F4	428.2 ± 4.0
F5	436.6 ± 4.7
F6	437.7 ± 4.9
F7	431.6 ± 4.1
F8	432.5 ± 4.2

All formulations passed weight variation test as per the pharmacopoeia limits of 5% as shown in the table.

6.3.2. THICKNESS TEST:

Table No 24: Thickness Test

FORMULATION CODE	THICKNESS WITH ± SD (cm) FOR 6 TABLETS
F1	0.567 ± 0.017
F2	0.560 ± 0.010
F3	0.559 ± 0.009
F4	0.555 ± 0.007
F5	0.560 ± 0.010
F6	0.562 ± 0.010
F7	0.559 ± 0.007
F8	0.566 ± 0.016

The thickness of all formulations is within the limits as shown in the table.

6.3.3. HARDNESS TEST:

Table No 25: Hardness Test

FORMULATION CODE	HARDNESS WITH ± SD Kg/cm^2 FOR 6 TABLETS
F1	3 ± 0.25
F2	2.5 ± 0.37
F3	4 ± 0.64
F4	3.5 ± 0.46
F5	4 ± 0.64
F6	3 ± 0.42
F7	3 ± 0.42
F8	5 ± 0.80

The hardness of formulation carried out found that it was 2.5 ± 0.37 Kg/cm^2 to 5 ± 0.80 Kg/cm^2 for formulation F2 and F8 all other formulations are within the limits as shown in the table.

6.3.4. FRIABILITY TEST:

Table No 26: Friability test

FORMULATION CODE	FRIABILITY (%) FOR 6 TABLETS
F1	0.68 %
F2	0.68 %
F3	0.45 %
F4	0.22 %
F5	0.28 %
F6	0.48 %
F7	0.68 %
F8	0.45 %

Friability test for formulation was carried out and found it was 0.68% - 0.22% for formulation F1and F4 and all other formulation are within this limit as shown in the table.

6.3.5. DISINTEGRATION TEST:

Table No 27: Disintegration Test

FORMULATION CODE	TIME (min)
F1	16
F2	18
F3	20
F4	22
F5	19
F6	22
F7	23
F8	27

The disintegration test for formulation was carried out and found it was 16-27 minutes for formulation F1and F8 and all other formulation is within this limit as shown in the table.

6.3.6. FLOATING LAG TIME AND CAPACITY:

Table No 28: Floating lag time and capacity

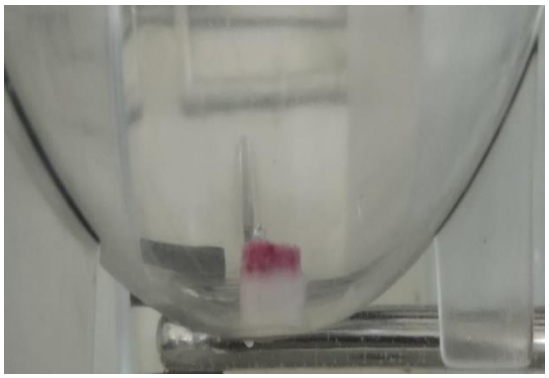
FORMULATION CODE	FLOATING LAG TIME (sec)	FLOATING CAPACITY (hours)
F1	120	< 15
F2	130	< 15
F3	60	< 15
F4	180	< 15
F5	240	< 15
F6	128	< 15
F7	149	< 15
F8	220	< 15

Floating capacity of all formulations is above 15 hours and floating lag time is 60 – 240 seconds

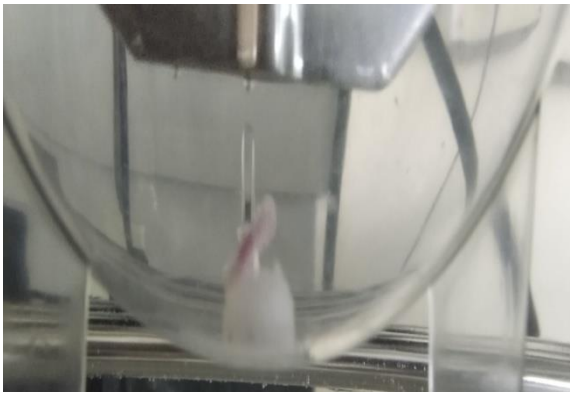
6.4. *IN VITRO* EVALUATION:

After 1 minutes

After 2 minutes

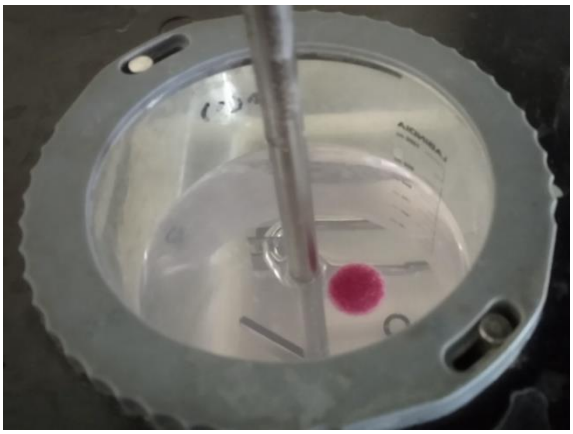


After 3 minutes



After 4 minutes

After 5 minutes (1st layer)



After 5 minutes (2nd layer)

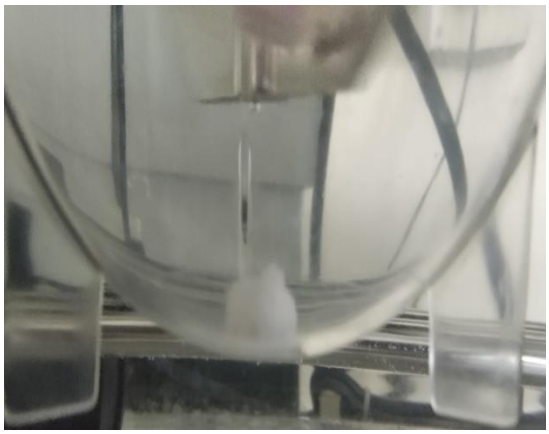


Figure No 22: *In vitro* drug release of bilayer tablet

DISSOLUTION STUDIES:

In vitro drug release profile for formulation F1 is given in below table

Table No 29: *In* vitro drug release for F1

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	1.5	-	5		67.5	-	18	
2	2	2	-	8		90	-	28.8	
3	3	2	-	-	13.4	90	-	-	48.2
4	4	2	-	-	13.4	90	-	-	48.2
5	5	2	-	-	13.6	90	-	-	48.9
6	6	2.2	-	-	16.2	99	-	-	58.3
7	7	2.2	-	-	17.6	99	-	-	63.3
8	8	2.2	-	-	18.4	99	-	-	66.2
9*	15	-	-	-	2.4	-	-	-	86.4

*15^{th} hour is done separately in pH 7.4

In vitro drug release profile for formulation F2 is given in below table

Table No 30: *In vitro* drug release for F2

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	1.1	-	5.8		49.5	-	19.4	
2	2	1.5	-	10.4		67	-	37.4	
3	3	2	-	-	13.2	90	-	-	47.5
4	4	2.2	-	-	15.6	99	-	-	56.1
5	5	2.2	-	-	16.2	99	-	-	58.3
6	6	2.2	-	-	18.8	99	-	-	67.6
7	7	2.2	-	-	19.4	99	-	-	69.8
8	8	2.2	-	-	20.6	99	-	-	74.1
9*	15	-	-	-	2.6	-	-	-	93.6

*15^{th} hour is done separately in pH 7.4

In vitro drug release profile for formulation F3 is given in below table

Table No 31: *In vitro* drug release for F3

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	0.7	-	6.4		31.5	-	23	
2	2	1.1	-	8.6		49.5	-	30.9	
3	3	1.5	-	-	12.2	67	-	-	45.3
4	4	1.5	-	-	15.2	67	-	-	54.7
5	5	2	-	-	18	90	-	-	64.8
6	6	2	-	-	18.6	90	-	-	66.9
7	7	2.2	-	-	20.6	99	-	-	74.1
8	8	2.2	-	-	21	99	-	-	75.6
9*	15	-	-	-	2.6	-	-	-	93.6

*15^{th} hour is done separately in pH 7.4

In vitro drug release profile for formulation F4 is given in below table

Table No 32: *In vitro* drug release for F4

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	0.7	-	8.4		31.5	-	30.2	
2	2	1.5	-	9		67	-	32.4	
3	3	2	-	-	12.2	90	-	-	43.9
4	4	2	-	-	13.2	90	-	-	47.5
5	5	2	-	-	13.2	90	-	-	48.2
6	6	2.2	-	-	13.4	99	-	-	61
7	7	2.2	-	-	17	99	-	-	61.2
8	8	2.2	-	-	20.2	99	-	-	72.7
9*	15	-	-	-	2.6	-	-	-	93.6

*15^{th} hour is done separately in pH 7.4

In vitro drug release profile for formulation F5 is given in below table

Table No 33: *In vitro* drug release for F5

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	1.5	-	6.8		67	-	24.4	
2	2	2	-	9.2		90	-	33.1	
3	3	2	-	-	10.4	90	-	-	37.4
4	4	2.2	-	-	13	99	-	-	46.8
5	5	2.2	-	-	16.2	99	-	-	58.3
6	6	2.2	-	-	18.8	99	-	-	67.6
7	7	2.2	-	-	19	99	-	-	68.4
8	8	2.2	-	-	22.6	99	-	-	81.3
9*	15	-	-	-	2.8	-	-	-	100.8

*15^{th} hour is done separately in pH 7.4

In vitro drug release profile for formulation F6 is given in below table

Table No 34: *In vitro* drug release for F6

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	1.5	-	10.2		67	-	36.7	
2	2	2	-	14.4		90	-	51.8	
3	3	2.2	-	-	0.6	99	-	-	2
4	4	2.2	-	-	0.8	99	-	-	2
5	5	2.2	-	-	0.8	99	-	-	2
6	6	2.2	-	-	1	99	-	-	3
7	7	2.2	-	-	1.4	99	-	-	5.4
8	8	2.2	-	-	1.8	99	-	-	6.4
9	15	-	-	-	-	-	-	-	-

In vitro drug release profile for formulation F7 is given in below table

Table No 35: *In vitro* drug release for F7

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	1.1	-	6		49.5	-	21.6	
2	2	1.5	-	8.8		67	-	31.6	
3	3	1.5	-	-	9	67	-	-	32.4
4	4	2	-	-	12	90	-	-	43.2
5	5	2	-	-	13.2	90	-	-	47.5
6	6	2	-	-	15.8	90	-	-	56.8
7	7	2	-	-	16.2	90	-	-	58.3
8	8	2.2	-	-	19.2	99	-	-	69.1
9*	15	-	-	-	2.4	-	-	-	86.4

*15^{th} hour is done separately in pH 7.4

In vitro drug release profile for formulation F8 is given in below table

Table No 36: *In vitro* drug release for F8

S.NO	TIME (hours)	CONCENTRATION (mcg/ml)				PERCENTAGE DRUG RELEASE (%)			
		GLIMEPIRIDE		METFORMIN		GLIMEPIRIDE		METFORMIN	
		pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH7.4	pH 1.2	pH 7.4
1	1	1.1	-	6		49.5	-	21.6	
2	2	1.5	-	8.6		67	-	30.9	
3	3	1.5	-	-	11.4	67	-	-	41
4	4	2	-	-	13	90	-	-	46.8
5	5	2	-	-	17.2	90	-	-	61.9
6	6	2	-	-	17.6	90	-	-	63.3
7	7	2.2	-	-	17.8	99	-	-	64
8	8	2.2	-	-	19.6	99	-	-	70.5
9*	15	-	-	-	2.6	-	-	-	93.6

*15^{th} hour is done separately in pH 7.4

Comparison of percentage drug release of Glimepiride:

Table No 37: Comparison of percentage drug release of Glimepiride

FORMULATION CODE	PERCENTAGE DRUG RELEASE OF GLIMEPIRIDE IN HOURS
F1	99% in 8 hours
F2	99% in 8 hours
F3	99% in 8 hours
F4	99% in 8 hours
F5	99% in 8 hours
F6	99% in 8 hours
F7	99% in 8 hours
F8	99% in 8 hours

In vitro dissolution study was carried out for all formulation F1-F8 and that all formulations shows drug release for 8 hours which proves that floating tablet controls the drug release for prolonged period of time.

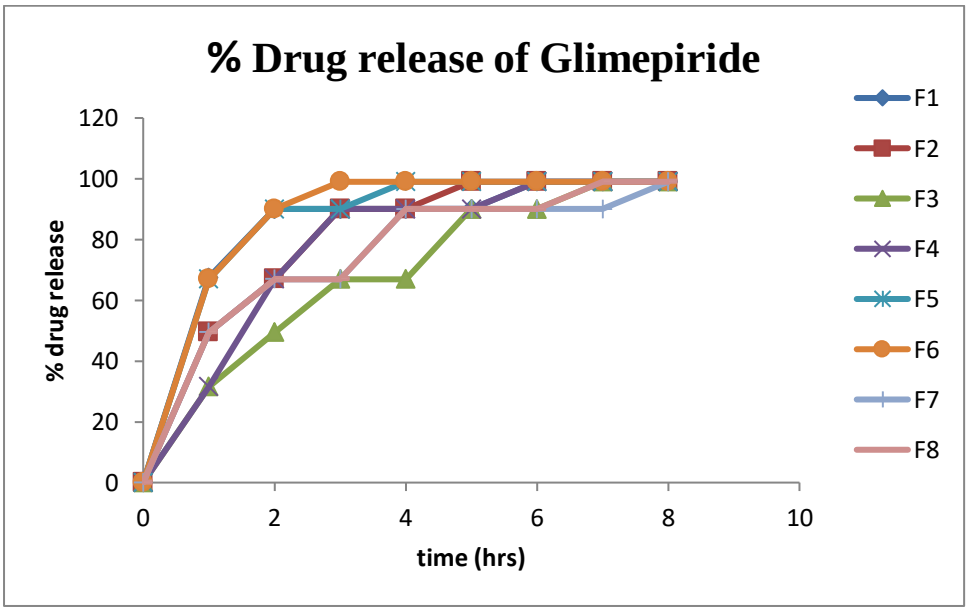


Figure No 23: Comparison of percentage Drug release of Glimepiride

Comparison of percentage drug release of Metformin:

Table No 38: Comparison of percentage drug release of Metformin

FORMULATION CODE	PERCENTAGE DRUG RELEASE OF GLIMEPIRIDE IN HOURS
F1	86.4% in 15 hours
F2	93.6% in 15 hours
F3	93.6% in 15 hours
F4	93.6% in 15 hours
F5	100.8% in 15 hours
F6	6.4% in 15 hours
F7	86.4% in 15 hours
F8	93.6% in 15 hours

In vitro dissolution study was carried out for all formulation F1-F8 and that formulations shows drug release in 15 hours which proves that sustained release tablet controls the drug release.

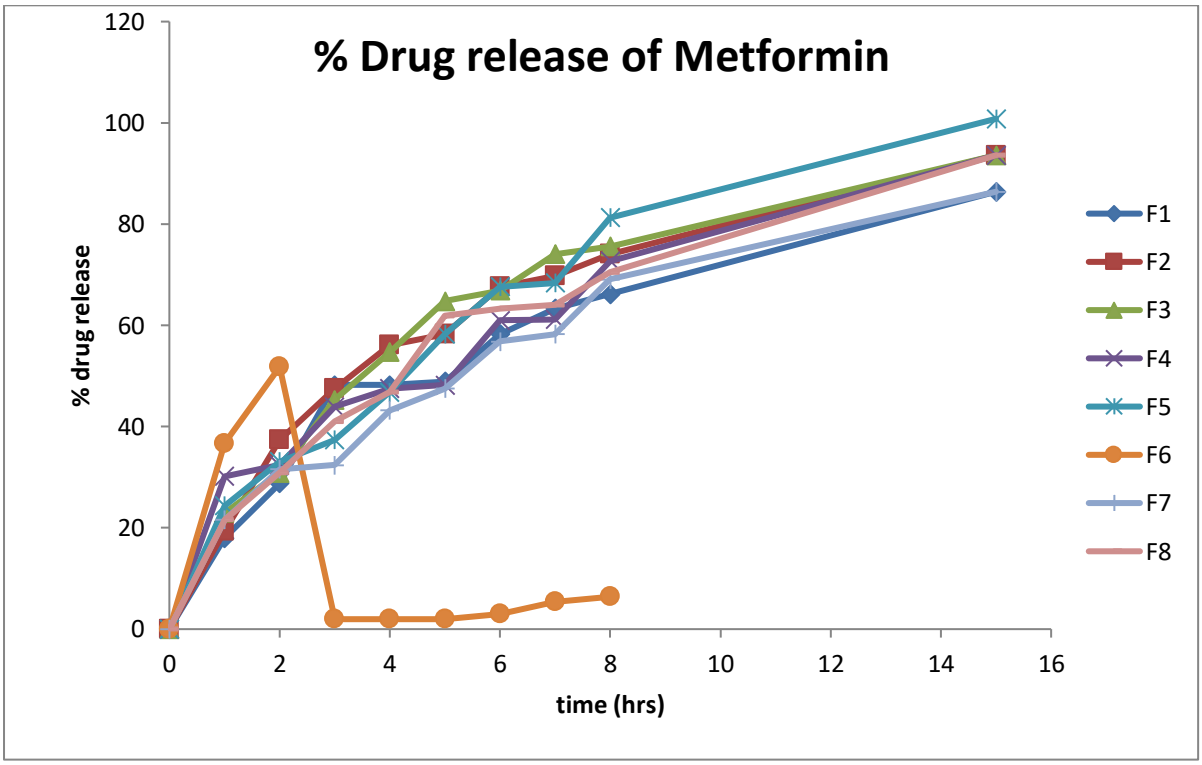


Figure No 24: Comparison of percentage Drug release of Metformin

6.5. KINETICS STUDY OF DRUG RELEASE

The release kinetics study is performed for best formulation. The drug release of best formulation is fitted with different kinetics models. Formulation F2 is selected as best formulation and kinetics study, zero order, first order, Higuchi, Korsemeyer peppas are done for F2 formulation.

FIRST ORDER KINETICS STUDY FOR GLIMEPIRIDE:

The first order kinetics of drug release means that the rate of drug release is proportional to the remaining concentration of drug at any time period. The F2 formulation obeys first order kinetics model, thus shown in the figure.

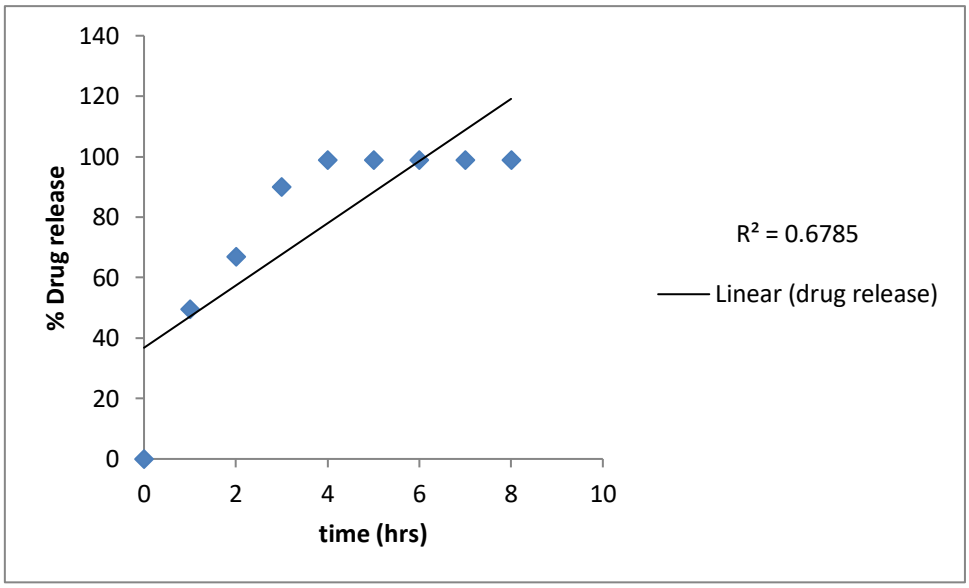


Figure No 25: First order kinetics of Glimepiride-F2

ZERO ORDER KINETICS STUDY FOR METFORMIN:

The zero order kinetics of drug release signifies that the cumulative drug release is proportional to time, which means that the rate of drug release remains constant with time. . The F2 formulation obeys zero order kinetics model, thus shown in the figure.

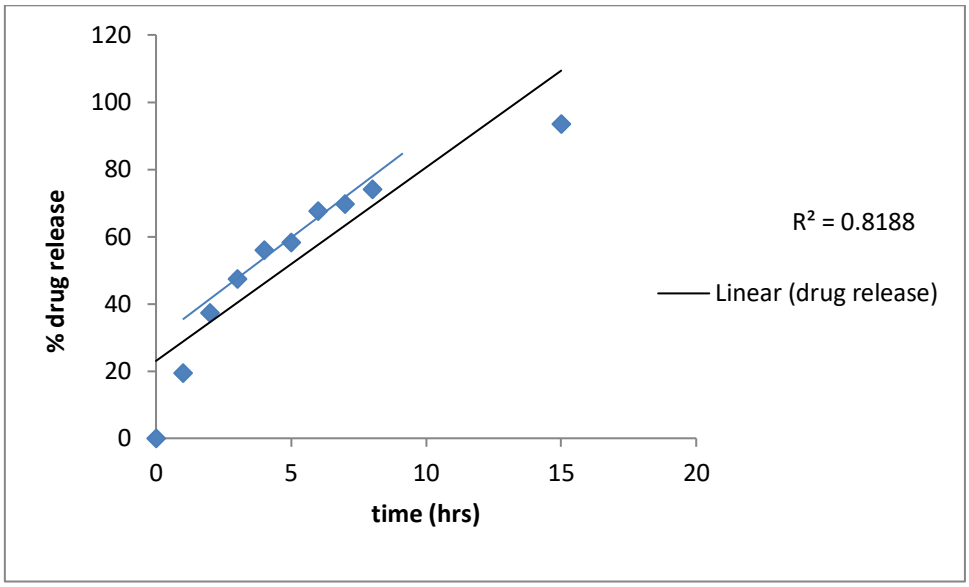


Figure No 26: Zero order kinetic of Metformin-F2

HIGUCHI KINETICS STUDY:

The diffusion process of drug release is Higuchi kinetics. The Higuchi describes the cumulative drug release is proportional to the square root of time. Higuchi is done for formulation F2, the graph is shown in the figure no 27 and table no 39 for Glimepiride, figure no 28 and table no 40 for Metformin.

Table No 39: Higuchi data for Glimepiride

SQUARE ROOT OF TIME	CUMULATIVE % DRUG RELEASE (%)
1	49.5
1.4	67
1.7	90
2	99
2.2	99
2.4	99
2.6	99
2.8	99

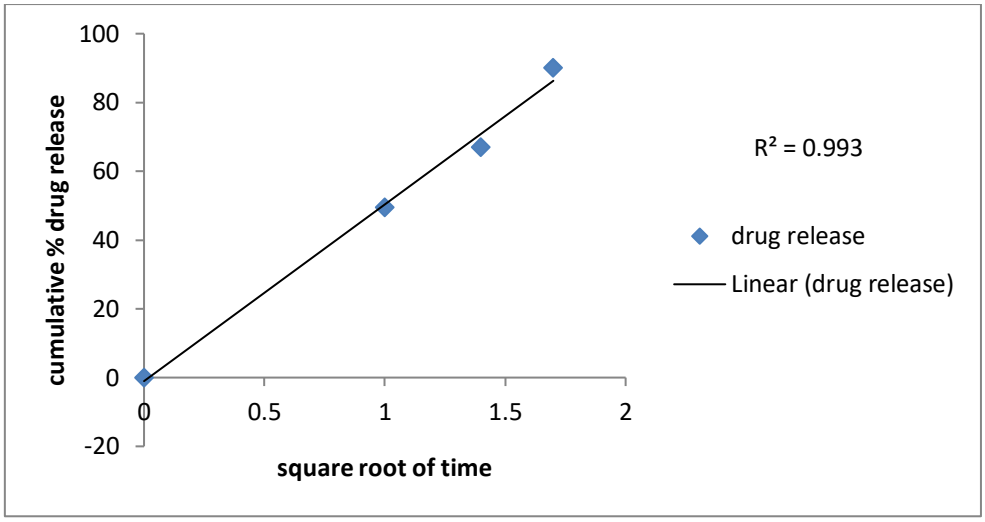


Figure No 27: Higuchi plot for Glimepiride-F2

Table No 40: Higuchi data for Metformin

SQUARE ROOT OF TIME	CUMULATIVE % DRUG RELEASE (%)
1	19.4
1.4	37.4
1.7	47.5
2	56.1
2.2	58.3
2.4	67.6
2.6	69.8
2.8	74.1
3.8	93.6

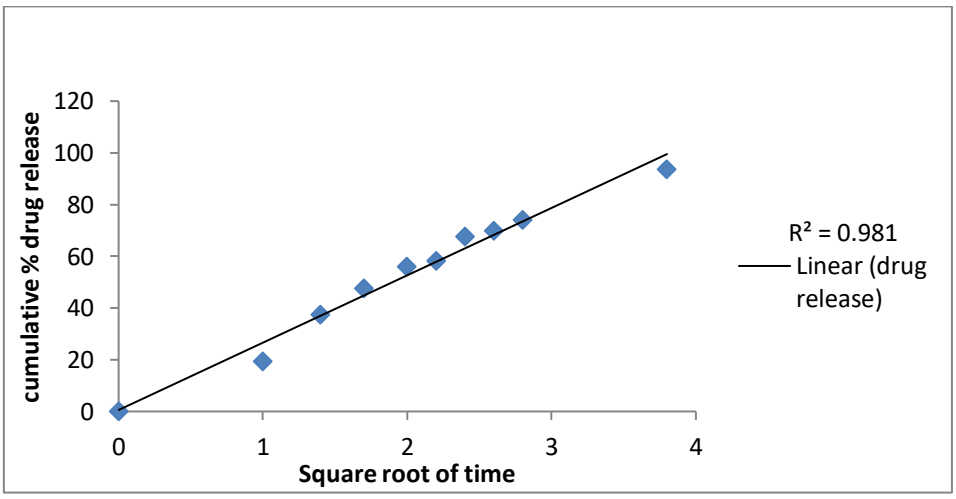


Figure No 28: Higuchi plot for Metformin-F2

KORSEMEYER PEPPAS KINETICS STUDY:

Korsemeyer peppas describes the log cumulative drug release is proportional to log time. Korsemeyer peppas is done for formulation F2, the graph is shown in the figure no 29 and table no 41 for Glimepiride, figure no 30 and table no 42 for Metformin.

Table No 41: Korsemeyer peppas data for Glimepiride

LOG TIME	LOG CUMULATIVE % DRUG RELEASE (%)
0	1.694
0.301	1.826
0.477	1.954
0.607	1.995
0.698	1.995
0.778	1.995
0.845	1.995
0.903	1.995

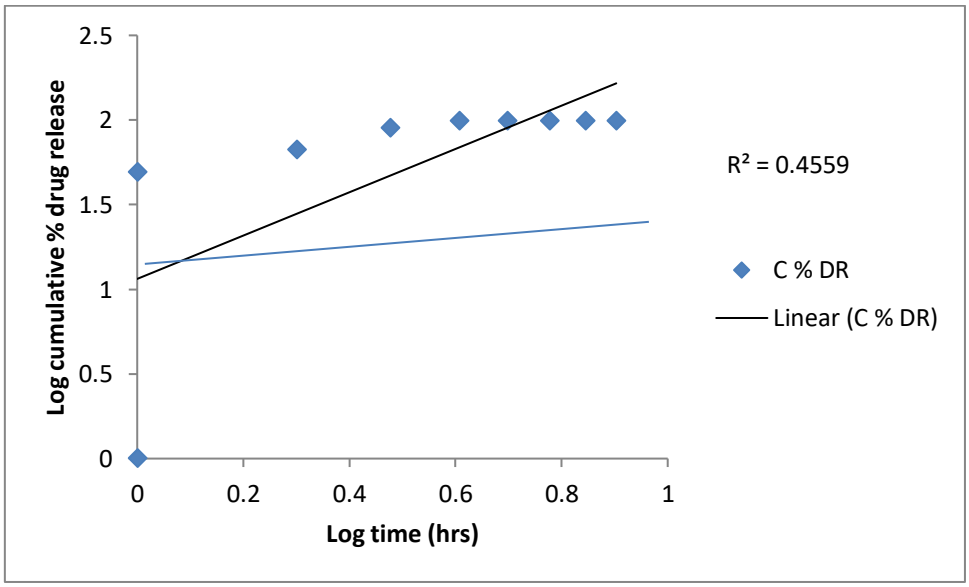


Figure No 29: Korsemeyer peppas plot for Glimepiride-F2

Table No 42: Korsemeyer peppas data for metformin

LOG TIME	LOG CUMULATIVE % DRUG RELEASE (%)
0	1.278
0.301	1.572
0.477	1.676
0.607	1.748
0.698	1.765
0.778	1.829
0.845	1.843
0.903	1.869
1.176	1.971

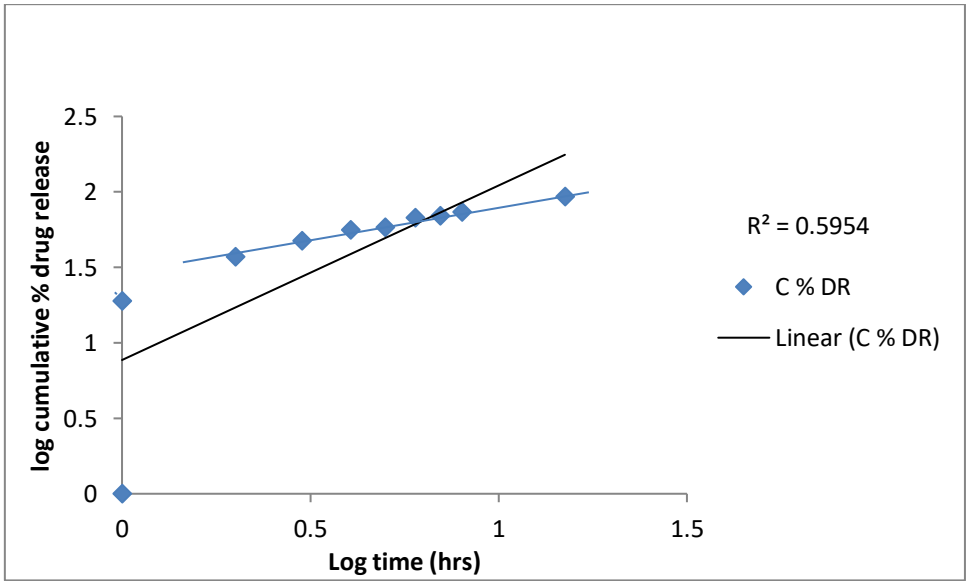


Figure No 30: Korsemeyer peppas plot for Metformin-F2

Table 43: Higuchi and Korsemeyer peppas plot for bilayer tablet

Study	r^2- value		n - value	
	Glimepiride	Metformin	Glimepiride	Metformin
Higuchi	0.998	0.981	-	-
Korsemeyer peppas	-	-	0.982	0.989

CONCLUSION

7. CONCLUSION

The Glimepiride floating tablet is prepared with various polymer of guar gum; xanthan gum and carbopol with excipients talc, magnesium stearate, and sodium bicarbonate are compressed and taken as first layer. The Metformin sustained release is also prepared by different polymer ratio of HPMC, methyl cellulose and PVP with excipients microcrystalline cellulose, talc, magnesium stearate are compressed and taken as second layer of tablet. The first and second layer of tablet is combined as bilayer tables.

Evaluation of bilayer tablet such as weight variation, thickness, hardness, friability, disintegration and floating lag time and floating capacity is carried out and shown that all the formulation are within the limit.

Among all formulations F2 was selected based on invitro dissolution study with drug release up to 15 hours for metformin sustained release layer and 8 hours for glimepiride floating layer in the bilayer tablets. The release kinetics study was done for best formulation F2 and follows first order for Glimepiride and zero order for Metformin. Which was studied for release mechanism; Higuchi shows higher linear with regression value of 0.993 for glimepiride and 0.981 for metformin respectively, which indicates drug release from the both layer is by diffusion principle (r^2 is more than 0.98) and further it is confirmed by peppas n-value 0.982 for glimepiride and 0.989 for metformin, so it is considered as non-fickian type of drug release.

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