# CERTIFICATE

This is to certify that the research project work entitled **"Formulation and Evaluation of Bi-layer Tablet of Metformin and Glimepiride"** was carried out by **Mr. Avinash verma** for the partial fulfillment of the requirement for the award of degree in **Master of Pharmacy in Pharmaceutics** at R & D Department, Dr. Morepean lab. Pvt. Ltd., Parwanoo (Himanchal) and RVS College of Pharmacy, Sulur, Coimbatore, under my guidance and supervision

INSTITUTIONAL GUIDE

**Mrs. R. Ramya**, M.Pharm
Asst. Professor,
Department of Pharmaceutics,
R.V.S.College of Pharmaceutical sciences
Sulur, Coimbatore.

**Date:**

**Place:**

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**Dr. R. Venkatanarayanan, M.Pharm. Ph.D.,**
The Principal,
RVS College of Pharmaceutical Sciences,
Sulur, Coimbatore.

**Date:**

**Place:**

# EVALUATION-CERTIFICATE

This is to certify that the dissertation work entitled **"Formulation and Evaluation of Bi-layer Tablet of Metformin and Glimepiride"** is a bonafide work done by **Mr. Avinash Verma** in partial fulfillment of the requirement for the award of **MASTER OF PHARMACY** in Pharmaceutics and carried out in the Department of Pharmaceutics, R.V.S College of Pharmaceutical Sciences, Sulur, Coimbatore under the supervision and guidance of **Mrs. R. Ramya,** Asst. Professor, Department of Pharmaceutics**.**

**INTERNAL EXAMINER** **EXTERNAL EXAMINER**

**Date:** **Date:**

**Place:** **Place:**

## ACKNOWLEDGEMENT

First and foremost I thank **Lord Ganesh** for my successful completion of this work.

I sincerely acknowledge my deep sense of gratitude and hearty thanks to **Mrs. R. Ramya. Asst. Professor Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, Sulur. Coimbatore**, for her valuable guidance encouragement and continued support throughout the course of this work. I also thank her for her valuable suggestions and advises and stimulating criticism

I am highly indebted to **Dr. R. Venkatanarayanan**, Principal, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore for providing necessary facilities, encouragement and continued support throughout the course of this work.

I wish to place on record my sincere thanks to **Mr. T. Akelesh M.Pharm, DIH, Asst. Professor, and Mr. Barish M.Pharm, Asst. Professor, DCH., RVS College of Pharmaceutical Sciences, Coimbatore** for their valuable advice, help and support during my project work.

Let me extend my gratefulness to **Mr. A. K. Sinha, President**, of Dr. Morpean, **Mr. Amit Upadhayay, Assistant Manager (R & D),** and **Mr. Neeraj Sharma,** Research Executive Dr. Morpean lab. Pvt Ltd.,

I am thankful to the **HRD of Dr. Morpean Research Centre**, Parwanoo, Solan, Himanchal for giving me an opportunity to carry out the project work in R & D Centre.

I sincerely acknowledge my deep sense of gratitude and hearty thanks to my colleagues for encouraging each and every day

Last but not the least I place my thanks to my family, my father **Mr. S.P. Verma** and my mother **Mrs. Kishan kali** who have been supportive, ever loving. Because of whom I am able to reach where I am today. My Brother Atul verma, my sweet sister Miss. Rashmi verma, who is back bone of life.

**Mr. AVINASH VERMA**

# Content

# ABBREVIATIONS

| | | |
|---|---|---|
| NDA | : | New Drug Application |
| AND | : | Abbreviated New |
| IND | : | Investigation New Drug |
| API | : | Active Pharmaceutical Ingredients |
| Di | : | Loading Dose |
| Dm | : | Sustained Dose |
| NIDDM | : | Non- Insulin Dependent Diabetes Mellitus |
| ATP | : | Adenosine tri Phosphate |
| FDA | : | Food and Drug Administration |
| mg | : | Milli gram |
| ml | : | Milli litre |
| min | : | Minutes |
| sec | : | Seconds |
| % | : | Percentage |
| µg/ml | : | Microgram per ml |
| Fig | : | Figure |
| RH | : | Relative Humidity |
| RT | : | Room Temperature |
| HPMC | : | Hydroxy Propyl Methyl Cellulose |
| Rt | : | Reference Test |
| Tt | : | Test |
| AUC | : | Area Under Curve |
| $C_{max}$ | : | Maximum Plasma Concentration |
| $t_{max}$ | : | Time to Maximum Plasma Concentration |
| IV | : | Intravenous |
| $V_d$ | : | Volume of Distribution |
| LOD | : | Loss on Drying |
| CL | : | Clearance |
| IPA | : | Isopropyl Alcohol |
| rpm | : | Revolution per minute |
| I P | : | Indian Pharmacopoeia |

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# INTRODUCTION [1,2]

There are certain conditions where it is desirable to extend the dosing interval of many pharmaceuticals while maintaining the initial plasma concentration achievable with conventional tablets. This would provide immediate and extended therapeutic effects and reduces the number of dosage necessary; they're by making therapy more convenient. This can be done by formulating tablets containing two layers, one containing the immediate release layer and one containing the sustained release layer. Thus a Bi-layer tablet can achieve the initial plasma concentration achievable with conventional tablets and maintain for long time as sustained release tablets.

Bi-layers tablet is defined as tablets consisting of two discrete zones consisting of same or different active pharmaceutical ingredients intended for therapeutic action. Bi-layer tablets consist of two layers

1. **Immediate release layer-** contains loading dose
2. **Controlled release layer –** contains maintenance dose.

**Immediate release layer** of the dosage form containing the loading dose that delivers the entirely of its drug content at once after administration for the purpose of providing a rapid rise of drug concentration in the blood stream.

**Sustained release layer** of the dosage form contains the maintenance dose that gradually release its drug content over a given period of time after administration for the purpose of providing a constant concentration of drug in to the blood stream.

**The Blood Level Time Profile of a Bi-layer Tablet**

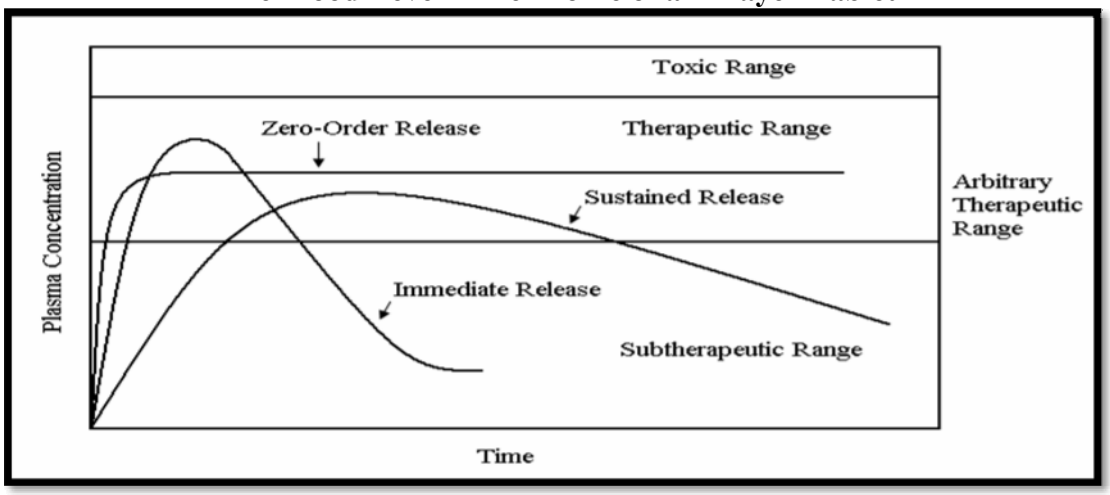


**Figure No 1: A Blood Level Time Profile for an Ideal Bi-layer Tablet**

**Reasons for Preparing Bi-layer Tablets [3]: -**

1. To separate physically and chemically incompatible ingredients
2. Two different drugs can be administered together which causes better control of disease and increase the patient compliance

   e.g Nasal decongestant and antihistamine
3. To produce repeat action or prolonged action product.

   The immediate release layer achieves the therapeutic drug in the plasma and the sustained release layer maintained a steady state plasma concentration.

**Bi-layer Tablets: Quality and GMP-Requirements** [4]

To produce a quality Bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the Bi-layer tablet
- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- High yield
- Accurate and individual weight control of the two layers

These requirements seem obvious but are not so easily accomplished.

**Kinetic Pattern of Drug Release** [5, 6]**:** It is assumed that the drug, which is to be incorporated in to an ideal Bi-layer tablet dosage form, confers upon the body, the characteristics of a one compartment open model. The basic kinetic design of such a product is represented:

**Kinetic Pattern of Drug Release required for Ideal Bi-layer Tablets:-**

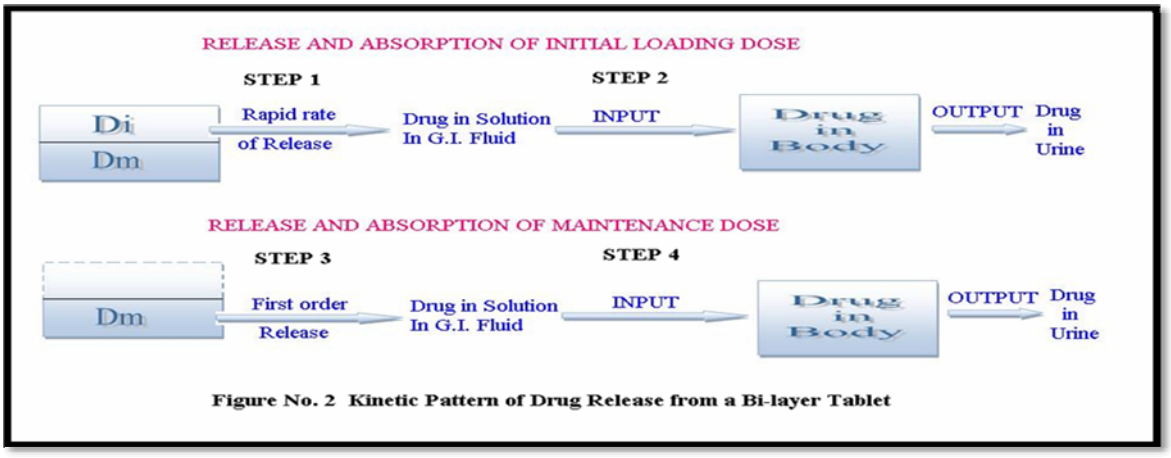


**Figure No. 2 Kinetic Pattern of Drug Release from a Bi-layer Tablet**

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of two portion, one that provide the initial priming or loading dose ($D_i$) and one that provide the maintenance or sustained dose ($D_m$)

The initial priming dose of drug $D_i$ is released rapidly in to the gastrointestinal fluids immediately following administration of the dosage form. The release dose is required to be absorbed in to the body compartment rapidly following first order kinetic process. The aim of the initial rapid release and subsequent absorption of the initial priming dose is the rapid attainment of a therapeutic concentration of the drug in the body. The priming dose provides a rapid onset of the desired therapeutic response in the patient.

Following this period of rapid drug release, the portion $D_m$ of drug remaining in the dosage form is released at a slow but defined rate. In order to maintain a constant plasma level of drug, the maintenance dose the dosage form according to zero order kinetics must release $D_m$. It thus follows that the rate of release of drug will remain constant and be independent of the amount of maintenance dose remaining in the dosage form an any given time

Two further conditions must be fulfilled in order to ensure that the therapeutic concentration of drug in the body remains constant.

1. The zero order rate of release of the drug from the maintenance dose must be rate determining with respect to the rate at which the released drug subsequently absorbed in to the body. The kinetic of absorption of the maintenance dose will be characterized by the same zero order release rate constant
2. The rate at which the maintenance dose released from the dosage form and hence the rate of absorption of drug into body, must be equal to the rate of drug output from the body when the concentration of drug in the body is the required therapeutic value.

In practice, the design of an ideal Bi-layer tablet is capable of releasing the maintenance dose at a precise controlled rate which is in mass balance with the rate of drug elimination corresponding to the required therapeutic concentration of the drug in the plasma, is difficult to achieve, also there are problems in achieving and maintaining dose of drug in the presence of all the variable physiological conditions associated with the gastrointestinal tract.

**CONSIDERATIONS FOR THE FORMATION OF SUSTAINED RELEASE FORMULATION [6]:**

- If the active compound has a long half-life (over 6 hours), it is sustained on its own.
- If the pharmacological activity of the active compound is not related to its blood levels, time releasing then has no purpose.
- If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
- Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.

The difference between controlled release and sustained release is that controlled release is a perfectly zero order release; that is, the drug releases over time irrespective of concentration. Sustained release implies slow release of the drug over a time period. It may or may not be controlled release.

**Formulation: -**

For good quality tablets with sharp definition between the layers, special care must be taken as: -

1. Dusty fines must be limited, fine smaller than 100# mesh should be kept at a minimum.
2. Maximum granules size should be less than 16# mesh for a smooth, uniform scrape off at the die.
3. Low moisture is essential if incompatibilities are used.
4. Weak granules that break down easily must be avoided; excessive amount of lubricant, especially magnesium Stearate should be avoided for better adhesion of the layers.
5. Formulation of multi layer tablet is more demanding than that of single layer tablets for this reason selection of additives is critical.

**Pharmacological Properties and Therapeutic uses:**

Oral hypoglycemic agents are commonly prescribed drugs that find utility in controlling the symptoms of diabetes in the 80% of patients having NIDDM. Since insulin

resistance an impaired insulin secretion are key factors in the pathogenesis of NIDDM. Treatment should be directed toward restoring metabolic normality by improving insulin secretion and reducing insulin resistance. These goals are accomplished through the use of oral hypoglycemic agents. Specially the sulfonylurea.

**Mechanism (s) of Sulfonylurea Hypoglycemia:**

The sulfonylurea produces the hypoglycemia actions via several mechanisms that can be broadly sub-classified as pancreatic and extra-pancreatic:

A. **Pancreatic Mechanism:** All sulfonylurea hypoglycemics inhibit the efflux of $K^+$ ($K^+$ channel blockers) from pancreatic β-cells via a sulfonylurea receptor, which may be closely linked to an ATP-sensitive $K^+$-channel. The inhibition of efflux of $K^+$ leads to depolarization of the β-cell membrane and as a consequence, voltage-dependent $Ca^+$-channels on the β-cell membrane then open to permit entry of $Ca^+$, the resultant increased binding of $Ca^+$ to Calmodulin results in activation of kinases associated with endocrine secretory granules thereby promoting the exocytosis of insulin-containing secretory granules:

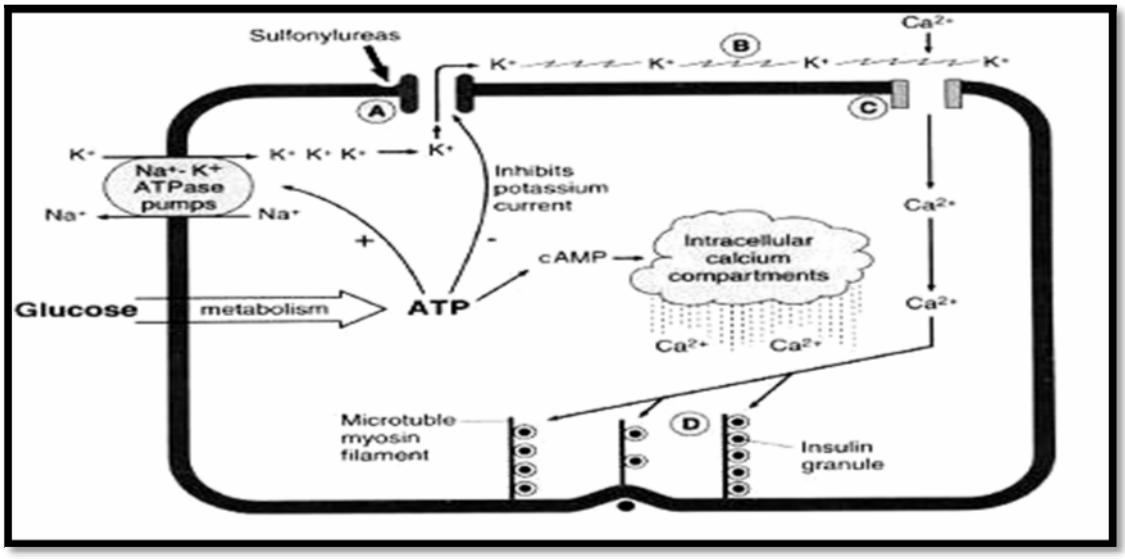



**Fig No. 3 Pancreatic Mechanism of Sulfonylurea Hypoglycemia**

B. **Extra-Pancreatic Mechanisms:**

The sulfonylurea also reduces serum glucagon levels possibly contributing to its hypoglycemic effects. The precise mechanism by which this occurs remains unclear

but may result from indirect (secondary) inhibition due to enhanced release of both somastatin and insulin.

Sulfonylurea may also potentiate insulin action at targeting tissues (Drug dependent characteristic).

Glimepiride is a sulfonylurea ant diabetic agent, which decreases blood glucose concentrations.

The primary mechanism of action of Glimepiride appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. Glimepiride acts in concert with glucose by improving the sensitivity of beta cells to physiological glucose stimulus, resulting in insulin secretion in the rhythm of meals. In addition, extra pancreatic effects (e.g. reduction of basal hepatic glucose production and increased peripheral tissue sensitivity to insulin and glucose uptake) may also play a limited role in the activity of Glimepiride.

In nonfasting diabetic patients, the hypoglycemic action of a single dose of Glimepiride persists for 24 hours.

Evidence from in vitro and animal studies suggests that there is lower glucagons secretion with Glimepiride than glibenclamide and this may give rise to a prolonged reduction of blood glucose levels without increased plasma insulin levels. The clinical significance of these findings is yet to be clarified. A long-term, randomized, placebo controlled clinical trial demonstrated that Glimepiride therapy improves postprandial insulin/ C-peptide responses and overall glycaemic control without producing clinically meaningful increases in fasting insulin/ C-peptide levels.

The efficacy of Glimepiride is not affected by age, gender or weight. Glimepiride therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profile of patients. The physiological response to acute exercise (i.e. reduction of insulin secretion) is still present during Glimepiride therapy.

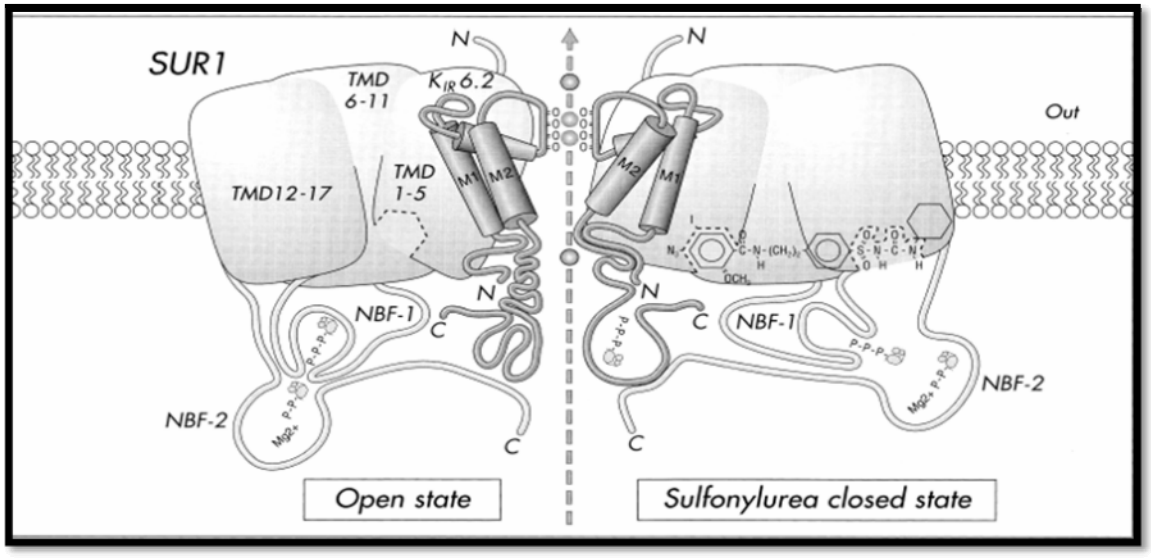



**Fig No. 4 Extra-Pancreatic Mechanism of Sulfonylurea Hypoglycemia**

## Glimepiride and Metformin Hydrochloride Extended Release Tablets

### 1. Description

Bi-layer tablet contains two oral Anti-hyperglycaemic drugs Glimepiride and Metformin hydrochloride extended release used in the management of Type-2-diabetes (NIDDM). The primary mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Hence, the combination of Glimepiride and Metformin extended release complements each other and provides better glycaemic control in management of Type 2 diabetes and probably in the prevention of its associated macro vascular and micro vascular complications.

### 2. Pharmacology

### 2.1 Pharmacodynamics

**Glimepiride**

The primary mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning 2 pancreatic β-cells. In addition, extra pancreatic effects may also play a role in the activity of sulphonylureas such as Glimepiride.

**Metformin**

It improves glucose tolerance in patients with Type 2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

**2.2 Pharmacokinetics**

**2.2.1 Absorption**

**Glimepiride**

Glimepiride show significant absorption with NIDDM patients within 1 hour after administration and peak drug levels ($C_{max}$) at 2 to 3 hours. When Glimepiride was given with meals, the mean $T_{max}$ (time to reach $C_{max}$) was slightly increased (12%) and the mean $C_{max}$ and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

**Metformin extended release**

The absolute bioavailability of a Metformin 500-mg tablet given under fasting conditions is approximately 50-60%. Following a single oral dose of Metformin extended release; $C_{max}$ is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of Metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 μg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively. After repeated administration of extended release, Metformin did not accumulate in plasma.

**2.2.2 Distribution**

**Glimepiride**

After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

**Metformin extended release**

Distribution studies with Metformin extended release have not been conducted. Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound.

**2.2.3 Metabolism**

**Glimepiride**

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of Glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes.

**Metformin extended release**

Metabolism studies with Metformin extended release have not been conducted.

**2.2.4 Excretion**

**Glimepiride**

When Glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in faeces and M1 and M2 (predominant) accounted for about 70% of that recovered in faeces. No parent drug was recovered from urine or faces.

After IV dosing in patients, no significant biliary excretion of Glimepiride or its M1 metabolite has been observed.

**Metformin**

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Renal clearance of Metformin is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

## Dosage and Administration

Dosage should be individualized on the basis of both effectiveness and tolerance. The combination should be given once daily with meals and should be started at a low dose. The initial recommended dose is one tablet once daily with breakfast or first main meal of the day.

**Maximum Recommended Dose:**

The maximum recommended dose for Glimepiride is 8 mg daily. The maximum recommended daily dose for Metformin extended release is 2000 mg in adults.

**CONTRAINDICATIONS**

- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Congestive heart failure requiring pharmacologic treatment.
- Known hypersensitivity to this product or any of its components.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

**STORAGE:** Store in a cool and dry place.

## Scope and Objective of the Study

Objective of the study is to formulate Metformin and Glimepiride in Bi-layer tablet dosage form and evaluate different process Parameters. As Metformin and Glimepiride have more solubility and absorption in intestine.

Literature survey reveals that several formulation methods of Bi-layer tablet such as Wet Granulation and Dry Granulation have been reported for Formulation of Metformin and Glimepiride. Most of reported methods for estimation of Metformin and Glimepiride are Wet Granulation. But the formulation has been developed by Direct Compression Method in place of Wet and Dry granulation

To achieve this goal, various prototype trials were taken and evaluated with respect to the various quality parameters such as Bulk Density, Sieve Analysis, Drug Uniformity, and Dissolution.

Presently many brands are available in market, but present study carried out for developing of Metformin and Glimepiride Bi-layer tablets as generic product, which is cheaper, safe and better than other marketed products.

Under this consideration, the overall objective of present work is:

- Pre formulation study of Metformin and Glimepiride (i.e. API)
- Selection of excipients which are stable and compatible with API
  (by Carrying out Drug-excipients compatibility study)
- Formulation and development of conventional dosage form.
- To study the effect of variation in different processing parameters on final formulation

To Plan for Scale up Batch

## PLAN OF WORK

To achieve this objective, the following plan of work was made.

1. Literature Survey
2. Analysis of Innovator Tablets
    (a) Glycomet GP-1mg (USV)
    (b) Gluconorm-G1 (Lupin)
3. Preformulation Study
    (a) Compatibility Study
    (b) API Characterization
4. Formulation and Evaluation of Tablet
    (I) Pre-compression parameters
        (a) Loss on Drying.
        (b) Density Analysis
        (c) Compressibility Index and Hausner's Ratio.
        (d) Sieve Analysis
    (II) Post- compression Parameters.
        (a) Physical Appearance
        (b) Weight Variation
        (c) Thickness
        (d) Hardness
        (e) Friability
        (f) Disintegration Test
        (g) In-vitro Dissolution Study
        (h) Drug content Uniformity Test.
5. Comparison with Reference Listed drug
6. Stability Study of the Formulation
7. Plan of Scale Up-Batch.

## Literature Survey

1. **H.O. Ammar, H.A. Salama[14], et. al.,** Glimepiride is one of the third generation sulfonylureas used for treatment of type 2-diabetes. Poor aqueous solubility and slow dissolution rate of the drug lead to irreproducible clinical response or therapeutic failure in some cases due to subtherapeutic plasma drug levels. Consequently, the rationale of this study was to improve the biological performance of this drug through enhancing its solubility and dissolution rate. Phase solubility diagrams revealed increase in solubility of the drug upon cyclodextrin addition. In conclusion, the association of water soluble polymers with Glimepiride–CyD systems leads to great enhancement in dissolution rate, increased duration of action and improvement of therapeutic efficacy of the drug.

2. **Lian-Dong Hu., Yang Liu[15]., et. al.,** Metformin hydrochloride (MH) sustained-release pellets were successfully prepared by centrifugal granulation. Seed cores preparation, drug layering, talc modification and coating of polymeric suspensions were carried out in a centrifugal granulator. Talc modification was performed before coating in order to overcome the high water solubility of metformin. The influence of surface modification by talc, the effects of Eudragit_ types and ratios, as well as the correlation between in vitro release and in vivo absorption. Combined use of two Eudragit_ polymers with different features as coating materials produced the desired results. Restricted delivery of metformin hydrochloride to the small intestine from differently coated pellets resulted in increased relative bioavailability and a sustained release effect. The adoption of several different pH dissolution media established a better relationship between the in vitro release and in vivo absorption of the sustained-release pellets.

3. **G. Di Colo, S. Falchi, Y. Zambito[16],** Compressed matrix tablets based on pH-sensitive poly(ethylene oxide)–Eudragit L100 compounds have shown in vitro a compliance with the above requirement. The polymer compounds were prepared by a coevaporation process. The release pattern of Metformin hydrochloride from matrices depended on the PEO–EUD L ratio in the coevaporate. The 1:1 (w/w) ratio

was unable to control Metformin hydrochloride release in simulated gastric fluid (SGF, pH 1.2), because the matrix material was excessively hydrophilic. Nevertheless, the release rate in SGF could be modulated by increasing the EUD L fraction in the coevaporate. With a PEO (M , 400 kDa)–EUD L (1:2, w/w) ratio the percent dose released in 2 h to SGF, where the coevaporate was insoluble, was around 23 or 50% with 10 or 20% loading dose.

4. **Shweta Arora, Rakesh K. Sharma[17], et., al.,** Various grades of low-density polymers were used for the formulation of this system. They were prepared by physical blending of Metformin and the polymers in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in simulated fed state gastric fluid (citrate phosphate buffer pH 3.0). Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethyl cellulose gave the best in vitro percentage release and were taken as the optimized formulation. By fitting the data into zero order, first order and Higuchi model it was concluded that the release followed zero order release, as the correlation coefficient (R2 value) was higher for zero order release. It was concluded from R2 values for Higuchi model that drug release followed fickian diffusion mechanism. There was an increase in AUC in optimized HBS capsules of metformin when compared with immediate release formulation.

5. **Ganesh Rajput, Dr. Jayvadan Patel[18]., et. al.** The present investigation is aimed to formulate floating tablets of Metformin hydrochloride using an effervescent approach for gastro retentive drug delivery system. Floating tablets were prepared using directly compressible method using polymers HPMC K 100M and HPMC K 4M for their gel-forming properties. Formulations were optimized using optimized polymers viscosity of HPMCK4M and HPMCK100M mixture. It was concluded that polymer viscosity had major influence on drug release from hydrophilic matrix tablets as well as on floating lag time. When polymer viscosity increase the similarity factor f2 was increased hence, it concluded that the polymer viscosity

affected the similarity factor f2. The similarity factor f2 was carried out for optimized batch and the theoretical dissolution profile. The different ratios of HPMC K 4M and HPMC K 100M were evaluated to achieve apparent viscosity to 66633 cps. The optimized batch showed the highest f2=82 value, it contained 37.34mg of HPMC K 4M and 212.66mg of HPMC K100M.

6. **Jingshu Piao, Ji-Eun Lee[19].,** Mucoadhesive polymer-coated pellets containing metformin hydrochloride were prepared by the powder-layering technique using a centrifugal fluidizing (CF)-granulator. Four high-viscosity polymers were applied to make the pellets: 1) hydroxymethylcellulose (HPMC), 2) sodium alginate (Na-Alg), 3) HPMC/Carbopol, and 4) sodium carboxylmethylcellulose (Na-CMC). The physical crushing test, mucoadhesive test, zeta-potential test, in vitro release study and observation of gastroretention state of the dosage form were performed to investigate the pellets. The strong adhesive interaction between the Na-CMC-coated pellets and the mucin disc was obtained by mucoadhesive test. Na-Alg was most effective among the polymers used in changing the value of zeta potential of the mucin solution by the interaction between a polymer and a mucin particle. Results from drug dissolution study showed that over 95% of the drug from all the four pellets was released before 2 h, while Na-CMC- and Na-Alg-coated pellets showed a moderate sustained-release in SGF (simulated gastric fluid) and SIF (simulated intestine fluid), respectively. In conclusion, Na-CMC and Na-Alg seem to be promising candidates for mucoadhesive formulation and further studies to improve the sustained-release property are underway for achieving the ultimate goal of once-a-day formulation of metformin hydrochloride.

7. **Uttam Mandal, Tapan Kumar Pal[20],** The emerging new fixed dose combination of Metformin hydrocholride (HCl) as sustained release and glipizide as immediate release were formulated as a bilayer matrix tablet using hydroxy propyl methyl cellulose (HPMC) as the matrix-forming polymer, and the tablets were evaluated via in vitro studies. Three different grades of HPMC (HPMC K 4M, HPMC K 15M, and HPMC K 100M) were used. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. In vitro release studies were

carried out at a phosphate buffer of pH 6.8 with 0.75% sodium lauryl sulphate w/v using the apparatus I (basket) as described in the United States Pharmacopeia (2000). The release kinetics of Metformin were evaluated using the regression coefficient analysis. There was no significant difference in drug release for different viscosity grade of HPMC with the same concentration. Tablet thus formulated provided sustained release of Metformin HCl over a period of 8 hours and glipizide as immediate release.

8. **Fiona Palmer, Marina Levina and Ali Rajabi-Siahboomi[21]**., Extended release (ER) formulation of metformin hydrochloride (HCl) presents the formulator with significant challenges due to its poor inherent compressibility, high dose and high water solubility. This study investigates the possibility for development of a direct compression ER matrix tablet using hypromellose.

9. **T. Kiran, M.Sadanandam[22], et.al.,** Surface solid dispersions using water-insoluble carriers like crospovidone, croscarmellose sodium, sodium starch glycolate, pre-gelatinized starch, potato starch and Avicel PH 101 were investigated to enhance the dissolution rate of the glimepiride, a poorly water insoluble drug. The effect of various carriers on dissolution profile was studied using presence absence model. The surface solid dispersion on crospovidone with drug to carrier ratio of 1:19 showed highest dissolution rate with the dissolution efficiency of 81.89% in comparison to pure drug (22.88%) and physical mixture (35.96%). The surface solid dispersion on crospovidone was characterized by powder X-ray diffractometry, differential scanning calorimetry, Fourier transform infrared spectroscopy, gas chromatography and scanning electron microscopy. The optimized dispersion was formulated into tablets by wet granulation method. These tablets, apart from fulfilling the official and other specifications, exhibited higher rates of dissolution and dissolution efficiency values.
10. **Ilic, R. Dreu, S. Srcic[23], et. al.,**Drug-free microparticles were prepared using a spray congealing process with the intention of studying the influence of processing parameters. By varying the atomizing pressure and liquid feed rate, microparticles with median sizes ($d_{(0.5)}$) from 58 to 278 μm were produced, with total process yields

ranging from 81% to 96%. An increased liquid feed rate was found to increase microparticle size, and higher atomizing pressures were found to decrease microparticle size. Greater change in microparticle size was achieved by varying atomizing pressure, which can be considered a dominant process parameter regarding microparticle size. In addition, microparticles with glimepiride, a model poorly water-soluble drug, were prepared by spray congealing using three different hydrophilic meltable carriers: Gelucire 50/13, poloxamer 188, and PEG 6000. Spherical microparticles with relatively smooth surfaces were obtained, with no drug crystals evident on the surfaces of drug-loaded microparticles. XRPD showed no change in crystallinity of the drug due to the technological process of microparticle production. All glimepiride loaded microparticles showed enhanced solubility compared to pure drug; however, Gelucire 50/13 as a carrier represents the most promising approach to the dissolution rate enhancement of glimepiride. The influence of storage (30 °C/65% RH for 30 days) on the morphology of glimepiride/Gelucire 50/13 microparticles was studied, and the formation of leaf-like structures was observed (a "blooming" effect)

11 **Uttam Mandal and Tapan Kumar Pal**[24], The emerging new fixed dose combination of Metformin hydrochloride (HCl) as sustained release and glipizide as immediate release were formulated as a bilayer matrix tablet using hydroxy propyl methyl cellulose (HPMC) as the matrix-forming polymer, and the tablets were evaluated via in vitro studies. Three different grades of HPMC (HPMC K 4M, HPMC K 15M, and HPMC K 100M) were used. All tablet formulations yielded quality matrix preparations with satisfactory tableting properties. In vitro release studies were carried out at a phosphate buffer of pH 6.8 with 0.75% sodium lauryl sulphate w/v using the apparatus I (basket) as described in the United States Pharmacopeia (2000). The release kinetics of Metformin was evaluated using the regression coefficient analysis. There was no significant difference in drug release for different viscosity grade of HPMC with the same concentration. Tablet thus formulated provided sustained release of Metformin HCl over a period of 8 hours and glipizide as immediate release.

12 **Ouyang Defang, Pan Weisan[25], et. al.,** A system that can deliver multi-drugs at a prolonged rate is very important to the treatment of various chronic diseases such as diabetes, asthma, and heart disease. Two controlled-release systems, which exhibited similar release profiles of Metformin and glipizide, i.e., elementary osmotic pump tablets (EOP) and bilayer hydrophilic matrix tablet (BT), were designed. The effects of pH and hydrodynamic conditions on drug release from two formulations were investigated. It was found that both drug releases from EOP were not sensitive to dissolution media pH and hydrodynamics change, while the release of glipizide from BT was influenced by the stirring rate. Moreover, in vivo evaluation was performed, relative to the equivalent dose of conventional metformin tablet and glipizide tablet, by a three-crossover study in six Beagle dogs. Cumulative percent input in vivo was compared to in vitro release profiles. The linear correlations of metformin and glipizide between fraction absorbed in vivo and fraction dissolved in vitro were established for EOP—a true zero-order release formula, whereas only nonlinear correlations were obtained for BT. In conclusion, drug release from EOP was both independent of in vitro and in vivo conditions, where the best sustained release effect was achieved, whereas the in vitro dissolution test employed for BT needed to be further optimized to be biorelevant.

13 **Sam Solomon, Senthamil Selvan[26], et. al.,** The aim of this study was to design an oral sustained release matrix tablet of Metformin HCl and to optimize the drug release profile using response surface methodology. Tablets were prepared by non aqueous wet granulation method using HPMC K-15 M as matrix forming polymer. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile .HPMC K 15 M (($X_1$) and PVP K 30 ($X_2$) were taken as the independent variable. The dependent Variables selected were % of drug released in 1 hr. ($rel_{1hr}$), % of drug released in 8 hrs ($rel_{8hr}$) and timer 50% drug release ($t_{50\%}$). Contour plots were drawn, and optimum formulations were selected by feasibility and grid search. The formulated tablets followed Higuchi drug release kinetics and diffusion was the dominant mechanism of drug release, resulting

in regulated and complete release within 8hrs. the polymer (HPMC K15M) and binder (PVP K 30) had significant ((P<0.05), Validation of optimization study, performed using 8 confirmatory runs, indicated very high degree of prognostic ability of response surface methodology, with mean percentage error (.S.D.) 0.0437+0.3285. Besides unraveling the effect of the 2 factors on the in vitro drug release, the study helped in finding the optimum formulation with sustained drug release.

14 **Ashutosh Mohapatra, Mukesh C Gohel[27], et. al.,** Metformin hydrochloride is an orally administered antihyperglycemic agent, used in the management of non insulin dependent (type-2) diabetes mellitus. Difficulty in swallowing (dysphagia) is common among all age group, especially in elderly and pediatrics. Unfortunately, a high percentage of patients suffering from type -2 diabetes are elderly people showing dysphasia. In this study, orally disintegrating tablets were prepared using direct compression and wet granulation method. First the tablets of Metformin were prepared using starch rx1500 and microcrystalline cellulose by direct compression. The tablets showed erosion behavior rather than disintegration. Then lactose was incorporated which created pores to cause burst release of drug. But these tablets did not give good mouth feel. thus pearlitol SD200(spray dried mannitol) was used to prepare tablets (LMCT 3 and MP 13) not only exhibited desired mouth feel but also disintegration time, invitro dispersion time, water absorption ratio, and in vitro drug release. All the batches contained 15% starch 1500 and 4% of croscarmellose sodium, the optimization bathes prepared by direct compression and wet granulation showed 85 % drug release at 4 min and 8 min, respectively. The strong saline and slight bitter taste of the drug masked using non nutritive sweetener and flavor

# DRUG PROFILE

## METFORMIN

**Description** : A Biguanide hypoglycemic agent used in the treatment of non-Insulin-dependent diabetes mellitus not responding to dietary modification. Metformin improves glycemic control by improving insulin sensitivity and decreasing intestinal absorption of glucose

**Drug Category** : Hypoglycemic Agents

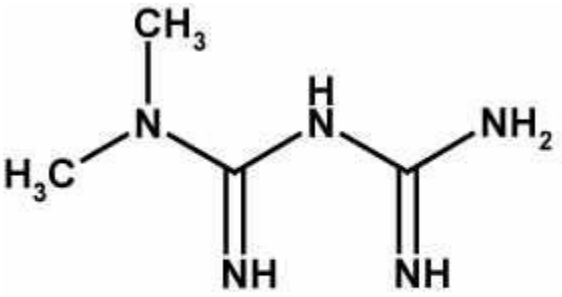
**Empirical Formula** : $C_4H_{11}N_5$

**Molecular Weight** : 129.1636

**IUPAC Name** : 3-(diaminomethylidene)-1,1-dimethylguanidine

**Half Life** : 6.2 hours

**Chemical Structure** :




Metformin

### Physical Properties of API

**Melting Point** : 223-226 $^{o}$C

**State** : Solid

| | | |
|---|---|---|
| **Solubility** | **:** | Freely soluble as HCl salt in water |

## Pharmacological Parameters

| | | |
|---|---|---|
| **Drug category** | **:** | Hypoglycemic Agents |
| **Route of administration** | **:** | Oral |
| **Pharmacology** | **:** | Metformin is an Anti-hyperglycemic agent, which improves glucose tolerance in patients with Type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other classes of oral Anti-hyperglycemic agents. Unlike sulfonylureas, Metformin does not produce hypoglycemia in either patients with Type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease. |
| **Mechanism of Action** | **:** | Metformin pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. |
| **Absorption** | **:** | Absorbed over 6 hours, bioavailability is 50 to 60% under fasting conditions. Food delays absorption. |
| **Protein Binding** | **:** | Metformin is negligibly bound to plasma proteins. |
| **Biotransformation** | **:** | Metformin is not metabolized |
| **Drug Interactions** | **:** | |

| Drug | | Interaction |
|---|---|---|
| **Cimetidine** | **:** | Cimetidine increases the effect of Metformin |
| **Glucosamine** | **:** | Possible hyperglycemia |

## DRUG PROFILE

**GLIMEPIRIDE**

**Description** **:** Glimepiride is the first III generation sulphonyl urea it is a very potent sulphonyl urea with long duration of action.

**Category** **:** Sulfonylureas, Anti-Arrhythmia Agents, Hypoglycemic Agents, Immunosuppressive Agents,

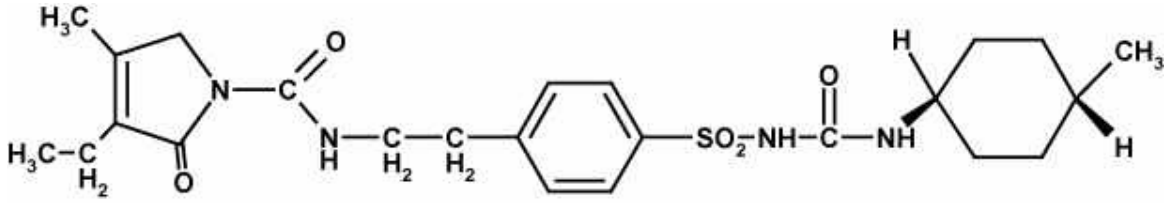
**Empirical Formula** **:** $C_{24}H_{34}N_4O_5S$

**Molecular Weight** **:** 490.6160

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

**Half Life** **:** 5 hours

**Chemical Structure** **:**



**Physical Properties of API**

| | | |
|---|---|---|
| **Color & Appearance** | **:** | It is a white, Odorless, crystalline powder |
| **Melting Point** | **:** | 207 $^{o}$C |
| **State** | **:** | Solid |
| **Solubility** | **:** | Insoluble in water and methanol |
| **pKa** | **:** | 6.2 |

## Pharmacological Parameters

| | | |
|---|---|---|
| **Drug category** | **:** | Sulfonylurea agent |
| **Route of administration** | **:** | Oral |
| **Pharmacology** | **:** | Glimepiride is a "second-generation" sulfonylurea agent. It is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin. |
| **Mechanism of Action** | **:** | Glimepiride is lowering blood glucose by stimulating the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin. It binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Membrane depolarization stimulates calcium ion influx through voltage-sensitive calcium channels. This increase in intracellular calcium ion concentration induces the secretion of insulin. |
| **Absorption** | **:** | Completely (100%) absorbed orally |
| **Protein Binding** | **:** | Over 99.5% bound to plasma protein. |
| **Drug Interactions** | **:** | |

| **Drug** | **Interaction** |
|---|---|

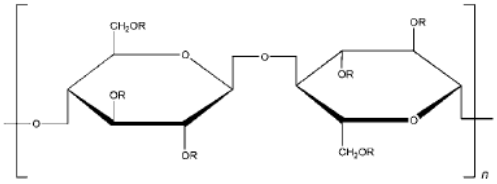
| | |
|---|---|
| **Cyclosporine** | The sulfonylurea increases the effect of cyclosporine |
| **Glucosamine** | Possible hyperglycemia |
| **Ketoconazole** | Ketoconazole increases the effect of rosiglitazone |
| **Repaglinide** | Similar mode of action - questionable association |
| **Rifampin** | Rifampin reduces levels and efficacy of rosiglitazone, rifampin decreases the effect of sulfonylurea |

## HYDROXYPROPYL METHYL CELLULOSE

**Chemical Name** : Cellulose hydroxyl propyl Methyl ether

**Molecular weight** : 10,000–1,500,000.

**Structural Formula** :




where R is H, $CH_3$, or $CH_3CH(OH)CH_2$

**Functional Categories** : Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

**Descriptions** : Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

### TYPICAL PROPERTIES

**Acidity/alkalinity** : pH 5.5–8.0 for a 1% w/w aqueous solution.

**Ash** : 1.5–3.0%, depending upon the grade and viscosity.

**Auto ignition temperature** : 360ºC

**Density (Bulk)** : 0.341 $g/cm^3$

**Density (Tapped)** : 0.557 $g/cm^3$

**Density (True)** : 1.326 $g/cm^3$

**Melting Point** : Browns at 190–200ºC; chars at 225–230ºC. Glass transition temperature is 170–180ºC.

**Specific Gravity** : 1.26

**Solubility** : Soluble in cold water, insoluble in chloroform, ethanol (95%), and ether

**Moisture content** : Hypromellose absorbs moisture from the atmosphere the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**Viscosity (dynamic)** : Solutions prepared Hypromellose 347 using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions

**Stability** : Solutions are stable at pH 3–11

**Storage Conditions** : 1. Hygroscopic after drying,
2. Increasing temperature reduces the viscosity.

**Safety** : 1. Nontoxic and Non-irritant material,
2. Excessive oral consumption has laxative effect.

**Applications in Pharmaceutical Formulation or Technology:**

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
- In oral products, Hypromellose is primarily used as a tablet Binder (2-5% w/w), in film-coating, and as a matrix for use in extended-release tablet formulations.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.
- Hypromellose is also used as a suspending and thickening agent in topical formulations.
- Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.
- Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.
- It is also widely used in cosmetics and food products.

**Table No. 1 MATERIALS USED**

| Sr.No. | Name | Category | Suppliers of material |
|---|---|---|---|
| **Sustained Release Layer** | | | |
| 1. | Metformin HCl | API | Morepen Labs.Ltd.Parwanoo |
| 2. | Methocel K100 M | Binder | Morepen Labs.Ltd.Parwanoo |
| 3. | Microcrystalline cellulose | Filler | Morepen Labs.Ltd.Parwanoo |
| 4. | Colloidal Silicon Dioxide | Glidant | Morepen Labs.Ltd.Parwanoo |
| 5. | Magnesium Stearate | Lubricant | Morepen Labs.Ltd.Parwanoo |
| **Immediate Release Layer** | | | |
| 1. | Glimepiride | API | Morepen Labs.Ltd.Parwanoo |
| 2. | Starch 1500 | Multi functional excipient | Morepen Labs.Ltd.Parwanoo |
| 3. | Microcrystalline cellulose | Filler | Morepen Labs.Ltd.Parwanoo |
| 4. | Colloidal Silicon Dioxide | Glidant | Morepen Labs.Ltd.Parwanoo |
| 5. | Magnesium Stearate | Lubricant | Morepen Labs.Ltd.Parwanoo |

**Table No. 2 EQUIPMENTS USED**

| Sr.No. | Equipments | Manufacturer | Capacity |
|---|---|---|---|
| 1. | Fluid bed Dryer | M/c S.B.Panchal & Co. | 1.25 kg |
| 2. | Planetary Mixer (PLM) | M/s Gansons | 5.0 Lit. |
| 3. | Disintegration Tester | M/s Electro Lab | N.A |
| 4. | Dissolution Tester | M/s Electro Lab (TDT-80L) | N.A |
| 5. | Shifter | M/s E.K.S Technique | Min Capacity 1.0 Lit. |
| 6. | LOD Tester | Mettler Toledo(HB 43) | N.A |
| 7. | Hardness Tester | M/s Tab Machine | N.A |
| 8. | Compression M/s (B Tooling) | M/s Clit | 10 Station |
| 9. | Compression M/s (D Tooling) | M/s Clit | 16 Station |
| 10. | Stirrer | M/s Remi motors | Type RQ-123, 38mm Propeller H.P-1/20 |
| 11. | Homogenizer | M/s Remi motors | Type RQ-127 Propeller H.P-1/8 |
| 12. | Vernier calipers | Mituto (Absolute digimatic) | N.A |
| 13. | Conventional coating pan, 12 & 16 inches | M/c Betochem eng. | 1.0 & 5.0 kg |
| 14. | Weighing Balance (Model No. AB 204) | M/c Mettler | Max. 210 gm Min. 10 mg |
| 15. | Weighing Balance (Model No. PB 302) | M/c Mettler | Max. 310 gm Min. 0.2 mg |
| 16. | I.R moisture analyzer, model No. LJ-16 | M/c Mettler | N.A |
| 17. | Humidity Chamber, 2 No. | M/c Newtronics | N.A |
| 18. | Oven $45^{o}$ C, 1 Number | M/c Sintex | N.A |
| 19. | Oven $45^{o}$ C, 2 Number | M/c Narang | N.A |
| 20. | Photo stability Chamber, 1 Number | M/c Newtronics | N.A |
| 21. | pH meter | M/c Electronic India | N.A |
| 22. | U.V. Spectrophotometer | M/c Parkin Elmer, Model-Lambda EZ 201 | N.A |

# Preformulation Study

Preformulation testing is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailability dosage forms that can be mass produced.

Following the identification of a new chemical entity that is suitable for development, the formulator will be called upon to produce dosage form. Initially this may involve production of injectable from suitable for early efficiency and toxicity testing and subsequently there will be a need to develop the final dosage form which generally will not be injectable. The challenge for the formulator is to develop the initial and final dosage form to the highest quality in shortest time. This process is best achieved when certain physicochemical properties of the drug substance are investigated, understood and efficiency utilized, this is Preformulation.

**Preformulation Study can divide into two Subclasses:**

1. **Compatibility Study**
2. **Active Pharmaceutical Ingredient (API) Characterization.**

**1. Compatibility Study:**

The Compatibility of drug and formulation components is an important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental condition and affect the shelf life of the product or any other unwanted effect on the formulation.

**2. Active Pharmaceutical Ingredient Characterization:**

- Organoleptic evaluation
- Color
- Taste
- Odour

**Need of Preformulation Studies:**

Scientific and regulatory justification of acquiring Preformulation data including the following:

- Establishment of drug specification intended for toxicological evaluation and clinical supply preparation
- Formulation of clinical supplies and establishment of their preliminary specification
- providing scientific data to support dosage from development and evaluation of product efficiency, quality, stability, and Bioavailability
- Evaluation of the stability of early development dosage forms.
- Fulfillment of the requirement of the chemistry manufacturing control section of the investigation new drug (IND) and subsequent new drug application (NDA) or Abbreviated new drug application (AND).

**Preformulation Study Include Investigation of –**

**1. Bulk Characterization**

- Crystalline and Polymorphism
- Hygroscopicity
- Fine Particle Characterization
- Bulk Density
- Powder Flow Properties

**2. Solubility Analysis**

- Ionization Constant- pKa
- pH Solubility Profile
- Common Ion Effect
- Solubilization
- Partition Coefficient
- Dissolution

**3. Stability Analysis**

- Solid state stability of drug alone

- Stability in presence of excipient (Compatibility Study)
- Solution state stability (Stability in G.I fluid & Granulating solvents).

**4. Photo Stability Studies**

**Analysis of Innovator Product:**

- Glycomet GP-1mg (USV)
- Gluconorm-G1 (Lupin)

A comparative analysis of innovator product and formulator product helps in calculation of the ($f_1$) dissimilarity and ($f_2$) similarity dissolution factor. Analysis of the innovator product was carried out for various physical parameter and In-vitro dissolution profile.

**Parameters:**

1. Shape
2. Thickness Test
3. Hardness Test
4. Friability Test
5. Weight Variation Test
6. In-vitro Dissolution Study
7. Drug Content Uniformity Test

**Table No. 3 Evaluation of Physical Property of Drug Excipients Mixtures:**

| Sr.No | Parameters | Gluconorm-G1 (Lupin) Batch No. J090718 | Glycomet GP-1mg (USV) Batch No. 28000264 |
|---|---|---|---|
| **1.** | Appearance | One side break line light pink& other side white caplet | One side break line light pink& other side off white caplet |

| | | | |
|---|---|---|---|
| **2.** | Thickness | 7.08mm | 6.90mm |
| **3.** | Diameter | 18.5mm | 17.03mm |
| **4.** | Hardness | 4 $kg/cm^2$ | 6 $kg/cm^2$ |
| **5.** | Friability | 0.9 % | 0.06 % |
| **6.** | Average weight | 1100 mg | 913 mg |

**1. Angle of Repose :**

Flowability of mixture was determined by calculating angle of repose by fixed height method. A funnel with 1 mm diameter of stem was fixed at a height of 3.0 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touch the stem of the funnel. A rough circle was drawn around the pile base and radius of the powder cone was measured Angle of repose was calculated from the average radius using the following formula.

**Table No. 4 Flow Characteristics**

| Angle of Repose | Flow Characteristics |
|---|---|
| < 25 | Excellent |
| 25-30 | Good |
| 30-40 | Passable |
| > 40 | Very Poor |

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

Where:

$\theta$ = Angle of Repose

h = Height of the Pile

r = Average Radius of the Powder Cone.

**Table No. 5 Angle of Repose of Metformin Blend:**

| Trials | Height (cm) | Radius (cm) | Angle of | Flow |
|---|---|---|---|---|

| | | | Repose (θ) | Characteristics |
|---|---|---|---|---|
| **Trial 1** | 3.0 | 5.5 | 28° 56' | Good |
| **Trial 2** | 3.0 | 5.3 | 29° 50' | Good |
| **Trial 3** | 3.0 | 5.4 | 29° 03' | Good |
| **Trial 4** | 3.0 | 5.2 | 30° 34' | Passable |
| **Trial 5** | 3.0 | 5.3 | 29° 50' | Good |

**Table No. 6 Angle of Repose of Glimepiride Blend**

| Trials | Height (cm) | Radius (cm) | Angle of Repose (θ) | Flow Characteristics |
|---|---|---|---|---|
| **Trial 1** | 3.0 | 5.8 | 27° 33' | Good |
| **Trial 2** | 3.0 | 5.7 | $27^0$ 60' | Good |
| **Trial 3** | 3.0 | 5.6 | 28° 14' | Good |
| **Trial 4** | 3.0 | 5.7 | 27° 60' | Good |
| **Trial 5** | 3.0 | 5.5 | 28° 59' | Good |

**2. Bulk Density:**

Bulk Density of all types of mixture was determined by pouring gently sample through a glass funnel into a 50 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk Density was calculated.

$$\text{Bulk Density (g/ml)} = \frac{\text{Weight of Sample}}{\text{Volume Occupied by the Sample}}$$

**Table No. 7 Bulk Density of Glimepiride Blend:**

| Trials | Weight of Blend (gm) | Volume of Blend (ml) | Bulk Density (gm/ml) |
|---|---|---|---|
| **Trial 1** | 25.98 | 50 | 0.519 |
| **Trial 2** | 26.12 | 50 | 0.522 |
| **Trial 3** | 26.08 | 50 | 0.521 |
| **Trial 4** | 26.53 | 50 | 0.530 |
| **Trial 5** | 26.48 | 50 | 0.529 |

**Table No. 8 Bulk Density of Metformin Blend:**

| Trials | Weight of Blend (gm) | Volume of Blend (ml) | Bulk Density (gm/ml) |
|---|---|---|---|
| **Trial 1** | 23.25 | 50 | 0.465 |
| **Trial 2** | 23.31 | 50 | 0.466 |
| **Trial 3** | 23.48 | 50 | 0.469 |
| **Trial 4** | 23.39 | 50 | 0.467 |
| **Trial 5** | 23.41 | 50 | 0.468 |

**3. Tapped Density:**

Tapped Density was determined by using electrolab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample in then tapped (250, 500 & 750 Tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2 %.A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and Tapped Density is calculated using following formula.

$$\text{Tapped Density (g/ml)} = \frac{\text{Weight of Sample}}{\text{Volume Occupied by the Sample}}$$

**Table No. 9 Tapped Density of Glimepiride Blend:**

| Trials | Weight of Blend (gm) | Volume of Blend (ml) | Tapped Density (gm/ml) |
|---|---|---|---|
| **Trial 1** | 25.98 | 41 | 0.633 |
| **Trial 2** | 26.12 | 41 | 0.637 |
| **Trial 3** | 26.08 | 40 | 0.652 |
| **Trial 4** | 26.53 | 41 | 0.647 |
| **Trial 5** | 26.48 | 41 | 0.645 |

**Table No. 10 Tapped Density of Metformin Blend:**

| Trials | Weight of Blend (gm) | Volume of Blend (ml) | Tapped Density (gm/ml) |
|---|---|---|---|
| **Trial 1** | 23.25 | 40 | 0.581 |

| | | | |
|---|---|---|---|
| **Trial 2** | 23.31 | 40 | 0.582 |
| **Trial 3** | 23.48 | 41 | 0.572 |
| **Trial 4** | 23.39 | 40 | 0.584 |
| **Trial 5** | 23.41 | 40 | 0.585 |

**4. Compressibility %:**

It is also one of the sample methods to evaluate flow of a powder by comparing the Bulk Density and Tapped Density. A useful Empirical guide is given by the Carr's Compressibility.

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

**Table No. 11 Compressibility Index of Glimepiride Blend**

| **Trials** | **Bulk Density (gm/ml)** | **Tapped Density (gm/ml)** | $\frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}}$ | **Compressibility Index (%)** | **Flow Character** |
|---|---|---|---|---|---|
| **Trial 1** | 0.519 | 0.633 | 0.1800 | 18.00 | Fair |
| **Trial 2** | 0.522 | 0.637 | 0.1805 | 18.05 | Fair |
| **Trial 3** | 0.521 | 0.652 | 0.2009 | 20.09 | Passable |
| **Trial 4** | 0.530 | 0.647 | 0.1808 | 18.08 | Fair |
| **Trial 5** | 0.529 | 0.645 | 0.1798 | 17.98 | Fair |

**Table No. 12 Compressibility Index of Metformin Blend**

| **Trials** | **Bulk Density (gm/ml)** | **Tapped Density (gm/ml)** | $\frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}}$ | **Compressibility Index (%)** | **Flow Character** |
|---|---|---|---|---|---|
| **Trial 1** | 0.465 | 0.581 | 0.1996 | 19.96 | Fair |
| **Trial 2** | 0.466 | 0.582 | 0.1993 | 19.93 | Fair |
| **Trial 3** | 0.469 | 0.572 | 0.1800 | 18.00 | Fair |
| **Trial 4** | 0.467 | 0.584 | 0.2003 | 20.03 | Passable |
| **Trial 5** | 0.468 | 0.585 | 0.2000 | 20.00 | Fair |

**Table No. 13 Relationship of Flow Character with Compressibility Index (%)**

| Compressibility Index (%) | Flow Character |
|---|---|
| ≤ 10 | Excellent |
| 11-15 | Good |
| 16-20 | Fair |
| 21-25 | Passable |
| 26-31 | Poor |
| 32-37 | Very poor |
| >38 | Very very poor |

**Conclusion:** The Flow Characteristic of both Metformin and Glimepiride Blend are fair.

**5. Hausner's Ratio:**

It provide an indication of the degree of densification which could result from vibration of feed hopper

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

**Lower Hausner's Ratio** ➔ Better Flowability

**Higher Hausner's Ratio** ➔ Poor Flowability

**Table No. 14 Hausner's Ratio of Glimepiride Blend**

| Trials | Bulk Density | Tapped Density | Hausner's Ratio | Flow Characteristics |
|---|---|---|---|---|

| | (gm/ml) | (gm/ml) | | |
|---|---|---|---|---|
| **Trial 1** | 0.519 | 0.633 | 1.21 | Fair |
| **Trial 2** | 0.522 | 0.637 | 1.22 | Fair |
| **Trial 3** | 0.521 | 0.652 | 1.25 | Fair |
| **Trial 4** | 0.530 | 0.647 | 1.22 | Fair |
| **Trial 5** | 0.529 | 0.645 | 1.21 | Fair |

**Table No. 15 Hausner's Ratio of Metformin Blend**

| Trials | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Hausner's Ratio | Flow Characteristics |
|---|---|---|---|---|
| **Trial 1** | 0.465 | 0.581 | 1.24 | Fair |
| **Trial 2** | 0.466 | 0.582 | 1.24 | Fair |
| **Trial 3** | 0.469 | 0.572 | 1.21 | Fair |
| **Trial 4** | 0.467 | 0.584 | 1.25 | Fair |
| **Trial 5** | 0.468 | 0.585 | 1.25 | Fair |

**Table No: 16 Relationship of Flow Character & Hauser's Ratio**

| Hausner's Ratio | Flow Character |
|---|---|
| 1.00-1.11 | Excellent |
| 1.12-1.18 | Good |
| 1.19-1.25 | Fair |
| 1.26-1.34 | Passable |
| 1.35-1.45 | Poor |
| 1.46-1.59 | Very poor |

**6. Sieve Analysis:**

The main aim of analysis is to determine the different size of drug particles present. A series of standard sieve were stacked one over the above so that sieve with larger pore size (Less sieve No.) occupy top position followed by a series of decreasing pore size (large sieve No.) towards the bottom.

**Procedure:**

The procedure involves the electromagnetic sieve shaking of the sample through the sieve of successively arranged sieve (sieve No 20, 30, 60, 80, 100 and receiver), and weight of the portion of the sample retained on each sieve and calculate percentage retained on each sieve.

**Results:**

50gm of both blend of Metformin and Glimepiride were analyzed separately on electromagnetic sieve shaking and weight of the portion of the sample retained on each sieve and calculate percentage retained on each sieve.

**Table No. 17 Results:**

| API + Excipients | Weight of material retained on sieve no 30 # | Weight of material retained on sieve no 40 # | Weight of material retained on sieve no 60 # | Weight of material retained on sieve no 80 # | Weight of material retained on sieve no above 80 # |
|---|---|---|---|---|---|
| **Metformin Blend** | 1.0 | 2.0 | 32.8 | 14.2 | - |
| **Glimepiride Blend** | - | 1.0 | 20.0 | 14.0 | 15.0 |

**Table No. 18 Sample Screen Analysis Data for Metformin Blend:**

| U.S Standard Sieve Size | Sieve opening (µm) | Mean of class interval (µm) | Granules weight on the smaller screen (gm) | Percentage (%) | Cumulative (%) weight |
|---|---|---|---|---|---|
| > 12 | 1680 | - | - | - | - |
| 12-20 | 1680-840 | 1260 | - | - | - |
| 20-40 | 840-420 | 630 | 1.0 | 1.0 | 50.0 |
| 40-70 | 420-210 | 315 | 20.0 | 20.0 | 49.0 |
| 70-140 | 210-105 | 157 | 29.0 | 29.0 | 29.0 |
| < 140 | < 108 | - | - | - | - |
| **Grand Total** | | | 50.0 | 50.0 | 50.0 |

**Table No. 19 Sample Screen Analysis Data for Glimepiride Blend:**

| U.S Standard Sieve Size | Sieve opening (µm) | Mean of class interval (µm) | Granules weight on the smaller screen (gm) | Percentage (%) | Cumulative (%) weight |
|---|---|---|---|---|---|
| > 12 | 1680 | - | - | - | - |
| 12-20 | 1680-840 | 1260 | - | - | - |
| 20-40 | 840-420 | 630 | 3.0 | 3.0 | 50.0 |
| 40-70 | 420-210 | 315 | 32.8 | 33.0 | 47.0 |
| 70-140 | 210-105 | 157 | 14.1 | 14.0 | 14.0 |

| | | | | | |
|---|---|---|---|---|---|
| < 140 | < 108 | - | - | - | - |
| **Grand Total** | | | 49.9 | 50.0 | 50.0 |

7. **Loss on Drying:**

Loss of drying is the loss of weight expressed as percentage W/W resulting from water and volatile matter of any kind that can be driven off under specified conditions the test is carried on a well mixed sample of the substance. If the substance is the form of large crystals, reduce the size by rapid crushing to a powder.

**Method:** 0.5 – 1.5 g of sample of blends was accurately weighed and the powder was kept in a Mettler Toledo Apparatus for 5 min. at 105°C and the moisture content was calculated.

**Table No. 20 Loss on Drying of Metformin Blend:**

| Trials | Sample | Initial weight (gm) | Final weight (gm) | LOD (%) |
|---|---|---|---|---|
| **Trial 1** | 1 | 0.534 | 0.517 | 3.18 |
| | 2 | 1.046 | 1.013 | 3.15 |
| | 3 | 1.522 | 1.475 | 3.08 |
| **Trial 2** | 1 | 0.508 | 0.491 | 3.34 |
| | 2 | 1.052 | 1.017 | 3.32 |
| | 3 | 1.510 | 1.020 | 3.24 |
| **Trial 3** | 1 | 0.512 | 0.496 | 3.12 |
| | 2 | 1.008 | 0.976 | 3.17 |
| | 3 | 1.534 | 1.485 | 3.19 |
| **Trial 4** | 1 | 0.521 | 0.507 | 2.68 |
| | 2 | 1.032 | 1.005 | 2.61 |
| | 3 | 1.520 | 1.480 | 2.63 |
| **Trial 5** | 1 | 0.520 | 0.508 | 2.30 |
| | 2 | 1.021 | 0.998 | 2.26 |
| | 3 | 1.560 | 1.525 | 2.24 |

**Table No. 21 Loss on Drying of Glimepiride Blend:**

| Trials | Sample | Initial weight (gm) | Final weight (gm) | LOD (%) |
|---|---|---|---|---|
| **Trial 1** | 1 | 0.502 | 0.485 | 3.38 |

| | | | | |
|---|---|---|---|---|
| | 2 | 1.064 | 1.029 | 3.28 |
| | 3 | 1.518 | 1.468 | 3.29 |
| **Trial 2** | 1 | 0.512 | 0.498 | 2.73 |
| | 2 | 1.036 | 1.010 | 2.50 |
| | 3 | 1.517 | 1.480 | 2.43 |
| **Trial 3** | 1 | 0.506 | 0.495 | 2.17 |
| | 2 | 1.024 | 1.002 | 2.14 |
| | 3 | 1.528 | 1.495 | 2.15 |
| **Trial 4** | 1 | 0.520 | 0.492 | 5.38 |
| | 2 | 1.043 | 0.987 | 5.36 |
| | 3 | 1.532 | 1.450 | 5.35 |
| **Trial 5** | 1 | 0.511 | 0.483 | 5.47 |
| | 2 | 1.002 | 0.947 | 5.39 |
| | 3 | 1.520 | 1.438 | 5.39 |

8. **Drug Excipients Compatibility (Stability in Presence of Excipients):**

A drug or active principal is most often delivered to patient along with other chemical substance within a pharmaceutical formulation, which should comply with strict specification, often prescribed by law. In order to be approved, formulation should warrant well defined level of stability, safety and efficacy. The desired level of stability is often difficult to achieve because the active principal may interact with the other substance of the formulation, the so called excipients which do not have a specified pharmaceutical activity.

Some time, this interaction is fundamental for a proper functioning of the drug delivery system (e.g. to speed up dissolution, or controlling release). In most cases of mechanical drug excipients mixture in the solid state, however we would like to predict possible negative effect of the inter reaction, faster degradation rate chemical changes etc. Most often, the negative effect of the drug excipients interaction in the solid state medicated by water and enhanced by an increased temperature in fact vapor released by the excipients may be absorbed /adsorbed by the drug or water bonded to the excipients may promote a reaction at the excipients drug inter phase in the first case (vapor mediated mechanism) the effect should be the more important at higher the concentration of the Excipients. In the second case, we often here partial salvation in the interphase are and even traces of water may place a major role in degradation of water- soluble through an increased mobility of drug –excipients which enhance their reactivity.

Owing to the length and complexity of the approval process, it is of paramount importance to address the drug-excipients. Compatibility issue from the early stage of Preformulation. The standard "Fast stability test" involve storing binary drug-excipients mixture under extreme temperature and humidity condition and periodically determining the drug concentration possible pitfall of this test is that concentration dependent effect are usually not identified, while some of the reaction observed at high temperature /humidity may not occurs in normal stage storage.

**Need of Drug Excipients Compatibility Study:**

1. To provide the information to the formulator which will help to select the Excipients for formulation of dosage form
2. To check whether the stability is ascertain during the toxicological study during the toxicological study.
3. To check the shelf life of drug in presence of excipients.
4. To check the loss of pharmaceutical elegance (fading of colored solution and tablets).
5. To check the bioavailability in presence of different excipients.
6. To check the loss of active ingredient.

In this study the excipients were selected which are generally used in tablets formulation. Ratio of drug Vs. excipients is taken as per their concentration in prototype development formula. To maximize possible physicochemical interaction, drug and excipients were mixed together into two ways as follow:

(1) Drug was mixed with Excipients in dry form kept in a colorless and transparent vial with rubber plug and aluminum seal.

(2) Drug was mixed with excipients in dry form then granulated with and IPA then dried, these granules are kept in colorless and transparent vial rubber plug and aluminum seal.

All the samples as described below were kept at:

- 25° C,

- 25° C / 60 % RH
- 40° C
- 40° C/ 75 % RH

**Incubation Conditions :** 25° C, 25° C/60 % RH, 40° C, 40° C/ 75 % RH
**Intervals:** 2 weeks, 4 weeks, 6 weeks
**Quantity:** Approx 100 mg/vial
**Packing Material:** USP Type-I clear and temperature glass vials of capacity 10ml, gray Butyl rubber plug and aluminum seals

**Table No. 22 Material Used in Order to Perform Preformulation Study**

| Sr.No. | Name | Category | Suppliers of Material |
|---|---|---|---|
| 1. | Metformin | API | Morepen Labs. Ltd. Parwanoo. |
| 2. | Glimepiride | API | Morepen Labs. Ltd. Parwanoo. |
| 3. | Methocel | Polymer | Morepen Labs. Ltd. Parwanoo. |
| 4. | MCC | Filler | Morepen Labs. Ltd. Parwanoo. |
| 5. | Colloidal Silicon Dioxide | Glident | Morepen Labs. Ltd. Parwanoo. |
| 6. | Magnesium Stearate | Lubricant | Morepen Labs. Ltd. Parwanoo. |
| 7. | Color | Colorant | Morepen Labs. Ltd. Parwanoo. |
| 8. | Starch 1500 | Filler | Morepen Labs. Ltd. Parwanoo. |

**Material Used in Order to Perform Preformulation Study:**

According to the functional category these excipients are mixed in different ratio with drug, these mixtures are kept in 25° C, 25° C/60 % RH, 40° C, 40° C/ 75 % RH. In a Type-I clear and transparent Glass vials of capacity 10ml.grey butyl rubber plugs and aluminum seals. The excipients are mixed with Metformin and Glimepiride and sample are withdrawn at the interval of 2 weeks, 4 weeks, 6 weeks and the sample are withdrawn and given to analytical development department for analysis of following parameters.

- Moisture contents
- Related Substance
- Assay
- Organoleptic Properties

**Table No. 23 Part – I Individual Excipients in Dry Form:**

| Sr.No. | Name of the Excipients |
|---|---|
| 1. | Metformin (Ratio: 100%) |
| 2. | Glimepiride (Ratio: 100%) |
| 3. | Methocel (Ratio: 100%) |
| 4. | Microcrystalline Cellulose (Ratio: 100%) |
| 5. | Colloidal Silicon Dioxide (Ratio: 100%) |
| 6. | Magnesium Stearate (Ratio: 100%) |
| 7. | Color (Ratio: 100%) |

**Table No. 24 Part – II Metformin: Excipients in Dry Form:**

| Sr.No. | Name of the Excipients |
|---|---|
| 1. | Glimepiride (X=20, Ratio- 10 : 10) |
| 2. | Methocel (X= 5, Ratio- 10 : 2.5 ) |
| 3. | Microcrystalline Cellulose(MCC-102) (X=30, Ratio-10 : 10 ) |
| 4. | Colloidal Silicon Dioxide (X= 1,Ratio- 10 : 0.5 ) |
| 5. | Magnesium Stearate (X= 1,Ratio- 10 : 0.5 ) |

**Table No. 25 Part – III Glimepiride: Excipients in Dry Form:**

| Sr.No. | Name of the Excipients |
|---|---|
| 1. | Metformin (X=20, Ratio- 10 : 10) |
| 2. | Starch 1500 (X= 5, Ratio- 10 : 2.5 ) |
| 3. | Microcrystalline Cellulose (MCC-102) (X=30, Ratio-10 : 10 ) |
| 4. | Colloidal Silicon Dioxide (X= 1,Ratio- 10 : 0.5 ) |
| 5. | Magnesium Stearate (X= 1,Ratio- 10 : 0.5 ) |
| 6. | Color (X= 1,Ratio- 10 : 0.5 ) |

**Table No.26 Part – IV Metformin: Excipients in Wet Form Dried at 40° C, (LOD: 1-3%):**

| Sr.No. | Name of the Excipients |
|---|---|
| 1. | Glimeperide (X=20, Ratio- 10 : 10) |
| 2. | Methocel (X= 5, Ratio- 10 : 2.5 ) |
| 3. | Microcrystalline Cellulose (MCC-102) (X=30, Ratio-10 : 10 ) |
| 4. | Colloidal Silicon Dioxide (X= 1,Ratio- 10 : 0.5 ) |
| 5. | Magnesium Stearate (X= 1,Ratio- 10 : 0.5 ) |

**Table No. 27 Part – V Glimepiride: Excipients in Wet Form Dried at 40° C, (LOD: 1-3%):**

| Sr.No. | Name of the Excipients |
|---|---|
| 1. | Metformin (X=20, Ratio- 10 : 10) |
| 2. | Starch 1500 (X= 5, Ratio- 10 : 2.5 ) |
| 3. | Microcrystalline Cellulose (MCC-102) (X=30, Ratio-10 : 10 ) |
| 4. | Colloidal Silicon Dioxide (X= 1,Ratio- 10 : 0.5 ) |
| 5. | Magnesium Stearate (X= 1,Ratio- 10 : 0.5 ) |
| 6. | Color (X= 1,Ratio- 10 : 0.5 ) |

**Results:**

**Table No. 28 Drug- Excipients Compatibility Study:**

| Sr. No | Drug + Excipients | Drug Excipients Ratio | Parameters | Initial Value of Parameters | Condition | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 40° C/75% RH | | 25° C/60% RH | |
| | | | | | 2weeks | 4weeks | 2weeks | 4weeks |
| 1. | Metformin + Methocel | 1: 2.5 | Moisture content | 5.60 | 5.18 | 4.87 | 4.72 | 5.21 |
| | | | Assay (%) | 101.21 | 100.0 | 99.78 | 100 | 101.68 |
| 2. | Metformin + Microcrystalline Cellulose | 1:2 | Moisture content | 4.23 | 4.23 | 4.12 | 4.02 | 4.31 |
| | | | Assay | 99.95 | 99.76 | 99.80 | 99.90 | 99.68 |
| 3. | Metformin + Colloidal Silicon Dioxide | 1:0.1 | Moisture content | 3.68 | 3.62 | 3.42 | 3.12 | 3.60 |
| | | | Assay | 100.25 | 99.85 | 100.02 | 100 | 98.80 |
| 4. | Metformin + Magnesium Stearate | 1:0.1 | Moisture content | 2.87 | 2.52 | 2.32 | 2.78 | 2.70 |
| | | | Assay | 102.08 | 98.74 | 100.21 | 100.00 | 99.92 |

**Conclusion:** Metformin HCl is compatible with the all excipients and not shown any impurities

**Table No. 29 Drug- Excipients Compatibility Study:**

| Sr.No | Drug + Excipients | Drug Excipients Ratio | Parameters | Initial Value of Parameters | Condition | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 40° C/75% RH | | 25° C/60% RH | |
| | | | | | 2weeks | 4weeks | 2weeks | 4weeks |
| 1. | Glimepiride + Starch 1500 | 1:0.5 | Moisture content | 2.36 | 1.87 | 2.10 | 2.28 | 2.30 |
| | | | Assay | 102.65 | 100.02 | 100.0 | 99.85 | 100 |
| 2. | Glimepiride + Microcrystalline Cellulose | 1:2 | Moisture content | 3.56 | 2.36 | 2.20 | 3.21 | 3.48 |
| | | | Assay | 99.78 | 98.56 | 99.28 | 99.66 | 99.25 |
| 3. | Glimepiride + Colloidal Silicon Dioxide | 1:0.1 | Moisture content | 2.35 | 1.89 | 2.10 | 2.27 | 2.18 |
| | | | Assay | 101.35 | 99.02 | 100 | 101.00 | 100 |
| 4. | Glimepiride + Magnesium Stearate | 1:0.1 | Moisture content | 2.25 | 1.95 | 2.00 | 2.17 | 2.19 |
| | | | Assay | 102.48 | 100.02 | 101.2 | 101.67 | 100 |

**Conclusion:** Glimepiride stable with all excipients, No affect of moisture on assay.

**ORGANOLEPTIC PROPERTIES OF DRUG IN PRESENCE OF EXCIPIENTS AT DIFFERENT INTERVAL**

**Table No. 30 Change in Color at Different Time Interval in Presence of Excipients:**

| Sr.No. | Name of the Material | Initial Color | Change in Colors | | |
|---|---|---|---|---|---|
| | | | 2 weeks | 4 weeks | 6 weeks |
| 1. | Metformin + Methocel | White | -- | -- | -- |
| 2. | Methocel | White | -- | -- | -- |
| 3. | Metformin + Microcrystalline Cellulose | White | -- | -- | -- |
| 4. | Microcrystalline Cellulose | White | -- | -- | -- |
| 5. | Metformin + Colloidal Silicon Dioxide | White | -- | -- | -- |
| 6. | Colloidal Silicon Dioxide | White | -- | -- | -- |
| 7. | Metformin + Magnesium Stearate | White | -- | Brown | Brown |
| 8. | Magnesium Stearate | White | -- | -- | -- |
| 9. | Metformin+ Starch 1500 | White | -- | -- | -- |
| 10. | Starch 1500 | White | -- | -- | -- |

**Conclusion:**

Metformin is stable with most of the excipients in case of magnesium Stearate ,causing the discoloration of the product, the change in color was observed that will not affect the stability of the product so use of magnesium Stearate as lubricant in less quantity to avoid discoloration.

**Table No. 31 Change in Color at Different Time Interval in Presence of Excipients:**

| Sr.No. | Name of the Material | Initial Color | Change in Colors | | |
|---|---|---|---|---|---|
| | | | 2 weeks | 4 weeks | 6 weeks |
| 1. | Glimepiride + Starch 1500 | White | -- | -- | -- |
| 2. | Starch 1500 | White | -- | -- | -- |
| 3. | Glimepiride + | White | -- | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| | Microcrystalline Cellulose | | | | |
| 4. | Microcrystalline Cellulose | White | -- | -- | -- |
| 5. | Glimepiride + Colloidal Silicon Dioxide | White | -- | -- | -- |
| 6. | Colloidal Silicon Dioxide | White | -- | -- | -- |
| 7. | Glimepiride + Magnesium Stearate | White | -- | -- | -- |
| 8. | Magnesium Stearate | White | -- | -- | -- |
| 9. | Glimepiride + Color | Red | -- | -- | -- |

**Conclusion:** Glimepiride is stable with all the excipients.

**Table No. 32 Formulation of Metformin HCl Layer:**

| **Method of Formulation** | | Direct compression | Direct compression | Direct compression | Direct compression | Direct compression |
|---|---|---|---|---|---|---|
| **Trial No.** | | **Trial-1** | **Trial-2** | **Trial-3** | **Trial-4** | **Trial-5** |
| **Sr. No** | **Ingredients** | | | | | |
| **1** | Metformin HCl | 500 | 500 | 500 | 500 | 500 |
| **2** | Methocel K100 M | 288 | 288 | 315 | 300 | 297.50 |
| **3** | Microcrystalline cellulose | 50.75 | 50.75 | 23.75 | 40.25 | 44.00 |
| **4** | Colloidal Silicon Dioxide | 5.00 | 5.00 | 5.0 | 4.25 | 4.25 |
| **5** | Magnesium Stearate | 5.00 | 5.00 | 5.0 | 4.25 | 4.25 |
| Total weight (mg) | | 848.75 | 848.75 | 848.75 | 848.75 | 850 |

**Table No. 33 Formulation of Glimepiride Layer:**

| **Method of Formulation** | | Wet granulation | Wet granulation | Wet granulation | Direct compression | Direct compression |
|---|---|---|---|---|---|---|
| **Trial No.** | | **Trial - 1** | **Trial - 2** | **Trial - 3** | **Trial - 4** | **Trial - 5** |
| **Sr. No** | **Ingredients** | | | | | |
| **1.** | Glimepiride | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| **2.** | Lactose monohydrate | 80.0 | 65 | 75 | -- | -- |
| **3.** | Microcrystalline cellulose Plain | 115.9 | 131.85 | 120 | -- | -- |
| **4.** | Sodium starch Glycolate | 28 | 25 | 30 | -- | -- |
| **5.** | Color | 0.060 | 0.1 | 0.2 | -- | -- |
| **6.** | Poly vinayl pyrolidone K-30 | 18.0 | 20.0 | 180 | -- | -- |
| **7.** | Sodium starch Glycolate | 5.0 | 5.0 | 5.3 | -- | -- |
| **8.** | Color (Iron red oxide) | 0.04 (Supra) | 0.05 (Supra) | 0.05 (Supra) | 0.10 ( Lake) | 0.15 (Lake) |
| **9** | Starch 1500 | -- | -- | -- | 60.0 | 45 |
| **10** | Microcrystalline cellulose Rank | -- | -- | -- | 186..9 | 201.85 |
| **11** | Colloidal Silicon Dioxide | -- | -- | -- | 1.0 | 1.0 |
| **12** | Magnesium Stearate | 2.0 | 2.0 | 0.5 | 1.0 | 1.0 |
| **Total Weight (mg)** | | 250 | 250 | 250 | 250 | 250 |

**Methodology of Metformin Layer Preparation:**

**Direct compression:**

- Weigh accurate quantity of Metformin layer based on its potency

- Weigh and add Methocel, Microcrystalline Cellulose, and Colloidal Silicon Dioxide through sieve size 40 and Magnesium Stearate through sieve size 60.
- Mix all ingredients well in planetary mixture for 15 min at impeller speed 100 rpm.
- After mixing blend the same in Octagonal Blender for 20 min. after that Magnesium Stearate which was sieved from sieve size 60 was added and blend all material for 5 min.
- Final blend was compressed by 18.5 X 9 mm caplet one side break line, other side plane punches in Cadmech Compression Machine.
- Same method was applied for Trial 1, 2, 3 & 4
- In Trial 5 method was adapted which was same as direct compression the difference lies that the release rate of Metformin is sustained.
- This blend was compressed by adding adequate quantity of lubricant mentioned above in Cadmech Compression Machine.

**Methodology for Glimepiride Layer Preparation:**

**Wet Granulation:**

- Weigh accurate quantity of Glimepiride based on its potency.
- Weigh and add Methocel, Microcrystalline Cellulose, and Colloidal Silicon Dioxide through sieve size 40 and Magnesium Stearate through sieve size 60.
- Mix all ingredients well in planetary mixture for 15 min at impeller speed 100 rpm.
- After mixing blend the same in Octagonal Blender for 20 min, after that Magnesium Stearate which sieved from sieve size 60 was added and blend all material for 5 min.
- Final blend was compressed by 18.5 X 9 mm caplet one side break line, other side plane punches in Cadmech compression machine.
- Same method was applied for Trial 1, 2 & 3.
- In wet granulation the results are not satisfactory so the direct compression method applied in next batches

**Direct compression**

- In Trial 4 method was adapted which is direct compression the difference lies that the release rate of Metformin is not Satisfactory.

- In Trial 5 method was adapted which is direct compression the difference lies that the release rate of Metformin and other parameters is Satisfactory.
- This blend was compressed by adding adequate quantity of lubricant mentioned above in Cadmech Compression Machine.

**Methodology:**

In this process the granules of each blend were filled separately in the hopper in Double rotatory compression machine. Machines were engineered to compress each layer separately before the deposition of the next granulation, with a final compression for the complete tablet. Since in this machine, the excess granulation from each feed frame could not be permitted to circulate around the turret and commingle, wipe off blades covering the entire face of the die table has been installed. The excess was thus directed into pots at the side of the press and manually returned to appropriate hopper. Suction tubes were needed to remove any fine dust that escapes under the scraper blades. The arrangement described above is installed on the presses, prevent one granulation from contaminating the other.

**Table no. 34 Optimization formula for the development of scale up Batches**

| Sr.No | Ingredients | Specification | mg/tab |
|---|---|---|---|
| 1. | Metformin HCl | I.P | 500 |
| 2. | Methocel K100 M | I.P | 297.50 |
| 3. | Microcrystalline cellulose | I.P | 44.0 |
| 4. | Colloidal Silicon Dioxide | I.P | 4.25 |
| 5. | Magnesium Stearate | I.P | 4.25 |
| 6. | Glimepiride | I.P | 1 |
| 7. | Colloidal Silicon Dioxide | I.P | 1.0 |
| 8. | Microcrystalline cellulose | I.P | 236.85 |
| 9. | Starch 1500 | I.P | 60 |
| 10. | Color (Iron red oxide) | I.P | 0.15 |
| 11. | Magnesium Stearate | I.P | 1.0 |

## Evaluation

**Post Compression Parameters:**

1. **Shape of Tablets:**

   Randomly picked tablets from each formulation were examined for the shape of the tablets

2. **Weight Variation Test:**

   Twenty tablets were weighed and the average weight was calculated. The individual weight was compared with the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablets differs by more than two tablets the percentage limit. The following percentage deviation in weight variation is allowed according to USP.

**Table No.: 35 Limits of weight variation according to tablets weight**

| Sr. No | Average weight of tablet | Percentage weight variation |
|---|---|---|
| 1. | 130 mg or less | 10 % |
| 2. | More than 130 mg and less than 324 mg | 7.5 % |
| 3. | 324 mg or more | 5 %\ |

In all the formulation the tablets weight is more than 324 mg or more, hence 5% maximum difference allowed.

**Table No. 36 Weight Variation Test**

| Sr.No | Trial-1 | Trial-2 | Trial-3 | Trial-4 | Trial-5 |
|---|---|---|---|---|---|
| **1.** | 1102 | 1088 | 1109 | 1110 | 1099 |
| **2.** | 1125 | 1109 | 1094 | 1080 | 1089 |
| **3.** | 1086 | 1121 | 1102 | 1085 | 1124 |
| **4.** | 1094 | 1102 | 1099 | 1100 | 1088 |
| **5.** | 1110 | 1089 | 1089 | 1124 | 1109 |
| **6.** | 1091 | 1125 | 1110 | 1089 | 1105 |
| **7.** | 1089 | 1085 | 1080 | 1125 | 1110 |
| **8.** | 1121 | 1127 | 1085 | 1085 | 1080 |
| **9.** | 1109 | 1086 | 1100 | 1127 | 1085 |
| **10.** | 1085 | 1086 | 1124 | 1086 | 1100 |
| **11.** | 1102 | 1109 | 1088 | 1082 | 1124 |
| **12.** | 1086 | 1094 | 1109 | 1109 | 1089 |
| **13.** | 1124 | 1102 | 1121 | 1094 | 1125 |
| **14.** | 1100 | 1099 | 1102 | 1102 | 1085 |
| **15.** | 1080 | 1089 | 1089 | 1099 | 1127 |
| **16.** | 1099 | 1110 | 1125 | 1089 | 1086 |
| **17.** | 1109 | 1080 | 1085 | 1124 | 1082 |
| **18.** | 1127 | 1085 | 1127 | 1088 | 1100 |
| **19.** | 1089 | 1100 | 1086 | 1109 | 1125 |
| **20.** | 1088 | 1124 | 1082 | 1105 | 1085 |
| **Average weight** | 1100.8 | 1100.5 | 1100.3 | 1100.6 | 1100.85 |

**3. Uniformity of Thickness:**

Ten tablets were picked from formulation randomly and thickness was measured individually using Vernier-caliper. It is expressed in millimeter and average was calculated.

**Table No. 37 Uniformity of Thickness**

| Sr.No | Trial -1 | Trial -2 | Trial -3 | Trial -4 | Trial -5 |
|---|---|---|---|---|---|
| **1.** | 6.41 | 6.44 | 6.4 | 6.48 | 6.48 |
| **2.** | 6.38 | 6.48 | 6.41 | 6.41 | 6.47 |
| **3.** | 6.39 | 6.41 | 6.43 | 6.48 | 6.45 |
| **4.** | 6.31 | 6.45 | 6.47 | 6.41 | 6.42 |
| **5.** | 6.33 | 6.43 | 6.42 | 6.4 | 6.44 |
| **Average** | 6.36 | 6.44 | 6.42 | 6.43 | 6.45 |

**4. Hardness Test:**

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in $kg/cm^2$. Ten tablets were randomly picked and hardness of the same tablets from each formulation was determined. The average value was also calculated.

**Table No. 38 Hardness Test**

| Sr. No. | Trial-1 | Trial-2 | Trial-3 | Trial-4 | Trial-5 |
|---|---|---|---|---|---|
| **1.** | 8.0 | 6.0 | 5.0 | 7.0 | 6.0 |
| **2.** | 8.0 | 7.0 | 6.0 | 6.0 | 6.0 |
| **3.** | 7.0 | 5.5 | 7.0 | 6.0 | 5.0 |
| **4.** | 8.0 | 6.0 | 6.0 | 5.0 | 7.0 |
| **5.** | 7.0 | 6.0 | 6.0 | 6.0 | 6.0 |
| **Average** | 8 | 6 | 6 | 6 | 6 |

**5. Friability Test:**

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed and transferred into Friabilator which was operated at 25 rpm for 4 minutes. The tablets were weighed again and calculate the friability by this formula:

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

**Table No. 39 Friability Test**

| Sr. No | Trial-1 | Trial-2 | Trial-3 | Trial-4 | Trial-5 |
|---|---|---|---|---|---|
| **1.** | 0.75 | 0.37 | 0.52 | 0.16 | 0.11 |
| **2.** | 0.68 | 0.31 | 0.58 | 0.11 | 0.13 |
| **3.** | 0.71 | 0.38 | 0.51 | 0.17 | 0.09 |
| **4.** | 0.78 | 0.33 | 0.55 | 0.14 | 0.12 |
| **5.** | 0.74 | 0.35 | 0.52 | 0.18 | 0.14 |
| **Average** | 0.732 | 0.348 | 0.536 | 0.152 | 0.118 |

## Results:

**Table No. 40 The Post Compression Parameter are evaluated.**

| Sr. No. | Parameters | Specification | Results |
|---|---|---|---|
| **1.** | Appearance | One side break line & other side plain caplet | One side break line & other side plain caplet |
| **2.** | Thickness | 6.5 mm | 6.45mm |
| **3.** | Diameter | 18.50 mm | 18.5 mm |
| **4.** | Hardness | NLT 2.0 kg/cm$^2$ | 6.0 kg/cm$^2$ |
| **5.** | Friability | NMT 1% | 0.118 % |
| **6.** | Average Weight | 1100 mg | 1100.85mg |

**Content Uniformity of Glycomet GP-1mg (USV):**

**Standard Preparation of Glimepiride:**

Weigh and accurately transferred 10.7 mg of Glimepiride working standard into a 50 ml volumetric flask and make up the volume with mobile phase up to 50 ml, from the above stock solution, take 5ml in 100 ml volumetric flask and make up the volume with the mobile phase.

**Sample Preparation of Glimepiride:**

Take 1 intact Bi-layer tablet of Glimepiride and Metformin in 100 ml volumetric flask, dissolve in 25 ml of mobile phase make up the volume with mobile phase

**Fig No. 5 Content Uniformity Chromatogram of Glycomet GP-1mg (USV)**

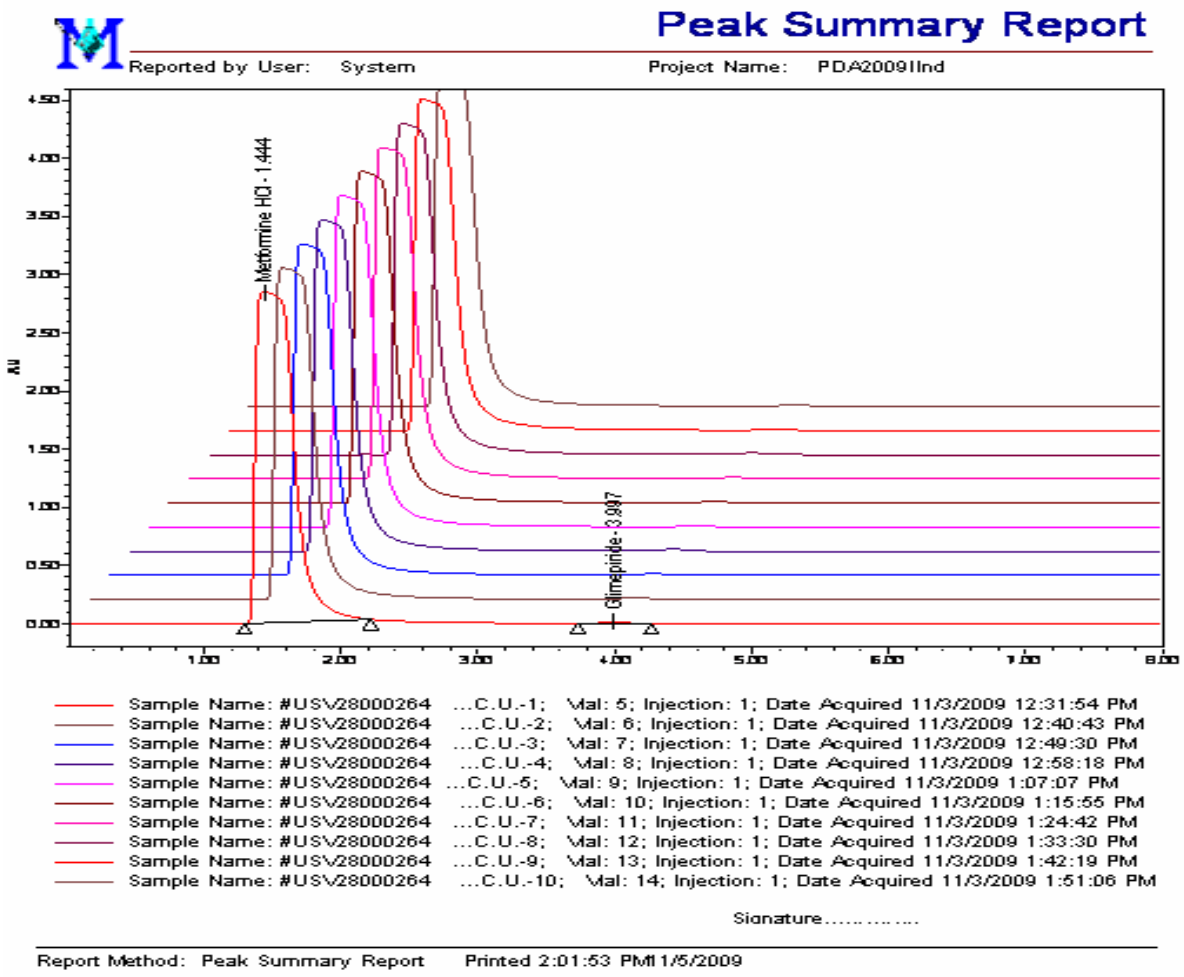


**Table No 41 Content Uniformity Peak Summary with Statistics of Glycomet GP-1mg (USV)**

# Peak Summary Report

Reported by User: System Project Name: PDA2009IInd

## Peak Summary with Statistics

### Name: Glimepiride

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #USV28000264 ...C.U.-1 | 5 | 1 | Glimepiride | 3.997 | 181420 | 0.33 | 16274 |
| 2 | #USV28000264 ...C.U.-2 | 6 | 1 | Glimepiride | 3.998 | 195320 | 0.35 | 18312 |
| 3 | #USV28000264 ...C.U.-3 | 7 | 1 | Glimepiride | 3.988 | 181196 | 0.32 | 15658 |
| 4 | #USV28000264 ...C.U.-4 | 8 | 1 | Glimepiride | 3.984 | 196132 | 0.35 | 17906 |
| 5 | #USV28000264 ...C.U.-5 | 9 | 1 | Glimepiride | 3.983 | 180921 | 0.32 | 15356 |
| 6 | #USV28000264 ...C.U.-6 | 10 | 1 | Glimepiride | 3.979 | 178195 | 0.31 | 15180 |
| 7 | #USV28000264 ...C.U.-7 | 11 | 1 | Glimepiride | 3.984 | 179243 | 0.31 | 15261 |
| 8 | #USV28000264 ...C.U.-8 | 12 | 1 | Glimepiride | 3.978 | 176079 | 0.31 | 14684 |
| 9 | #USV28000264 ...C.U.-9 | 13 | 1 | Glimepiride | 3.978 | 178592 | 0.31 | 14960 |
| 10 | #USV28000264 ...C.U.-10 | 14 | 1 | Glimepiride | 3.979 | 181588 | 0.32 | 15031 |
| Mean | | | | | 3.985 | 182868.5 | | |
| Std. Dev. | | | | | 0.007 | 6997.2 | | |
| % RSD | | | | | 0.19 | 3.8 | | |

## Peak Summary with Statistics

### Name: Metformine HCl

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #USV28000264 ...C.U.-1 | 5 | 1 | Metformine HCl | 1.444 | 54508109 | 99.67 | 2857294 |
| 2 | #USV28000264 ...C.U.-2 | 6 | 1 | Metformine HCl | 1.442 | 55431259 | 99.65 | 2852346 |
| 3 | #USV28000264 ...C.U.-3 | 7 | 1 | Metformine HCl | 1.438 | 55957589 | 99.68 | 2849535 |
| 4 | #USV28000264 ...C.U.-4 | 8 | 1 | Metformine HCl | 1.429 | 56224695 | 99.65 | 2874829 |
| 5 | #USV28000264 ...C.U.-5 | 9 | 1 | Metformine HCl | 1.437 | 56519832 | 99.68 | 2848692 |
| 6 | #USV28000264 ...C.U.-6 | 10 | 1 | Metformine HCl | 1.429 | 56808874 | 99.69 | 2879182 |
| 7 | #USV28000264 ...C.U.-7 | 11 | 1 | Metformine HCl | 1.429 | 57297338 | 99.69 | 2892474 |
| 8 | #USV28000264 ...C.U.-8 | 12 | 1 | Metformine HCl | 1.440 | 56775180 | 99.69 | 2849052 |
| 9 | #USV28000264 ...C.U.-9 | 13 | 1 | Metformine HCl | 1.441 | 57149601 | 99.69 | 2848978 |
| 10 | #USV28000264 ...C.U.-10 | 14 | 1 | Metformine HCl | 1.442 | 57208499 | 99.68 | 2850203 |
| Mean | | | | | 1.437 | 56388097.7 | | |
| Std. Dev. | | | | | 0.006 | 887308.2 | | |
| % RSD | | | | | 0.41 | 1.6 | | |

**Calculation:**

Quality Control Department
Analytical Data Report

MOREPEN

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | **Specification No.** | | | |
| Product | : | **Glycomet GP-1mg(USV)** | | Date | 03.11.2009 | |
| Batch No | : | 28000264 | | | | |
| **Uniformaty of content** | | | | | | |
| Standard Preparation | | | | | | |
| Wt. Of Standard | | 10.7 mg | ⟶ | 50ml with mobile phase | | |
| | | 5 ml | ⟶ | 100 ml with mobile phase | | |
| Test | | 1 Tablet | ⟶ | 100 ml with mobile phase | | |
| Calculation | | | | | | |

*Area Sample* *W1* *5* *P*

*, ---------- X ----------X----------X ---------- X 100*

*Area Standard* *50* *W2* *100*

*1* *10.7* *5* *100* *99.15*

*,----------X----------X----------X----------X ----------x* *100*

*193143* *50* *100* *1* *100*

**Factor** = **0.000549285** %

| | | **Area** | | *% Drug Release* |
|---|---|---|---|---|
| 1) Factor | X | 181420 | = | *99.65* |
| 2) Factor | X | 195320 | = | *107.29* |
| 3) Factor | X | 181196 | = | *99.53* |
| 4) Factor | X | 196132 | = | *107.73* |
| 5) Factor | X | 180921 | = | *99.38* |
| 6) Factor | X | 178195 | = | *97.88* |
| 7) Factor | X | 179243 | = | *98.46* |
| 8) Factor | X | 176079 | = | *96.72* |
| 9) Factor | X | 178592 | = | *98.10* |
| 10) Factor | X | 181588 | = | *99.74* |

**MIN** **96.72** **%** **MAX** ***107.7*** **%**

**Analysed By** **Checked BY**

**Assay of Glycomet GP-1mg (USV)**

**Standard preparation of Glimepiride:** Weigh and accurately transferred 10.5 mg of Glimepiride and 490.6 mg of Metformin working standard into a 100 ml volumetric flask and make up the volume with mobile phase up to 100 ml

**Sample preparation of Glimepiride:** Weigh accurately 20 tablets each containing 500mg Metformin and 1 mg Glimepiride crush them in to fine powder. Weight equivalent to Metformin and Glimepiride, transfer the powder to 100 ml volumetric flask. Filter the solution through 0.45 µ GFC filter paper

**Procedure:** Assay was carried out in HPLC (water system) including pump, photodiode array detector. Separately injected 10µl of the standard and the sample preparation in to the liquid chromatography and record the area for the major peak.

The chromatographic conditions described under may be used.

| | | |
|---|---|---|
| System | : | Waters 2695 |
| Column | : | A Stainless steel column C18 (250 X 4.6 mm), 5 µm |
| Flow Rate | : | 1.5ml/min |
| Mobile Phase | : | Acetonitrile (600) + Methanol (400) |
| Wavelength | : | 228 nm |
| Injection Volume | : | 10 µl |
| Run Time | : | 8 min |
| Column Temperature | : | 48°C |

**Fig No. 6 Blank Chromatogram of Glycomet GP-1mg (USV)**

Sample Report

Reported by User: System

Project Name: PDA2009IInd

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Blank Glimeperide+Metformine | Acquired By: | System |
| Sample Type: | Unknown | Date Acquired: | 11/3/2009 11:03:39 AM |
| Vial: | 1 | Acq. Method Set: | MOREPEN |
| Injection #: | 1 | Date Processed: | 11/5/2009 1:49:51 PM |
| Injection Volume: | 10.00 ul | Processing Method: | GLIMIPEN MF |
| Run Time: | 8.0 Minutes | Channel Name: | 2487Channel 1 |
| Sample Set Name: | GLIMIPEN MF | Proc. Chnl. Descr.: | 228 |

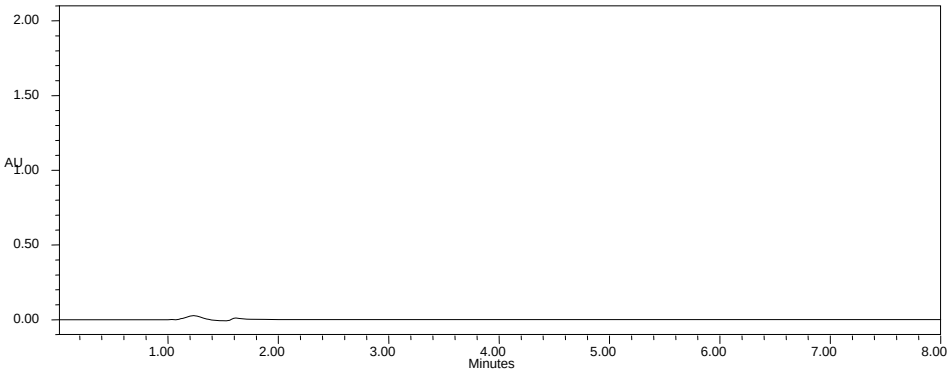
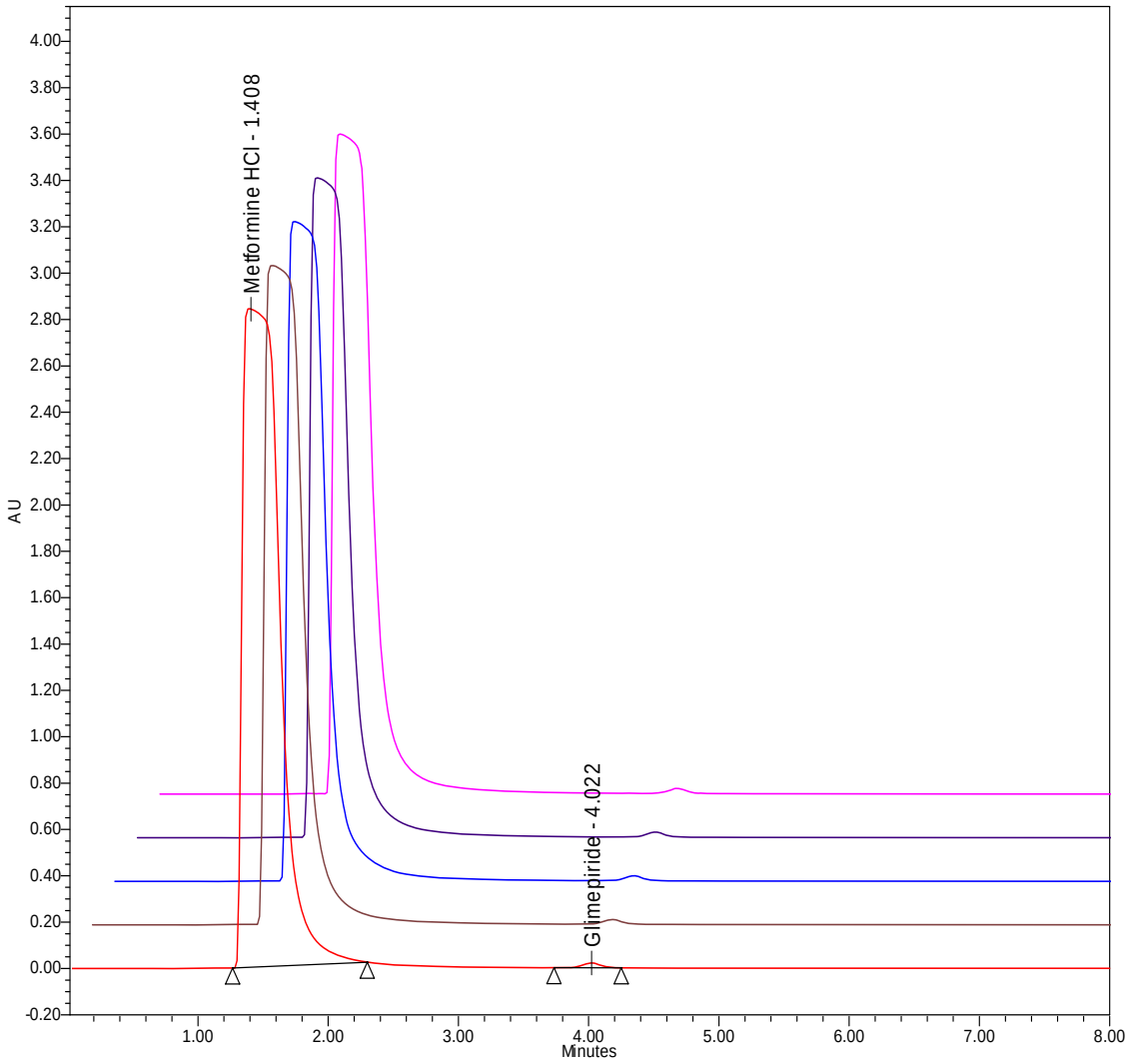


**Fig No. 7 Standard Chromatogram of Glycomet GP-1mg (USV)**

# Peak Summary Report

Reported by User: System  Project Name: PDA2009IInd




Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 1; Date Acquired 11/3/2009 11:12:26 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 2; Date Acquired 11/3/2009 11:21:12 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 3; Date Acquired 11/3/2009 11:29:57 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 4; Date Acquired 11/3/2009 11:38:56 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 5; Date Acquired 11/3/2009 11:47:42 AM

Signature.....

**Table No. 42 Standard Peak Summary with Statistics Glycomet GP-1mg (USV)**

# Peak Summary Report

Reported by User: System Project Name: PDA2009IInd

**Peak Summary with Statistics**

**Name: Glimepiride**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | STD. Glimepiride+Metformine | 2 | 1 | Glimepiride | 4.022 | 193503 | 0.35 | 20555 |
| 2 | STD. Glimepiride+Metformine | 2 | 2 | Glimepiride | 4.009 | 192717 | 0.35 | 20565 |
| 3 | STD. Glimepiride+Metformine | 2 | 4 | Glimepiride | 3.993 | 193277 | 0.35 | 21016 |
| 4 | STD. Glimepiride+Metformine | 2 | 5 | Glimepiride | 3.989 | 192085 | 0.35 | 21079 |
| 5 | STD. Glimepiride+Metformine | 2 | 3 | Glimepiride | 4.000 | 194133 | 0.35 | 21013 |
| Mean | | | | | 4.003 | 193143.0 | | |
| Std. Dev. | | | | | 0.013 | 779.3 | | |
| % RSD | | | | | 0.33 | 0.4 | | |

**Peak Summary with Statistics**

**Name: Metformine HCl**

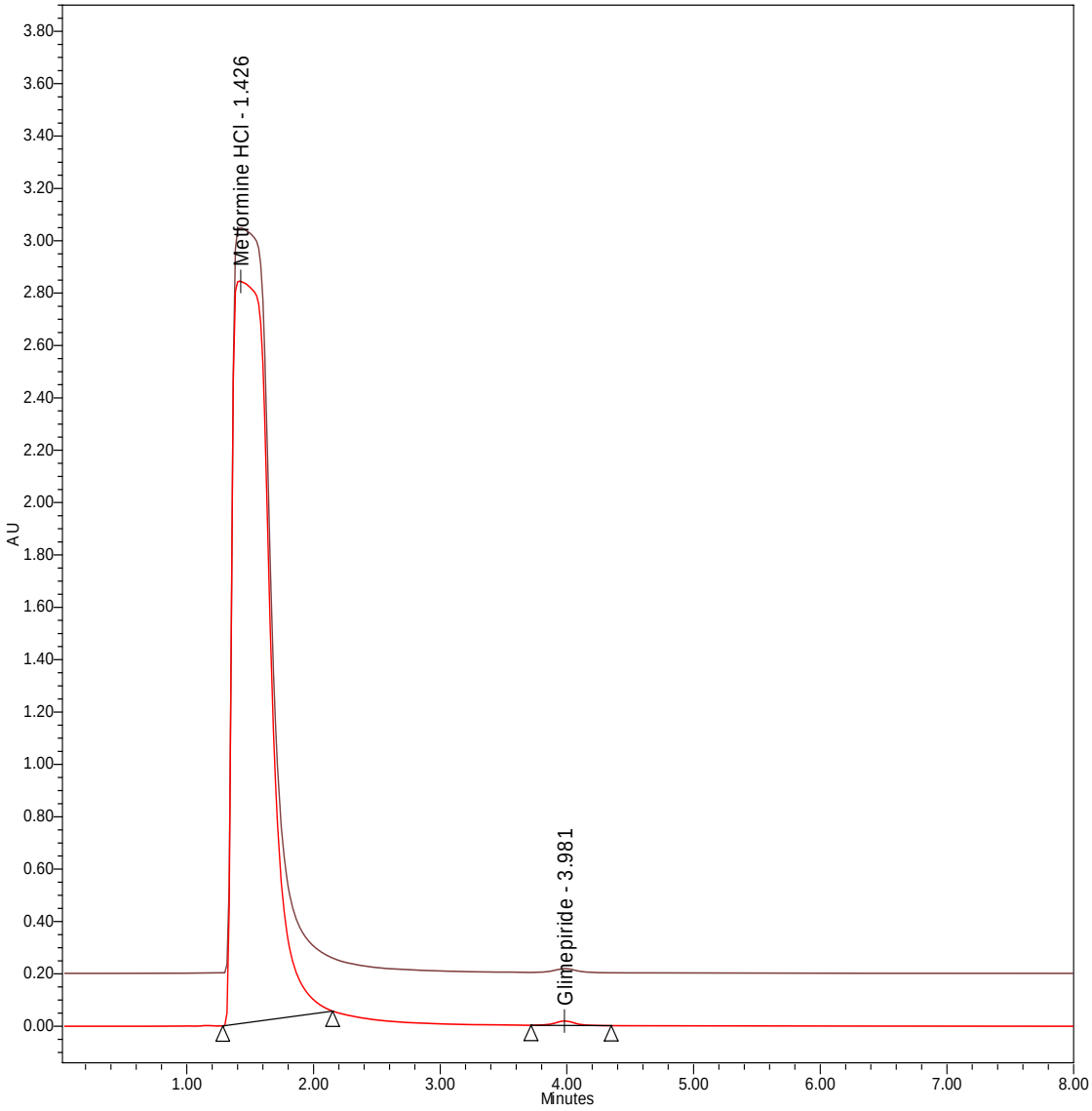
| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | STD. Glimepiride+Metformine | 2 | 1 | Metformine HCl | 1.408 | 55682737 | 99.65 | 2843879 |
| 2 | STD. Glimepiride+Metformine | 2 | 5 | Metformine HCl | 1.411 | 55332874 | 99.65 | 2850927 |
| 3 | STD. Glimepiride+Metformine | 2 | 4 | Metformine HCl | 1.410 | 55344703 | 99.65 | 2846095 |
| 4 | STD. Glimepiride+Metformine | 2 | 3 | Metformine HCl | 1.396 | 55177401 | 99.65 | 2904167 |
| 5 | STD. Glimepiride+Metformine | 2 | 2 | Metformine HCl | 1.409 | 55201356 | 99.65 | 2836561 |
| Mean | | | | | 1.407 | 55347814.0 | | |
| Std. Dev. | | | | | 0.006 | 201802.4 | | |
| % RSD | | | | | 0.43 | 0.4 | | |

**Fig.No. 8 Assay Chromatogram of Glycomet GP-1mg (USV)**

# Peak Summary Report

Reported by User: System

Project Name: PDA2009IInd




Sample Name: #USV28000264 ...Assay; Vial: 4; Injection: 1; Date Acquired 11/3/2009 12:14:19 PM

Sample Name: #USV28000264 ...Assay; Vial: 4; Injection: 2; Date Acquired 11/3/2009 12:23:05 PM

Signature.....

**Table No. 43 Assay Peak Summary with Statistics of Glycomet GP-1mg (USV)**

# Peak Summary Report

Reported by User: System  Project Name: PDA2009IInd

**Peak Summary with Statistics**

**Name: Glimepiride**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #USV28000264 ...Assay | 4 | 1 | Glimepiride | 3.981 | 181374 | 0.32 | 16854 |
| 2 | #USV28000264 ...Assay | 4 | 2 | Glimepiride | 3.983 | 179675 | 0.31 | 15719 |
| Mean | | | | | 3.982 | 180524.3 | | |
| Std. Dev. | | | | | 0.001 | 1201.3 | | |
| % RSD | | | | | 0.02 | 0.7 | | |

**Peak Summary with Statistics**

**Name: Metformine HCl**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #USV28000264 ...Assay | 4 | 1 | Metformine HCl | 1.426 | 57059385 | 99.68 | 2839368 |
| 2 | #USV28000264 ...Assay | 4 | 2 | Metformine HCl | 1.428 | 57055520 | 99.69 | 2846095 |
| Mean | | | | | 1.427 | 57057452.8 | | |
| Std. Dev. | | | | | 0.002 | 2733.2 | | |
| % RSD | | | | | 0.13 | 0.0 | | |

Signature.....

Calculation:

**Content Uniformity of Gluconorm-G1 (Lupin)**

**Standard preparation of Glimepiride:**

Weigh and accurately transferred 10.7 mg of Glimepiride working standard into a 50 ml volumetric flask and make up the volume with mobile phase up to 50 ml, from the above stock solution take 5ml in 100 ml volumetric flask and make up the volume with the mobile phase.

**Sample preparation of Glimepiride:**

Take 1 intact Bi-layer tablet of Glimepiride and Metformin in 100 ml volumetric flask, dissolve in 25 ml of mobile phase make up the volume with mobile phase

**Fig No. 9 Content Uniformity Chromatogram of Gluconorm-G1 (Lupin)**

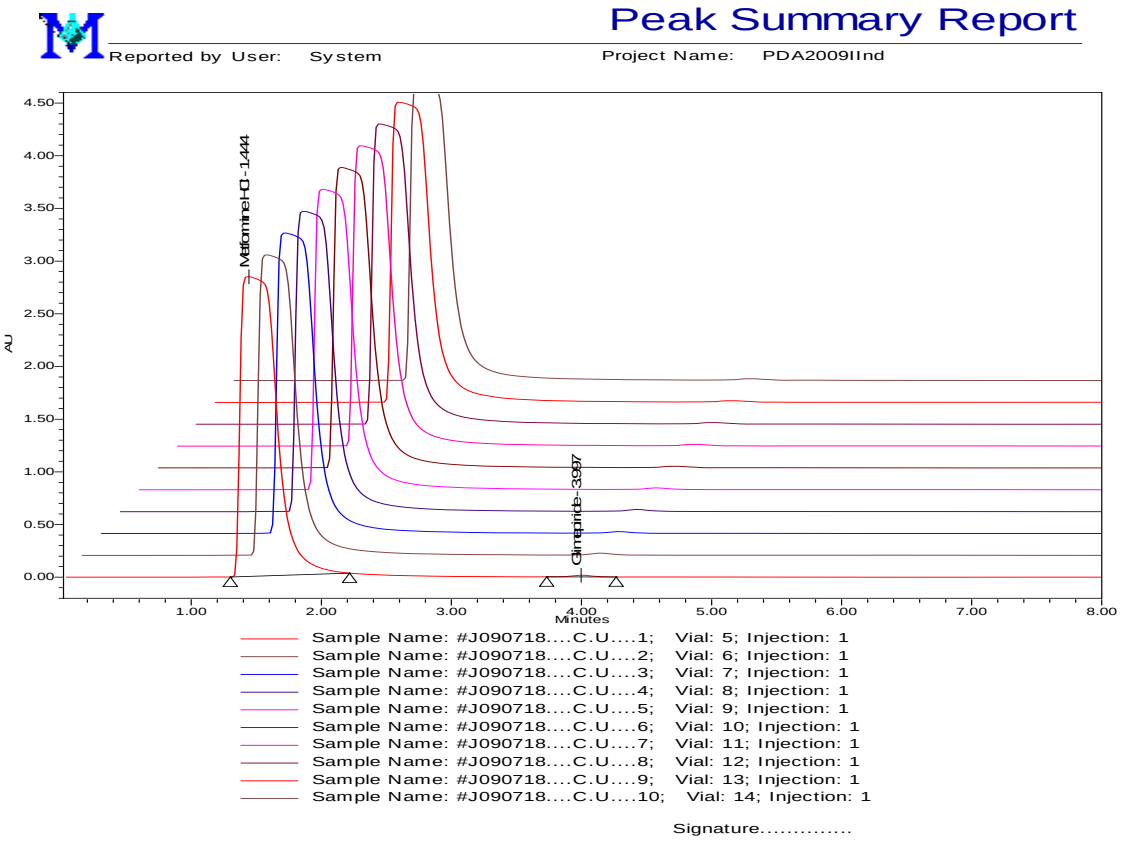


**Table No 44 Content Uniformity Peak Summary with Statistics of Gluconorm-G1 (Lupin)**

# Peak Summary Report

Reported by User: System Project Name: PDA2009IInd

## Peak Summary with Statistics

### Name: Glimepiride

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #J090718....C.U....1 | 5 | 1 | Glimepiride | 3.997 | 174594 | 0.32 | 16085 |
| 2 | #J090718....C.U....2 | 6 | 1 | Glimepiride | 3.998 | 197983 | 0.36 | 18375 |
| 3 | #J090718....C.U....3 | 7 | 1 | Glimepiride | 3.988 | 181751 | 0.34 | 15670 |
| 4 | #J090718....C.U....4 | 8 | 1 | Glimepiride | 3.984 | 198743 | 0.36 | 17984 |
| 5 | #J090718....C.U....5 | 9 | 1 | Glimepiride | 3.983 | 176271 | 0.32 | 15246 |
| 6 | #J090718....C.U....6 | 10 | 1 | Glimepiride | 3.979 | 178195 | 0.32 | 15180 |
| 7 | #J090718....C.U....7 | 11 | 1 | Glimepiride | 3.984 | 179608 | 0.32 | 15292 |
| 8 | #J090718....C.U....8 | 12 | 1 | Glimepiride | 3.978 | 173951 | 0.31 | 14754 |
| 9 | #J090718....C.U....9 | 13 | 1 | Glimepiride | 3.978 | 179503 | 0.32 | 15059 |
| 10 | #J090718....C.U....10 | 14 | 1 | Glimepiride | 3.979 | 179180 | 0.32 | 14976 |
| Mean | | | | | 3.985 | 181977.9 | | |
| Std. Dev. | | | | | 0.007 | 8960.8 | | |
| % RSD | | | | | 0.19 | 4.9 | | |

## Peak Summary with Statistics

### Name: Metformine HCl

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #J090718....C.U....1 | 5 | 1 | Metformine HCl | 1.444 | 53874193 | 99.68 | 2854271 |
| 2 | #J090718....C.U....2 | 6 | 1 | Metformine HCl | 1.442 | 55431259 | 99.64 | 2852346 |
| 3 | #J090718....C.U....3 | 7 | 1 | Metformine HCl | 1.429 | 53501847 | 99.66 | 2868746 |
| 4 | #J090718....C.U....4 | 8 | 1 | Metformine HCl | 1.429 | 54362824 | 99.64 | 2865774 |
| 5 | #J090718....C.U....5 | 9 | 1 | Metformine HCl | 1.429 | 55047877 | 99.68 | 2873418 |
| 6 | #J090718....C.U....6 | 10 | 1 | Metformine HCl | 1.429 | 55265451 | 99.68 | 2872275 |
| 7 | #J090718....C.U....7 | 11 | 1 | Metformine HCl | 1.429 | 55462597 | 99.68 | 2884211 |
| 8 | #J090718....C.U....8 | 12 | 1 | Metformine HCl | 1.429 | 55702627 | 99.69 | 2891853 |
| 9 | #J090718....C.U....9 | 13 | 1 | Metformine HCl | 1.429 | 55947064 | 99.68 | 2894245 |
| 10 | #J090718....C.U....10 | 14 | 1 | Metformine HCl | 1.429 | 55440279 | 99.68 | 2895357 |
| Mean | | | | | 1.432 | 55003601.8 | | |
| Std. Dev. | | | | | 0.006 | 814791.5 | | |
| % RSD | | | | | 0.41 | 1.5 | | |

Calculation :

**Assay of Gluconorm-G1 (Lupin)**:

**Standard preparation of Glimepiride:**

Weighed and accurately transferred 10.6 mg of Glimepiride and 490.5 mg of Metformin working standard into a 100 ml volumetric flask and make up the volume with mobile phase up to 100 ml

**Sample preparation of Glimepiride:**

Weighed accurately 20 tablets each containing 500mg Metformin and 1 mg Glimepiride crush them in to fine powder. Weight equivalent to Metformin and Glimepiride, transfer the powder to 100 ml volumetric flask. Filter the solution through 0.45 µ GFC filter paper

**Procedure:** Assay was carried out in HPLC (water system) including pump, photodiode array detector. Separately injected 10µl of the standard and the sample preparation in to the liquid chromatography and record the area for the major peak.

The chromatographic conditions described under may be used.

| | | |
|---|---|---|
| System | : | waters 2695 |
| Column | : | A Stainless steel column C18 (250 X 4.6 mm), 5 µm |
| Flow Rate | : | 1.5ml/min |
| Mobile Phase | : | Acetonitrile (600) + Methanol (400) |
| Wavelength | : | 228 nm |
| Injection Volume | : | 10 µl |
| Run Time | : | 8 min |
| Column Temperature | : | 48°C |

**Fig.No. 10 Blank chromatogram of Gluconorm-G1 (Lupin)**

Sample Report

Reported by User: System

Project Name: PDA2009IInd

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Blank Glimeperide+Metformine | Acquired By: | System |
| Sample Type: | Unknown | Date Acquired: | 11/3/2009 11:03:39 AM |
| Vial: | 1 | Acq. Method Set: | MOREPEN |
| Injection #: | 1 | Date Processed: | 11/5/2009 1:49:51 PM |
| Injection Volume: | 10.00 ul | Processing Method: | GLIMIPEN MF |
| Run Time: | 8.0 Minutes | Channel Name: | 2487Channel 1 |
| Sample Set Name: | GLIMIPEN MF | Proc. Chnl. Descr.: | 228 |

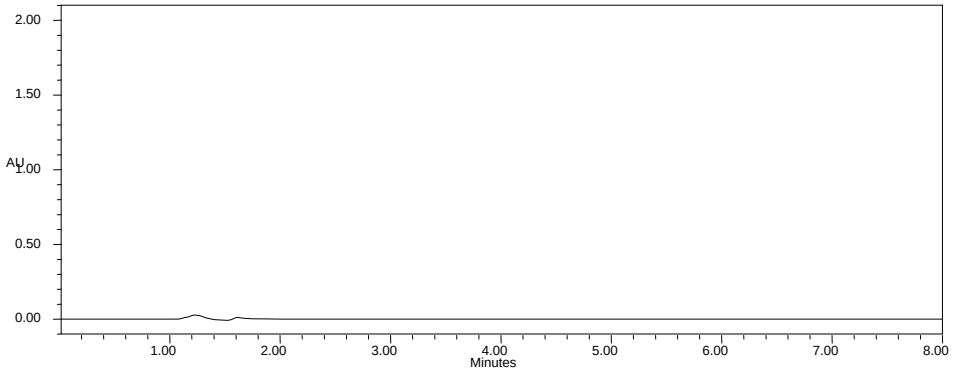
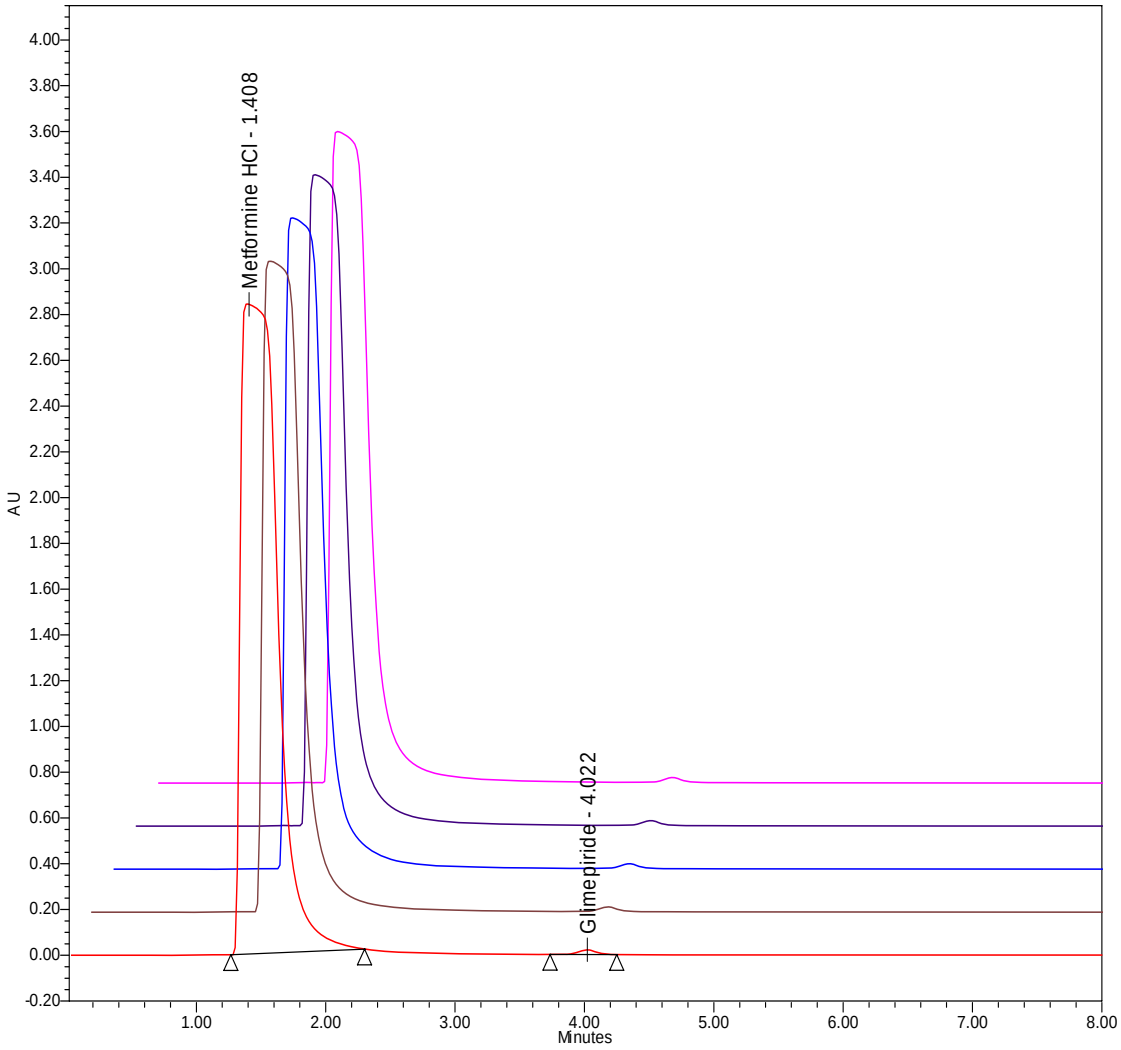


**Fig No. 11 Standard Chromatogram of Gluconorm-G1 (Lupin)**

# Peak Summary Report

Reported by User: System  Project Name: PDA2009IInd




Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 1; Date Acquired 11/3/2009 11:12:26 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 2; Date Acquired 11/3/2009 11:21:12 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 3; Date Acquired 11/3/2009 11:29:57 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 4; Date Acquired 11/3/2009 11:38:56 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 5; Date Acquired 11/3/2009 11:47:42 AM

Signature.....

**Table No. 45 Standard Peak Summary with Statistics of Gluconorm-G1 (Lupin)**

# Peak Summary Report

Reported by User: System  Project Name: PDA2009IInd

**Peak Summary with Statistics**

**Name: Glimepiride**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | STD. Glimepiride+Metformine | 2 | 1 | Glimepiride | 4.022 | 200215 | 0.36 | 20798 |
| 2 | STD. Glimepiride+Metformine | 2 | 2 | Glimepiride | 4.009 | 201510 | 0.36 | 20895 |
| 3 | STD. Glimepiride+Metformine | 2 | 4 | Glimepiride | 3.993 | 200055 | 0.36 | 21304 |
| 4 | STD. Glimepiride+Metformine | 2 | 5 | Glimepiride | 3.989 | 203987 | 0.36 | 21556 |
| 5 | STD. Glimepiride+Metformine | 2 | 3 | Glimepiride | 4.000 | 200812 | 0.36 | 21267 |
| Mean | | | | | 4.003 | 201315.8 | | |
| Std. Dev. | | | | | 0.013 | 1599.0 | | |
| % RSD | | | | | 0.33 | 0.8 | | |

**Peak Summary with Statistics**

**Name: Metformine HCl**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | STD. Glimepiride+Metformine | 2 | 1 | Metformine HCl | 1.408 | 55738711 | 99.64 | 2844130 |
| 2 | STD. Glimepiride+Metformine | 2 | 5 | Metformine HCl | 1.411 | 55925214 | 99.64 | 2854601 |
| 3 | STD. Glimepiride+Metformine | 2 | 4 | Metformine HCl | 1.410 | 55866322 | 99.64 | 2849064 |
| 4 | STD. Glimepiride+Metformine | 2 | 3 | Metformine HCl | 1.409 | 55842572 | 99.64 | 2846227 |
| 5 | STD. Glimepiride+Metformine | 2 | 2 | Metformine HCl | 1.409 | 56047841 | 99.64 | 2842163 |
| Mean | | | | | 1.409 | 55884132.0 | | |
| Std. Dev. | | | | | 0.001 | 113666.4 | | |
| % RSD | | | | | 0.09 | 0.2 | | |

**Fig.No. 12 Assay Chromatogram of Gluconorm-G1 (Lupin)**

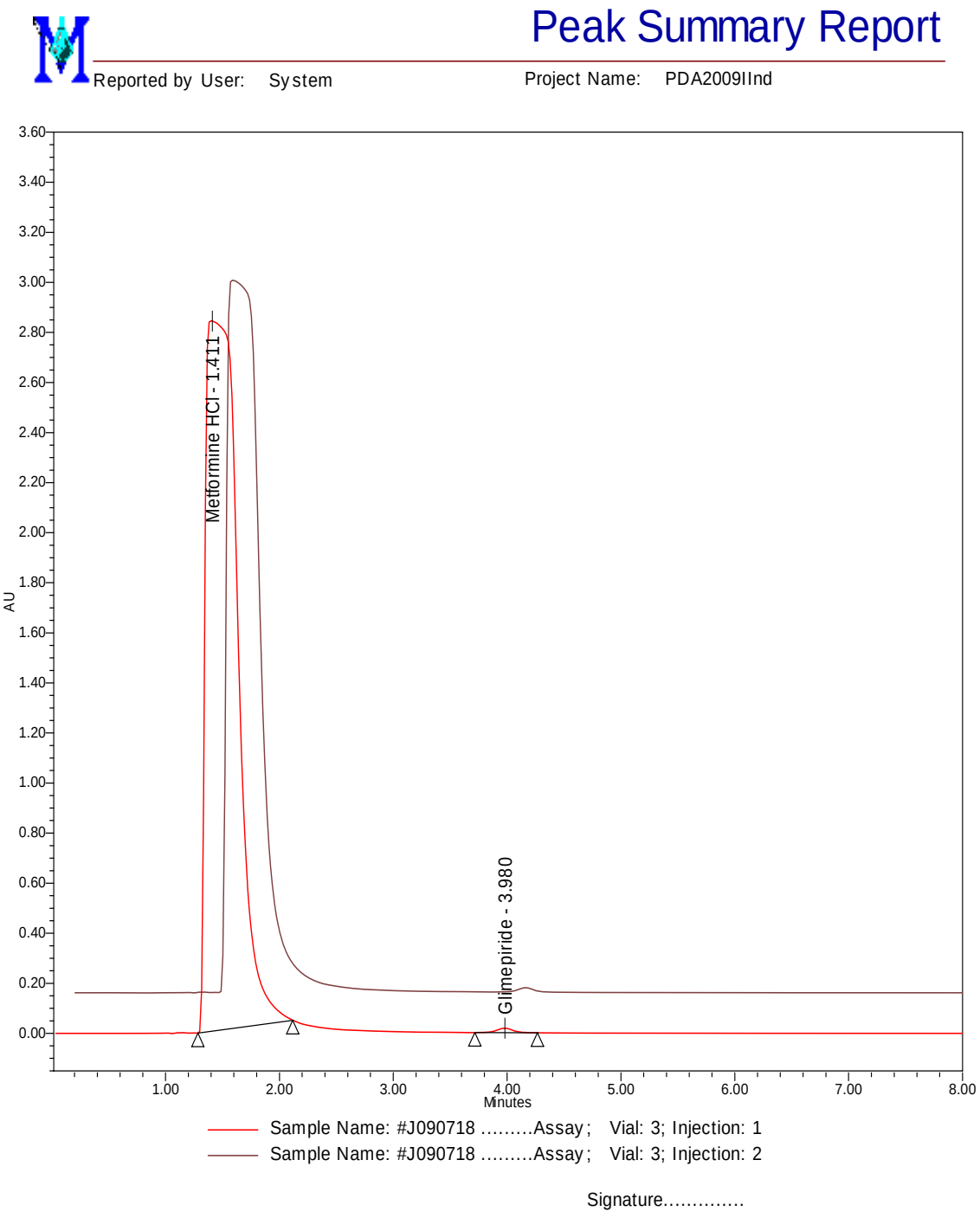


**Table No. 46 Assay Peak Summary with Statistics of Gluconorm-G1 (Lupin)**

# Peak Summary Report

Reported by User: System

Project Name: PDA2009IInd

**Peak Summary with Statistics**

**Name: Glimepiride**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #J090718 .....Assay | 3 | 1 | Glimepiride | 3.980 | 178966 | 0.32 | 17938 |
| 2 | #J090718 .....Assay | 3 | 2 | Glimepiride | 3.975 | 177049 | 0.32 | 17788 |
| Mean | | | | | 3.978 | 178007.6 | | |
| Std. Dev. | | | | | 0.004 | 1355.2 | | |
| % RSD | | | | | 0.09 | 0.8 | | |

**Peak Summary with Statistics**

**Name: Metformine HCl**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #J090718 .....Assay | 3 | 1 | Metformine HCl | 1.411 | 55610910 | 99.68 | 2851846 |
| 2 | #J090718 .....Assay | 3 | 2 | Metformine HCl | 1.411 | 55622233 | 99.68 | 2856570 |
| Mean | | | | | 1.411 | 55616571.6 | | |
| Std. Dev. | | | | | 0.000 | 8006.4 | | |
| % RSD | | | | | 0.02 | 0.0 | | |

**Calculation:**

**Content Uniformity of Morpean Trial:**

**Standard preparation of Glimepiride:**

Weighed and accurately transferred 10.9 mg of Glimepiride working standard into a 50 ml volumetric flask and make up the volume with mobile phase up to 50 ml, from the above stock solution take 5ml in 100 ml volumetric flask and make up the volume with the mobile phase.

**Sample preparation of Glimepiride:**

Take 1 intact Bi-layer tablet of Glimepiride and Metformin in 100 ml volumetric flask, dissolve in 25 ml of mobile phase make up the volume with mobile phase

**Fig No. 13 Content Uniformity Chromatogram of Morpean Trial**

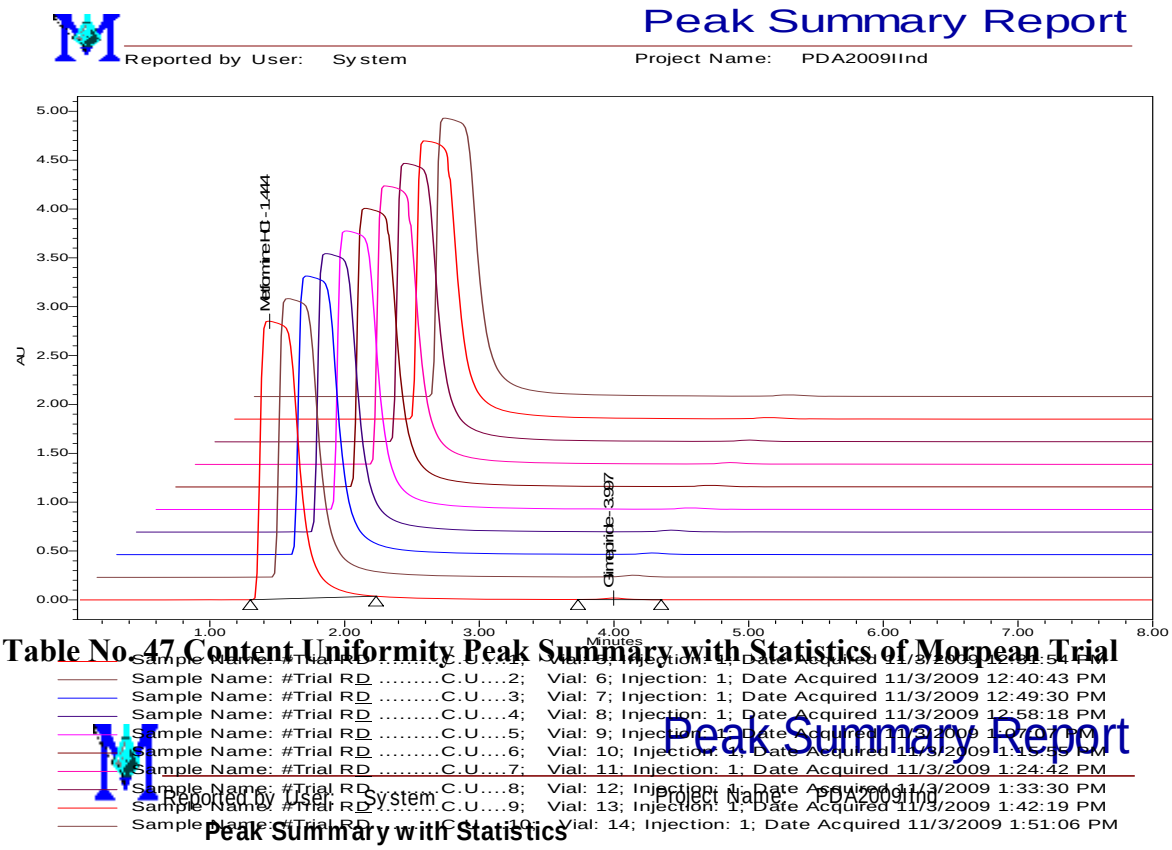



**Table No. 47 Content Uniformity Peak Summary with Statistics of Morpean Trial**

Peak Summary Report

Reported by User: System Project Name: PDA2009IInd

**Peak Summary with Statistics**

**Name: Glimepiride**

Signature.....

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #Trial R&D .....C.U....1 | 5 | 1 | Glimepiride | 3.997 | 181100 | 0.33 | 16266 |
| 2 | #Trial R&D .....C.U....2 | 6 | 1 | Glimepiride | 3.998 | 195320 | 0.36 | 18312 |
| 3 | #Trial R&D .....C.U....3 | 7 | 1 | Glimepiride | 3.988 | 180229 | 0.32 | 15603 |
| 4 | #Trial R&D .....C.U....4 | 8 | 1 | Glimepiride | 3.984 | 196132 | 0.35 | 17906 |
| 5 | #Trial R&D .....C.U....5 | 9 | 1 | Glimepiride | 3.983 | 181834 | 0.32 | 15386 |
| 6 | #Trial R&D .....C.U....6 | 10 | 1 | Glimepiride | 3.979 | 182106 | 0.32 | 15271 |
| 7 | #Trial R&D .....C.U....7 | 11 | 1 | Glimepiride | 3.984 | 183698 | 0.33 | 15391 |
| 8 | #Trial R&D .....C.U....8 | 12 | 1 | Glimepiride | 3.978 | 177515 | 0.32 | 14838 |
| 9 | #Trial R&D .....C.U....9 | 13 | 1 | Glimepiride | 3.978 | 179503 | 0.32 | 15059 |

Report Method: Peak Summary Report Printed 2:31:31 PM 11/3/2009

Calculation:

**Assay of Morepen Trial-5:**

**Standard preparation of Glimepiride:**

Weighed and accurately transferred 11.0 mg of Glimepiride and 495.6 mg of Metformin working standard into a 100 ml volumetric flask and make up the volume with mobile phase up to 100 ml

**Sample preparation of Glimepiride:**

Weighed accurately 20 tablets each containing 500mg Metformin and 1 mg Glimepiride crush them in to fine powder. Weight equivalent to Metformin and Glimepiride, transfer the powder to 100 ml volumetric flask. Filter the solution through 0.45 µ GFC filter paper

**Procedure:** Assay was carried out in HPLC (water system) including pump, photodiode array detector. Separately injected 10µl of the standard and the sample preparation in to the liquid chromatography and record the area for the major peak.

The Chromatographic conditions described under may be used.

| | | |
|---|---|---|
| System | : | Waters 2695 |
| Column | : | A Stainless steel column C18 (250 X 4.6 mm), 5 µm |
| Flow Rate | : | 1.5 ml/min |
| Mobile Phase | : | Acetonitrile (600) + Methanol (400) |
| Wavelength | : | 228 nm |
| Injection Volume | : | 10 µl |
| Run Time | : | 8 min |
| Column Temperature | : | 48°C |

**Fig. No. 14 Blank Chromatogram of Morpean Trial**

Sample Report

Reported by User: System

Project Name: PDA2009IInd

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | Blank Glimeperide+Metformine | Acquired By: | System |
| Sample Type: | Unknown | Date Acquired: | 11/3/2009 11:03:39 AM |
| Vial: | 1 | Acq. Method Set: | MOREPEN |
| Injection #: | 1 | Date Processed: | 11/5/2009 1:49:51 PM |
| Injection Volume: | 10.00 ul | Processing Method: | GLIMIPEN MF |
| Run Time: | 8.0 Minutes | Channel Name: | 2487Channel 1 |
| Sample Set Name: | GLIMIPEN MF | Proc. Chnl. Descr.: | 228 |

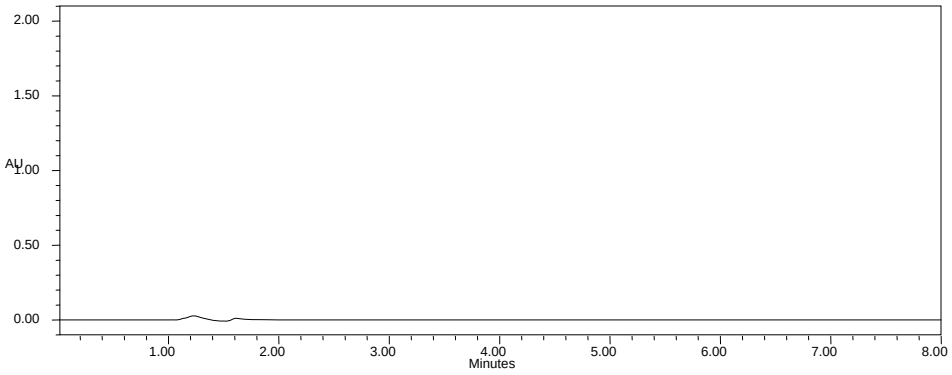
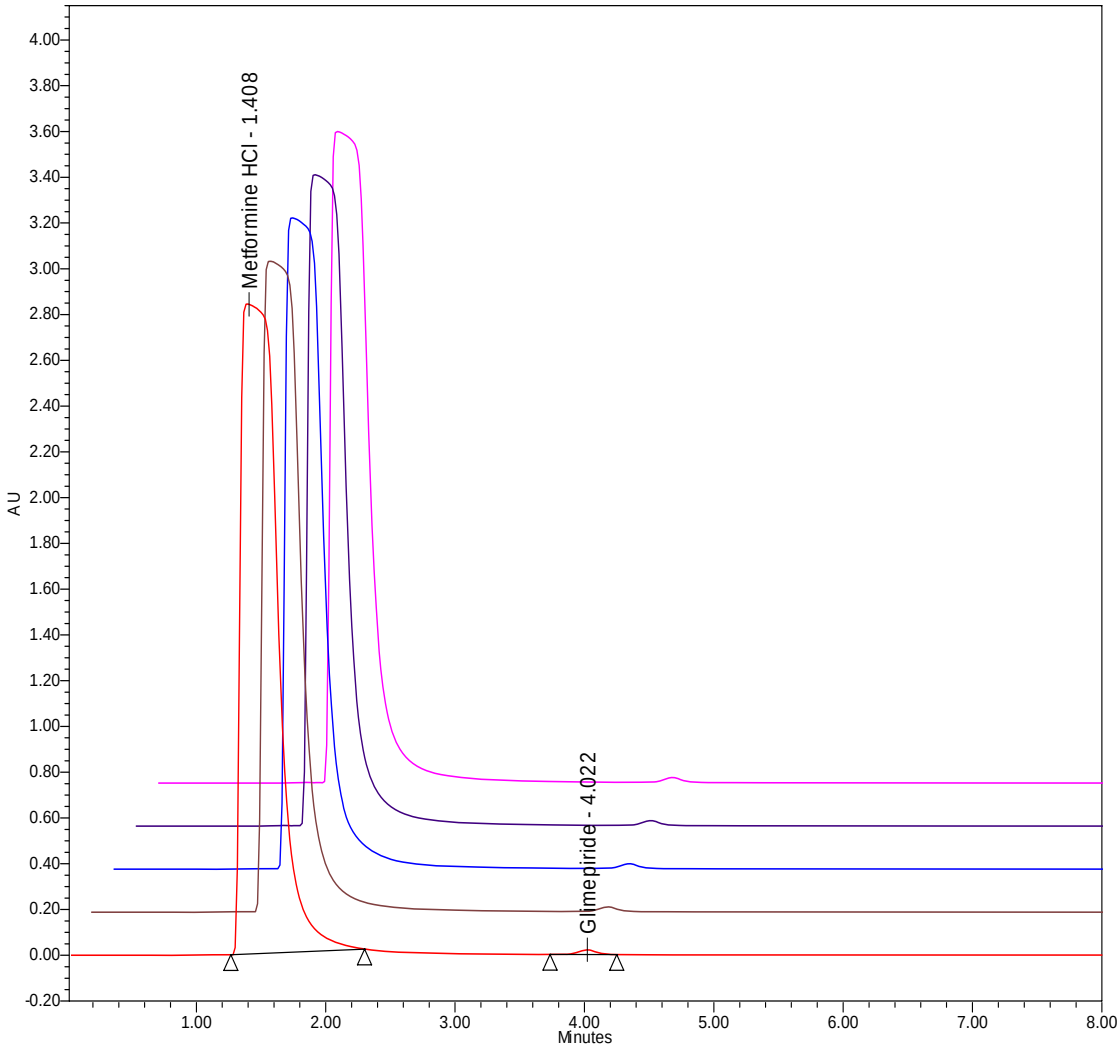


**Fig No. 15 Standard Chromatogram of Morpean Trial**

# Peak Summary Report

Reported by User: System

Project Name: PDA2009IInd




Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 1; Date Acquired 11/3/2009 11:12:26 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 2; Date Acquired 11/3/2009 11:21:12 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 3; Date Acquired 11/3/2009 11:29:57 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 4; Date Acquired 11/3/2009 11:38:56 AM
Sample Name: STD. Glimepiride+Metformine; Vial: 2; Injection: 5; Date Acquired 11/3/2009 11:47:42 AM

Signature.....

**Table No. 48 Standard Peak Summary with Statistics of Morpean Trial**

# Peak Summary Report

Reported by User: System

Project Name: PDA2009IInd

**Peak Summary with Statistics**

**Name: Glimepiride**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | STD. Glimepiride+Metformine | 2 | 1 | Glimepiride | 4.022 | 200215 | 0.36 | 20798 |
| 2 | STD. Glimepiride+Metformine | 2 | 2 | Glimepiride | 4.009 | 201510 | 0.36 | 20895 |
| 3 | STD. Glimepiride+Metformine | 2 | 4 | Glimepiride | 3.993 | 200055 | 0.36 | 21304 |
| 4 | STD. Glimepiride+Metformine | 2 | 5 | Glimepiride | 3.989 | 203987 | 0.36 | 21556 |
| 5 | STD. Glimepiride+Metformine | 2 | 3 | Glimepiride | 4.000 | 200812 | 0.36 | 21267 |
| Mean | | | | | 4.003 | 201315.8 | | |
| Std. Dev. | | | | | 0.013 | 1599.0 | | |
| % RSD | | | | | 0.33 | 0.8 | | |

**Peak Summary with Statistics**

**Name: Metformine HCl**

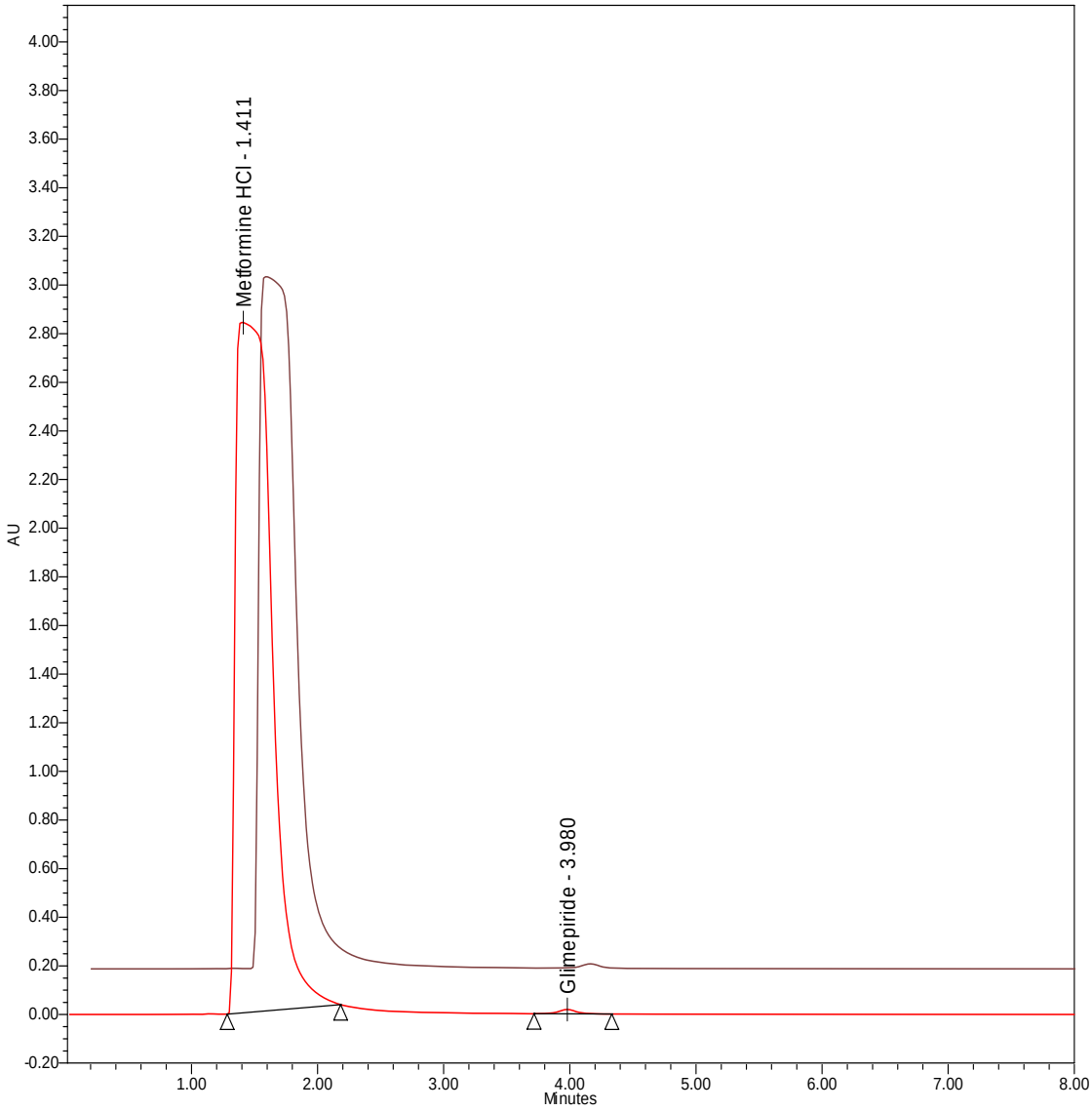
| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | STD. Glimepiride+Metformine | 2 | 1 | Metformine HCl | 1.408 | 55738711 | 99.64 | 2844130 |
| 2 | STD. Glimepiride+Metformine | 2 | 5 | Metformine HCl | 1.411 | 55925214 | 99.64 | 2854601 |
| 3 | STD. Glimepiride+Metformine | 2 | 4 | Metformine HCl | 1.410 | 55866322 | 99.64 | 2849064 |
| 4 | STD. Glimepiride+Metformine | 2 | 3 | Metformine HCl | 1.409 | 55842572 | 99.64 | 2846227 |
| 5 | STD. Glimepiride+Metformine | 2 | 2 | Metformine HCl | 1.409 | 56047841 | 99.64 | 2842163 |
| Mean | | | | | 1.409 | 55884132.0 | | |
| Std. Dev. | | | | | 0.001 | 113666.4 | | |
| % RSD | | | | | 0.09 | 0.2 | | |

**Fig. No. 16 Assay Chromatogram of Morpean Trial**

# Peak Summary Report

Reported by User: System

Project Name: PDA2009IInd




Sample Name: #Trial RD .....Assay; Vial: 3; Injection: 1; Date Acquired 11/3/2009 11:56:30 AM

Sample Name: #Trial RD .....Assay; Vial: 3; Injection: 2; Date Acquired 11/3/2009 12:05:29 PM

Signature.....

**Table No. 49 Assay Peak Summary with Statistics of Morpean Trial**

# Peak Summary Report

Reported by User: System

Project Name: PDA2009IInd

**Peak Summary with Statistics**

**Name: Glimepiride**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #Trial R&D .....Assay | 3 | 1 | Glimepiride | 3.980 | 181072 | 0.32 | 17995 |
| 2 | #Trial R&D .....Assay | 3 | 2 | Glimepiride | 3.975 | 180454 | 0.32 | 17882 |
| Mean | | | | | 3.978 | 180763.0 | | |
| Std. Dev. | | | | | 0.004 | 436.3 | | |
| % RSD | | | | | 0.09 | 0.2 | | |

**Peak Summary with Statistics**

**Name: Metformine HCl**

| | Sample Name | Vial | Inj | Name | Retention Time (min) | Area | % Area | Height |
|---|---|---|---|---|---|---|---|---|
| 1 | #Trial R&D .....Assay | 3 | 1 | Metformine HCl | 1.411 | 56010285 | 99.68 | 2854120 |
| 2 | #Trial R&D .....Assay | 3 | 2 | Metformine HCl | 1.411 | 56068512 | 99.68 | 2859077 |
| Mean | | | | | 1.411 | 56039398.3 | | |
| Std. Dev. | | | | | 0.000 | 41172.4 | | |
| % RSD | | | | | 0.02 | 0.1 | | |

Calculation:

**IN VITRO DISSOLUTION TEST (By U.V)**

**Comparative study of innovator product and optimization formulation**

**Dissolution of Metformin drug:**

Dissolution study of tablet performed in USP II (Paddle) dissolution test apparatus (Electro lab TDT 08L) using 900ml of Phosphate buffer as a dissolution media. The tablet was loaded in to each basket of dissolution apparatus; the temperature of dissolution media was maintained at 37°C ± 0.5°C with stirring speed of 100 rpm through out the study. Aliquots of dissolution media containing 10 ml of sample were taken at time interval of 1, 2, 4, 6, 8 hours and 10 ml of fresh dissolution media maintaining at the same temperature was replace after each withdrawal. The samples were analyzed by U.V Spectroscopy at 232nm. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug release at different time intervals.

**Dissolution Parameters:**

| | | |
|---|---|---|
| Medium | : | 6.8 gm of Ortho-Phosphoric acid Solution (6.8mg in 1000 ml ). Adjust to pH 6.8 by NaOH. |
| Quantity | : | 900 ml |
| Apparatus | : | Apparatus II (Paddle). |
| rpm | : | 100 |
| Time | : | 1, 2, 4, 6, & 8 hours or required intervals. |
| Temperature | : | 37 ± 0.5ºC. |

**Preparation of 6.8-pH Phosphate Buffer Medium:**

6.8 gm of Ortho-Phosphoric acid added to the 1000 ml volumetric flask and make up the volume with 1000 ml-Distilled water

**Standard Solution Preparation:**

Take 25 mg of Metformin working standard into 50 ml volumetric flask, dissolve and make up to the volume with distilled water, from that take 2 ml of sample and again dissolved in to 50 ml of Distilled water.

Taken the absorbance at 232 nm of the prepared samples in U.V spectrophotometer

| Sr. No | Concentration (µg/ml) | Absorbance (nm) |
|---|---|---|
| **1.** | 2.5 | 0.285 |
| **2.** | 5 | 0.475 |
| **3.** | 7.5 | 0.682 |
| **4.** | 10 | 0.851 |
| **5.** | 12.5 | 1.067 |
| **6.** | 15 | 1.240 |

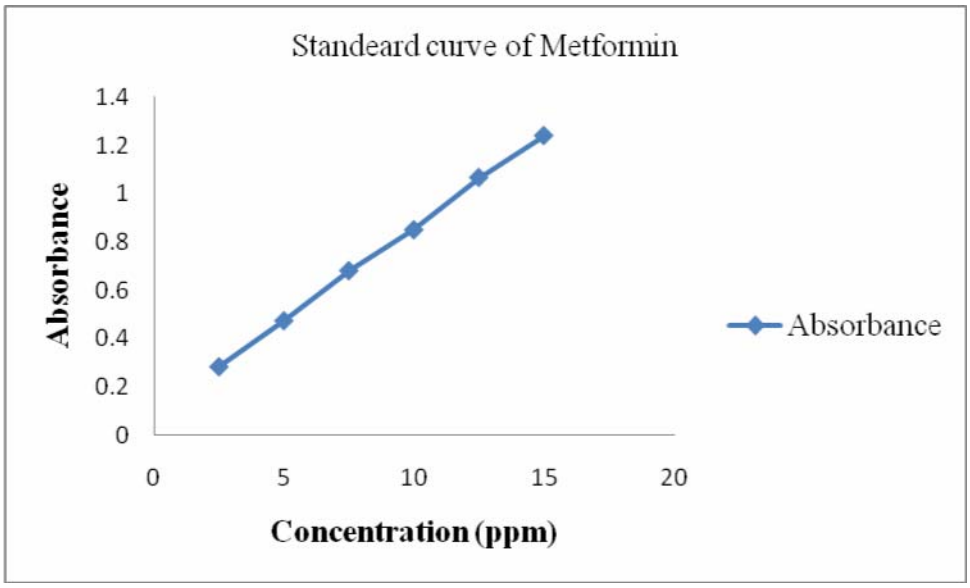



**Fig No.17 Standard curve of Metformin**

$$Factor = \frac{1}{A\,s} \times \frac{W_1}{50} \times \frac{1}{50} \times \frac{900}{L.C} \times \frac{P_1}{100} \times 100$$

**Where:**

$W_1$ = Weight of working standard

L.C = Label claim in mg

$P_1$ = % potency of working standard

$A_S$ = Absorbance of the Metformin standard sample.

$$Factor = \frac{1}{0.821} \times \frac{25.6}{50} \times \frac{1}{50} \times \frac{900}{500} \times \frac{98.94}{100} \times 100$$

$$Factor = 111.063$$

**Table No. 50 Dissolution Study of Metformin (USV)**

| Absorbance x factor (% release) | % Release after 1 hour | % Release after 2 hour | % Release after 4 hour | % Release after 6 hour | % Release after 8 hour |
|---|---|---|---|---|---|
| $A_1$ x F | 39.15 | 60.3 | 68.5 | 78.62 | 89.81 |
| $A_2$ x F | 41.59 | 61.19 | 71.49 | 79.89 | 90.6 |
| $A_3$ x F | 42.87 | 58.58 | 72.18 | 79.52 | 89.41 |
| $A_4$ x F | 36.31 | 59.97 | 71.35 | 81.85 | 90.62 |
| Average | 39.98 | 60.01 | 70.88 | 79.97 | 90.11 |

**Fig.No. 18 Dissolution Profile of Glycomet GP-1mg (USV)**

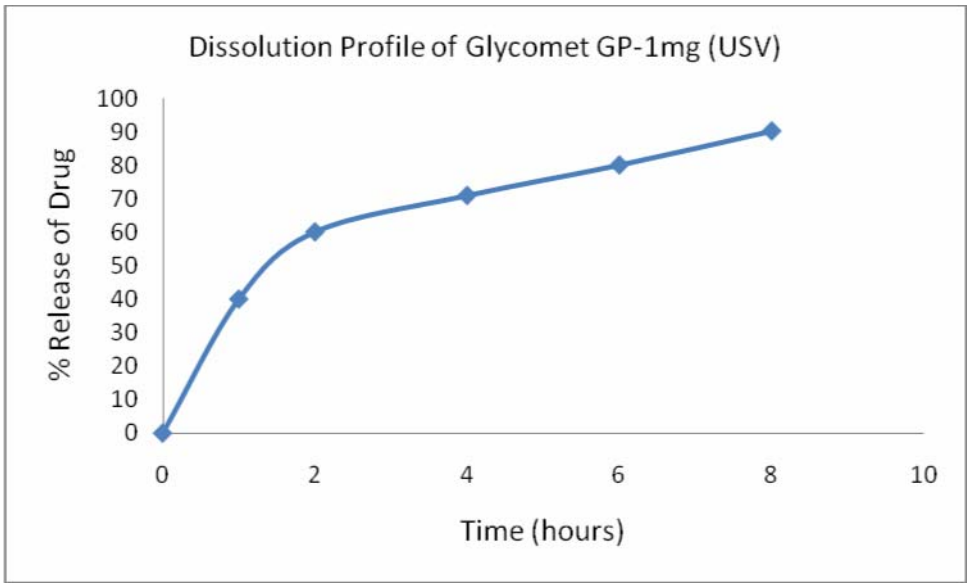



**Table No. 51 Dissolution study of Gluconorm-G1 (Lupin)**

| Absorbance x factor (% release) | % Release after 1 hour | % Release after 2 hour | % Release after 4 hour | % Release after 6 hour | % Release after 8 hour |
|---|---|---|---|---|---|
| $A_1$ x F | 39.24 | 58.57 | 70.25 | 79.64 | 90.25 |
| $A_2$ x F | 42.16 | 60.35 | 69.46 | 80.11 | 92.36 |
| $A_3$ x F | 38.53 | 61.01 | 71.25 | 81.37 | 90.47 |
| $A_4$ x F | 40.55 | 62.27 | 70.58 | 82.04 | 91.58 |
| Average | 40.12 | 60.55 | 70.38 | 80.79 | 91.16 |

**Fig. No. 19 Dissolution Profile of Gluconorm-G1 (Lupin)**

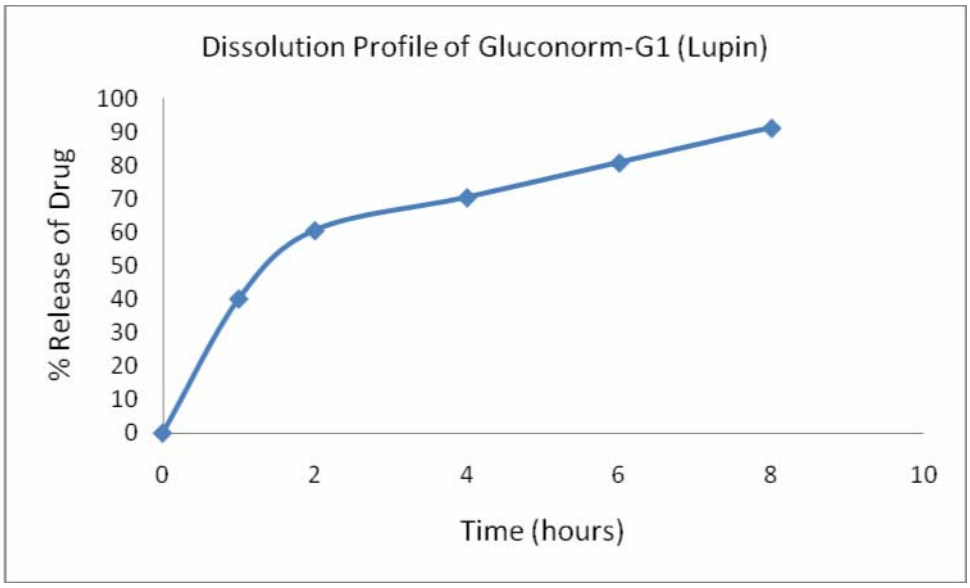
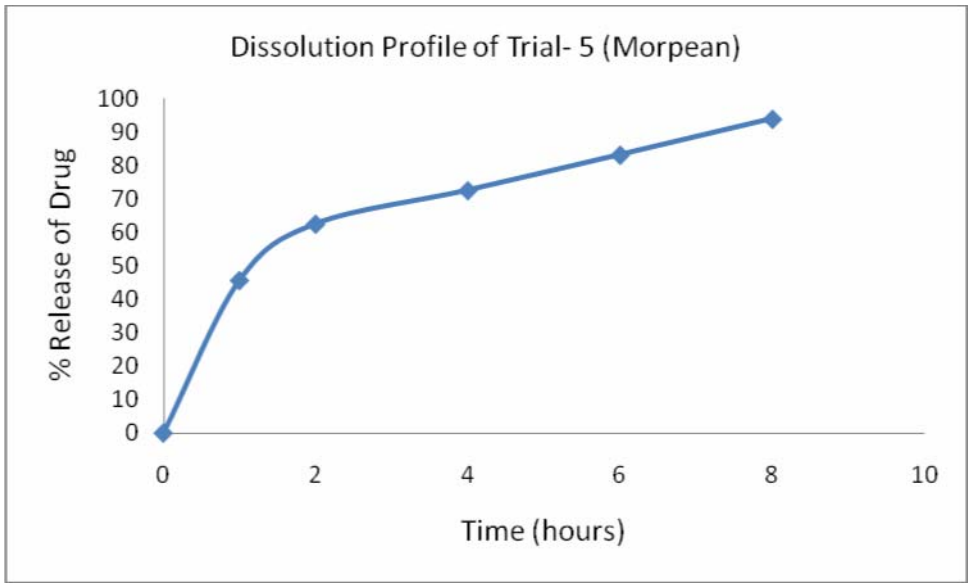



**Table No. 52 Dissolution Study of Trial-5 (Morpean lab.)**

| Absorbance x factor(% release) | % Release after 1 hour | % Release after 2 hour | % Release after 4 hour | % Release after 6 hour | % Release after 8 hour |
|---|---|---|---|---|---|
| $A_1$ x F | 46.09 | 58.53 | 71.56 | 82.63 | 92.39 |
| $A_2$ x F | 46.09 | 62.97 | 71.37 | 82.6 | 97.06 |
| $A_3$ x F | 45.09 | 63.52 | 72.85 | 83.67 | 92.41 |
| $A_4$ x F | 45.31 | 64.86 | 74.3 | 83.62 | 93.62 |
| Average | 45.64 | 62.47 | 72.52 | 83.13 | 93.87 |

**Fig. No. 20 Dissolution Profile of Trial- 5 (Morpean)**




**Calculation of Dissimilarity ($f_1$) and Similarity ($f_2$) factor:**

**Dissimilarity factor:**

It was calculated in the comparison with reference or innovator product to know the dissimilarity

*The dissimilarity factor ($f_1$) should be always less then 15($f_1$< 15)*

$$F_1 \equiv \frac{\sum R_{t1} - T_t}{\sum R_{t1}} \times 100$$

**Similarity factor ($f_2$):**

The similarity factor ($f_2$) was defined as the logarithm reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products. This was calculated to compare the test with reference release profiles

*The Similarity factor ($f_2$) should be always greater then 50 ($f_2$ >50)*

The method is more adequate to compare dissolution profile when more than three or four dissolution time points are available and can only be applied if average difference between $R_t$ and $T_t$ is less then 100. If this difference is higher than 100, normalization of data is required.

$$F_2 \equiv 50 \times \log 10 \frac{100}{\sqrt{1 + 1/n \times \sum (R_t - T_t)^2}}$$

**Conclusion:**

**Tablet No. 53 for Metformin**

| Time(hours) | $Rt_1$ USV | $Rt_2$ LUPIN | Tt | $Rt_1$-$T_t$ | $Rt_2$-Tt | $\sum(Rt_1-Tt)^2$ | $\sum(Rt_2-Tt)^2$ |
|---|---|---|---|---|---|---|---|
| **1** | 39.98 | 40.12 | 45.64 | -5.66 | -5.52 | 32.035 | 30.4704 |
| **2** | 60.01 | 60.55 | 62.47 | -2.46 | -1.92 | 6.0516 | 3.6864 |
| **4** | 70.88 | 70.38 | 72.52 | -1.64 | -2.14 | 2.6896 | 4.5796 |
| **6** | 79.97 | 80.79 | 83.13 | -3.16 | -2.34 | 9.9856 | 5.4756 |
| **8** | 90.11 | 91.16 | 93.87 | -3.76 | -2.71 | 14.137 | 7.3441 |
| **Average** | ∑340.95 | ∑343 | | ∑-16.68 | ∑-14.63 | ∑64.8988 | ∑51.5561 |

$$F_1 \equiv \frac{\sum R_{t1} - T_t}{\sum R_{t1}} \times 100$$

$$F_1 \equiv 4.26$$

$$F_1 \equiv 4.89$$

$$F_2 \equiv 50 \times \log 10 \frac{100}{\sqrt{1 + 1/n \times \sum (R_t - T_t)^2}}$$

$$F_2 \equiv 78.24$$

$$F_2 \equiv 70.30$$

**Comparative Dissolution Profile of Metformin Drug**

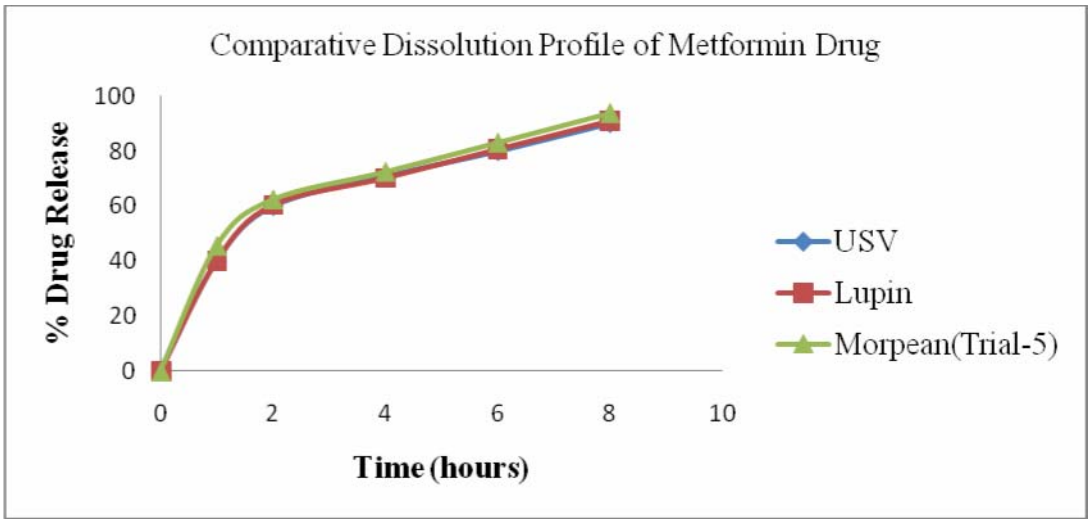



**Fig.No. 21Comparative Dissolution Profile of Metformin Drug**

## Stability Study

The stability with respect to the Dosage from refer to the Chemical and physical integrity of the damage form and stability of the dosage form to maintain protection against microbiological contamination.

It is also defined as the time laps during which drug retains same physical and chemical properties those possess at the time of manufacturing.

The main purpose of conducting stability testing for Pharmaceutical Product:

- To ensure the efficacy, safety and Quality testing of active drug substance and dosage form
- To establish Shelf Life or Expiration Period
- To support label claim

**ICH Guidelines for Stability Testing:**

The International Conference on Harmonization (ICH) brings together experts from Pharmaceutical and regulatory authorities of Europe, Japan and other countries to discuss

scientific and technical aspects of product registration. Whole world is divided into four climatic zone in order to harmonize and simplify the stability testing.

**Table No. 54 List of Countries according to Climatic Zone**

| Regions | Zone I & Zone II | Zone III & Zone IV |
|---|---|---|
| Europe | All countries | |
| America | Canada, Mexico United states | Brazil, Jamaica, Cuba |
| Asia | Afghanistan, China, Japan, Korea, Iran, Israel, Turkey | Hong Kong, Bangladesh, India, Pakistan, Singapore, Saudi Arabia |
| Africa | Egypt, South Africa, Zimbabwe | Kenya, Libya, Sudan, Nigeria |
| Australia Ocean | Australia, New Zeeland | Fiji Tonga |

**Table No. 55**
**Worldwide zones and the Temperature and Humidity conditions as per ICH Guidelines**

| Zones | Mean Kinetic Temperature | Yearly Average Humidity |
|---|---|---|
| Zone I(Temperate) | 21°C | 45% |
| Zone II(Mediterranean) | 25°C | 60% |
| Zone III(Hot & Dry) | 30°C | 35% |
| Zone IV(Hot & Humid) | 80°C | 70% |

The recommended storage test condition for different types of stability studies is given as in following manner:

**Table.No.56**

| Study | Intended storage condition of finished production | | | Maximum periods Covered by data at Submission |
|---|---|---|---|---|
| | Room Temp | Refrigerator (general case) | Freezer | |
| Long term study | 25 ± 2°C/60± 5%R.H. Or 30 ± 2°C/60 ± 5%R.H. | 5 ± 3°C | -20±5°C | 12 Months |
| Intermediate Stability Study | 30 ± 2°C/60 ± 5%R.H. | -- | -- | 6 Months |
| Accelerated Stability Study | 40 ± 2°C/5 ± 5%R.H. | If available 25 ±2°C/60±5%R.H. otherwise 30±2°C/65±5%R.H. | -- | 6 Months |

If 30°C / 65% R.H.is the long term stability condition, there are no intermediate conditions

Acceptance criteria for stability study at the point of data submission

- For each test included in the product, a suitable acceptance criterion should be fixed.
- The criteria for quantitative result will be in the term of numerical limits i.e. dissolution rate drug assay in terms of % for solids and water loss in term of liquids.
- For quantitative tests, the criteria may be in the term of pass or fail.

According to ICH Guidelines "Significant changes" in accelerated stability study is defined as-

- 5% potency loss from the initial assay value of a batch.
- Specified degradation product exceeding its acceptable criteria.
- Failure to meet specification for appearance, physical properties and functionality test.
- Failure to meet specification limit for pH
- Failure to meet specification limit for dissolution of tablets.
- A 5% loss in water from its initial value is considered a significant change for a product packaged in semi permeable container, intended to be stored at room temperature, refrigerator and freezer.

**Testing Frequency:**

- According to ICHQ1A and CPMP- QWP/556/96 Guidelines for real time testing during first year sampling should be done for every six months and after two years sampling should be done in a year.
- Accelerated testing should be done for at least 6 month according to ICHQ1A,and sampling point of 0, 3 & 6 months, whereas WHO Guidelines suggest 0, 1, 2, 3 & 6 months sampling Intervals.
- For intermediate testing, according to ICHQ1A sampling intervals are 0, 6, 9, 12 months.

**Test Procedure and Test Criteria:**

The Stability Assay is conducted by keeping the drug substance or the product in final containers or packing and under the selected storage conditions. Samples are withdrawn at the prescribed sampling intervals and subjected to analysis, sampling for analysis are generally taken from previously unopened containers, however samples can be taken from previously opened containers in case of products packaged in unit of use of containers intended for dispensing to multiple patients or for repacking. The dosage units should be sampled from the container randomly with each dosage form unit having an equal chance of being included in the sample

**Evaluation:**

A systemic approach should be adopted in the presentation and evaluation of the stability information, which should include results from the chemical, physical and microbiological tests including particular attributes of the dosage form

**Accelerated Stability Study:**

**Table No.57 Stability data for Exposing sample at 40°C / 75% R.H for 1 month**

| Sr. No. | Testes | Observation |
|---|---|---|
| **1.** | Color | No Change |
| **2.** | Moisture Content | 3.21 |
| **3.** | Impurity | No |
| **4.** | Assay (Metformin) | 98.48 |
| **5.** | Assay (Glimepiride) | 98.16 |

**Table No.58 Dissolution Profile for Exposed sample at 40°C/75 % R.H. for 1 Month**

| Time(hours) | % Drug Release of Metformin |
|---|---|
| **1** | 40.12 |
| **2** | 60.55 |
| **4** | 70.38 |
| **6** | 80.79 |
| **8** | 91.16 |

**Table No.59 Stability data for Exposing at 25°C / 60% R.H for 1 month**

| Sr. No. | Testes | Observation |
|---|---|---|
| **1.** | Color | No Change |
| **2.** | Moisture Content | 3.38 |
| **3.** | Impurity | No |
| **4.** | Assay (Metformin) | 99.60 |

| | | |
|---|---|---|
| **5.** | Assay (Glimepiride) | 99.42 |

**Table No. 60 Dissolution Profile for Exposed sample at 25°C/60 % R.H. for 1 Month**

| Time(hours) | % Drug Release of Metformin |
|---|---|
| **1** | 45.52 |
| **2** | 62.38 |
| **4** | 72.45 |
| **6** | 83.08 |
| **8** | 92.87 |

# Results and Discussion

1. **Preformulation Study:**

The present investigation was carried out to develop Bi-layer tablet dosage form of Metformin and Glimepiride drug. The tablets are prepared by using different excipients.

**1.1 Compatibility Study:**

**Drug: Excipients Compatibility** study of Metformin and Glimepiride with different categories of excipients was carried out. The study was carried out at different conditions of temperature and humidity like 40°C / 75% R.H., 2-8°C, at room temperature and noted their physical appearance, impurity level and water content after 2 weeks, 4weeks, and compared with initial value as shown in **Table No. 29 & 30**. Organoleptic properties of drug in presence of excipients was carried out at different interval and compared with initial color as shown in **Table No. 31 & 32**

**2. API Characterization Study :**

**2.1 Sieve Analysis of API:**

The sieve analysis carried out by using mechanical shaker, the particle size of Metformin and Glimepiride were analyzed separately on Electromagnetic sieve shaking and weighing of the portion of the sample retained on each sieve and calculated percentage retained on each sieve **Table No. 17, 18 & 19**

**2.2 Powder Flow Properties:**

The Metformin and Glimepiride drug show poor flow properties. In order to overcome this direct compression Technique was adopted and the result of improved flow shown in **Table No. 7 & 8** indicates that drug has improved flow property.

**3. Evaluation of Formulation Parameters:**

Evaluation was divided mainly in to:

- **Pre-Compression Parameters**
- **Post Compression Parameters**

Pre compression parameters include loss on drying of dried granules and final blend, Bulk density, Tapped Density, Carr's Index, Housner's ratio and sieve analysis. In post compression parameters Average Weight, Thickness, Hardness, Disintegration Time and Friability were determined.

**3.1 Pre Compression Parameters:**

**Loss on drying (LOD):**

Sample of Metformin blend was kept in an oven at 60°C for 2 hours and decrease in weight of sample were observed. Sample of Metformin blend was kept in an oven at 40° C for 2 hours and decrease in weight of sample was observed. Usually 3 samples are taken to observe the Loss on Drying as shown in **Table No. 21** shows for % LOD in a particular limit.

**Powder Flow Characteristics:**

The flow characteristics of final blend of both Metformin and Glimepiride drug was shown in **Table No. 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 & 16**

- Bulk density for Metformin and Glimepiride in the range of **0.465-0.530** gm/ml
- Tapped density in the range **0.572 – 0.633** gm/ml
- Carr's index ranging **17.98- 20.09 %**
- Hausner's ratio in the range **1.21-1.25** shows the good flow characteristics.

**3.2 Post Compression Parameters:**

**Weight Variation:**

In Trial 1-5, weight variation was determined given in **Table No. 36**, but in final trial tablet ranging 1100.85 mg (Average weight -1100 mg /tab), which is less than 5%, indicate that the variation in the weight of the tablets is within standard official limits.

**Thickness Evaluation:**

Thickness of tablets was carried out by Vernier calipers. Thickness of tablets shows very slight deviation in both strengths given in **Table No. 37**

**Hardness Test:**

Hardness of the tablets was measured in Newton (N) unit in digital hardness tester. The hardness of tablets found to be uniform within range given in **Table No. 38** indicates that the prepared tablets are mechanically stable.

**Friability Test:**

The friability was carried out by using Roche Friabilator. The % friability of tablets was ranging **0.11-0.14 %** for 1100.85 mg tablet and given in **Table No.39** they are less than the standard limit of 1% indicates that the prepared tablets are mechanically stable.

**Drug Content Uniformity:**

The drug uniformity of Glimepiride found in given limit in ranging from **95-105 %**, which is within the range of 95.43**-105.4 %**. It indicates uniformity distribution of drug in the table of each formulation.

**In vitro Drug release Studies:**

Dissolution study of Metformin performed in USP-II (Paddle) Dissolution test apparatus (Electro lab TDT08L) using 900ml of acetate buffer as a dissolution media. The tablets was loaded into an each basket of dissolution apparatus, the temperature of dissolution media was maintained at 37°C with stirring speed 100 rpm throughout the study. As show in **Table No.52**

**$F_2$ Value:**

Similarity factor ($F_2$) was calculated between innovator formulation and our formulation. Similarity factor value in the range of 50-100 indicates that there is similarity in the release profile of the formulations.

$F_2$ Value of both Metformin and Glimepiride was found to be satisfactory, as $F_2$ values for Metformin is **78.24** respectively given in **Table No.53** and **Figure No.21** Show the dissolution profile.

## 4. Stability Study:

The stability studies of final trial was done for 3 months by packing in high density polyethylene (HDPE) container in humidity chamber (40°C/75%RH)

The results given in **Table No. 57, 58, 59 & 60** for 1 month, show all parameters of formulation including physical parameters, impurity profile, content uniformity and dissolution profile were within specification limit. So therefore it indicates that optimization formulations were stable.

# Conclusion

- Drug excipients compatibility study with Metformin-Glimepiride was conducted with different excipients and compatible excipients were used.
- Trial –V that compose of Metformin, Glimepiride, MCC Rank-Q-102, Colloidal Silicon Dioxide, Hydroxyl Propyl Methyl Cellulose, Magnesium Stearate and Starch, shows better compatibility.
- The result of this study shows that in case of all tablets formulation, the trial –V formulation shows better results in pre-compression as well as in post compression parameters
- Trial-V also shows better Metformin-release profile in phosphate buffer media
- In the stability study under storage condition $40^{o}C/75\%RH$ after 1 month shows that the formulation trial –V has better result under official limit for pre-compression and post compression parameters.
- The optimized Metformin and glimepiride Bi-layer tablet satisfies the entire official requirement for a generic product, which is found not only stable but also comparable with innovator product

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