A potential breakthrough in the enhancement of Glimepiride solubility and dissolution rate by Binary and Ternary solid dispersion technique and *in- vitro* comparison with marketed formulation

THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE

OF

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FACULTY OF ENGINEERING AND TECHNOLOGY

SUBMITTED BY

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FACULTY OF ENGINEERING AND TECHNOLOGY JADAVPUR UNIVERSITY

KOLKATA 700032

2023

Dedicated to my family, my guide and to my nation…

CERTIFICATE

Department of Pharmaceutical Technology

Jadavpur University

Kolkata-700032

This is to certify that the dissertation entitled ***"A potential breakthrough in the enhancement of Glimepiride solubility and dissolution rate by Binary and Ternary solid dispersion technique and in- vitro comparison with marketed formulation"*** *submitted to Department of Pharmaceutical Technology, Jadavpur University in partial fulfilment of the requirements for completion of the degree of* ***Master of Pharmacy*** *is a record of original research work carried out by Mr Rideb Chakraborty under my guidance and supervision in Department of Pharmaceutical Technology.*

I further certify that neither this dissertation nor any part of it has been submitted to any other University or Institute for award of any degree or diploma. I am pleased to forward this dissertation for evaluation.

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DECLARATION OF ORIGINALITY AND COMPLIANCE OF ACDEMIC ETHICS

*I hereby declare that the dissertation entitled "**A potential breakthrough in the enhancement of Glimepiride solubility and dissolution rate by Binary and Ternary solid dispersion technique and in- vitro comparison with marketed formulation**" is a bonafide and genuine research work carried out by me under the supervision of Dr. Ketousetuo Kuotsu, Associate professor, Department of Pharmaceutical Technology Jadavpur University. All information in this document have been obtained and presented in accordance with the academic rules and ethical conduct. I also declare that as required by these rules and conduct; I have fully cited and referenced all the materials and results that are not original to this work.*

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Place: Kolkata

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(Mr. Rideb Chakraborty)

PREFACE

The thesis is performed for the partial requirement of the degree of Master of Pharmacy. The present research work entitled ***"A potential breakthrough in the enhancement of Glimepiride solubility and dissolution rate by Binary and Ternary solid dispersion technique and in- vitro comparison with marketed formulation"*** was designed to establish the comparative solubility and dissolution rate enhancement using two different water soluble carriers for the poorly water soluble drug Glimepiride employing binary and ternary solid dispersion method.

In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37°C (7, solubility of drug is slightly increased to 0.02 mg/ml. These poorly water soluble drugs provide challenges to deliver them in an active and absorbable form to the desired absorption site using physiologically safe excipients. This poor solubility may cause poor dissolution and unpredicted bioavailability. It is practically insoluble in water and other aqueous media. However, the drawback of this potentially useful hypoglycemic agent is that it is highly hydrophobic and practically insoluble in water. The primary mechanism of action of glimepiride for lowering blood glucose levels seems to be dependent on stimulating the release of insulin from the functioning pancreatic cells. Glimepiride acts by binding to ATP sensitive potassium channel receptors on the pancreatic cell surface, which reduces potassium conductance causing depolarization of the membrane. Calcium ion reflux is stimulated by the membrane depolarization through voltage sensitive calcium channels. This increased intracellular calcium ion concentration induces the secretion of insulin.

This thesis is divided Ito 12 chapters describing fundamentals, materials methodology, results and discussion, conclusion, references and appendix.

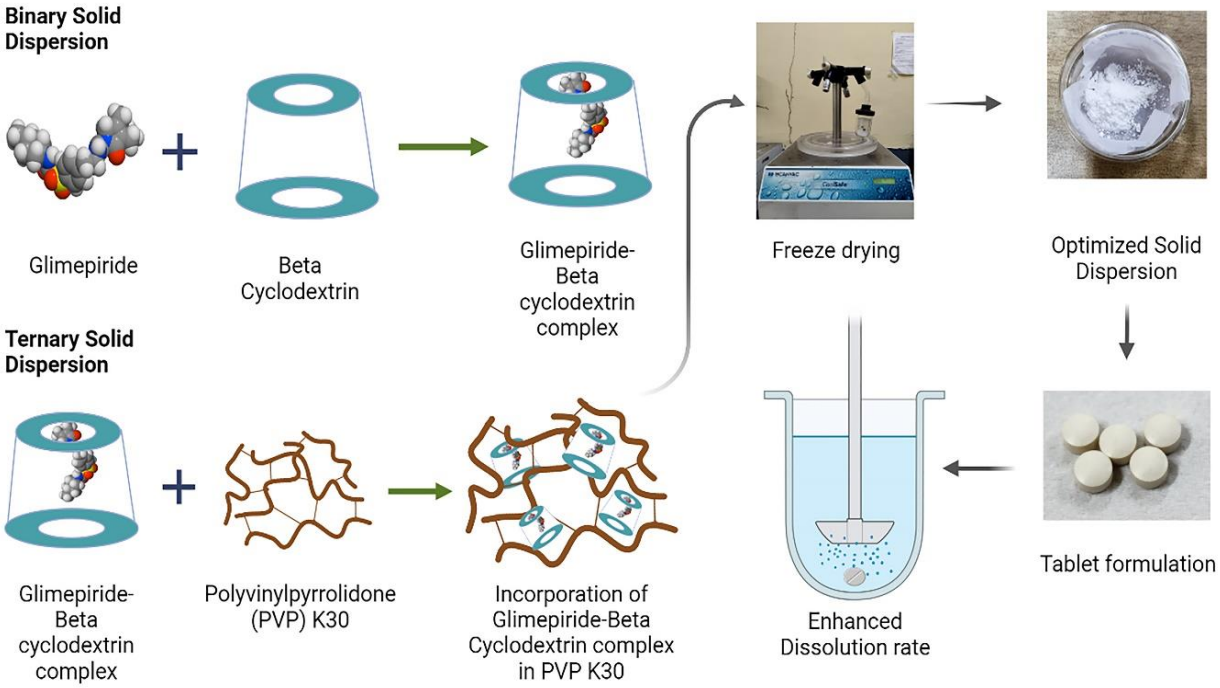
ABSTRACT

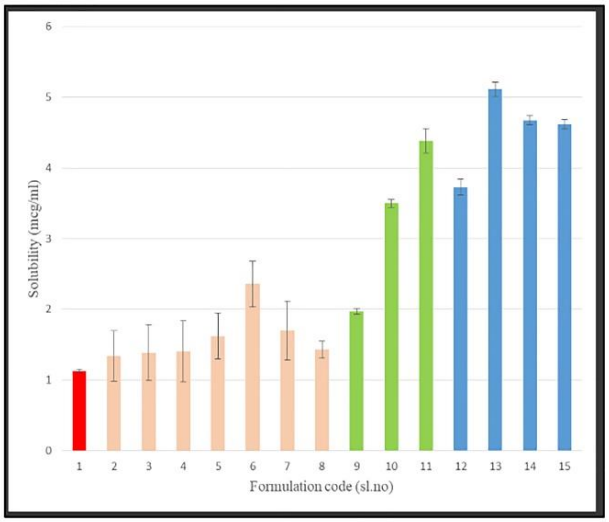
Glimepiride, an anti-diabetic and third-generation sulfonylurea drug belonging to class II BCS (Biopharmaceutical Classification System) type, is characterized by its low solubility and high permeability. In order to increase glimepiride's aqueous solubility and hence increase its bioavailability, the goal of this study was to formulate the drug as binary and ternary solid dispersion employing water-soluble carriers. Three binary solid dispersions of glimepiride were prepared by solvent evaporation technique using β-cyclodextrin with different drug carrier ratios. After optimizing the binary solid dispersion concerning solubility improvement, four different ratios of ternary solid dispersion employing polyvinylpyrrolidone-K30 (PVP-K30) were fabricated with the optimized solid dispersion to determine solubility. The combination of the glimepiride and βcyclodextrin systems significantly increases the solubility and in the case of ternary solid dispersion, the solubility is increased even more. The enhancement of the solubility is influenced by the carrier's concentration. FTIR, XRD, and DSC studies were performed for a better understanding of the characterization of optimized solid dispersion and to know if there are any significant interactions with water-soluble carriers or with excipients. A total of four tablet formulation batches were prepared and *in-vitro* comparisons were carried out with commercially available immediate-release formulation, and the explicit in-vitro drug release result suggested that formulating glimepiride in ternary solid dispersion has enhanced the solubility and dissolution rate drastically.

KEYWORDS

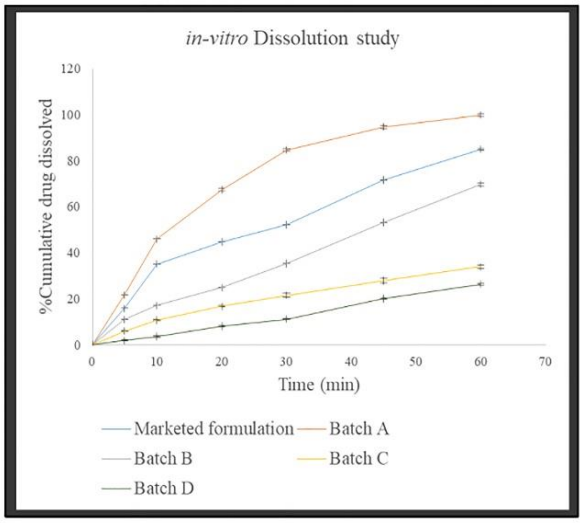
Type II diabetes mellitus, BCS Class II drug, Glimepiride, Binary and Ternary solid dispersion, Solubility enhancement.

GRAPHICAL ABSTRACT





Enhanced solubility



Enhanced Dissolution Rate

CONTENTS

1. INTRODUCTION

It's safe to say that diabetes mellitus (DM) is one of the oldest human disorders. About 3000 years ago, it was first mentioned in an Egyptian manuscript. The distinction between type 1 and type 2 DM was defined in crystal plain terms in 1936. In 1988, type 2 diabetes was initially identified as a part of the metabolic syndrome. The most prevalent kind of DM, type 2 (formerly known as non-insulin dependent DM), is characterized by hyperglycemia, insulin resistance, and relative insulin insufficiency. The interplay of genetic, environmental, and behavioral risk factors leads to type 2 diabetes.

Type 1 Diabetes Mellitus (T1DM)

The autoimmune death of insulin-producing beta cells in the pancreatic islets characterizes type 1 diabetes mellitus (T1DM), which makes up 5% to 10% of all cases of diabetes. Consequently, there is a complete lack of insulin. Autoimmunity has been linked to a mix of genetic predisposition and environmental triggers including virus infection, toxins, or certain dietary components. Though it can happen to anyone at any age, T1DM is most frequently found in children and teenagers.

Type 2 Diabetes Mellitus (T2DM)

About 90% of all instances of diabetes are Type 2 diabetes mellitus (T2DM). Insulin resistance is the term used to describe the reduced insulin response in T2DM. Since insulin is ineffective in this condition, the body produces more insulin to maintain glucose homeostasis at first, but over time, this diminishes, leading to T2DM. T2DM is most frequently diagnosed in those over the age of 45. Nevertheless, it is becoming more common in kids, teenagers, and young adults as a result of increased obesity rates, inactivity rates, and calorie-dense diets.

Gestational Diabetes Mellitus

Pregnancy-related hyperglycemia is categorized as gestational diabetes mellitus (GDM), often known as pregnancy-related hyperglycemia. Although it can happen at any moment while a woman is pregnant, GDM typically affects women in their second and third trimesters. The American Diabetes Association (ADA) estimates that 7% of all pregnancies are complicated by GDM. Future onset of type 2 diabetes mellitus is more likely among GDM-positive women and their offspring.

Hypertension, preeclampsia, and hydramnios can all worsen GDM and increase the need for surgical treatments. The fetus may be larger and heavier than normal (macrosomia) or have congenital abnormalities. Such newborns may already have respiratory distress syndrome, which can lead to childhood and adolescent obesity. Older age, obesity, excessive gestational weight gain, history of congenital anomalies in previous children, or stillbirth, or a family history of diabetes are risk factors for GDM.

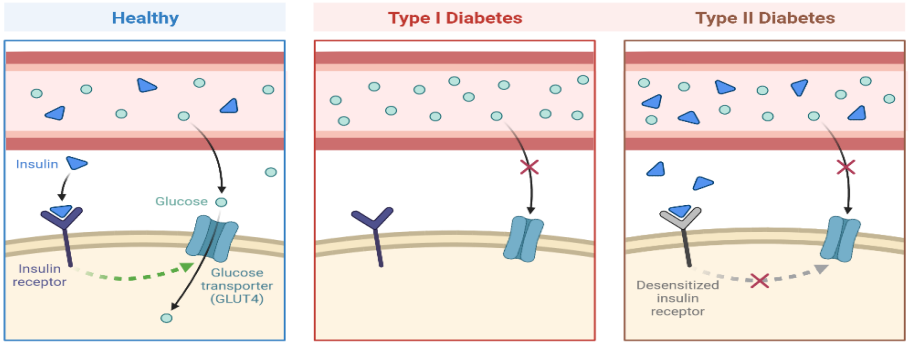
Monogenic Diabetes

This particular form of diabetes is brought on by a single genetic mutation in an autosomal dominant gene. Neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY) are two examples of monogenic diabetes. Monogenic diabetes accounts for 1% to 5% of all instances of diabetes. A hereditary condition called MODY typically manifests before the age of 25.

Secondary Diabetes

Secondary diabetes results from the aggravation of other pancreatic conditions including pancreatitis, hormonal imbalances like Cushing disease, or medications like corticosteroids.

People with type 2 DM are more prone to a variety of short- and long-term problems, which frequently result in early death. Patients with type 2 DM likely to have higher morbidity and mortality rates due to the condition's prevalence, sneaky onset, and tardy diagnosis, particularly in resource-constrained developing nations like Africa.



Healthy condition versus type I Diabetes versus type II Diabetes

Genetics and lifestyle choices are the main causes of type 2 diabetes. It is well recognized that a variety of lifestyle factors play a significant role in the emergence of type 2 DM. These include a sedentary lifestyle, smoking, excessive alcohol consumption, and physical inactivity. It has been discovered that obesity has a role in about 55% of type 2 DM cases. Type 2 DM in children and adolescents is thought to have increased as a result of the rise in juvenile obesity between the 1960s and 2000s. Toxins from the environment could be part of the reason why type 2 DM rates have recently increased. The prevalence of type 2 diabetes and urine concentrations of bisphenol A, a component of various plastics, have been found to have a weakly positive connection.

Type 2 diabetes is strongly heritable genetically, and having first-degree relatives who have the disease significantly raises the likelihood of getting it. Monozygotic twin concordance is about 100%, and roughly 25% of people with the condition have a family history of diabetes mellitus. Type-2 DM is defined by insulin insensitivity as a result of insulin resistance, diminishing insulin production, and eventually failing pancreatic beta-cells. Recently, genes have been found to be strongly related with developing type 2 DM. As a result, less glucose is transported into the liver, muscle, and fat cells. With hyperglycemia, there is an increase in the breakdown of fat. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM.

Because of this malfunction, meals do not reduce the levels of glucagon and hepatic glucose that grow during fasting. Hyperglycemia happens as a result of low insulin levels and increased insulin resistance. Important gastrointestinal mediators of insulin release and, in the case of GLP-1, glucagon suppression, are incretins. Although type 2 DM patients have reduced GIP activity, they nevertheless retain GLP-1's insulinotropic effects, making GLP-1 a potentially helpful therapeutic alternative. However, in vivo, DPP-IV rapidly inactivates GLP-1, much like it does with GIP.

A sulfonyl urea called glimepiride is used to treat type II diabetes. The chemical name for glimepiride is C24H34N4O5S, and it has a molecular weight of around 490.617 g/mol. It falls under the Biopharmaceutical Classification System's Class II. It is hardly soluble in various organic solvents and buffers, but entirely insoluble in water and acidic solutions. It is taken orally and is insoluble in water, soluble in methylene chloride (Dichloromethane), soluble in methanol, and soluble in dimethyl sulfoxide (DMSO). The solubility of glimepiride is poor and pH dependant. At 37°C (7, the drug's solubility is significantly enhanced to 0.02 mg/ml) glimepiride has very poor solubility in acidic and neutral aqueous solutions. These poorly water soluble drugs provide challenges to deliver them in an active and absorbable form to the desired absorption site using physiologically safe excipients. This poor solubility may cause poor dissolution and unpredicted bioavailability. It is practically insoluble in water and other aqueous media. However, the drawback of this potentially useful hypoglycemic agent is that it is highly hydrophobic and practically insoluble in water.

The primary mechanism of action of glimepiride for lowering blood glucose levels seems to be dependent on stimulating the release of insulin from the functioning pancreatic cells. Glimepiride acts by binding to ATP sensitive potassium channel receptors on the pancreatic cell surface, which reduces potassium conductance causing depolarization of the membrane. Calcium ion reflux is stimulated by the membrane depolarization through voltage sensitive calcium channels. This increased intracellular

calcium ion concentration induces the secretion of insulin. It can be employed for concomitant use with metformin, thiazolidinedione, insulin and alpha-glucosidase inhibitors for treatment of type-2 (noninsulin dependent) diabetes mellitus. It is completely absorbed from the gastrointestinal tract when it is administered orally. The possible side effects are severe hypoglycemic reactions with coma, seizure, or other neurological impairment. The other reported side effects of sulfonylureas includes clolestatic jaundice, nausea and vomiting, aplastic and hemolytic anemias, agranulocytosis, generalized hypersensitivity reactions, and rashes.

The drug molecules are classified as per the biopharmaceutics classification system (BCS), wherein a drug is considered as poorly aqueous soluble when the highest dose strength is not completely soluble in 250 mL aqueous media over the pH ranges of 1–8 at 37 °C. The BCS categorizes drug substances based on the solubility and permeability profile of drug substance as following classes:

• Class I: high solubility, high permeability

• Class II: low solubility, high permeability

• Class III: high solubility, low permeability

• Class IV: low solubility, low permeability

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion but it is problematic if the drug is poorly soluble or poor membrane penetrability. Almost more than 90% drugs are orally administered. Drug absorption, sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. More than 40% of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties.

The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. A lot of techniques used to overcome the poor aqueous solubility of active pharmaceutical ingredients (API) has been investigated in drug research and development such as salt formation, prodrug formation, particle size reduction, complexation, micelles, microemulsions, nanoemulsions, nanosuspensions, solid lipid nanoparticle, and solid dispersion (SD). SD is considered one of the most successful strategies to improve the dissolution profile of poorly soluble drugs. It is a method to alter the solid state at the particle, or molecular level involves a physical change in the drug and is an attractive option for improving drug solubility. GLIMEPIRIDE belongs to Biopharmaceutics Classification System class-II drug and has lower solubility and poor dissolution rate and as a result low bioavailability (BA). The drug development scientist can enhance the BA using SD technique. Various group of scientist are working in the field of SD, and good achievements were gained. The

API in SDs can be dispersed as separate molecules, amorphous particles, or crystalline particles while the carrier can be in the crystalline or amorphous state.

Numerous studies on SD have been published and have showed many advantageous properties of SD in improving the solubility and dissolution rate of poorly soluble drugs. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Solid dispersion is defined as "a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by melting (fusion), solvent or melting solvent method".

Need to increase solubility of a poorly soluble drug

The term, "solubility" is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. USP and BP classify the solubility regardless of the solvent used, just only in terms of quantification and have defined the criteria as given in below table

Expression for approximate solubility according to USP and IP solubility criteria.

Description	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Insoluble	>10,000

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. According to the equation of Noyes and Whitney, this may be achieved by an increase in the surface area of the drug which is accessible for the dissolution medium and an enhancement of its solubility. Beside enhancement of wettability or micronisation of drug substances in order to increase the surface area,

and replacement of crystalline drugs by amorphous material in order to increase the solubility, the application of solid dispersion is a method to affect both, surface area and solubility. The dispersivity of the drug in the carrier ranges beginning from a suspension of course drug particles to a suspension of fine drug particles and finally to a drug within the carrier, where a single drug molecules are dispersed in the carrier material. As particle size decreases in the order mentioned above, the drug surface area which is accessible for the dissolution medium increases in the same order. Furthermore, the solubility of the drug in the dissolution medium is influenced by the interaction of one drug molecule with the surrounding molecules.

Techniques for solubility enhancement

There are various techniques available to improve the solubility of poorly soluble drugs.

I. Physical modification

A. Particle size reduction

a. Micronisation

b. Nan suspension

B. Modification of the crystal habit

a. Polymorphs

b. Pseudo polymorphs

C. Complexation

a. Use of complexing agent

D. Solubilization by surfactants

a. Microemultion

b. Self microemulsifying drug delivery system

E. Drug dispersion in carriers

a. Solid solution

b. Solid dispersion

II. Chemical modification

A. pH adjustment

B. Salt formation

C. Co-crystallization

D. Co-solvency

Solid dispersion

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles Solid dispersions have been known to be one amongst the recent means of improving the dissolution rate by enhancement of solubility, and hence the bioavailability of poorly water soluble drugs. 1961, Sekiguchi et al. developed the concept of solid dispersion of poorly water soluble drug. According, to – Chiou and Riegeman Solid dispersions are "The dispersion of one or more active ingredients in an inert carrier or matrix, where the active ingredients could exist in finely crystalline, solubilised or amorphous state." solid dispersion is a very useful method for pharmaceutical point of view because of its capability to solve the solubility problems by using solid dispersion method.

A common methods used for preparation of solid dispersion

- Fusion method
- Solvent method
- Melting solvent method
- Supercritical fluid method
- Electro spinning method.
- Solvent evaporation method
- Melt agglomeration method
- Lyophillization Techniques
- Spray-Drying method
- Dropping method solution
- Melt extrusion method
- Gel entrapment technique
- Kneading technique
- Co-precipitation method
- Co-grinding method

1. Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. The first solid dispersions are created for pharmaceutical applications were prepared by the fusion method.

Advantage:

The main advantage of direct melting method is its simplicity and economy. In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.

Disadvantages:

Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions.

2. Solvent method

The first step in the solvent method is the preparation of a solution containing both matrix and material and drug. The second step involves the removal of solvent resulting in the formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges. First challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution and solid dispersions are obtained.

Advantages

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

Disadvantages

The disadvantages include the higher cost of preparation, the difficulty in completely removing liquid solvent and possible adverse effect of the supposed negligible amount of the solvent on the chemical stability of the drug are some of the disadvantages of this method.

3. Melting solvent method

In this method drug is first dissolved in a suitable liquid solvent solution is then incorporated directly into the melt of polyethylene glycol obtainable below 700c without removing the liquid solvent. It has been shown that 5- 10 %(w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

Advantages

In this method that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

Disadvantages

As the practical point of view, the melting-solvent method is limited to drugs with a low therapeutic dose, e.g. Below 50 mg.

Moreover, it is impossible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol.

The feasibility of the method has been demonstrated on spironolactone polyethylene glycol 6000 systems.

4. Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide, which h is used as either a solvent for drug and matrix or as an ant solvent. When supercritical C02 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles

are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as "solvent free". The technique is known as Rapid Expansion of Supercritical Solution.

Advantages

The supercritical anti solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles.

The general term for this process is precipitation with compressed anti oven. More specific examples of PCA are Supercritical Anti Solvent when supercritical CO2 is used or Aerosol Solvent Extraction System, and solution Enhanced Dispersion by supercritical fluids.

Disadvantages

Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix which are more in cost.

5. Electrospinning method

Electrospining is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through millimeter scale nozzles. This process involves the application of a strong electrostatic field over a conductive capillary attaching to reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical Value, a charged polymer jet is ejected from the apex of cone. The ejected charge jet is then carried to the collection screen via the electrostatic force. The Columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried.

Advantages

This technique has tremendous potential for the preparation of Nano fibers and controlling the release of biomedicine. Process is simplest, the cheapest.

This technique can be utilized for the preparation of solid dispersions in future.

Disadvantages

Less economical for all the drugs and carriers.

6. Solvent evaporation method

Solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is latter evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature. A basic process of preparing solid dispersions of this type consists of dissolving the drug and thy polymeric carrier in a common solvent, such as ethanol, chloroform mixture of ethanol and dichloromethane .Normally, the resulting films are pulverized and milled.

7. Melt agglomeration method

This technique has been used to prepare where in the binder acts as a carrier. In addition, are prepared either by Heating binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer. A rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a high binder content can be incorporated in the agglomerates. In addition the melt in procedure also results in homogenous distribution of drug agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion. The mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

8. Lyophillization techniques

Lyophillization has been thought of a molecular mixing technique. The drug and carrier are co dissolved in a common solvent, Frozen and sublimed to obtain a lyophilized molecular dispersion.

9. Spray-drying method

Drug is dissolved in suitable solvent and required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

10.Dropping method solution

The dropping method, developed by Ulrich et al., (1997) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvent and, therefore, has none of the problems associated with solvent evaporation.

11.Melt extrusion method

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g. sustained-release pellets.

12.Gel entrapment technique

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

13.Kneading technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

14.Co-precipitation method

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

15.Co-grinding method

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Ex. chlordiazepoxide solid dispersion was prepared by this method.

Several methods are used in solid dispersion preparations, such as hot melt extrusion, supercritical fluid method and solvent evaporation method. The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature

2. LITERATURE REVIEW

Abdul Basit *et al* discussed, Beta Cell secretagogues are helpful for attaining adequate glycaemic control since type 2 diabetes mellitus is characterized by insulin resistance and increasing cell failure. A second-generation sulfonylurea called glimepiride encourages the release of insulin from pancreatic cells. Compared to other sulfonylureas, glimepiride generally had a lower risk of hypoglycaemia and less tendency to cause weight gain in clinical trials. As glimepiride has no negative effects on ischemia preconditioning, its usage may be safer in patients with cardiovascular disease. It is a helpful, affordable therapeutic option for controlling type II diabetes mellitus because it lowers fasting plasma glucose, post-prandial glucose, and glycosylated haemoglobin levels.

S Akhter *et al* discussed, the principal factor limiting the oral bioavailability of glimepiride (GMP) is its poor water solubility. Due to the glimepiride's poor water solubility and slow rate of dissolution, sub therapeutic plasma drug levels can sometimes result in an unpredictable clinical response or therapeutic failure and this work showed that following solid dispersion, the drug converted to an amorphous state employing PEG as a water soluble carrier. Also, it was clear that solid dispersions boost the bioavailability of medications when taken orally by making drug particles more soluble.

S Sareen *et al* aimed to combine contemporary research on solid dispersion technology for solubility enhancement with a focus on the mechanisms underpinning it, various preparation techniques, and evaluation criteria. For different novel chemical entities, solubility behaviour is the greatest challenge because 60% of the new prospective products have solubility issues. This is the main factor keeping novel drug compounds from reaching their full potential or the market. There are numerous methods to increase the solubility of drugs, including salt formation, solid dispersion, particle size reduction, nano suspension, use of surfactants, etc. From this article, it can be inferred that solid dispersion is a crucial strategy for increasing the bioavailability of medications with limited water solubility.

Maulvi, F.A *et al* discussed in addition to overcoming the drawbacks of earlier methods, solid dispersion (SD) provides a practical and affordable way to increase the bioavailability of medications that are poorly water-soluble. The selected kneading method was selected because it is economical, environmentally friendly, and prevents drug heat deterioration, the use of organic solvent, and the need for expensive equipment. Additionally, the solid dispersion powders made using this process and particular polymers are physico-chemically stable and simple to shape into tablet dosage form using the direct compression method.

A Mehta *et al* discussed that investigational tablet formulation and the commercial product were then characterized for their different physicochemical attributes, including weight variation, friability percentage, disintegration, and in vitro dissolution profiles. In order to rule out any interactions between the drug and the polymer, IR spectroscopy, XRD, and DSC revealed no change in the crystal structure of glimepiride. Glimepiride's ability to dissolve in solid dispersion products has significantly improved (>85% in 5 minutes). Moreover, solid dispersion-containing tablets showed a better

dissolving profile than commercial tablets. As a result, the solid dispersion technique can be utilized to enhance glimepiride disintegration.

A.Sharma *et al* discussed, according to their experiment, solvent evaporation was used to create solid PVP K30 dispersions. Drug-carrier interaction, drug content, solubility, and dissolution rate were all characterized for the physical mixture and solid dispersion (s). As the concentration of polymers rose, the solubility of the medication rose as well. In comparison to the pure drug and physical mixture, the dissolution rate for BCS Class II drug from its solid dispersion was significantly increased. The drug was in the amorphous form, as seen by the X-ray diffraction pattern and DSC thermograms, which supported the faster dissolution rate of solid dispersions. When stored under accelerated conditions, the solid dispersion remained stable. A promising method to increase the solubility and dissolution rate of carvedilol is the solid dispersion approach using PVP K30 as a carrier.

3.1. AIM AND OBJECTIVE:

The aim of this research work is to employ the solid dispersion technique for improving the bioavailability by enhancing the solubility and dissolution rate of poorly water soluble drug Glimepiride.

The aim of this research work can be broadly classified in following aims such as:

i. Enhancing the solubility profile of Glimepiride using Binary solid dispersion technique taking β-cyclodextrin as a carrier.
ii. Enhancing the solubility profile of Glimepiride using Ternary solid dispersion technique taking β -cyclodextrin and Polyvinylpyrrolidone K30 (PVP K30) as carriers.
iii. Optimization, characterization, solubility study and *in-vitro* dissolution study of the formulations.
iv. *in-vitro* dissolution study with commercially available immediate release (IR) tablet formulation.

3.2. PLAN OF WORK

i. Determination of absorbance maxima of Glimepiride
ii. Development of calibration curve of Glimepiride at pH 1.2, 6.8 and at neutral aqueous media using JASCO V- 550 double beam UV spectrophotometer.
iii. Preparation of binary solid dispersion of Glimepiride and Beta-cyclodextrin using solvent evaporation method, where ethanol was being used as a solvent for drug Glimepiride and purified water for Beta-cyclodextrin in difference ratios.
iv. Preparation of ternary solid dispersion of Glimepiride-Beta-cyclodextrin-PVPK30 using solvent evaporation method, where ethanol was being used as a solvent for drug Glimepiride and purified water for Beta-cyclodextrin and PVPK30 in different ratios.
v. Comparative solubility study of formulated binary and ternary solid dispersions and optimization.
vi. Identification of crystallinity of pure drug and amorphous state of optimized solid dispersion using X-Ray diffraction (XRD) technique.
vii. Drug excipients compatibility study using Fourier transform infrared spectroscopy (FTIR) after keeping the formulation under 40°C, 75% RH FOR 6 months.
viii. Determination of pre-formulation parameters of tablet formulation batches.
ix. Preparation of tablets by direct compression method using 10 station compression machine (Rimek minipress-1 Karnavati Engineering Ltd, Mehsana, Gujarat).
x. Evaluation of post compression parameters such as thickness, hardness, friability, uniformity of drug content, weight variation, disintegration time.
xi. Stability study of the optimized formulation.
xii. *in-vitro* dissolution study of prepared tablet batches and commercially available IR tablet formulation.

4. MATERIALS:

I. Glimepiride (GLIMI, M.W: 490.617 g/mol, received from Sigcap India/ Dr. Reddy's Lab as gift sample).
II. β-cyclodextrin (BCD, M.W: 1134.98 g/mol, HiMedia Laboratories Pvt.Ltd)
III. Polyvinylpyrrolidone K30 (PVP K30, M.W: 40,000).
IV. Microcrystalline cellulose (MCC, SRL Laboratories Pvt.Ltd)
V. Crosscarmellose sodium (was purchased from Loba chemicals Pvt.Ltd),
VI. Talcom powder (Talc), NICE chemical Pvt. Ltd, Kerala, India) Ethanol (99.9%, analytical AR grade)
VII. Purified water, all reagents and solvents were of analytical grade.

5. METHOD:

5.1. Preparation of standard solution:

Standard stock solution (100 µg/mL) was prepared by transferring 10 mg of glimepiride into a 100 mL volumetric flask and volume was made up to 100ml using pH 1.2 acidic buffer, and the mixture was sonicated to dissolve. Aliquots of these standard solution was transferred using A-grade bulb pipette into 100 mL volumetric flasks and made up to volume with the same media to get final concentration of 2.0 – 10.0 µg/ml.

5.2. Determination of absoption maxima:

Standard solution (8 µg/mL) was taken and scanned from 200 to 400 nm keeping pH 1.2 acidic media as blank using UV Visible spectrophotometer (JASCO V550).

5.3. Development of calibration curve at different aqueous pH:

Calibration curves for Glimepiride were prepared in pH 1.2, 6.8 and purified water, keeping 228nm as fixed wavelength in the concentration range of 2.0 – 10.0 µg/ml using UV Visible spectrophotometer (JASCO V550).

5.4. Determination of saturation solubility:

To determine saturation solubility, an excess amount of the drug GLIMI was added to 10 mL of pH 1.2 acidic buffer in stopper volumetric flasks. The solution was then sonicated for 10min at room temperature. The flask is then put into a water bath with a constant temperature of 37±0.5°C and shaken for 30 minutes at time intervals until equilibrium is reached. After that, the solutions were appropriately diluted and filtered through the Whatman filter paper of pore size 11µ. Using a UV spectrophotometer (JASCO V550), absorbance was measured in triplicate at 228 nm absorption maxima to determine the amount of drug dissolved in it [8] [9].

5.5. Preparation of physical mixture:

Binary physical mixtures (PM) of GLIMI were prepared by mixing glimepiride with the BCD in ratios of 1:1 w/w (PM1), 1:3 w/w (PM2), and 1:5 w/w (PM3) in a mortar until homogenous binary mixtures were obtained. The resulting mixture was then sieved using a 120-mesh screen. Similarly, ternary PMs were obtained by the same procedure using GLIMI, BCD, and PVPK30 in ratios of 1:3:0.5 w/w (PM4), 1:3:1 w/w (PM5), 1:3:1.5 w/w (PM6), 1:3:2 w/w (PM7). The powders were then stored in screw cap bottles at room temperature until further analysis [10].

5.6. Preparation of solid dispersion:

Both Binary and Ternary SDs were prepared by solvent evaporation technique using ethanol and distilled water in a 3:1 v/v ratio as a solvent where ethanol is utilized to solubilize the drug GLIMI as it is very poorly water-soluble and distilled water is utilized to solubilize water soluble carriers properly. To evaporate the solvent from the homogenous solution of drug and carriers heating was continued at 65±0.5°C with continuous stirring at 300rpm using a magnetic stirrer until the solvent is evaporated completely and a semisolid mass is obtained. Freeze-drying is performed (using Scanvac Coolsafe Lyophilizer) at -50°C temperature and a deep vacuum of 200mbar was applied for 24 hours for converting the semisolid mass of the drug and carrier to dry amorphous SD powder. Next, the amorphous SDs were sieved using a 120 mesh screen to obtain fine uniform SD powder [11] [12] [13].

(A) (B) (C)

Fig 1: Representation diagram of solid dispersion using solvent evaporation method.

A: Clear solution of GLIMI and carriers, B: Solvent evaporated by applying heat at 65±0.5°C with continuous stirring at 300rpm using a magnetic stirrer, C: Final solid dispersion obtained after complete removal of solvent by freeze-drying (lyophilisation)

5.6.1. Preparation of Binary SD by solvent evaporation technique using BCD:

Binary SDs of GLIMI and BCD were prepared in weight ratios of 1:1 w/w (SD1), 1:3 w/w (SD2), 1:5 w/w (SD3) using solvent evaporation method and ethanol-water system (3:1 v/v ratio) as solvent. After obtaining dried amorphous SD powder solubility study was performed to optimize the best binary SD batch out of these three different ratios [14][15].

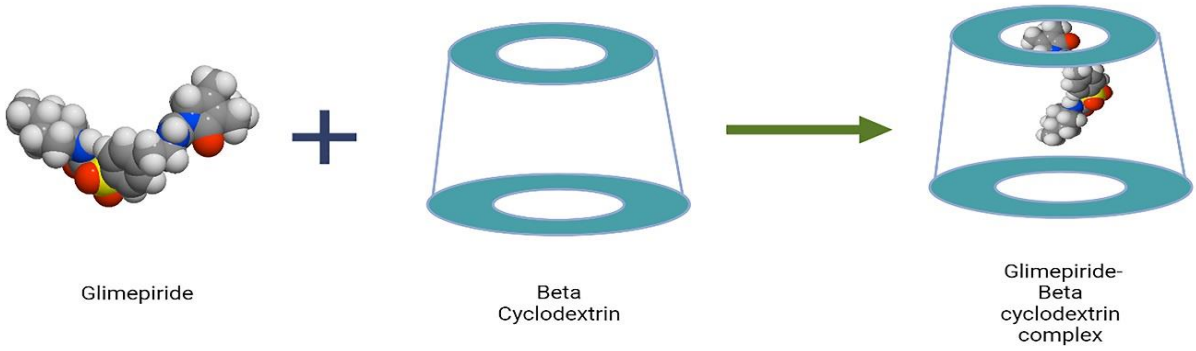


Fig 2: Graphical representation of Glimepiride-β-cyclodextrin Binary Solid Dispersion

5.6.2. Preparation of Ternary SD by solvent evaporation technique using BCD and PVPK30:

Ternary SDs were prepared by adding water-soluble carrier PVPK30 in the system with the previously optimized ratio of binary SD of GLIMI-BCD (SD2). At first, the drug was solubilized in ethanol in a beaker and the water-soluble carrier BCD and PVP K30 were solubilized in distilled water separately in two beakers to form three different homogenous solutions of GLIMI, BCD, and PVPK30. Next, with continuous heat and stirring these three solutions were mixed and the process continued until the complete removal of solvent, then freeze-drying, and sieving using a 120 mesh screen were performed to obtain a uniform fine powder of ternary SD. This process was performed for three different weight ratios of PVP K30 of 0.5% w/w (SD4), 1% w/w (SD5), 1.5% w/w (SD6), and 2% w/w (SD7) with the optimized binary solid dispersion batch [16][17][18][19]. **[Table 1]**

5.7. Solubility study:

Equivalent weight of each binary and ternary SD to 4mg glimepiride was added to 10mL pH 1.2 media and were sonicated for 1 hour at 25°C and then shaken in mechanical shaker for 48 hours. Samples were then filtered through pore size of 0.45µm, and the filtrates were suitably diluted and subjected to UV spectrophotometer analysis at a wavelength of 228 nm to determine the solubility [20].

5.8. Fourier-transform infrared spectroscopy (FTIR):

Perkin Elmer (Massachusetts, USA) spectrophotometer was used for the FTIR analysis, and the percentage transmittance was recorded between wave number of 4500 and 500 cm-1. The steps involved mixing powder samples of the pure drug GLIMI (A), a physical mixture of the drug and both carriers (B), SD5 (C), and SD5 with excipients (D) in Potassium bromide (KBr), and then compressing the mixture into a disc. The spectrum was acquired after the pellet was positioned in the path of the light. This test is intended to reveal any potential interactions between pure API and excipients and carriers.[21]

5.9. X-ray diffraction (XRD):

Using Rigaku Miniflex Diffractmeter (Rigaku corporation, Tokyo, Japan), the powder X-ray diffraction patterns of the pure drug (A1), SD5 (B1), and SD5 with excipients were recorded. The samples were scanned at a scanning rate of 4°/min over a 2 range of 5-70°. Although the natural state of the pure drug GLIMI is crystalline, in order to effectively produce SD and enhance solubility, it must be in an amorphous state. This transition from crystal to amorphous is identifiable by checking for sharp peaks in the crystal drug sample.[22]

5.10. Differential scanning calorimetry (DSC):

DSC study of pure drug GLIMI and SD5 with excipients were carried out by taking two to ten mg of sample into a hermetically sealed aluminum pan. In standard DSC mode nitrogen gas was purged into the chamber at 25 ml/min by heating each sample at 20° to 250°c at 10°c/min and the cooling process was also carried out at the same condition. Here, an empty aluminum pan was used as a reference [23].

5.11. Preparation of tablet formulation:

90 mg tablets of GLIMI were prepared by direct compression method using Microcrystalline cellulose (MCC) as a diluent, talc, and magnesium stearate as lubricant and anti-adherent for tablet compression. Compression was performed in ten station compression machine (Rimek Minipress-1, Karnavati Engineering Ltd. Mehsana, Gujarat) using a 7mm circular punch with a compression force of 5-6 kg/cm2. A total of four batches of tablets were formulated including two batches of pure drug using (Batch C) and without using Crosscarmellose sodium (Batch D) and other two batches using optimized SD5 with (Batch A) or without Crosscarmellose sodium (Batch B). Pure Glimepiride 4 mg and SD5 equivalent weight 4 mg of the drug were utilized to formulate the tablets. To manufacture immediate-release tablets, super-disintegrant Crosscarmellose sodium is used [24]. Except for talc and magnesium stearate, all of the ingredients were ground together in a pestle and mortar and then passed through

mesh number 60. After 5 minutes of mixing, talc and magnesium stearate were added. The SD5 formulation was selected because it had the best solubility profile. For batches, A and B, 4mg equivalent SD was taken, and for batches C and D, 4mg of pure GLIMI was taken for direct compression. **[Table 2]**

5.11.1. Pre-compression evaluation of tablet blend:

Before compressing the tablet various pre-compression properties were determined for tablet blends such as bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose. There can be multiple process parameters responsible for variations in characteristics of blend and that can hamper the quality of final tablet formulation [25]

5.11.1.1. Bulk density:

Bulk density is a property of powders, granules and other "divided solids, especially used in reference to mineral components (soil, gravel), chemical substances, (pharmaceutical) ingredients, food products or any other masses of corpuscular or particulate matter. It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter particle void volume, amd internal pore volume. It was measured by pouring the weighed powder from sieve no. #20 into a measuring cylinder and the initial bulk volume is recovered.

Bulk density is not an intrinsic property of a material; it can change depending on how the material is handled. For example, a powder poured into a cylinder will have a particular bulk density; if the cylinder is disturbed, the powder particles will move and unusually settle closer together, resulting in a higher bulk density. For this reason, the bulk density of powders is usually reported both as "freely settled" (or poured density) and tapped density (where the tapped density refers to the bulk density of the powder after a specified compaction process, usually involving vibration of the container.

Bulk density of the powder is calculated by

$$D_b = M/V_b$$

Where, M and V_b are the mass and volume of the powder respectively.

5.11.1.2. Tapped density:

It is the ratio of the total mass of the tapped volume of powder. Volume was measured by tapping the powder for 750 times and the tapped volume was recovered if the difference between these two is less than 2% and if the difference is more than 2%, tapping is continued for 1250 times and tapped volume is noted. The tapping was continued until the difference of the volume is less than 2%. It is expressed in g/ml and is given by

$$D_t = M/V_t$$

Where M and V_t is the mass and volume of the powder respectively.

5.11.1.3. Compressibility index:

Compression is an important parameter that a powder/ granule undergoes prior to compression. The compressibility index of the powder was determined by Carr's compressibility index (%);

$$[(D_t-D_b) \times 100]/ D_t$$

Carr's index	Type of flow
5-15	Excellent
15-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor

5.11.1.4. Hausner's ratio:

Hausner's ratio is an ease of index of powder flow. It is calculated by using following formula

Hausner's ratio= Tapped Density/ Bulk Density

Flow character	Hausner's ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very poor	1.46-1.59
Very very poor	>1.60

5.11.1.5. Angle of repose:

Funnel method was used to measure the angle of repose of powder. The accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel

just touches the apex of the heap of the powder. The diameter of the powder cone was measured and angle of repose was calculated using following equation.

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

Angle of repose	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

5.11.2. Evaluation of glimepiride tablets:

In-vitro disintegration time, friability, hardness, thickness, content uniformity and weight variation were all assessed for all produced tablets. Using the Roche friabilator, friability was calculated. Erwaka's digital hardness tester was used to measure hardness. Using a digital slide caliper, thickness and diameter were measured and *in-vitro* disintegration study was performed using Veego disintegration apparatus.

5.11.2.1. Hardness test:

Tablet hardness tester (erwaka digital hardness tester) was used to determine the crushing strength. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded.

5.11.2.2. Friability:

Roche Friabilator was used to assess the friability of tablets. Ten tablets were put into the friabilator after being originally weighed (W1). The friabilator was turned 100 times in 4 minutes at a speed of 25 rpm. It makes use of a drum with an internal diameter of 283 to 291mm and a depth of 36 to 40mm. The drum has a detachable side. A curved projection that curves from the center of the drum to the outside wall and has an interior radius between 75.5 and 85.5 mm tumbles the tablets with each rotation of the drum. The horizontal axis of a machine that revolves at a speed of 25 rpm is where the drum is mounted. Thus, the tablets turn and roll, slide, and fall with each turn. The tablets consequently roll or slide and land on the drum wall or against one another with each revolution. To determine the ultimate weight (W2) of the tablets, they were weighed once more.

Percentage weight loss= [(W1-W2)/W1] x 100

5.11.2.3. Thickness and diameter:

Thickness and diameter of the tablets were determined by using digital slide calipers. Test was carried out in triplicate to know the deviation of each batch.

5.11.2.4. Content uniformity:

For drug content uniformity calculation each batch's 10 randomly chosen tablets were weighed, with the average weight determined, and then ground into a fine powder in a mortar and pestle. The weight equivalent to 5 milligrams of GLIMI was calculated. With the use of a magnetic stirrer, the weighed amount was dissolved in 5 ml of dichloromethane in a separate 10 ml volumetric flask. The volume was then increased to 10 ml using methanol, and the solution was filtered. In a different volumetric flask, an aliquot of 0.2 ml of this solution was diluted with methanol to make 10 ml. At 228 nm, the content of tablet was measured using a UV spectrophotometer [26][27][28].

5.11.2.5. Weight variation:

Using an analytical weighing balance (Mode: AY-200, Shimadzu), 20 tablets from each formulation were individually weighed. Calculations were made to determine the average weights of each tablet batch and the standard deviation from the mean value. The weight variation's percentage difference must stay within allowed limits.

Tablet weight (IP/BP)	limit	Tablet weight (USP)
80mg or less	±10%	130mg or less
80 to 250 mg	±7.5%	130mg to 324mg
>250 mg	±5%	More than 324

5.11.2.6. in-vitro disintegration:

in-vitro disintegration study was carried out using veego digital disintegration apparatus, it has Six plastic tubes with the top and bottoms open are held on a basket rack. A screen with a 10-mesh mesh

covers the bottom. At 37 °C, a pH 1.2 buffer solution is submerged in the rack. It moves at a set pace up and down. One tablet was put into each tube, and it was seen that they all broke apart and passes through the screen and this particular time point was recorded.

5.11.3. *In-vitro* dissolution study:

Using USP type II dissolution apparatus and 900 ml of pH 1.2 buffer as the dissolution medium, every batch of formulation underwent an in-vitro dissolution study. The temperature was maintained at 37°±0.5°C and 50 rpm. At 5, 10, 20, 30, 45, and 60 minutes, 5 ml of aliquots were taken out and replenished with 5 ml of fresh, pH 1.2 dissolving media. The obtained samples were then analyzed at 228nm using a UV-visible spectrophotometer (JASCO V550) using the same pH 1.2 buffer as the blank after the suitable dilution (if required). At various time intervals, the release profile data was analyzed for cumulative Percentage dissolved.

The drug dissolution studies were carried out in triplicate (n=3) for batches of pure drug glimepiride tablet formulation (Batch C and D) and batches of solid dispersion (SD5) tablet batches (Batch A and B), where Batch B and D are formulated without super-disintegrant (Crosscarmellose sodium). The same dissolution study was also carried out for marketed immediate release glimepiride tablets for a better comparative result. [29][30][31]

5.11.4. Stability study:

Stability studies were carried out as per the ICH guidelines. The excipient to be used were placed inside sealed 40ml HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) at 40°±0.5°C/ 75±5% RH for 6 months. The sample were withdrawn and evaluated for the content and *in-vitro* release at pre-determined time intervals (1 month, 3 month and 6 month). The variations are analysed and compared with the freshly prepared formulation.

5.11.5. Drug release kinetics study:

The drug release pattern from the formulation was measured by plotting the in-vitro drug release studies in various kinetic models such as zero order (percentage cumulative drug released versus time), first order(logarithmic value of cumulative amount of drug remained versus time), Higuchi model(cumulative amount of drug released versus square root of time), Korsmeyer-Peppas model(logarithmic value of cumulative amount of drug released versus logarithmic value of time) and Hixon-Crowell model(cube root of percentage drug remained versus time. The linearity of the plots was evaluated from the calculated R^2 values.

5.11.5.1. Zero order:

Zero order model drug dissolution from dosage forms that do not disintegrate and release the drug slowly can be represented by the equation:

$$Q_t = Q_0 + K_{0t}$$

Where Q_t is the amount of drug dissolved in time t,

Q_0 is the initial amount of the drug in solution (most times, $Q_0 = 0$) and,

K_0 is the zero-order release constant expressed in units of concentration/ time.

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted as cumulative percentage drug released versus time.

This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal system, as well as matrix tablet with low soluble drugs in coated forms, osmotic system etc.

5.11.5.2. First order:

This model has also been used to describe absorption and/ or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$dC/ dt = -Kc$$

Where, K is the first order rate constant, the above equation can be expressed as

$$\log C = \log C0 - (Kt/ 2.303)$$

Where C0 is the initial concentration of drug, K is the first order rate constant, and t is the time.

The data obtained are plotted as log cumulative percentage undissolved drug versus time, which yield a straight line with a slope of –K/ 2.303.

This relationship can be used to describe the drug dissolution in pharmaceutical dosage form such as those containing water soluble drugs in porous matrices.

5.11.5.3. Higuchi model:

In 1963, Higuchi developed several theoretical models to study the release of water soluble and poorly water soluble drugs incorporated in semi-solid/solid matrices.

Mathematical expression were obtained for drug particle dispersed in a uniform matrix behaving as the diffusion media. It is used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms.

$$Q= K_b t^{1/2}$$

Where K_b is the release rate constant for Higuchi model.

5.11.5.4. Korsmeyer peppas model:

In 1983, Korsmeyer peppas *et al*. developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t) which can be described as,

$$\ln(Qt/Q\infty)= \ln K+ n \ln t$$

Where, $(Qt/Q\infty)$ is the fraction of drug release at time t and K is the rate constant comprising the structural and geometric characteristics of the formulation and n is the release exponent.

For the determination of exponent n, the portion of the release curve where $Qt/Q\infty < 0.6$ should only be used. This model can used to analyse the release of pharmaceutical dosage forms when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

N= 0.45 indicates Fickian diffusion, 0.45<n<1 indicates anomalous transport or non Fickian diffusion (both diffusion and errosio0, n= or> 1 indicates case-II transport (erosion of the polymeric chain)

5.11.5.5. Hixson and Crowell model:

Hixson and Crowell were developed a model in 1931. When there is an alteration in the size (diameter) of the particles and surface area of the tablets there occurs the delivery of the drug from the system. Hixson and Crowell cube root law explains the release of drugs from the system where there is change in diameter of the particles and surface area of the particles [26]. The Hixson Crowell model states that the drug particles and dissolution rate are assumed as the rate of drug release is limited and not by the diffusion [34]. Hence, this model results in proportion between the cube root of its volume and surface area of particle. It is expressed by an equation,

$$C_0^{1/3}- C_t^{1/3}= Kt$$

Where,
C_t= Amount of drug released in time t
C_o= Initial amount of drug in the tablet
K= Rate constant

6. INFORMATION ABOUT DRUG, EXCIPIENTS AND EQUIPMENTS

6.1. Drug information:

First introduced in 1995, glimepiride is a member of the second generation sulfonylurea (SU) drug class used for the management of type 2 diabetes mellitus (T2DM) to improve glycemic control. Type 2 diabetes is a metabolic disorder with increasing prevalence worldwide. It is characterized by insulin resistance in accordance with progressive beta cell failure and long term micro and macro vascular complications that lead to co-morbidities and mortalities. Sulfonylureas are one of the secretagues widely used for the management of type 2 diabetes mellitus to lower blood glucose level. The main effect of SU's is thought to be effective when residual pancreatic beta cells are present, as they work by stimulating the release of insulin from the pancreatic beta cells and they are also thought to exert extra-pancreatic effects, such as insulin mediated peripheral glucose uptake.

Glimepiride works by stimulating the secretion of insulin granules from pancreatic islet beta cells by blocking ATP sensitive potassium channel (K_{ATP} channels) and causing depolarization of the beta cells. Compared to glipizide, another second SU drug, glimepiride has a longer duration of action. It is sometime classified as 3rd generation SU because it has larger substitutions than other 2nd generation SUs. Compared to other SUs, glimepiride was associated with lower risk of developing hypoglycaemia and weight gain in clinical trial s as well as fewer cardiovascular effects than other SUs due to minimal effects on ischemic preconditioning of cardiac myocytes. It is effective in reducing fasting plasma glucose, postprandial glucose and glycosylated haemoglobin levels and it considered to be a useful, cost effective treatment option for managing type 2 diabetes mellitus. Glimepiride was approved by the food and drug administration (FDA) in the US in 1995 for the treatment of T2DM.

CAS Id: 10238-21-8

IUPAC name:

3-Ethyl-4-methyl-N-[2-(4-{[(trans-4-methylcyclohexyl)carbamoyl]sulfamoyl}phenyl)ethyl]-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide

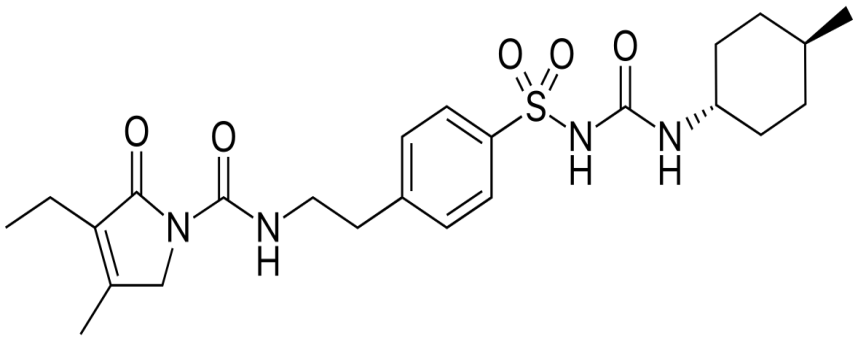
Physical state: Solid.

Melting point: 207°C

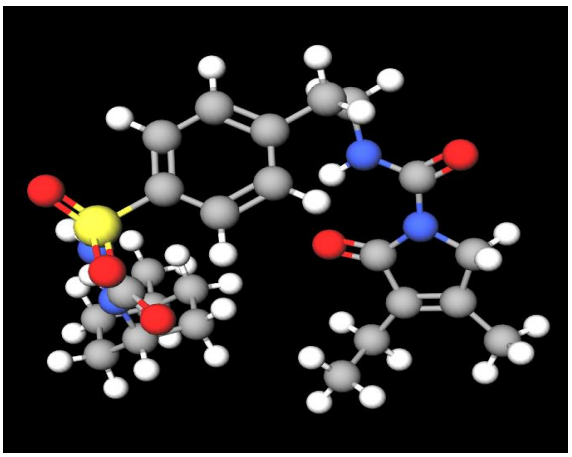
Water solubility: 0.0075 mg/ml

Octanol/ water partition coefficient: logP3.5

Structure:



2D Structure of Glimepiride

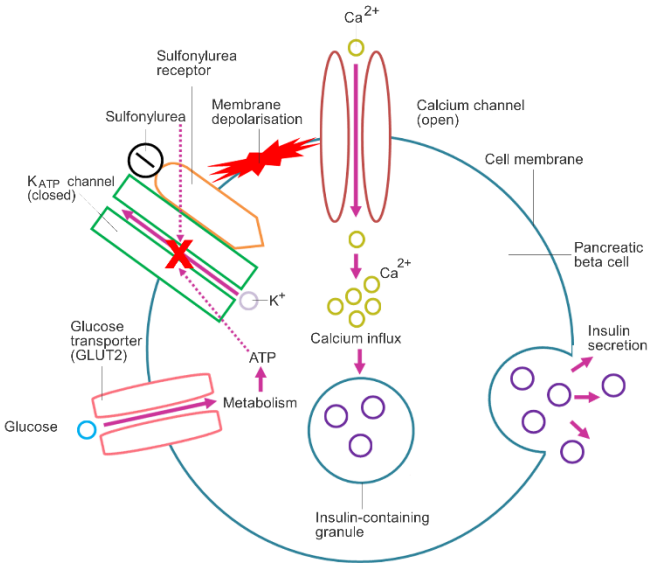


3D structure of Glimepiride

Mechanism of action:

ATP-sensitive potassium channels on pancreatic beta cells that are gated by intracellular ATP and ADP. The hetero-octomeric complex of the channel is composed of four pore-forming Kir6.2 subunits and four regulatory sulfonylurea receptor (SUR) subunits. Alternative splicing allows the formation of channels composed of varying subunit isoforms expressed at different concentrations in different tissues. In pancreatic beta cells, ATP-sensitive potassium channels play a role as essential metabolic sensors and regulators that couple membrane excitability with glucose-stimulated insulin secretion (GSIS). When there is a decrease in the ATP: ADP ratio, the channels are activated and open, leading to K+ efflux from the cell, membrane hyperpolarization, and suppression of insulin secretion. In contrast, increased uptake of glucose into the cell leads to elevated intracellular ATP:ADP ratio, leading to the closure of channels and membrane depolarization. Depolarization leads to activation and opening of the voltage-dependent Ca2+ channels and consequently an influx of calcium ions into the cell. Elevated intracellular calcium levels causes the contraction of the filaments of actomyosin

responsible for the exocytosis of insulin granules stored in vesicles. Glimepiride blocks the ATP-sensitive potassium channel by binding non-specifically to the B sites of both sulfonylurea receptor-1 (SUR1) and sulfonylurea receptor-2A (SUR2A) subunits as well as the A site of SUR1 subunit of the channel to promote insulin secretion from the beta cell.



Mechanism of action of Glimepiride

Pharmacodynamics:

Glimepiride stimulates the secretion of insulin granules from the pancreatic beta cells and improves the sensitivity of peripheral tissues to insulin to increase peripheral glucose uptake, thus reducing plasma blood glucose levels and glycated hemoglobin (HbA1C) levels. A multi-center, randomized, placebo-controlled clinical trial evaluated the efficacy of glimepiride (1–8 mg) as monotherapy titrated over 10 weeks compared with placebo in T2DM subjects who were not controlled by diet alone. In this study, there was a reduction in fasting plasma glucose (FPG) by 46 mg/dL, post-prandial glucose (PPG) by 72 mg/dL, and HbA1c by 1.4% more than the placebo. In another randomized study comprising of patients with T2DM receiving either placebo or one of the three doses (1, 4, or 8 mg) of glimepiride during a 14-week study period, all glimepiride regimens significantly reduced FPG, PPG, and HbA1c values ($P < 0.001$) compared to placebo by the end of the study period. The 4- and 8-mg doses of glimepiride were more effective than the 1-mg dose; however, the 4-mg dose provided a nearly maximal antihyperglycemic effect.

Half-life:

The elimination half-life of glimepiride is approximately 5 to 8 hours, which can increase up to 9 hours following multiple doses.

Clearance:

A single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, dose proportionality (4 and 8 mg) study in patients with type 2 diabetes (T2D) were performed. In these studies, the total body clearance was 52.1 +/- 16.0 mL/min, 48.5 +/- 29.3 mL/min in patients with T2D given a single oral dose, and 52.7 +/- 40.3 mL/min in patients with T2D given multiple oral doses. Following intravenous dosing in healthy subjects, the total body clearance was 47.8 mL/min.

Toxicity:

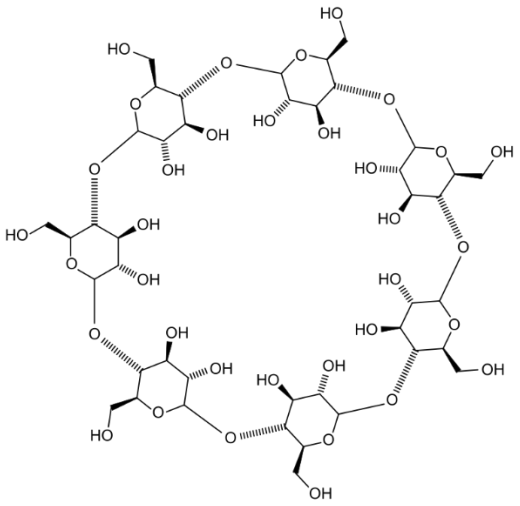
The oral LD50 value in rats is > 10000 mg/kg. The intraperitoneal LD50 value in rats is reported to be 3950 mg/kg. Although glimepiride is reported to have fewer risks of hypoglycemia compared to other sulfonylureas such as glyburide, over dosage of glimepiride may result in severe hypoglycemia with coma, seizure, or other neurological impairment may occur. This can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary since hypoglycemia may recur after apparent clinical recovery.

In a study of rats given doses of up to 5000 parts per million (ppm) in complete feed for 30 months, there were no signs of carcinogenesis. Meanwhile, the administration of glimepiride at a dose much higher than the maximum human recommended dose for 24 months in mice resulted in an increase in benign pancreatic adenoma formation in a dose-related manner, which was thought to be the result of chronic pancreatic stimulation. Glimepiride was non-mutagenic in *in vitro* and *in vivo* mutagenicity studies. In male and female rat studies, glimepiride was shown to have no effects on fertility.

6.2. Excipients information:

6.2.1. β-Cyclodextrin:

In β-cyclodextrin, the seven glucose subunits are linked end to end via α-1,4 linkages. The result has the shape of a tapered cylinder, with seven primary alcohols on one face and fourteen secondary alcohol groups on the other. The exterior surface of cyclodextrins is somewhat hydrophilic whereas the interior core is hydrophobic.



Structure of β-Cyclodextrin

Physical properties:

β-Cyclodextrin exists as a white (colorless) powder or crystals. The density of its saturated hydrate crystal (βCD·12H_2O) is 1.46 g/cm^3. β-Cyclodextrin is moderately soluble in water and glycerin; well soluble in dimethyl sulfoxide, dimethylformamide, pyridine, HFIP, and ethylene glycol; and insoluble in ethanol and acetone.

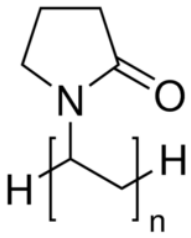
Synthesis of cyclodextrins:

Cyclodextrins are prepared by enzymatic treatment of starch.Commonly cyclodextrin glycosyltransferase (CGTase) is employed along with α-amylase. First starch is liquified either by heat

treatment or using α-amylase, then CGTase is added for the enzymatic conversion. CGTases produce mixtures of cyclodextrins, thus the product of the conversion results in a mixture of the three main types of cyclic molecules, in ratios that are strictly dependent on the enzyme used: each CGTase has its own characteristic α:β:γ synthesis ratio. Purification of the three types of cyclodextrins takes advantage of the different water solubility of the molecules: β-CD which is poorly water-soluble (18.5 g/L or 16.3mM) (at 25C) can be easily retrieved through crystallization while the more soluble α- and γ-CDs (145 and 232 g/L respectively) are usually purified by means of expensive and time consuming chromatography techniques. As an alternative a "complexing agent" can be added during the enzymatic conversion step: such agents (usually organic solvents like toluene, acetone or ethanol) form a complex with the desired cyclodextrin which subsequently precipitates. The complex formation drives the conversion of starch towards the synthesis of the precipitated cyclodextrin, thus enriching its content in the final mixture of products. Wacker Chemie AG uses dedicated enzymes, that can produce alpha-, beta- or gamma-cyclodextrin specifically. This is very valuable especially for the food industry, as only alpha- and gamma-cyclodextrin can be consumed without a daily intake limit.

6.2.2. PVPK30:

Povidone (polyvinylpyrrolidone, PVP) is used in the pharmaceutical industry as a synthetic polymer vehicle for dispersing and suspending drugs. It has multiple uses, including as a binder for tablets and capsules, a film former for ophthalmic solutions, to aid in flavoring liquids and chewable tablets, and as an adhesive for transdermal systems.



Povidone (polyvinylpyrrolidone, PVP K30)

Povidone k30 has the molecular formula of $(C6H9NO)_n$ and appears as a white to slightly off-white powder. Povidone formulations are widely used in the pharmaceutical industry due to their ability to dissolve in both water and oil solvents. The k number refers to the mean molecular weight of the povidone. Povidones with higher K-values (i.e., k90) are not usually given by injection due to their high molecular weights. The higher molecular weights prevent excretion by the kidneys and lead to accumulation in the body. The best-known example of povidone formulations is povidone-iodine, an important disinfectant.

Property	Description
Description	Fine, white to off white odourless, very hygroscopic, amorphous powder.
Molecular formula	$(C_6H_9NO)_n$
Molecular weight	2500–30,00,000 Da
CAS Number	9003-39-8
Non-proprietary name	Povidone (BP, USP, JP, PhEur)
Synonyms	Povidone, PVP, Polyvidone, Plasdone, Kollidon, Poly [1-(2-oxo-1-pyrrolidinyl) ethylene], 1-vinyl-2-pyrrolidinone polymer, 2-pyrrolidinone-1-ethenyl- homopolymer.
IUPAC	1-ethenylpyrrolidin-2-one
Melting point	Softens at 150 °C and decomposes after 180 °C.
pH	3-7 (varies with K-value and concentration of solution)
Solubility	Soluble in water, ethanol, methanol, chloroform, acids, and amines. Insoluble in ethers, hydrocarbons, some esters, some ketones, and mineral oil.
K-value range	10–120
Chemistry	PVP polymer is comprised of functional groups CO, C–N, CH_2 with a strong hydrophilic moiety – pyrrolidone and a strong hydrophobic moiety – alkyl group. The highest solubility of PVP in both water and non-aqueous solvents is attributed to the existence of highly polar amide moiety in pyrrolidone ring and a polar methylene and methine groups within the ring and along its backbone. The hydrophobic carbon chains show a steric hindrance effect.
Compatibility	Compatible in solution with a wide range of hydrophilic and hydrophobic, natural and synthetic resins; inorganic salts and other chemicals. PVP forms adducts in solution with sodium salicylate, salicylic acid, sulfathiazole, phenobarbital, tannin, and some other compounds. Due to the complex nature of thimerosal with povidone, the preservative action of the former agent is adversely affected.
Stability and storage	Chemically stable in dry form. Can be stored in ordinary conditions but in a tightly closed container as it is highly hygroscopic

6.2.3. Microcrystalline cellulose (MCC):

Microcrystalline cellulose (C6H10O5)n is refined wood pulp. It is a white, free-flowing powder. Chemically, it is an inert substance, is not degraded during digestion and has no appreciable absorption. In large quantities it provides dietary bulk and may lead to a laxative effect.

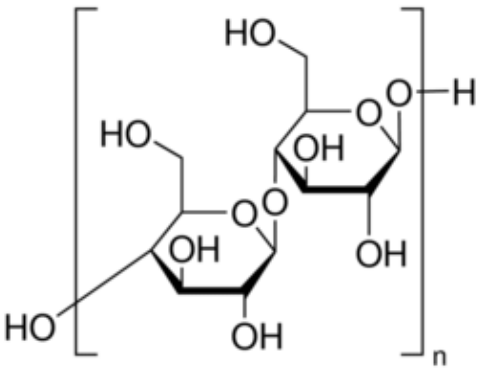
Microcrystalline cellulose is a commonly used excipient in the pharmaceutical industry. It has excellent compressibility properties and is used in solid dose forms, such as tablets. Tablets can be formed that are hard, but dissolve quickly. Microcrystalline cellulose is the same as cellulose, except that it meets USP standards.

It is also found in many processed food products, and may be used as an anti-caking agent, stabilizer, texture modifier, or suspending agent among other uses. According to the Select Committee on GRAS Substances, microcrystalline cellulose is generally regarded as safe when used in normal quantities.

Structure:

A naturally occurring polymer, it is composed of glucose units connected by a 1-4 beta glycosidic bond. These linear cellulose chains are bundled together as microfibril spiralled together in plant cell walls.

Each microfibril exhibits a high degree of three-dimensional internal bonding resulting in a crystalline structure that is insoluble in water and resistant to reagents. There are, however, relatively weak segments of the microfibril with weaker internal bonding. These are called amorphous regions; some argue that they are more accurately called dislocations, because of the single-phase structure of microfibrils. The crystalline region is isolated to produce microcrystalline cellulose.



Microcrystalline cellulose

Applications as a pharmaceutical excipient

Microcrystalline Cellulose is the most common binding and filling agent used to manufacture solid dose foods and pharmaceuticals. This is due to its compatibility and strength when turned in to a tablet whilst also dissolving easily when digested. It also acts great as a bulking agent if needed to increase the weight of formulation.

It's used as a disintegrant in formulations and speeds up the formed tablets deterioration allowing to work faster. MCC is directly compressible meaning it can be pressed into a tablet directly without any other ingredient, a huge benefit to this is that it does not have to be granulated which makes the encapsulating process more streamlined and efficient. MCC is safe to consume in normal quantities and is widely used as an excipient for its all around versatility

6.2.4. Talcum powder (Talc):

Magnesium silicate (MgSiO3) when hydrated is most commonly known as "talc". In the pharmaceutical industry it is used as an anticaking agent to improve powder flow in tablet compression. Talc is used cosmetically in talcum and baby powder as an adsorbent. Talc has been reported to be used in some food products, and is generally recognized as safe by the FDA.

Natural talc contains asbestos, a substance that may lead to lung cancer. However, talcum products used in cosmetics have been free of asbestos since the 1970s. Some studies have reported small increases in ovarian cancer with the use of asbestos-free talcum powder, but studies are conflicting and the results are not definitive. The American Cancer Society suggests corn starch-based cosmetics might be an alternative in those concerned about talc use.

6.2.5. Magnesium stearate:

Magnesium stearate [Mg(C18H3502)2 or octadecanoic acid] is a solid, white powder at room temperature. It is a FDA-approved inactive ingredient commonly used in the pharmaceutical industry as a lubricant and release agent in the manufacture of tablet, capsule, and powder dosage forms.

Magnesium stearate is generally recognized as safe by the FDA. Magnesium stearate exists as a salt form and is useful for it's lubricating properties for capsules and tablets in industry. It is used to help prevent pharmaceutical ingredients from adhering to industry equipment. Magnesium stearate may be derived from both plant and animal sources.

6.2.6. Crosscarmellose sodium

Croscarmellose sodium, or sodium CMC, is a cross-linked polymer of carboxymethylcellulose sodium. It appears as white, fibrous, free-flowing powder, and is used commonly as an FDA-approved disintegrant in pharmaceutical manufacturing. Disintegrants facilitate the breakup of a tablet in the intestinal tract after oral administration. Cross-linking allows enhanced bioavailability of the drug through superior drug dissolution. Without a disintegrant, tablets may not dissolve appropriately and may effect the amount of active ingredient absorbed, thereby decreasing effectiveness.

According to the FDA Select Committee on GRAS food substances, carboxymethylcellulose sodium is virtually unabsorbed. Caroxymethylcellulose sodium is generally regarded as safe when used in normal quantities.

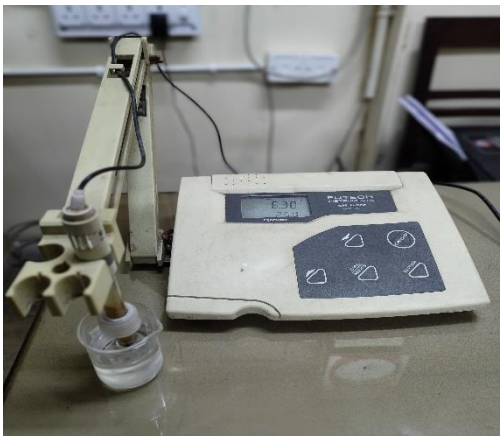
6.3. Equipments information:

Equipment	Manufacturer	Application
Weighing balance	Precisa	Measuring weight of powder sample.
UV Visible spectrophotometer	Model: JASCO V550	Quantitative determination of amount of UV or visible light absorbed by a compound, allowing to determine concentration of unknown sample by the principle of Beer-lambert law.
Magnetic stirrer	REMI	Mixing of solvent using constant temperature and rotation, allowing to evaporate solvent slowly from solvent system with continuous stirring.
Lyophilizer	Scanvac coolsafe Lyophilizer	Removing water from a sample after it is frozen and placed under vacuum, allowing the ice to change directly from solid to vapour without passing through liquid phase.
Digital pH meter	EUTECH instrument	Measuring pH of liquid sample accurately.
Tablet compression machine	REMIK	Compressing powder or granules into tablet.

Digital hardness tester	Veego	Determining tablet hardness point accurately.
Friabilator	Electrolab roche friabilator	Determining durability of tablets during transit.
Disintegration apparatus	Veego	Determining *In-vitro* breakdown time required for tablet formulation
Dissolution apparatus (USP Type II)	Labindia	Determining *in-vitro* time required for a formulation to dissolve in a particular media and to form solution.
Forier transform infrared spectrophotometer	Perkin Elmer, USA	Determining characteristic peaks of a compound by allowing the compound changing dipole moment by absorbing IR radiation.
X-Ray diffraction	Rigaku corporation	Determining crystalline or amorphous state of a sample by constructive interference of monochromatic X-Ray with the sample.
Differential scanning calorimetry	Perkin Elmer, USA	Measuring how physical properties of a sample changes along with temperature against them.
Stability chamber	Osworld	Testing of stability of a pharmaceutical product according to ICH guideline by using exaggerated storage condition.

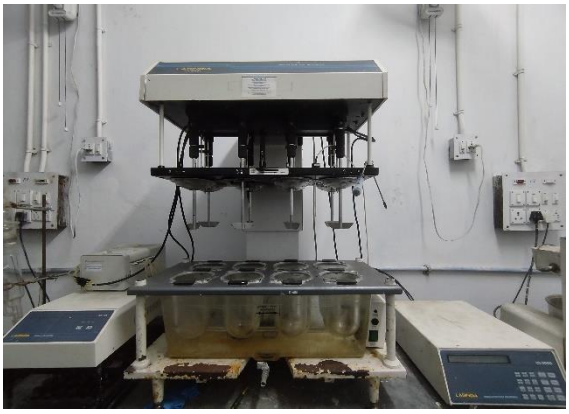
- **Some instruments that were used during the experiments**

Weighing machine: Precisa



Digital pH meter

JASCO V550 UV VIS Spectrophotometer



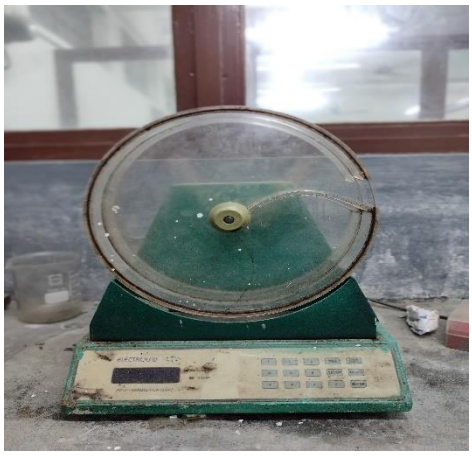
Labindia USP Type II Dissolution apparatus with Auto-sampling

REMI magnetic stirrer

Digital hardness tester

OSWORLD Accelerated stability chamber

VEEGO disintegration test apparatus



Roche Friabilator

Tablet punching machine: REMIK

Hot air oven

Scanvac coolsafe lyophilizer

7. TABLES AND GRAPHS

7.1. Tables:

Table 1: Formulation of solid dispersion

Sl.no.	Formulation code	Glimepiride:β-cyclodextrin (w/w)	Glimepiride:β-cyclodextrin: PVPK30 (w/w/w)
1	SD1	1:1	-
2	SD2	1:3	-
3	SD3	1:5	-
4	SD4	-	1:3:0.5
5	SD5	-	1:3:1
6	SD6	-	1:3:1.5
7	SD7	-	1:3:2

Table 2: Formulation design of Glimepiride tablets of pure API and solid dispersion of Glimepiride.

Ingredients	Batch A	Batch B	Batch C	Batch D
Glimepiride	-	-	4mg	4mg
SD5	20mg	20mg	-	-
MCC	62mg	66mg	78mg	82mg
Crosscarmellose sodium	4mg	-	4mg	-
Talc	2.4mg	2.4mg	2.4mg	2.4mg
Magnesium stearate	1.6mg	1.6mg	1.6mg	1.6mg
Total weight	90mg	90mg	90mg	90mg

Table 3: Solubility study of Glimepiride, Glimepiride physical mixture and glimepiride solid dispersion in acidic pH (pH 1.2)

Sl.no	Formulation code	Carrier used	Drug carrier ratio	Solubility in pH 1.2 (mcg/ml)
1	GLIMEPIRIDE	-	-	1.1269±0.0182
2	PM1	GLIMI:BCD	1:1	1.3392±0.3577
3	PM2	GLIMI:BCD	1:3	1.3829±0.3932
4	PM3	GLIMI:BCD	1:5	1.4026±0.4278
5	PM4	GLIMI:BCD:PVPK30	1:3:0.5	1.6191±0.3254
6	PM5	GLIMI:BCD:PVPK30	1:3:1	2.3560±0.3253
7	PM6	GLIMI:BCD:PVPK30	1:3:1.5	1.6960±0.4157
8	PM7	GLIMI:BCD:PVPK30	1:3:2	1.4291±0.1216
9	SD1	GLIMI:BCD	1:1	1.9663±0.0407
10	SD2	GLIMI:BCD	1:3	3.4993±0.0561
11	SD3	GLIMI:BCD	1:5	4.3862±0.1706
12	SD4	GLIMI:BCD:PVPK30	1:3:0.5	3.7259±0.1109
13	SD5	GLIMI:BCD:PVPK30	**1:3:1**	**5.1126±0.1004**
14	SD6	GLIMI:BCD:PVPK30	1:3:1.5	4.6750±0.0627
15	SD7	GLIMI:BCD:PVPK30	1:3:2	4.6195±0.0622

* n = 3; values are expressed as mean ± SD

Table 4: Characterization of tablet blends:

Formulation batch	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
A	0.380±0.005	0.395±0.002	1.04	4.21	22.34±0.01
B	0.412±0.003	0.426±0.004	1.03	2.66	23.73±0.02
C	0.406±0.001	0.417±0.002	1.02	2.44	24.08±0.01
D	0.396±0.002	0.413±0.001	1.044	4.55	25.28±0.01

* n = 3; values are expressed as mean ± SD

Table 5: Characterization of Glimepiride tablet formulations:

Formulation batch	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Weight (mg)	Friability (%)	In-vitro disintegration time (min)	Content uniformity
A	5.58±0.01	3.12±0.01	5.58±0.01	89.21±0.01	0.46	5.33±0.577	4.04±0.005
B	5.54±0.01	3.13±0.005	5.65±0.01	90.15±0.01	0.55	12±1	4.23±0.01
C	5.54±0.01	3.15±0.01	6.05±0.01	90.28±0.02	0.66	6±1	3.95±0.02
D	5.55±0.01	3.14±0.02	5.32±0.01	89.77±0.01	0.48	13±1	4.02±0.005

* n = 3; values are expressed as mean ± SD

Table 6: Percentage cumulative release of tablet formulations

Formulation	Percentage cumulative drug dissolved (%)						
	0 (min)	**5 (min)**	**10 (min)**	**20 (min)**	**30 (min)**	**45(min)**	**60(min)**
Marketed formulation	0	15.78±0.003	35.05±0.032	44.665±0.029	52.1519±0.0881	71.608±0.0873	84.976±0.274
Batch A	0	21.6±0.022	45.94±0.034	67.44±0.608	84.713±0.609	94.691±0.614	99.915±0.621
Batch B	0	10.866±0.008	17.05±0.008	24.87±0.009	35.26±0.015	53.14±0.089	69.75±0.589
Batch C	0	5.92±0.1931	10.621±0.25	16.73±0.35	21.51±0.82	27.86±0.83	33.86±0.82
Batch D	0	1.83±0.32	3.5±0.301	8.105±0.277	11.16±0.308	20.03±0.31	26.37±0.349

* n = 3; values are expressed as mean ± SD

Table 7: Stability and compatibility study of Glimepiride and carriers

		Time period			
Formulation	**Physical appearance**	**Initial condition**	**After 2 months**	**After 4 months**	**After 6 months**
Drug+ BCD	Physical state	Solid, powder	No change	No change	**No change**
	Colour	White	No change	No change	**No change**
DRUG+ PVPK30	Physical state	Solid, powder	No change	No change	**No change**
	Colour	White	No change	No change	**No change**

Table 8: Stability and compatibility study of optimized solid dispersion (SD5) and excipients:

			Time period		
Formulation	**Physical appearance**	**Initial condition**	**After 2 months**	**After 4 months**	**After 6 months**
Batch A	Nature	Solid state, powder	No change	No change	**No change**
	colour	White	No change	No change	**No change**
Batch B	Nature	Solid state, powder	No change	No change	**No change**
	colour	White	No change	No change	**No change**
Batch C	Nature	Solid state, powder	No change	No change	**No change**
	colour	White	No change	No change	**No change**
Batch D	Nature	Solid state, powder	No change	No change	**No change**
	colour	White	No change	No change	**No change**

Table 9: Correlation coefficients (R^2) of different drug release kinetics study:

Formulation	Correlation coefficient (R^2)				
	Zero order	**First order**	**Higuchi model**	**Korsmeyer-Peppas model**	**Hixon-Crowell model**
Marketed formulation	0.939	0.9765	0.9832	0.9265	0.9823
Batch A	0.8485	0.9799	0.9705	0.9671	0.9944
Batch B	0.9933	0.971	0.9356	0.8161	0.9849
Batch C	0.9673	0.9849	0.9844	0.9081	0.9797
Batch D	0.994	0.9885	0.8829	0.7382	0.9907

7.2. Diagrams and Graphs

Fig 3: Absorption maxima of Glimepiride in pH 1.2

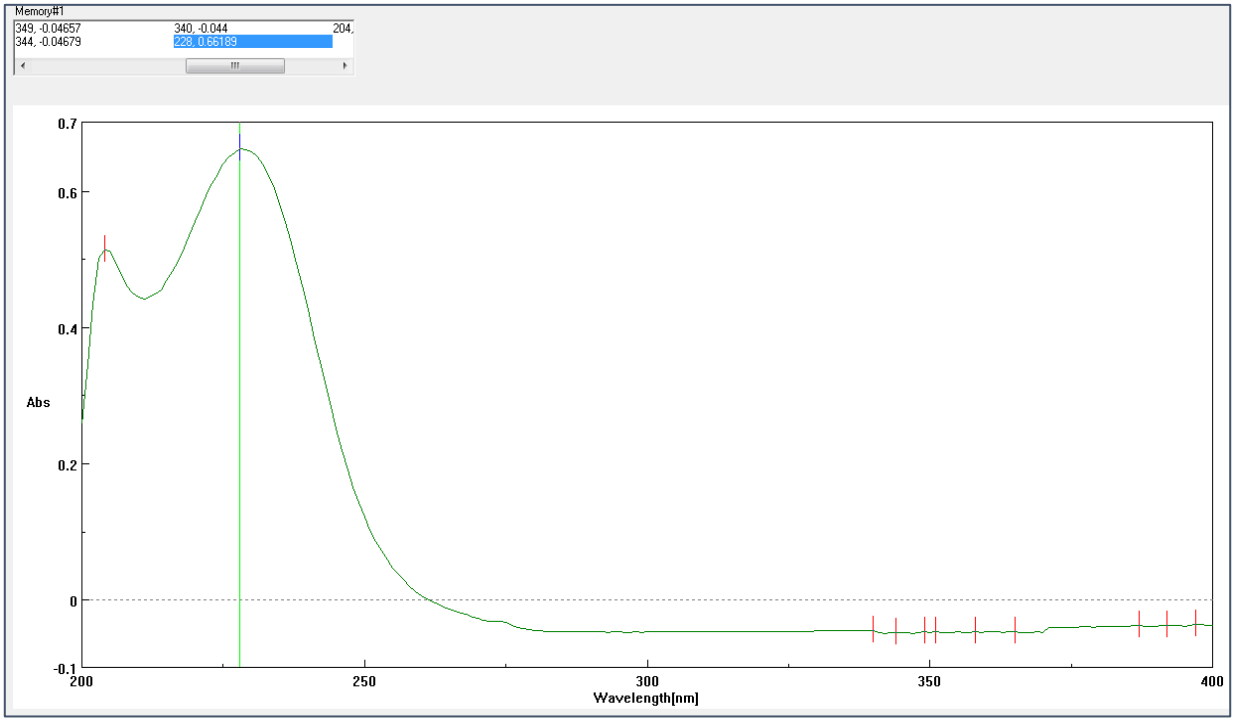
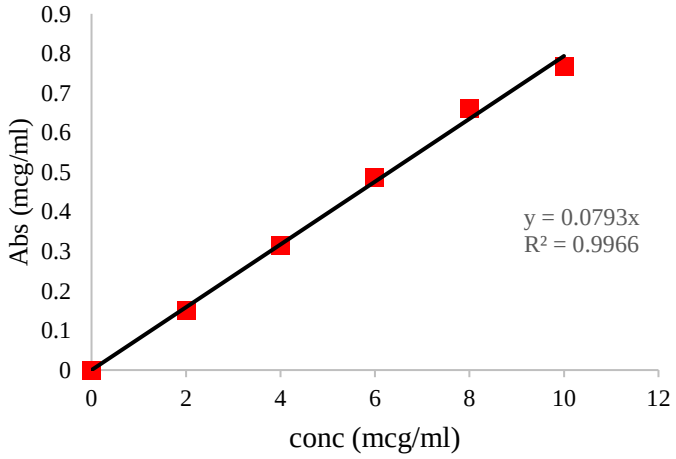
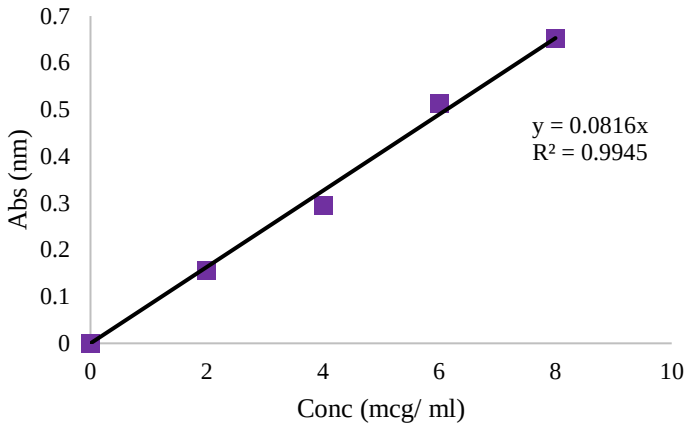


Fig4: Calibration curve at 0.1N HCl (pH 1.2)



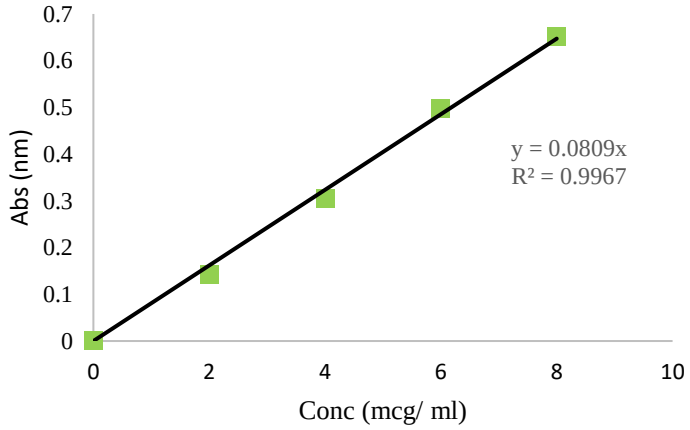
Conc (mcg/ml)	Abs(nm)
0	0
2	0.152
4	0.315
6	0.487
8	0.661
10	0.768

Fig 5: Calibration curve at pH 6.8



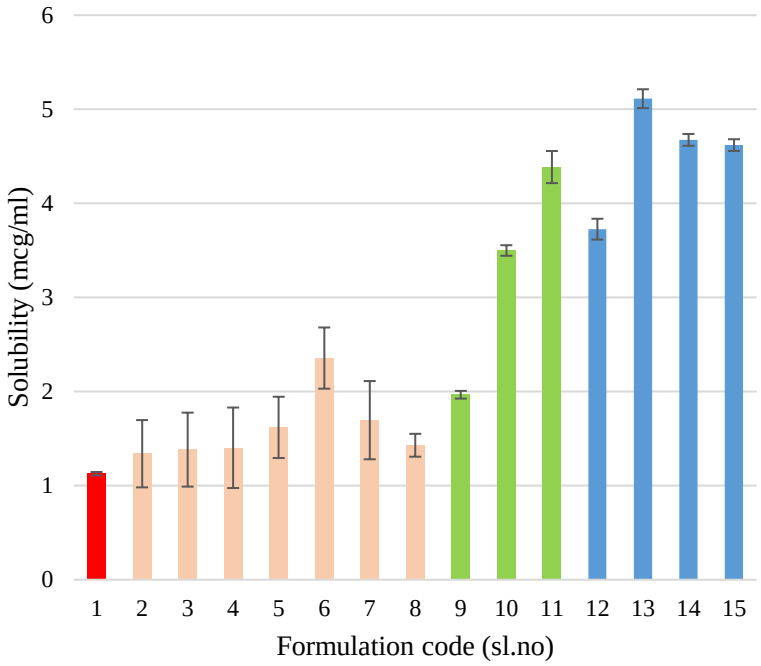
Conc(mcg/ml)	Abs(nm)
0	0
2	0.157
4	0.296
6	0.513
8	0.652

Fig 6: Calibration curve at neutral pH



Conc(mcg/ml)	Abs (nm)
0	0
2	0.142
4	0.305
6	0.498
8	0.652

Fig7: Bar diagram of solubility study of Glimepiride, Glimepiride physical mixture and glimepiride solid dispersion in acidic pH (pH 1.2)



* n = 3; values are expressed as mean ± SD

Fig 8: FTIR spectra of pure drug Glimepiride (A), Physical mixture of GLIMI: BCD: PVPK30 (B), SD5 (C), and SD5 with excipients (D)

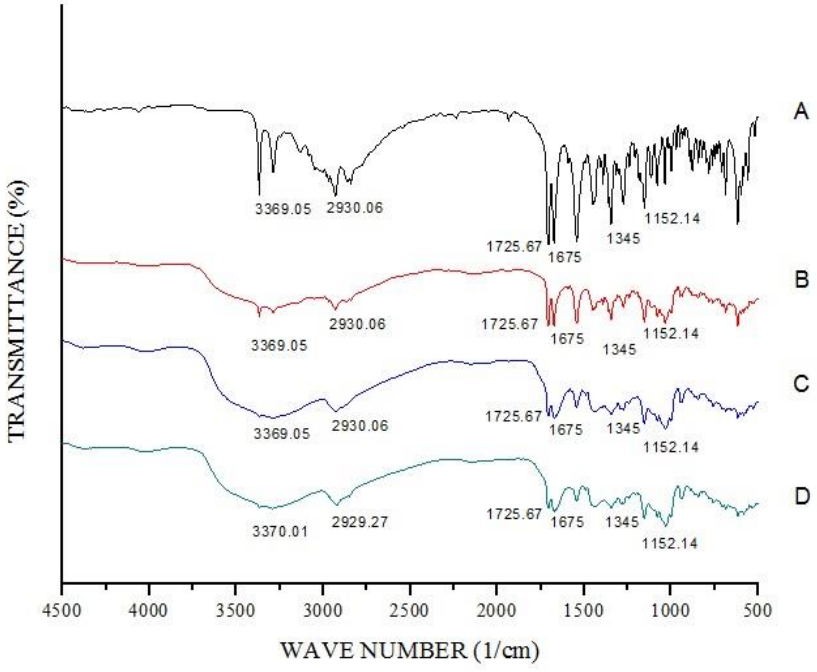


Fig 9: XRD pattern of Glimepiride (A1), SD5 (B1), and SD5 with excipients (C1)

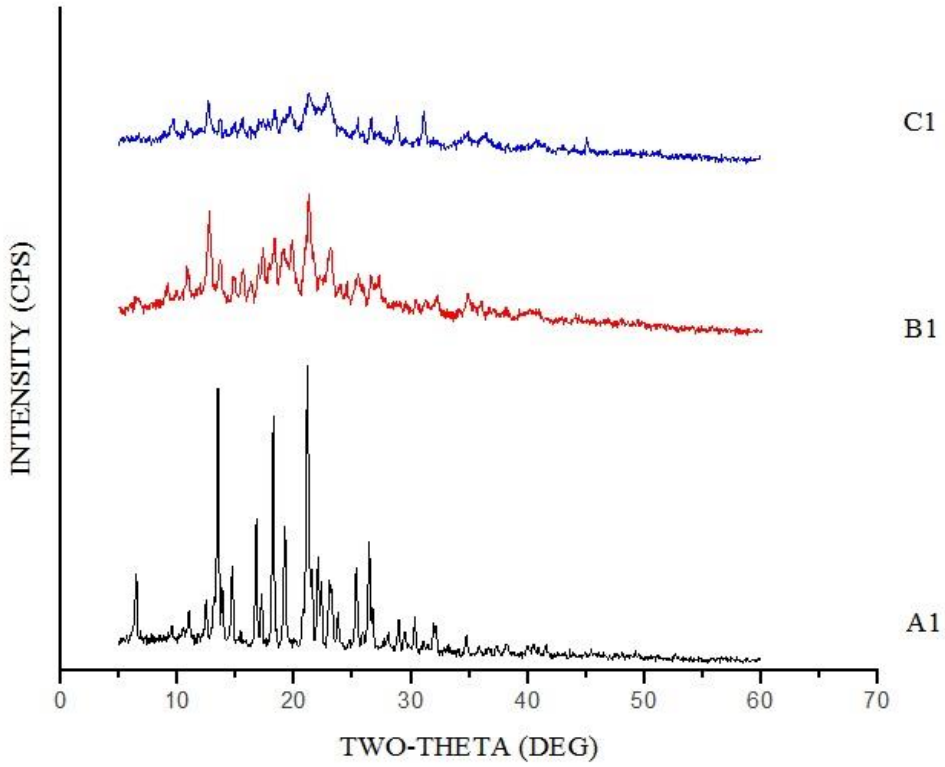


Fig 10: DSC thermogram of Glimepiride (A2)

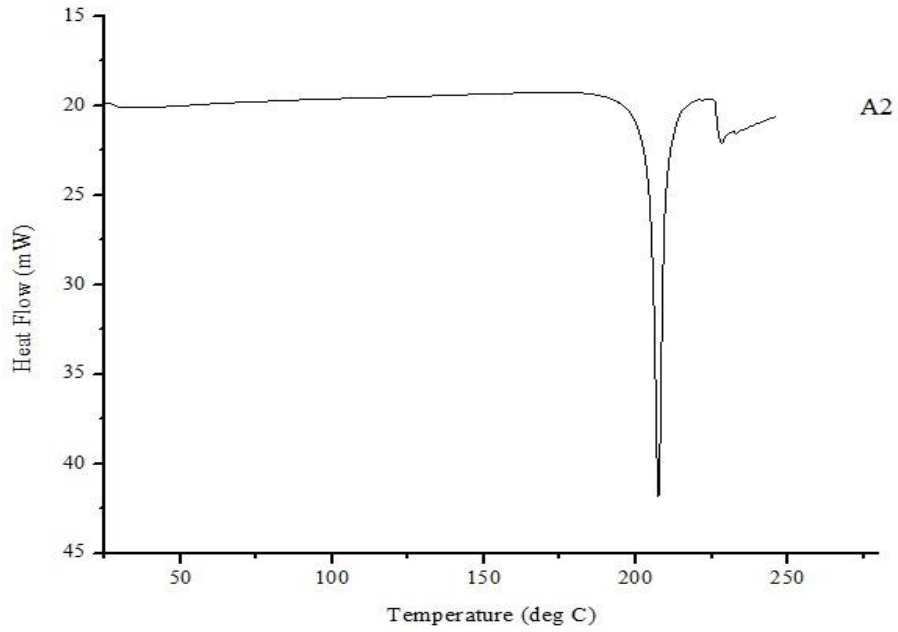


Fig 11: DSC thermogram of SD5 with excipients. (B2)

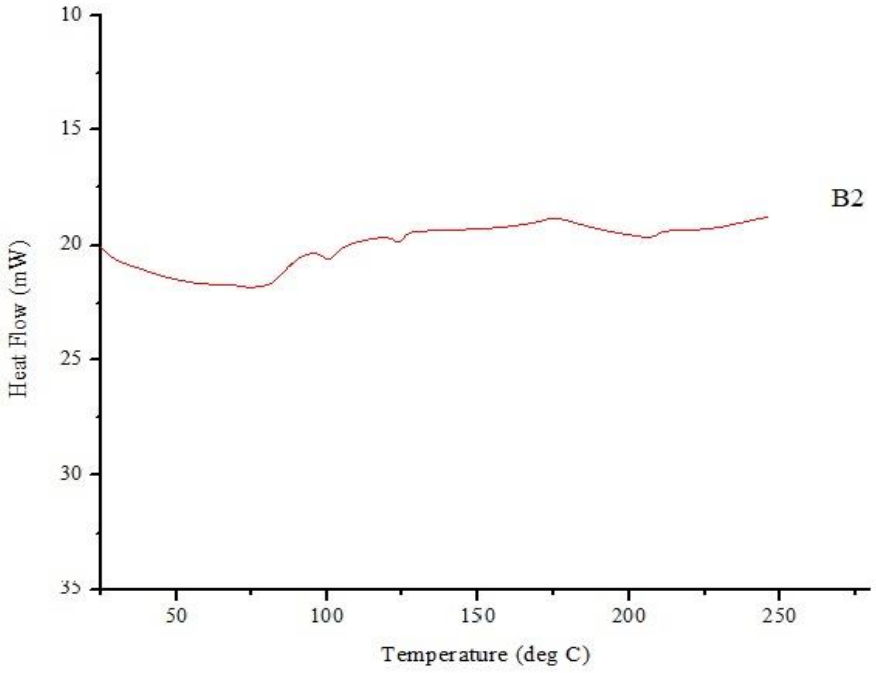
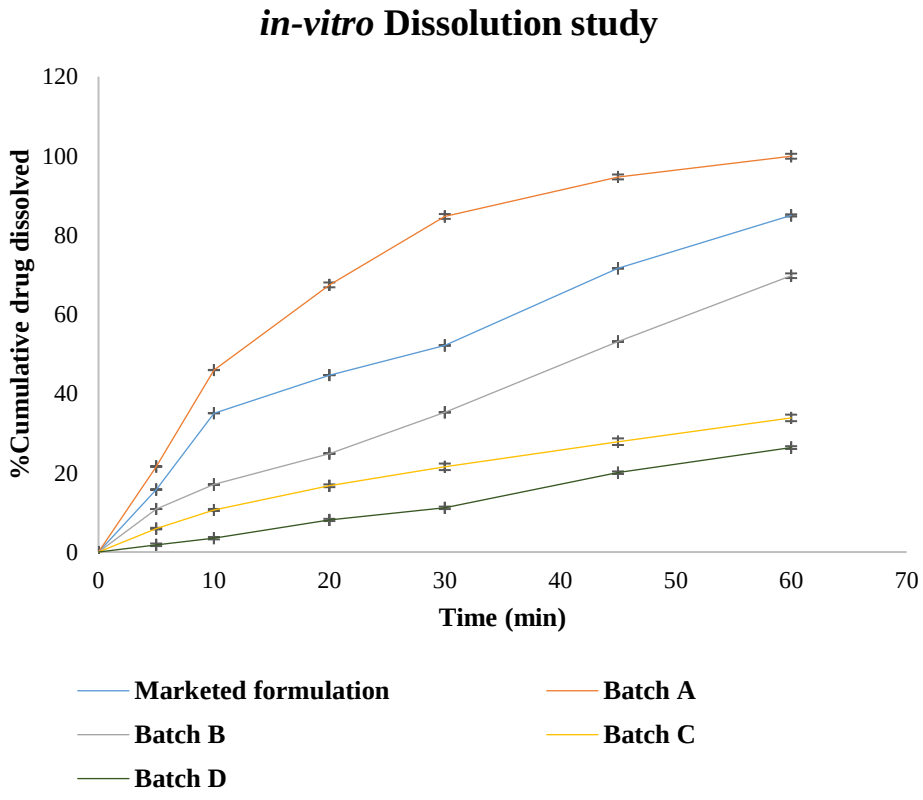


Fig 12: *in-vitro* dissolution study of Batch A, B, C, D and Marketed formulation of Glimepiride



- **Release kinetics of marketed tablet formulation:**

Fig 13: zero order release kinetic of marketed tablet formulation

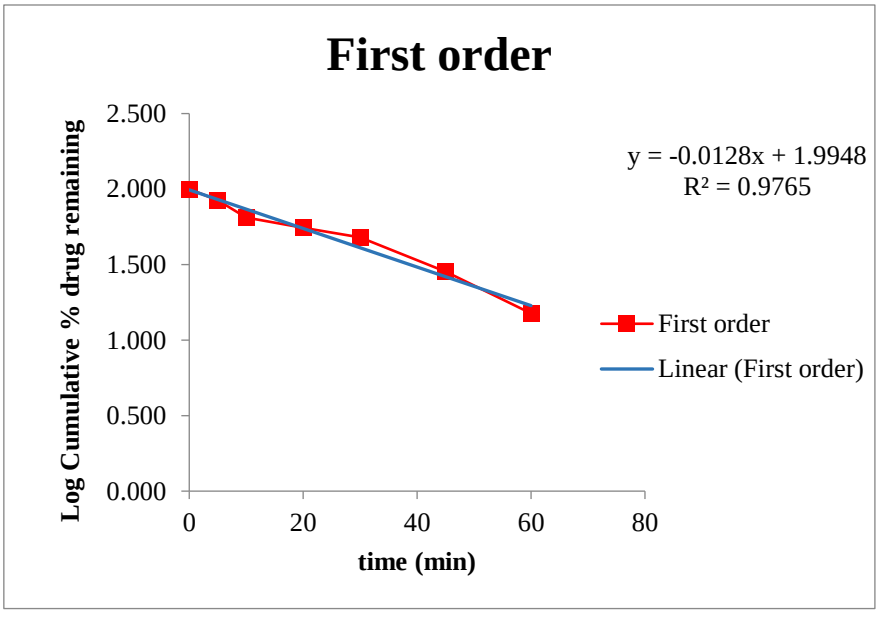


Fig 14: first order release kinetic of marketed tablet formulation

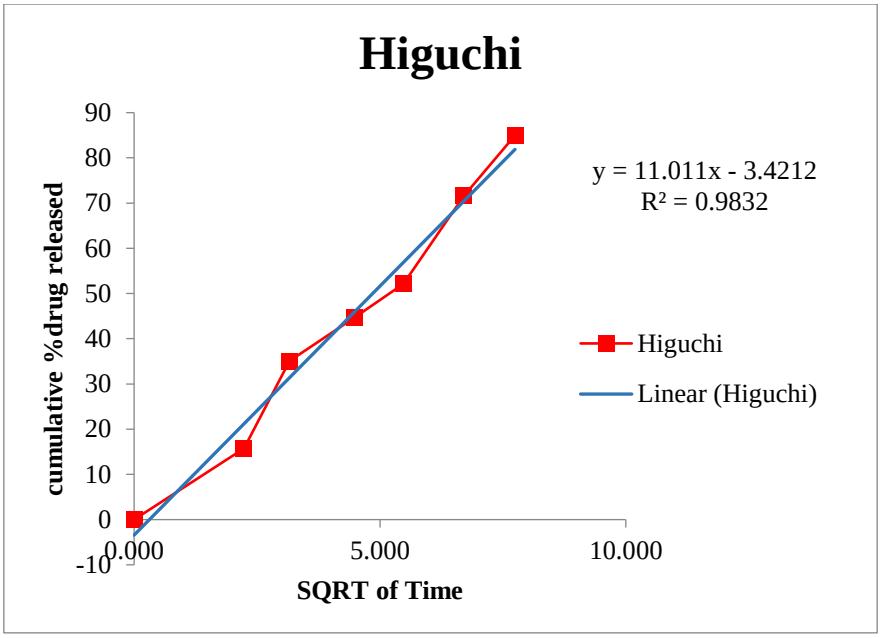


Fig 15: Higuchi model release kinetic of marketed tablet formulation

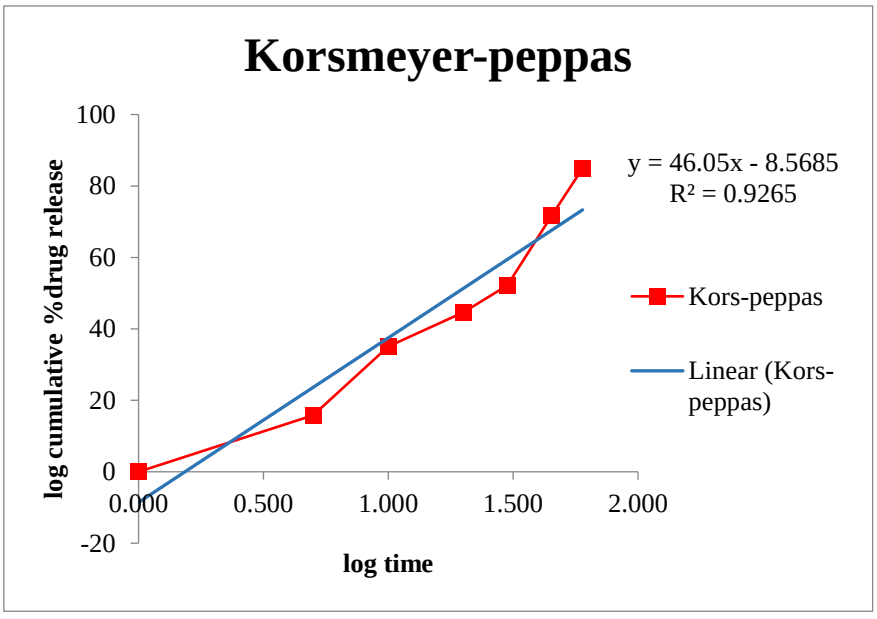


Fig 16: Korsmeyer-peppas model release kinetic of marketed tablet formulation

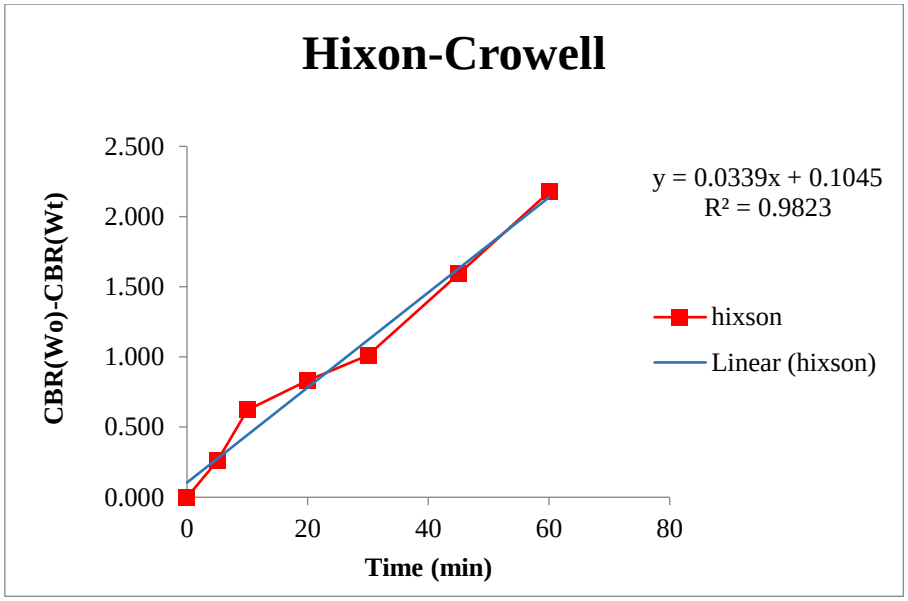


Fig 17: Hixon-Crowell model release kinetic for marketed tablet formulation

- **Release kinetics of tablet formulation (Batch A):**

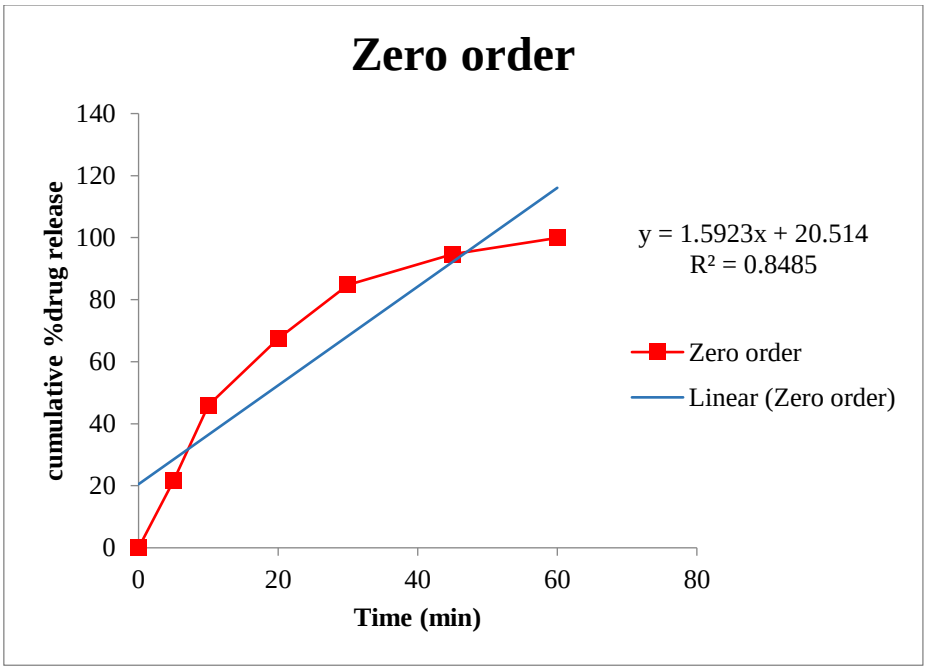


Fig 18: Zero order release kinetic of Batch A

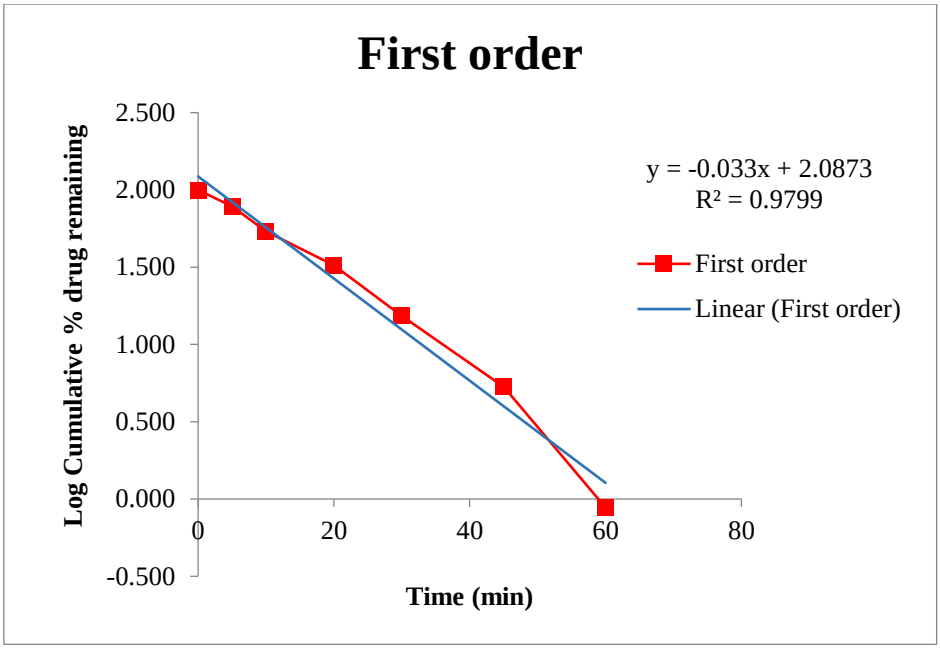


Fig 19: First order release kinetic of Batch A

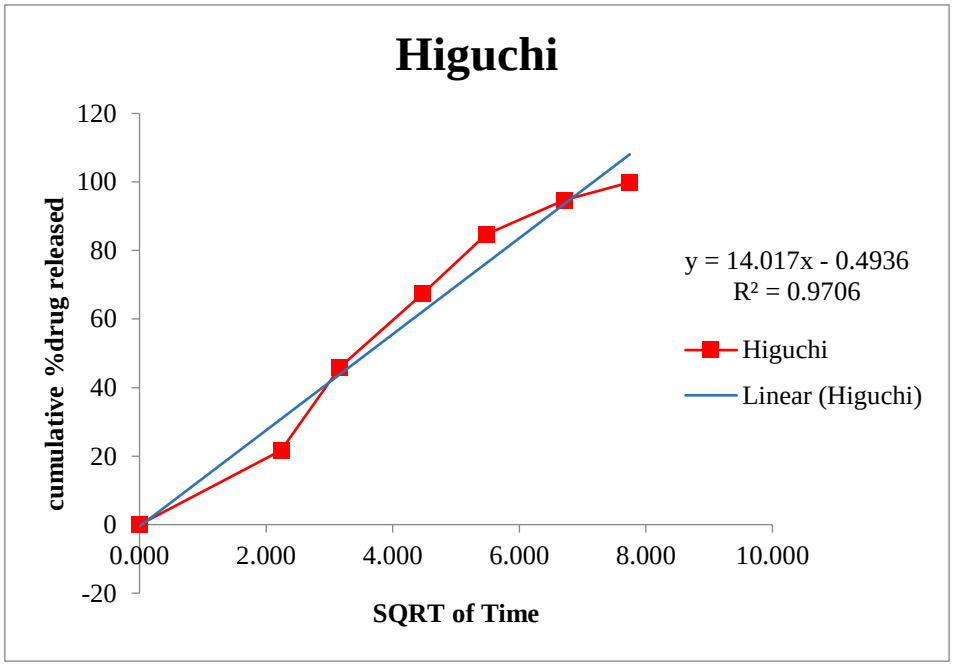


Fig 20: Higuchi model release kinetic of Batch A

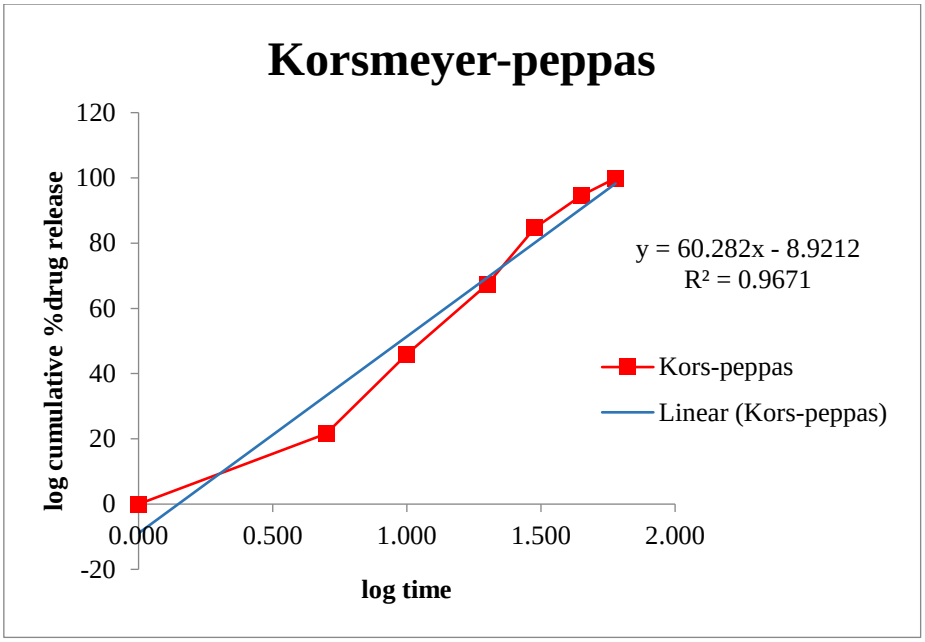


Fig 20: Korsmeyer-peppas model release kinetic of Batch A

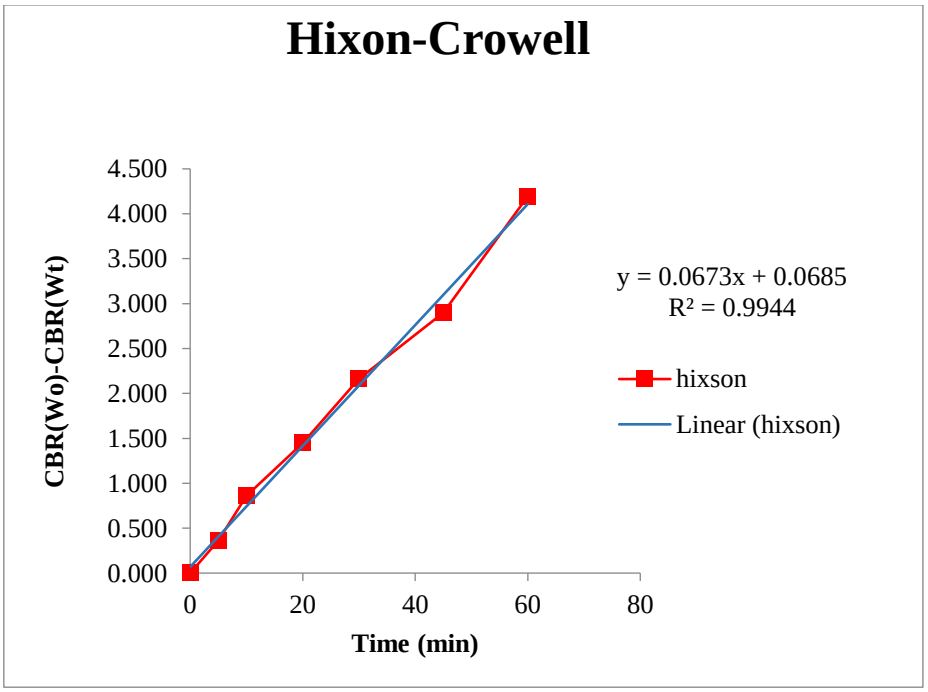


Fig 20: Hixon-crowell model release kinetic of Batch A

- **Release kinetics of tablet formulation (Batch B):**

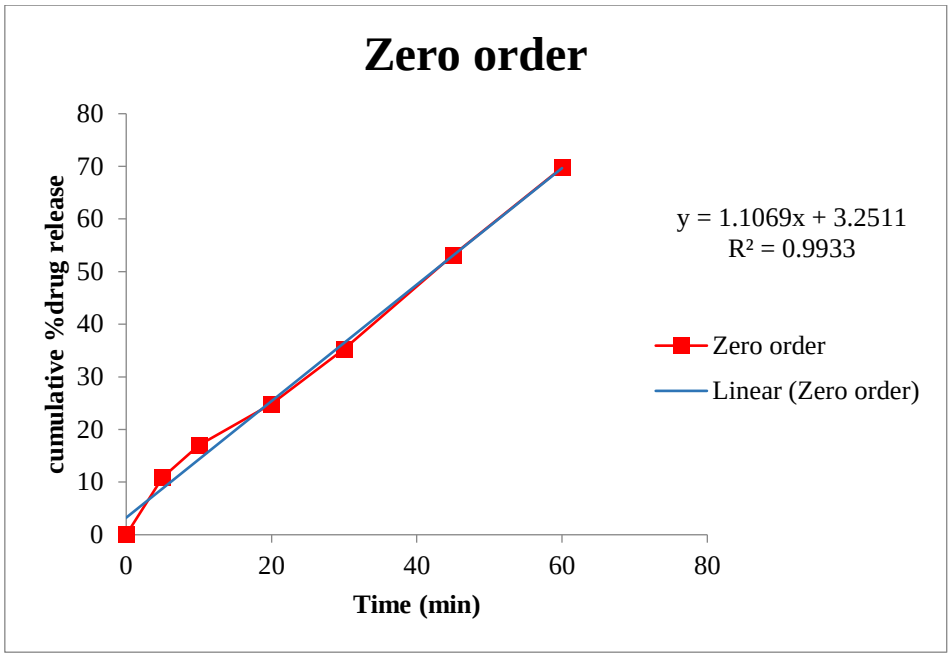


Fig 21: Zero order release kinetic of Batch B

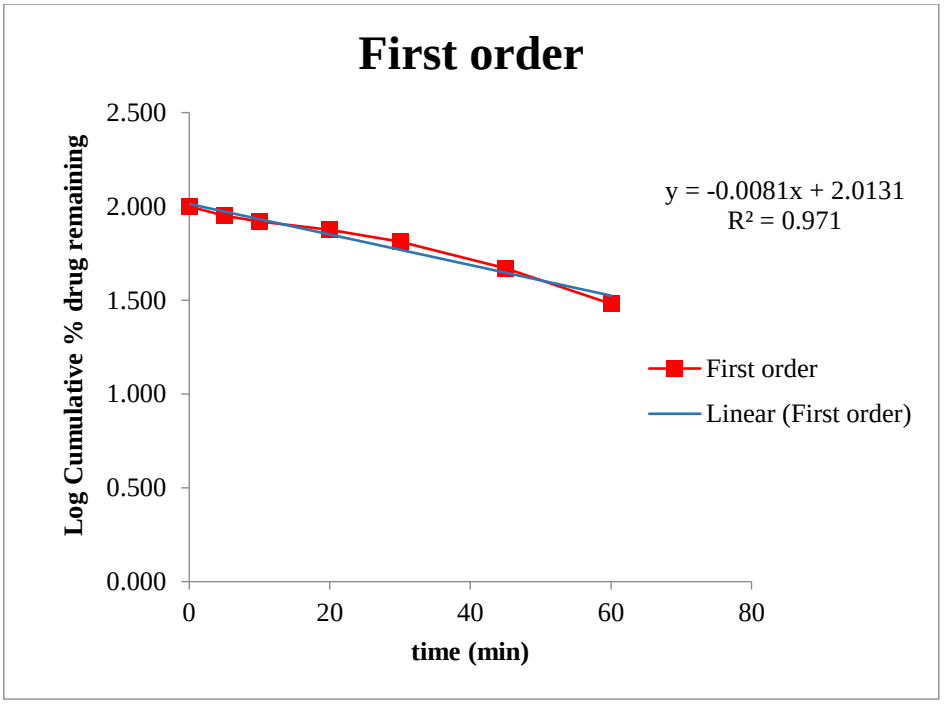


Fig 22: Zero order release kinetic of Batch B

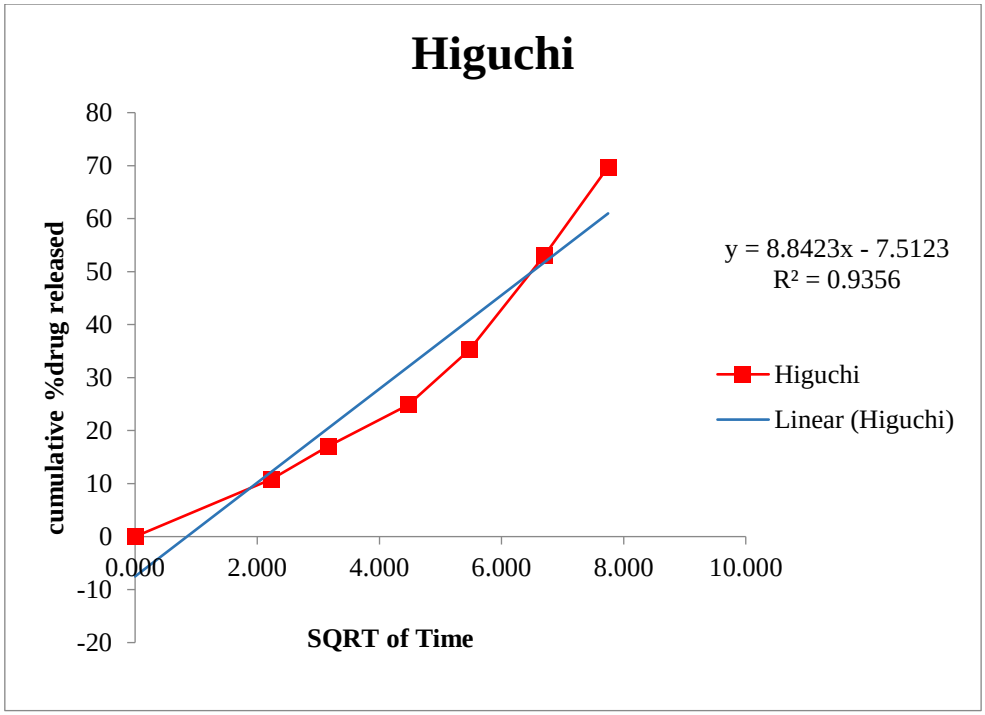


Fig 23: Higuchi model release kinetic of Batch B

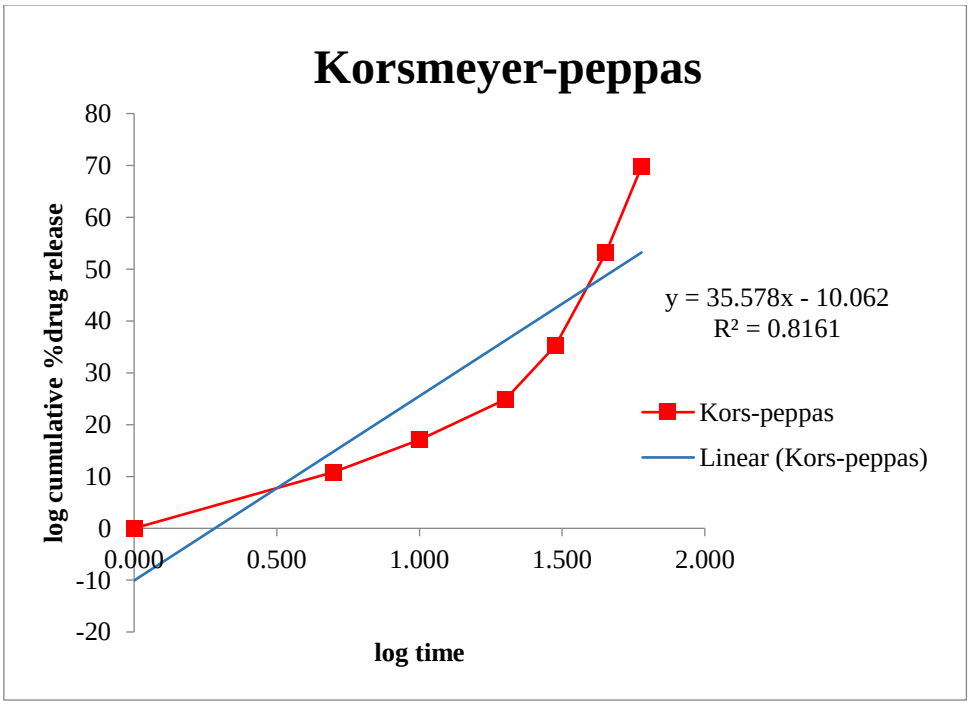


Fig 23: Korsmeyer-peppas model release kinetic of Batch B

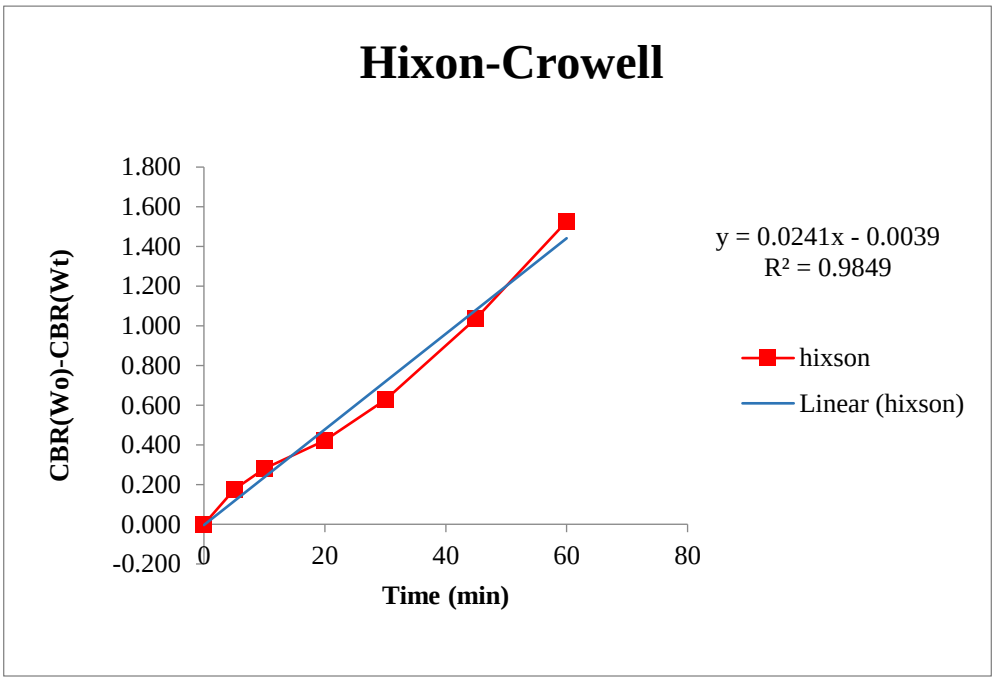


Fig 24: Hixon-Crowell model release kinetic of Batch B

- **Release kinetics of tablet formulation (Batch C):**

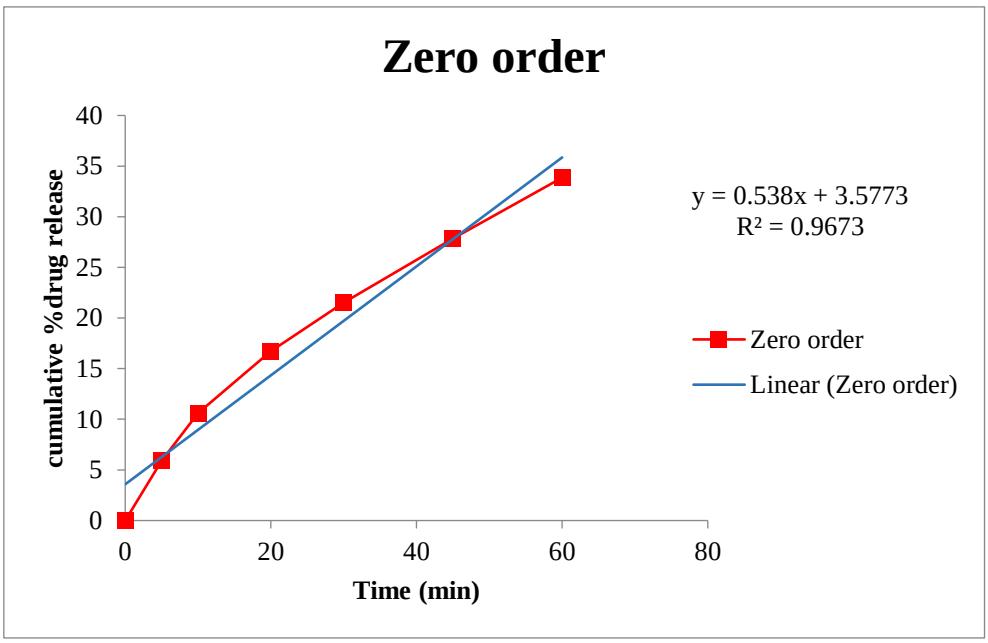


Fig 25: Zero order release kinetic of Batch C

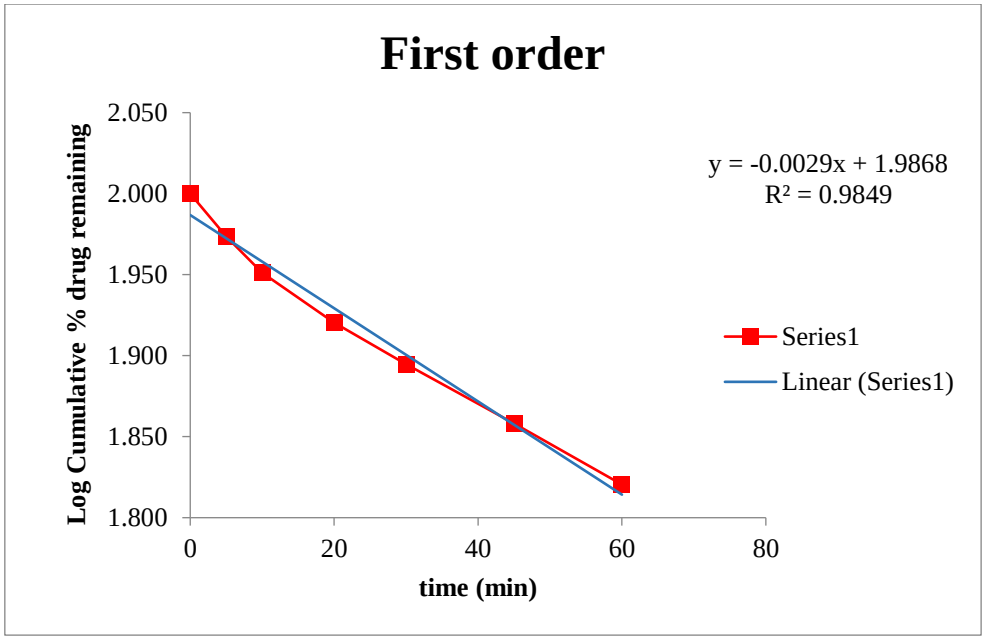


Fig 26: First order release kinetic of Batch C

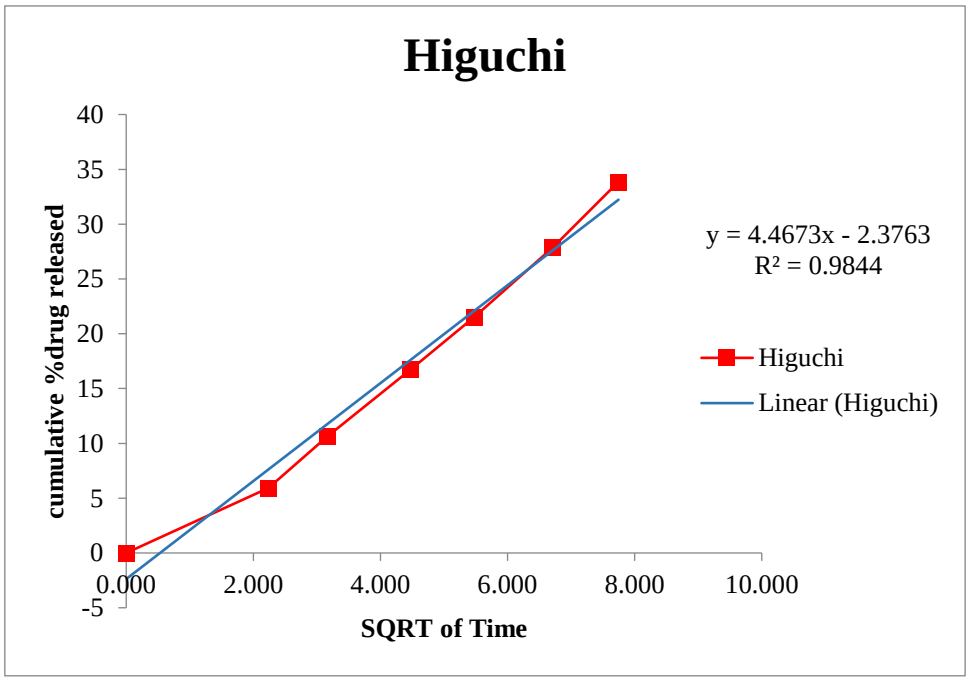


Fig 27: Higuchi model release kinetic of Batch C

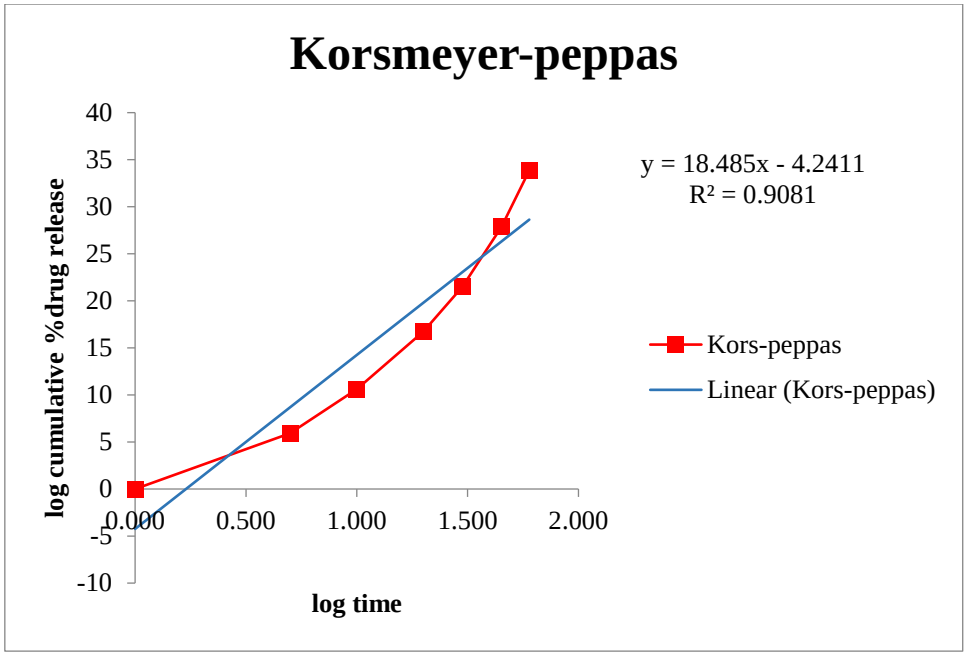


Fig 28: Korsmeyer-peppas model release kinetic of Batch C

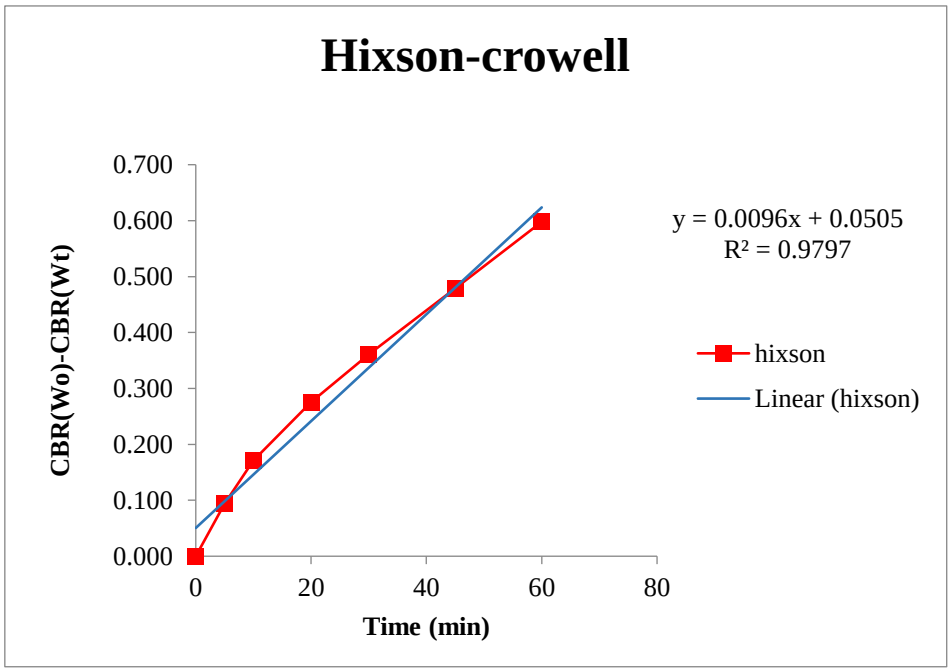


Fig 29: Hixson-crowell model release kinetic of Batch C

- **Release kinetics of tablet formulation (Batch D):**

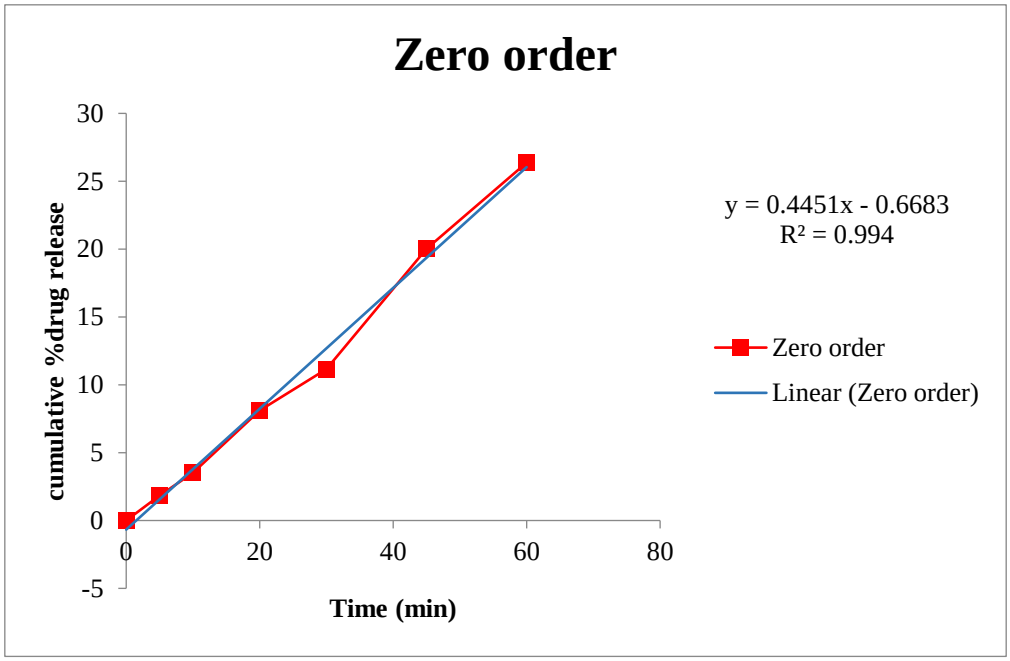


Fig 30: Zero order release kinetic of Batch D

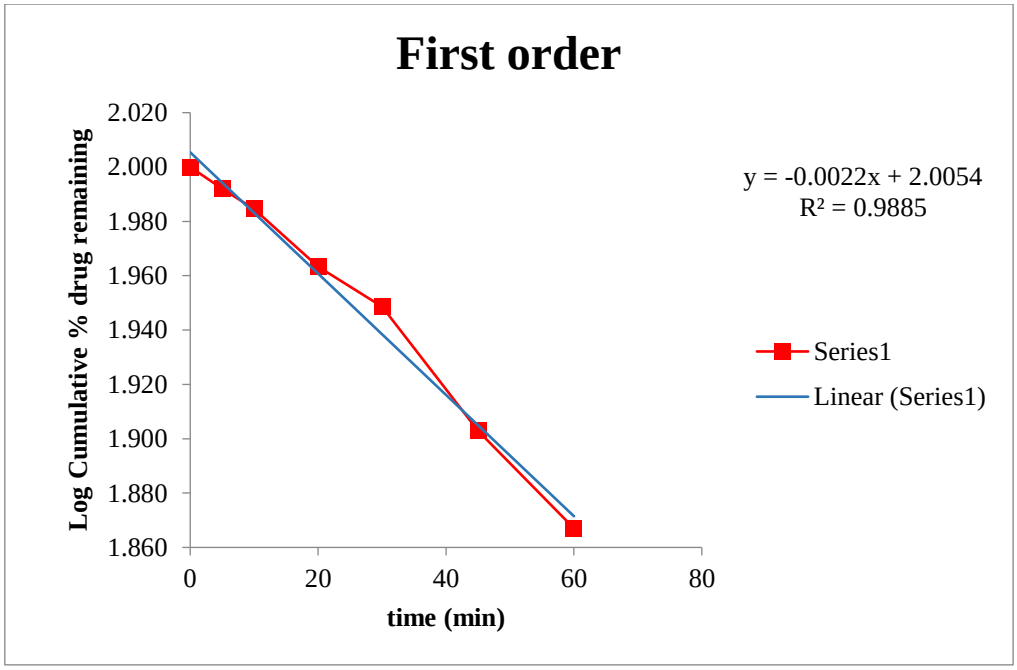


Fig 31: First order release kinetic of Batch D

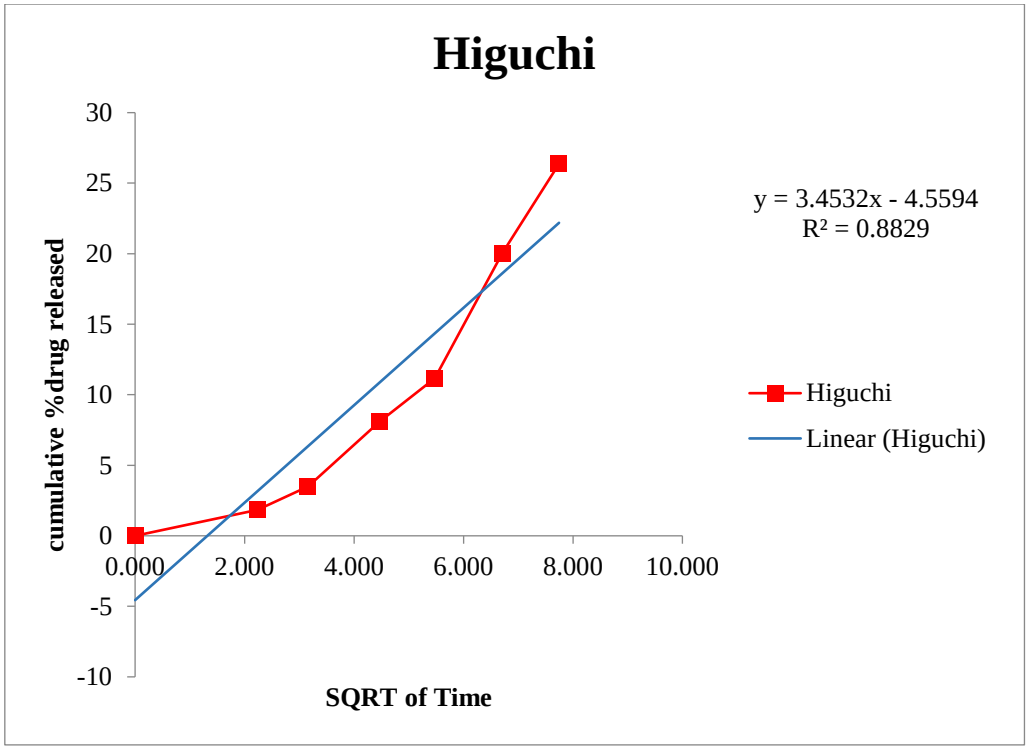


Fig 32: Higuchi model release kinetic of Batch D

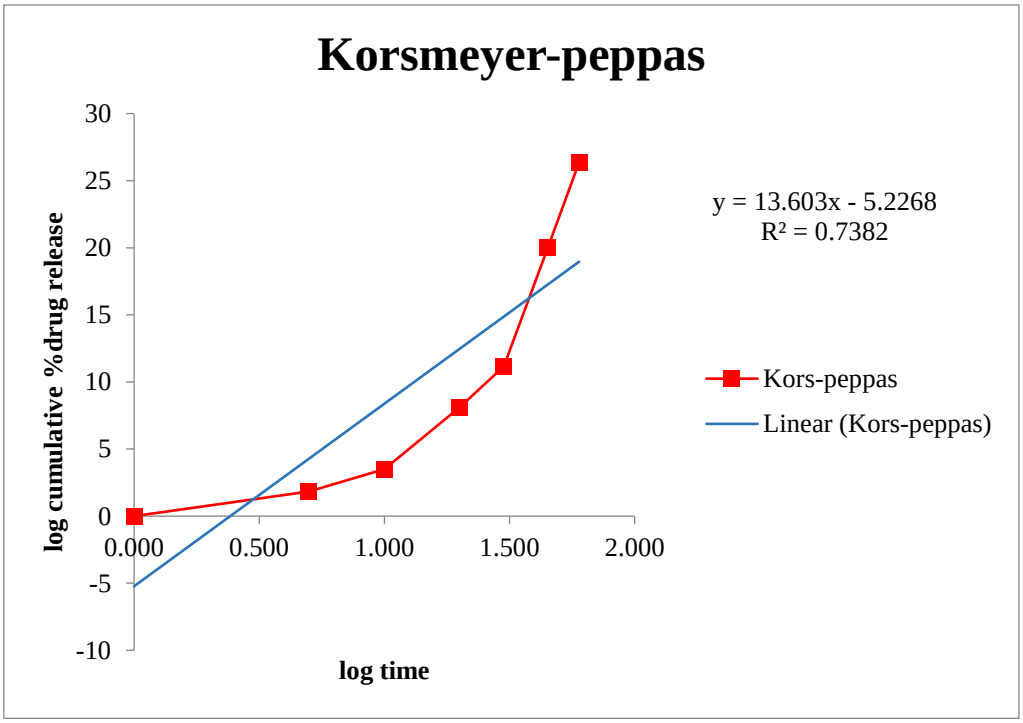


Fig 33: Korsmeyer-peppas model release kinetic of Batch D

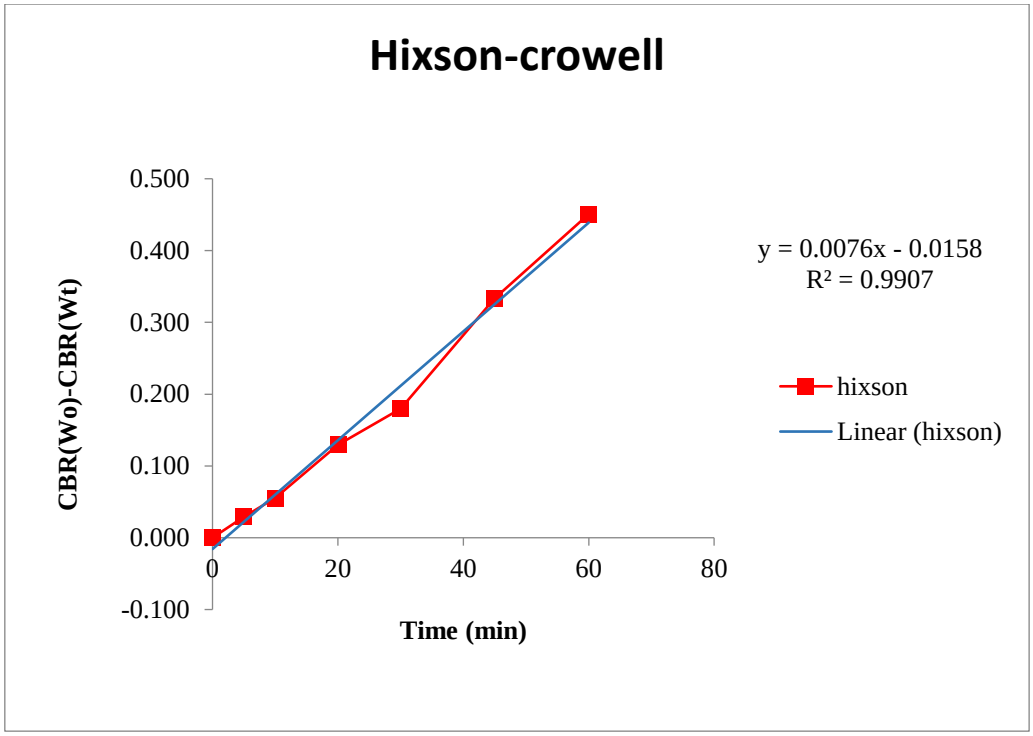


Fig 34: Hixson-crowell model release kinetic of Batch D

8. RESULT AND DISCUSSION:

8.1. Determination of absorption maxima of Glimepiride and Development of calibration curve at different aqueous pH:

The absorption maxima of glimepiride was found at 228nm wavelength using pH 1.2 media. [Fig 3], and calibration curve was prepared at pH 1.2, 6.8 and in neutral pH taking 228nm as fixed wavelength **[Fig 4, 5, 6**].

8.2. Determination of saturated solubility:

At a temperature of 37°C, saturation solubility of drug GLIMI was found to be 1.1378±0.0215mcg/ml in acidic HCL buffer (pH 1.2), 8.6437±2.7884mcg/ml in phosphate buffer (pH 6.8) and 12.0858±0.0362mcg/ml in purified water. Therefore drug GLIMI is showing pH dependent solubility while the drug is found to be very poorly soluble at acidic buffer but solubility is slightly increased in case of phosphate buffer.

8.3. Solubility study:

Solubility study for GLIMI, binary and ternary physical mixture (PM) of GLIMI, and binary and ternary solid dispersion (SD) of GLIMI was performed in triplicate (n=3) using acidic media (pH 1.2) and it was found that pure drug GLIMI is very poorly water-soluble and solubility is 1.1269±0.0182mcg/ml; however, very little solubility improvement was observed in case of both binary and ternary physical mixture. Solubility for PM1, PM2, PM3, PM4, PM5, PM6, and PM7 was found to be 1.3392±0.3577mcg/ml, 1.3829±0.3932mcg/ml, 1.4026±0.4278mcg/ml, 1.6191±0.3254mcg/ml, 2.3560±0.3253mcg/ml, 1.6960±0.4157mcg/ml and 1.4291±0.1216mcg/ml respectively. The solubility enhancement in the case of the physical mixture was not significant enough to be considered and thus rejected for further formulation development.

The enhancement of solubility in the case of binary solid dispersion of GLIMI and BCD was due to the formation of a guest-host complex. The hydrophobic interior of the BCD can keep the guest molecule, the drug, confined, while the BCD's hydrophilic exterior is soluble in water. This is made possible by the BCD's cylindrical shape. This complex increases the solubility of drugs, which in turn increases their bioavailability for water-insoluble drugs.

This solubility study aimed to find out the optimized binary solid dispersion ratio from SD1, SD2, and SD3 to fabricate ternary solid dispersion. According to the solubility data, the order of increasing solubility was observed as SD1<SD2<SD3. The solubility of SD2 was found to be 3.4993±0.0561mcg/ml which showed a significant increase from SD1 having a solubility of 1.9663±0.0407mcg/ml. Solubility increased even more in the case of SD3 but while comparing with

SD2 the enhancement of solubility is less significant therefore, SD2 is the most optimized batch of binary solid dispersion according to the solubility study.

Further solubility studies were performed using the best binary SD (SD2) to enhance the solubility profile even more than SD3 and SD4, and solubility enhancement of ternary SD was found in the increasing order of SD4<SD7<SD6<SD5; where the solubility for SD5 was found to be 5.1126±0.1004mcg/ml that was almost 4 fold solubility enhancement as compared to GLIMI. Therefore, SD5 was considered for further tablet formulation development. **[Table 3] [Fig 7]**

8.4. Fourier-transform infrared spectroscopy (FTIR):

According to Fig. 2, the pure glimepiride (A) showed distinctive sharp peaks at 3369.05 cm^{-1} and 2930.06 cm^{-1} due to N-H stretching, 1725 cm-1 and 1675 cm^{-1} due to carbonyl group, 1345 cm^{-1} showing C-N stretching vibration, and 1152.14 cm^{-1} due to S=O stretching vibration. This verified that the sample (A) is glimepiride. Same characteristic peaks are observed for sample B, C and D also that confirms that there is not any interaction between drug, carrier and excipients. In case of sample D, N-H stretching characteristic peak shifted to 2929.27 cm^{-1} from 2930.05 cm^{-1} and to 3370.01 cm^{-1} from 3369.05 cm^{-1}, as both of these observed characteristic peak shifts for sample D are within the range of particular functional groups and thus not significant. Solid dispersion SD5 (C), physical mixture (B), and SD5 with excipients all showed a noticeable reduction in the intensity of the characteristic peaks of Glimepiride in the infrared spectrum **[Fig 8].**

8.5. X-ray diffraction (XRD):

Comparing some characteristic peak heights in the diffraction of the SD5 (B1) and C1 with those of the pure drug glimepiride (A1) confirmed the transition from a crystalline to an amorphous form of the drug. With peak intensities of 1629, 1916, and 2303, respectively, pure drug glimepiride demonstrated sharp peaks of the diffraction angle of 2θ at 13.4°, 18.2°, and 21.1°, indicating the drug's crystalline nature. All of the pure drug's peaks could be seen in the XRD patterns of B1 and C1, but their intensity was noticeably decreased, indicating that the drug had been transformed from its crystalline form to an amorphous form **[Fig 9].**

8.6. Differential scanning calorimetry (DSC):

The DSC thermogram of Glimepiride (A2) showed a sharp endothermic melting point peak at 210°C that confirms the sample (A2) as a pure drug Glimepiride and also confirms the sample's crystalline nature; however, the characteristic peak corresponding to its melting point of Glimepiride was broadened with reduced intensity and got disappeared in the DSC thermogram of sample B2 that shows the transition from crystalline form to amorphous form **[Fig 10][Fig 11]**.

8.7. Pre-compression evaluation of tablet blend:

The bulk density of the tablet blend ranged between 0.380 and 0.412 gm/cm3, indicating that the tablets could be packaged well. The tapped density of the blend was found to be between 0.395 and 0.426gm/cm3. The range of Hausner's ratio was 1.02 to 1.044. The range of the compressibility index was 2.44 to 4.55. 22.34 to 25.28° was found to be the angle of repose. **[Table 4]**

8.8. Evaluation of Glimepiride tablet:

The tablet's average diameter was measured to be between 5.54 and 5.58 mm. The tablet's average thickness was determined to be between 3.12 and 3.15 mm. The prepared tablet had an average weight of between 89.21 and 90.28 mg. It was therefore anticipated that all of the tablets would have uniform weights and low standard deviation values that are within the USP-acceptable range. The manufactured tablet has a hardness that ranges from 5.32 to 6.05 kg/cm2, which is sufficient for processing. The durability of the manufactured tablets is demonstrated by the fact that none of the formulations had friability of more than 1.0%; resistance to weight loss demonstrates the tablet's resilience to abrasion during handling, packaging, and shipping. Ac-Di-Sol was employed as a super disintegrant in a concentration of 3.6% in the formulation of tablets for Batch A and Batch C. When compared to the Batch B and D formulations, which did not have super disintegrant added, the tablets containing super disintegrant exhibit better disintegration capabilities. These tablets' disintegration times ranged from 5.33 to 13 minutes. In addition to serving as a water-soluble carrier for SD, PVPK30 carrier effectively functions as strong binder, eliminating the need for an extra binding agent in tablet formulation.

All of the tablet formulations' drug content was measured spectrophotometrically at 228 nm, ranging from 3.95±0.02 to 4.23±0.01 mg per tablet batch. The uniformity of the drug content in the produced tablets was achieved as the standard deviation is found to be less than 0.005. **[Table 5].**

8.9. *In-vitro* dissolution study:

From the percentage dissolution of formulations [Table 6], only 26.37±0.349% drug release is observed from Batch D, and 33.86±0.82% release is observed from Batch C in 60 mins, so there is a very less amount of percentage drug release in the case of pure Glimepiride tablet batches and the release pattern is suggesting that there is not even any significant increase in percentage drug release using Crosscarmellose sodium, and thus pure glimepiride tablet batches (Batch C and D) can’t be considered to be an ideal immediate release tablet formulation.

Whereas, using solid dispersion (SD5) employed tablet formulations (Batch A and B) are showing better drug dissolution patterns as compared to pure Glimepiride formulations. 69.75±0.589% drug dissolution in 60mins is observed in the case of Batch B, and almost 10.866±0.008% dissolution is observed within 5 mins that is quite comparable with the marketed tablet formulation but marketed glimepiride tablet showing better results in 60 min duration and approximately 84.976±0.274% drug

is released; however, the best percentage cumulative drug dissolution is observed in case of Batch A where 99.915±0.621 % drug is dissolved in 60mins duration that is even better than marketed formulation (84.976±0.274% in 60 mins). Similarly, a significant rise in the percentage of cumulative drug dissolved is observed in the case of Batch A than in Batch B, C, and D and marketed formulation in 5mins, 10mins, 20mins, 30mins, 45 mins, and 60 mins time intervals. **[Table 6] [Fig 12]**

8.10. Stability study:

As shown in **Table 7, 8**, the solubility study was performed according to ICH guideline and results suggest that there are not any change in case of drug and carriers and also for each excipients with GLIMI after 6 months of stability study.

8.11. Release kinetics study:

The drug release pattern was also correlated with the established models of release kinetics namely Zero order, First Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas. R^2 values for the optimized tablet formulation (Batch A) are listed in **Table 9** and, for all graphs describing release patterns (Marketed tablet formulation, Batch A, B, C and D) refer to **Fig 13 to 34**.

9. CONCLUSION:

This study's primary goal was to develop solid dispersions utilizing water soluble carriers (BCD and PVPK30) in order to improve the drug GLIMI's poor water solubility. GLIMI is a BCS class II drug. The solubility of binary solid dispersions formulated from the GLIMI and BCD has increased significantly when compared to the pure drugs GLIMI alone. Binary SD of the drug carrier ratio of 1:3(SD2) is found to be the optimized batch of binary solid dispersion and further formulation development is carried out with this ratio by adding PVPK30 in different ratios to formulate ternary SD, and almost 4 fold of solubility enhancement is observed for the optimized batch of ratio 1:3:1 (SD5). Thus, it can be inferred from the study on solubility improvement that solubility is enhanced more in the case of the ternary solid dispersion of GLIMI than the binary solid dispersion of GLIMI. PVPK30 has thus been shown to be effective in improving the solubility profile of the GLIMI-BCD complex, but the improvement in solubility profile is dependent on carrier concentration for both carriers.

Another aim of this study was to formulate an optimized batch of tablet and to carryout *in-vitro* dissolution studies with marketed immediate release tablet formulation. According to the study, the drug solubility profile of the Batch A formulation is superior to that of the commercial tablet formulation. Aside from that, Batch B, where super-disintegrant was not used in the formulation, demonstrated a higher drug dissolution rate than Batch C and D. This shows that formulating the pure drug GLIMI as a solid dispersion is what increases the drug's dissolution rate, whereas batches (Batch C and D) of pure GLIMI tablet formulation exhibit a lower drug dissolution rate.

Hence, SD by solvent evaporation shows higher dissolution rate and solubility profile by in-vitro study, confirming that the solid dispersion would significantly increase the efficacy of a poorly water soluble drug in the coming years.

10. FUTURE SCOPE

This research work concluded in improving the solubility and dissolution rate of the drug, Glimepiride through solid dispersion technique using BCD and, PVPK30 as water soluble carriers, however further detailed research work is necessary for establishing this technique for improving the solubility and bioavailability of the drug. *in-vitro* analysis of these solid dispersion is required for further development of this formulation.

Animal studies can be utilized to check the therapeutic benefits of using solid dispersion technique. Further insights are required for precision and accuracy of the solid dispersion production which are required for scaling up of the process of this technique can be used to improve the solubility and bioavailability of the other BCS II drugs that are having the same issue of low solubility and poor dissolution rate.

11. REFERENCES:

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12. APPENDIX

12.1. Abbreviations:

T2DM: Type II diabetes mellitus

BCS: Biopharmaceuitcal classification system

BCD; β- Cyclodextrin

PVPK30: Polyvinylpyrrolidone K30

MCC: Microcrystalline cellulose

SD: Solid dispersion

PM: Physical mixture

GLIMI: Glimepiride

FTIR: Fourier-transform infrared spectroscopy

MW: Molecular Weight

XRD: X-ray diffraction

DSC: Differential Scanning Calorimetry