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Imeglimin- Novel Therapeutics Agents For Type 2 Diabetes

Sagar. B. Gore[a*], Swagti. A. Moon[b]

[a*] Student at Pratibhatai Pawar College of Pharmacy, Shrirampur. 413709

[b] Assistant Professor at Pratibhatai Pawar College of Pharmacy, Shrirampur. 413709

Corresponding Author: Sagar. B. Gore

ABSTRACT :

Type 2 Diabetes Mellitus (T2DM) is a chronic condition characterized by hyperglycemia resulting from insulin resistance, inadequate insulin production, and beta-cell dysfunction. This condition is influenced by a combination of genetic, metabolic, and environmental factors, with obesity, sedentary lifestyles, and unhealthy diets as primary contributors. Advances in pharmacological treatments have introduced novel drugs like Imeglimin, which targets the core defects of T2DM, including impaired insulin secretion, insulin resistance, and hepatic glucose overproduction. Imeglimin unique mechanism of action integrates mitochondrial function improvement, oxidative stress reduction, and beta-cell protection, distinguishing it from traditional anti-diabetic therapies. This review explores the pathophysiology of T2DM, risk factors, and the pharmacodynamics and pharmacokinetics of Imeglimin. It also highlights synthesis methods, evaluation parameters, and the therapeutic potential of Imeglimin in managing T2DM. The findings underscore Imeglimin promise as a versatile and well-tolerated addition to the diabetes treatment landscape, addressing unmet needs in T2DM management.

Keywords: Imeglimin, Insulin Sensitivity, Twymeeg, Beta-cell dysfunction, Type 2 diabetes .

1.INTRODUCTION :

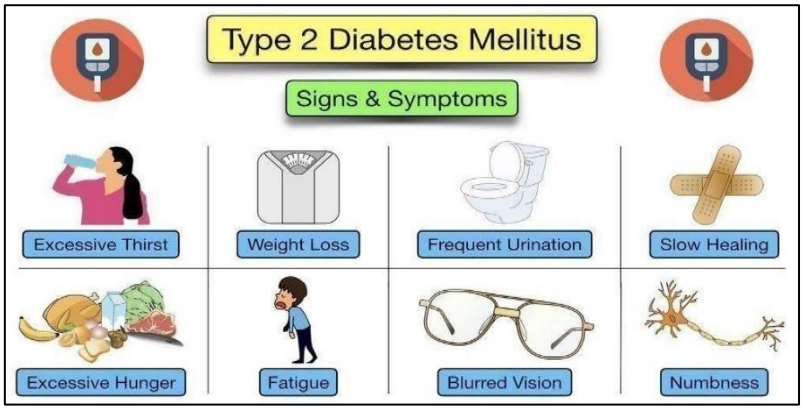
1.1 Type-2 Diabetes: -

Diabetes mellitus (DM) is a long-term condition where the blood sugar level is too high (called hyperglycemia) due to problems with insulin – either the body doesn't produce enough of it, or it doesn't use it properly. Over time, this imbalance can cause serious complications in both large and small blood vessels, which, if not managed well, can lead to frequent hospital visits and an increased risk of heart related diseases. Diabetes mellitus (DM) is likely one of the oldest known diseases. It was first mentioned in an Egyptian manuscript around 3,000 years ago. [(1)] In 1936, doctors clearly identified the difference between type 1 and type 2 diabetes.[2] Type 2 diabetes happens when the body doesn't produce enough insulin or can't use it properly due to problems with the pancreas and how cells respond to insulin. From 1980 to 2004, the number of people with type 2 diabetes has increased four times, largely due to more obesity, less physical activity, and an ageing population. [3]

1.2 Sign and symptoms of type 2 diabetes: -

- Polyuria (increased urine output)
- Fatigue
- Weight loss
- Excessive hunger
- Blurred vision
- Slow healing
- Recurrent skin infections
- Polydipsia ([4])

Fig 1 :-Type 2 Diabetes Mellitus Sign and Symptoms



1.3 Pathophysiology of type 2 Diabetes:

Type 2 diabetes mellitus (DM) happens when the body becomes less responsive to insulin. This is due to a combination of insulin resistance, reduced insulin production, and eventually, failure of the pancreatic beta cells, which make insulin. As a result, glucose transport into the liver, muscle, and fat cells decreases, and there is more breakdown of fat, leading to high blood sugar (hyperglycemia).

A newly recognized factor in type 2 DM is the malfunction of alpha cells, which impacts glucagon and liver glucose levels. Normally, these levels go down after eating, but in type 2 DM, they stay high due to inadequate insulin and increased insulin resistance, which contributes to high blood sugar. [(6)]

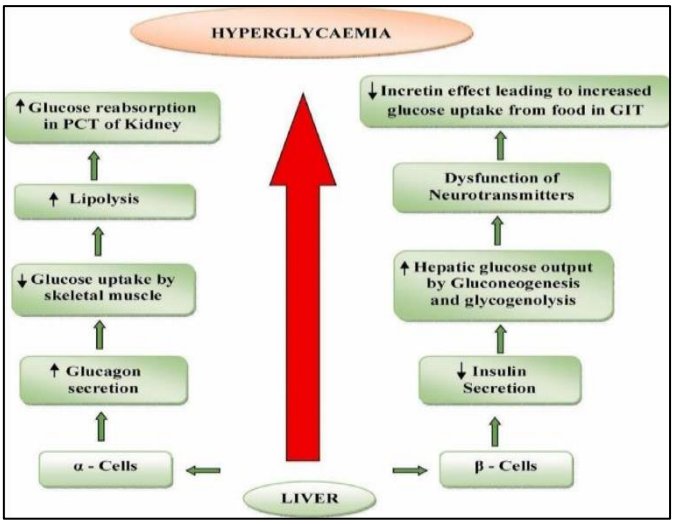


Fig 2: - Pathophysiology of T2DM -Ominous octet.

Alterations in how the body processes glucose happen because of a gradual decrease in how well b-cells work, which occurs alongside insulin resistance. The two main factors that control blood glucose levels are insulin secretion and insulin sensitivity. [(8)]

- **Beta-cell function: -**

Type 2 diabetes tends to worsen over time, primarily because of a steady decline in the ability of the pancreas's beta cells (b-cells) to function properly. Research has shown that diabetes and even prediabetes only develop when these b-cells can no longer compensate for insulin resistance in the body

For b-cells to produce enough insulin to handle this resistance, several factors are involved, like the number of b-cells (known as b-cell mass) and their ability to secrete insulin effectively. Both genetics and environmental influences can affect these factors.

Additionally, although conditions like insulin resistance and high fat levels in the blood (lipotoxicity) may contribute to the decline in b-cell function, there's evidence suggesting that some people may have an inherited risk that makes their b-cells more likely to fail. This pre-existing genetic risk could play a critical role in b-cell dysfunction and, consequently, the progression of diabetes. (8)

- **Insulin resistance :-**

Insulin resistance puts extra pressure on beta cells to produce more insulin, which contributes to their gradual failure in type 2 diabetes. We don't yet fully understand how insulin resistance leads to this beta cell failure, but one possible idea is that the same factors causing insulin resistance—like the harmful effects of excess fat (lipotoxicity)—may also directly damage beta cells. Obesity is the main factor leading to insulin resistance, and research shows it's crucial in determining how sensitive the body is to insulin. [(8)]

- **Risk Factors and Pathophysiology: -**

The risk of developing Type 2 Diabetes Mellitus (T2DM) comes from a mix of genetic, metabolic, and environmental factors that interact with each other. While some risk factors, like ethnicity and family history, cannot be changed and have a strong genetic basis, studies show that many cases of T2DM can be prevented. By managing key modifiable risk factors—such as maintaining a healthy weight, staying active, and eating a balanced diet—the likelihood of developing T2DM can be significantly reduced. [(9)]

- **Ethnicity and Family History/Genetic Predisposition: -**

The rates of type 2 diabetes (T2DM) vary widely around the world, influenced by factors like ethnicity and location. Studies show that Japanese, Hispanic, and Native American populations face the highest risks, while Asians have higher incidence rates compared to White Americans. In the UK, the risk is highest among the Black population. Although exact causes aren't fully understood, potential factors include modern lifestyles (which often led to obesity), socioeconomic influences, and genetic or environmental factors. [(9)]

- **Obesity, Low Physical Activity and Unhealthy Diet: -**

Obesity (defined as having a body mass index [BMI] of 30 kg/m² or more) is the main risk factor for type 2 diabetes (T2DM). It is closely linked with metabolic issues that lead to insulin resistance (IR). Research shows that as BMI increases, the age at which T2DM is diagnosed tends to decrease. Although the exact ways obesity causes T2DM and IR are not fully understood, there are many factors that contribute to the development of these conditions, including processes within individual cells and interactions between different organs.[(9)]

2. IMEGLIMIN: -

Imeglimin is a new type of drug from the glimins class, created to treat type 2 diabetes. It is a compound called tetrahydrotriazine, and its chemical name is (6R) -(+)-4-dimethylamino-2-imino6methyl-1,2,5,6tetrahydro1,3,5triazine hydrochloride. The goal of developing Imeglimin was to offer a safe and well-tolerated treatment with special features that can effectively address the metabolic issues in people with type 2 diabetes. It has already proven its effectiveness through extensive Phase I/II clinical trials. Imeglimin works differently from other oral diabetes medications, which means it might be safely and effectively combined with other drugs commonly used to treat type 2 diabetes and its related conditions. [(10)] Imeglimin helps the body use insulin better by reducing sugar production in the liver and improving how insulin works in the liver and muscles. It also helps the pancreas release more insulin when needed and protects the cells that make insulin. What makes Imeglimin stand out is that it also supports energy production in the body's cells, which is different from other diabetes medications. Low blood sugar is very rare with Imeglimin. It's a good choice for people who no longer respond to insulin therapy or can't reach their blood sugar goals with other medicines because it both improves insulin sensitivity and helps the body produce more insulin. [(11)]

Imeglimin is a medicine you take by mouth, and it stays in the body for 10–20 hours in healthy people. Only a few studies have looked at how the body absorbs and removes this drug. After taking Imeglimin, it gets absorbed in two ways, and this process takes up to 6 hours. How much of the drug enters the bloodstream (called bioavailability) depends on the dose. Larger doses mean less of the drug gets absorbed. Imeglimin doesn't stick much to proteins in the blood (only 1–8%). The drug is cleared from the body in two steps: a fast one followed by a slower one. The liver doesn't break it down much, so most of it leaves the body unchanged through urine. The amount of drug in the urine is the same as what the body absorbed. The way the body handles the drug is the same for both Caucasian and Japanese people. [(12)]

Imeglimin has a chemical structure called a cyclic 1,3,5-triazine, which contains a biguanide-like part, making it similar to metformin. The molecule can exist in at least three different forms, or tautomer's, due to the movement of hydrogen atoms between nitrogen atoms. These shifts cause changes between amino (–NH) and imino (–N=) groups. Imeglimin formula is C6N5H13. It has two extra carbon atoms compared to basic biguanides. One carbon helps form a six membered ring by connecting the two end nitrogen atoms, while the other adds a methyl (Me) group outside the ring. [(13)]

2.1 Structure of Imeglimin: -

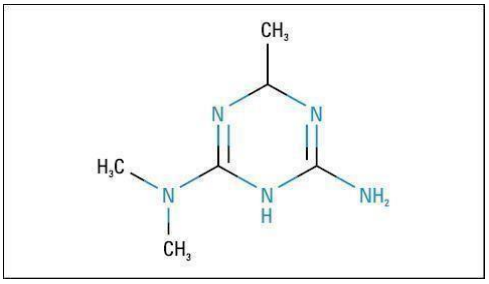


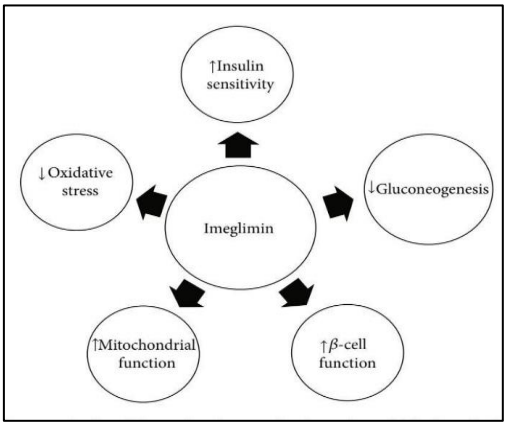
Figure 3. Chemical structure of Imeglimin (IMEG)

- **IUPAC name:** (4R)-6-N,6-N,4-trimethyl-1,4-dihydro-1,3,5-triazine-2,6-diamine; hydrochloride
- **Molecular formula:** C6H14ClN5
- **Molecular weight:** 191.66 gm/mol
- **Category:** Hypoglycemic agent
- **Dose:** 1500mg twice daily.
- **Description:** Available in white amorphous form.
- **Storage:** Sealed storage away from moisture.
- **Solubility:** Freely soluble in in water and organic solvent.
- **Melting Point:** 239.90˚C
- **Boiling point: -** 269.3–271.9°C.
- **Brand name:** Twymeeg [(14)]

3. MECHANISM OF ACTION: -

Emerging evidence from lab (in vitro) and animal/human studies (in vivo) suggests that Imeglimin has strong blood sugar-lowering effects and helps regulate glucose levels through various pathways. In the following sections, we will discuss the potential molecular mechanisms that explain how Imeglimin works (Figure 4).

Fig 4 Possible Molecular Mechanisms by Which Imeglimin Improves Glucose Homeostasis



3.1 Imeglimin Insulin Sensitivity: -

Imeglimin helps the body respond better to insulin, which is important for managing conditions like type 2 diabetes (T2DM) and gestational diabetes. In these conditions, the body's cells—like those in fat, muscles, and the heart—become resistant to insulin, making it harder for glucose (sugar) to enter the cells. Imeglimin works by boosting insulin's ability to do its job through different pathways. For example, it increases the activity of a protein called Akt, which is involved in insulin signaling. Studies, like one from 2015 by Vial and his team, showed that Imeglimin improved insulin sensitivity in mice on a high-fat diet. Another 2015 study by Pacini and his team found that Imeglimin also helped people with T2DM by making their beta cells more responsive to insulin. Although the exact ways Imeglimin works are still being explored, it may help by increasing the presence of Glut-4 (a protein that helps cells absorb glucose) and by improving insulin receptor function**.** [(15)]

3.2 Imeglimin and Gluconeogenesis.: -

Hepatic gluconeogenesis is a natural process where liver cells produce glucose from other sources. In people with diabetes, this process becomes too active, leading to high blood sugar levels. Imeglimin is a medication that has been used to reduce this excessive glucose production in the liver. In 2011, researchers led by Fouquieria showed that Imeglimin lowered glucose production by reducing the activity of two important enzymes (PEPCK and G6Pase) in liver cells from rats. In 2012, Wagner and colleagues found that Imeglimin improved blood sugar balance in diabetic mice by controlling glucose production in the liver. In 2014, Vial and his team discovered that Imeglimin also reduces glucose production by preventing lactic acid buildup in the liver through a mitochondrial pathway. All of this research suggests that Imeglimin helps lower blood sugar levels and reduce hyperglycemia by suppressing excess liver glucose production. [(15)]

3.3 Imeglimin, β-Cell Function, and Insulin Secretion: -

Research shows that Imeglimin helps protect beta cells and increase insulin production when glucose is present. In 2016, Perry and his team found that Imeglimin improves blood sugar levels and lowers HbA1c by increasing insulin release and helping pancreatic cells work better in diabetic mice. Another 2016 study by Hallakou-Bozec found that Imeglimin boosts insulin release after meals by using a process that depends on NAD and a salvage pathway, with stronger effects at higher doses in diabetic rats. In 2015, Pacini and his team showed that Imeglimin protected beta cells and improved their function, which helped regulate blood sugar in diabetic environments. In 2018, Lablanche and colleagues added more evidence, showing that Imeglimin prevents beta cell death by reducing damage from high glucose levels through its effects on mitochondria. They also found that Imeglimin increases the number of beta cells by blocking certain mitochondrial pores. Overall, growing research suggests that Imeglimin supports better blood sugar control by helping beta cells function more effectively. [(15)]

3.4 Imeglimin and Mitochondrial Function: -

Mitochondrial dysfunction is common in diabetes, which makes it harder for insulin-dependent cells like fat cells, heart cells, and muscle cells to respond properly to insulin. It also negatively affects pancreatic beta cells, reducing their ability to produce and release insulin in response to glucose. Preserving mitochondrial function is, therefore, important in managing diabetes. Some research suggests that Imeglimin can improve mitochondrial function in diabetic patients. For example, a 2015 study by Vial and colleagues showed that Imeglimin improved mitochondrial function by enhancing certain enzyme activities, promoting fatty acid breakdown, and balancing the composition of fats in the mitochondria of diabetic animals. This led to better glucose control. Another study by Detaille et al. in 2016 found that Imeglimin helped protect mitochondrial function in cultured human endothelial cells by regulating specific mitochondrial processes. [(15)]

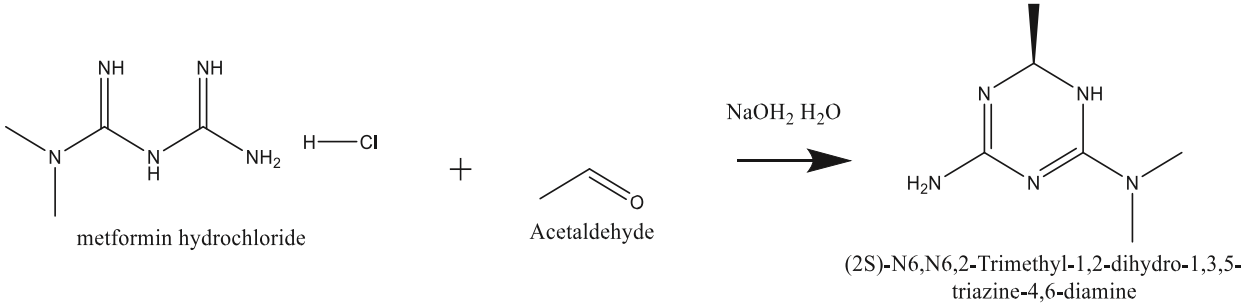
3.5 Imeglimin and Oxidative Stress: -

Oxidative stress is a condition where there is an imbalance between harmful free radicals and the body's antioxidant defenses. This imbalance plays a key role in the development of diabetes and its complications. Oxidative stress can interfere with insulin signaling, leading to insulin resistance. Recent studies suggest that Imeglimin, a drug, has antioxidant properties that help reduce the production of free radicals and restore balance in the body's redox state. For instance, in 2015, Vial and colleagues showed that Imeglimin lowered oxidative stress by reducing the production of free radicals in mitochondria, which improved blood sugar control. Similarly, in 2016, Detaille and his team found that Imeglimin decreased mitochondrial free radicals in human cells, further supporting its potential benefits. [(15)]

4. METHODS OF IMEGLIMIN: -

4.1 Synthesis of Imeglimin: -

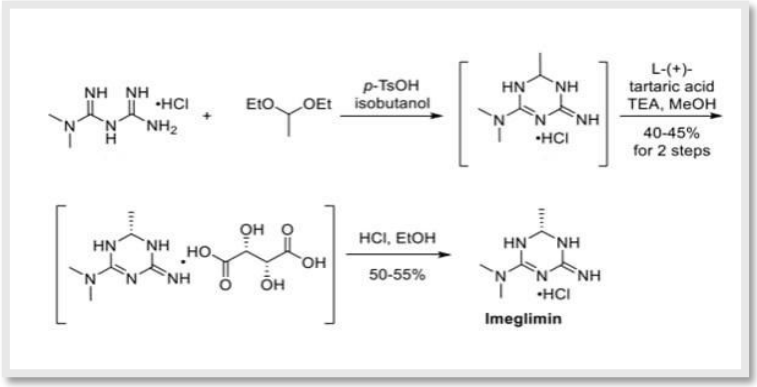
Fig 5: - Synthesis of Imeglimin drug[(16)]



4.2.Synthesis Steps of Imeglimin: -

Imeglimin hydrochloride is synthesized using metformin hydrochloride as a raw material by chemical reaction. The specific synthesis steps are as follows:

Fig 6- Synthesis Steps of Imeglimin



The image illustrates the synthesis pathway of Imeglimin, which involves the following steps:

a) Condensation Reaction:

React compound (a guanidine hydrochloride salt) with compound (ethyl isobutyrate) using p-toluene sulfonic acid (p-TsOH) as a catalyst in isobutanol as the solvent. This reaction forms the intermediate

b) Resolution with Tartaric Acid:

Intermediate is then reacted with L- (+)-tartaric acid, triethylamine (TEA), and methanol (MeOH) to form the chiral intermediate. This step yields 40-45% for the two reactions combined.

c) Hydrolysis and Salt Formation:

Treat intermediate with hydrochloric acid (HCl) in ethanol (EtOH). This final step produces Imeglimin hydrochloride with a yield of about 50-55%

This synthesis involves the formation of a guanidine intermediate, chiral resolution with tartaric acid, and final conversion to the hydrochloride salt form of Imeglimin. [17]

5. EVALUATION PARAMETERS OF IMEGLIMIN: -

5.1 Solubility: -

A. Solubility in organic solvents: -

Here's the solubility of Imeglimin in various organic solvents:

a) Methanol and Acetonitrile (Soluble):-

Solubility in methanol and acetonitrile suggests compatibility with polar organic solvents. Useful for analytical methods (e.g., HPLC or LC-MS) where these solvents are often used as mobile phases.

b) Acetone (Soluble):-

Solubility in acetone indicates moderate compatibility with non-polar organic solvents. Useful for solvent-based drug formulation processes like crystallization or purification.

c) Chloroform (Slightly Soluble):-

Minimal solubility in non-polar solvents like chloroform suggests limited hydrophobic character. Indicates Imeglimin is primarily hydrophilic in nature.

B. Solubility in water: -

Here's the solubility of Imeglimin in water:

- **Water (Freely Soluble):-**

a. Freely soluble drugs dissolve readily in water, making water-based formulations feasible.

b. This property supports the drug's potential for oral administration and absorption in aqueous biological environments like gastrointestinal tract.

C. Buffer Solubility:-

a. Acidic Buffers (pH 4-6):

Solubility is typically highest in this range. Likely due to protonation of the compound enhancing its hydrophilicity.

b. Neutral to Slightly Alkaline Buffers (pH 6-8):-

Moderate solubility is observed, making this range ideal for physiological studies.

c. Highly Alkaline Buffers (pH >8):-

Solubility may decline due to potential deprotonation of functional groups or reduced ionic interactions.[18]

5.2 Stability: -

Here's a detailed overview of the stability of Imeglimin:-

A. Temperature Stability:-

a. Short-term stability:

Imeglimin maintains its stability when exposed to temperatures between 25°C and 40°C for up to 6 hours. This indicates that the compound can tolerate brief periods of elevated temperatures without significant degradation

b. Long-term stability:

Over extended periods, Imeglimin remains stable when stored at 2°C to 8°C for up to 12 months. This suggests that refrigeration conditions are optimal for preserving its stability over time.

B. pH Stability:-

a. Stable pH range:-

Imeglimin is chemically stable within the pH range of 4.5 to 7.4, making it suitable for use in mildly acidic to neutral environments.

b. pH-dependent degradation:-

Beyond the stable pH range, degradation rates increase significantly. Acidic conditions (pH < 4.5) and basic conditions (pH > 7.4) accelerate the breakdown of Imeglimin, leading to the formation of degradation products.

C. Light Stability:-

a. Sensitivity to light exposure:-

Imeglimin is particularly sensitive to light, especially in the UV range at 254 nm, which can cause photochemical reactions.

b. Photodegradation:-

Prolonged exposure to light leads to photodegradation, resulting in chemical alterations and the formation of degradation products. This emphasizes the need for proper storage in light-protective packaging, such as amber-colored containers.

D. Oxidation Stability:-

a. Resistance to oxidative conditions:-

Imeglimin demonstrates stability under oxidative stress, including exposure to hydrogen peroxide (H_2O_2) and oxygen (O_2). This resistance to oxidation enhances its shelf life in aerobic environments.

b. Antioxidant properties:-

Imeglimin has intrinsic antioxidant properties, which may reduce the impact of oxidative stress on its stability, providing an additional layer of protection against degradation.[19]

5.3 Melting point: -

The melting point of Imeglimin is approximately 232–234°**.**
Importance of Melting Point for Imeglimin:

a. Drug Purity and Identification:-

The melting point is a key physical property used to confirm the identity and purity of Imeglimin during its manufacturing and quality control processes. Impurities can lower or broaden the melting point range.

b. Formulation Development:-

Knowledge of the melting point helps pharmaceutical scientists design formulations. It influences the choice of excipients and manufacturing methods, such as tableting or encapsulation.

c. Stability:-

A high melting point (like Imeglimin's) generally suggests good thermal stability, making it less likely to degrade at standard processing temperatures.

d. Storage and Handling:-

Stability at high temperatures ensures Imeglimin can be stored and transported without significant risk of melting or decomposition.

e. Crystallinity and Bioavailability:-

The melting point can give insights into the crystalline nature of Imeglimin, which can affect its dissolution rate and, ultimately, its bioavailability.[20]

5.4 Boiling point: -

The boiling point of Imeglimin is approximately 269.3–271.9°C.
Importance of Thermal Properties (Boiling Point):-

a. Formulation Stability:-

Thermal properties help in determining the conditions for drug stability during manufacturing, storage, and transport.

b. Pharmaceutical Processing:

Knowledge of thermal behavior (like melting or decomposition points) is critical in processes such as crystallization, drying, or sterilization.

c. Chemical Integrity: -

Ensuring that the compound remains chemically stable under different conditions prevents degradation and maintains efficacy.[21]

5.5 PKa:

Imeglimin has a pika of approximately 7.2. This value helps explain its ionization state and solubility properties, as it indicates that at physiological pH (~7.4), it exists in both ionized and unionized forms.

The pKa of a compound like Imeglimin can vary slightly depending on the solvent, ionic strength, and temperature, as these conditions influence the dissociation of its ionizable groups. Imeglimin has a guanidine moiety, which typically shows a basic pKa value (around 9.2).

A. Solvent:-

a) In aqueous solutions (water), the pKa of Imeglimin is around 9.2.
b) In less polar solvents or mixed solvents, the pKa could shift slightly, as the stabilization of charged species (protonated/deprotonated forms) depends on the solvent's polarity.

B. Ionic Strength:-

a) Increasing ionic strength (adding salts) can influence the activity coefficients of ions in solution, leading to slight shifts in the measured pKa
b) High ionic strength often stabilizes charged species, potentially lowering the pKa.

C. Temperature:-

Higher temperatures generally reduce pKa due to increased molecular motion and changes in the ionization equilibrium. For basic groups like guanidine, this effect might decrease the pKa by 0.01–0.03 units per degree Celsius.[22]

6. BRAND PRODUCTS OF IMEGLIMIN:-

6.1 Imenorm 500 mg Tablet:-

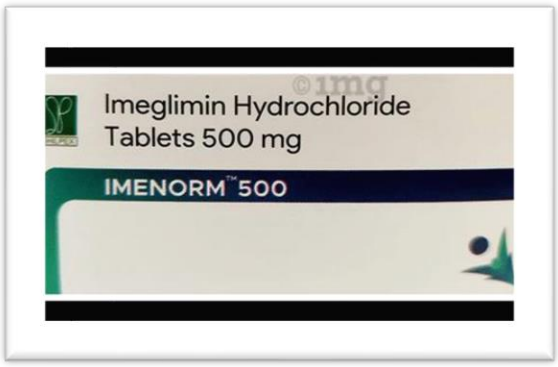


Fig 7 Imenorm 500 mg Tablet

- API (Active Pharmaceutical Ingredient) :-Imeglimin
- Manufacturer by: Shilpex Pharmysis
- Strength: - 500mg
- Medicine name: - Imenorm 500 [23]

6.2 Imezemic 500 mg tablet: -

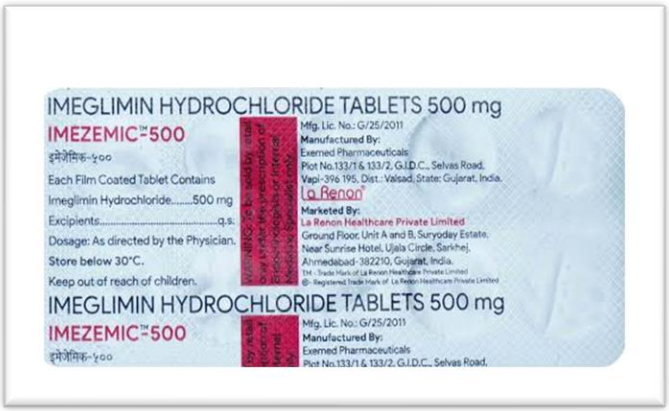


Fig 8 Imezemic 500 mg Tablet

- Medicine name: - Imezemic 500
- Manufactured by: - La Renon Healthcare Pvt Ltd

- API: - Imeglimin
- Markets: India, Asia-Pacific, Latin America, and other emerging markets
- Storage: - Store at 20-25°C (68-77°F) [24]

6.3 Lupimeg 500mg Tablet:

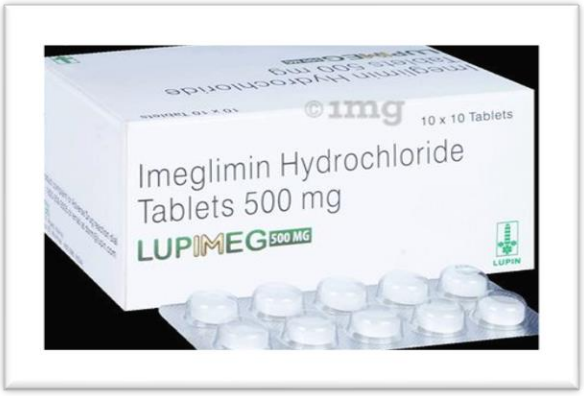


Fig 9 Lupimeg 500 mg Tablet

- Medicine name: - Lupimeg 500
- API: - Imeglimin
- Manufactured by: - Lupin Ltd
- Strength: - 500mg
- Storage: - Store at 20-25°C (68-77°F) [25]

6.4 Imextor 1000mg Tablet: -

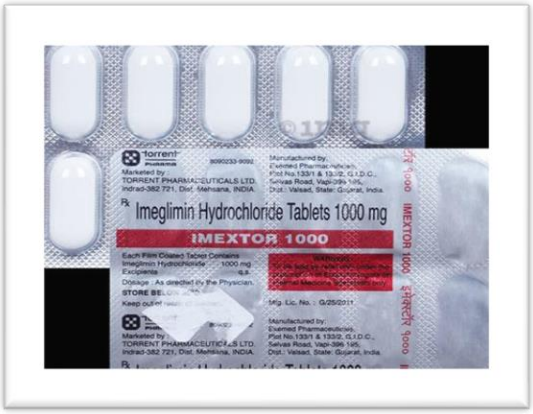


Fig 10 Imextor 1000 mg Tablet

- Medicine name: - Imextor 1000
- API: - Imeglimin
- Manufactured by: -Torrent Pharmaceuticals
- Directions for Use: -Imextor SR 1000 Tablet 10's should be taken as advised by your doctor. Do not take more than the recommended dose.
- Storage: - Store in a cool and dry place away from sunlight [26]

7. CONCLUSION:-

Type 2 Diabetes Mellitus (T2DM) remains a global health challenge driven by complex genetic, metabolic, and lifestyle factors. Understanding its pathophysiology, including insulin resistance, beta-cell dysfunction, and the role of hepatic glucose production, is critical for effective management. Imeglimin, a novel therapeutic agent, represents a significant advancement in T2DM treatment by targeting these fundamental defects through its multifaceted mechanisms. Its ability to enhance mitochondrial function, reduce oxidative stress, and protect beta-cell health offers a promising approach for improving glycemic control and addressing unmet needs in diabetes care. As research continues to refine our understanding of Imeglimin potential, its integration into clinical practice holds the promise of more comprehensive and individualized diabetes management. However, further long-term studies are needed to evaluate its efficacy, safety, and broader applications in diverse populations.

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