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A Review on Imeglimin Hydrochloride Immediate Release Tablet

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Keywords: Type 2 diabetes (T2DM) (Type 2 Diabetes Mellitus), Glucose-stimulated insulin secretion (GSIS), β-cell, Glucose, Immediate release tablets, Novel drug delivery, Mitochondrial function, Insulin.

ABSTRACT

The oral drug delivery method offers immediate release dosages as well as conventional solid dosages. In the numerous treatments for acute or chronic diseases, standard dose forms such capsules, solid pills; powder, solutions, emulsions, and aerosol suspension have been utilized for many years. These days, the dungarees market is the main place to find this composition as a pharmaceutical product. Nowadays, tablets are the most widely used and recently discovered dosage forms of all the dosages. Owing to its simplicity in self-administration, compactness, and production, as well as its ease of administration and manufacturing. The majority of pharmaceuticals products intended for oral administration that are currently sold dosage form, on the prescription and OTC markets are of the instant release variety, which are intended for immediate drug release for quick absorption. The term "immediate release tablets" refers to those that dissolve quickly and release the medication. An appropriate pharmaceutically suitable diluent or carrier that does not significantly slow down the rate of drug release and/or absorption can be used to deliver immediate release. This term does not include drug formulations that have been adjusted to provide for "controlled," "sustained," "prolonged," "extended," or "delayed" drug release. Imeglimin is the first medication in the "glimin" class of glucose-lowering medications. A novel drug for the treatment of type 2 diabetes mellitus. With type 2 diabetes, addressing abnormalities in both insulin secretion and sensitivity is a requirement for achieving optimal glucose management. Imeglimin's distinct mode of action targets the three pathophysiologic elements of type 2 diabetes – i) excessive hepatic glucose synthesis, ii) poor peripheral glucose uptake by insulin-sensitive tissues, iii) dysfunctional pancreatic beta-cells. Imeglimin primarily increases insulin action, including the capacity to reduce hepatic glucose production and enhance insulin gesturing in both the liver and skeletal muscle. It also increases glucose-stimulated insulin secretion (GSIS) and reserves the mass of beta-cells.

INTRODUCTION

Oral drug administration systems employ both conventional dosage forms and fast release dosage forms. In the treatment of acute and chronic disorders, conventional dose forms such tablets, capsules, pills, powders, solutions, emulsions, suspensions, and aerosols have been used for a very long time. These formulations remain the most significant pharmaceutical items on the market today. When a medication is provided using a conventional dosage form, the bloodstream concentration gradually rises to a therapeutic level, is maintained for a while, and then finally decreases to a sub therapeutic level, rendering the medication pharmacologically inactive.

There is a maximum safe concentration and a minimum effective concentration for each specific medicine. Fluctuations in plasma concentration may cause drug levels to swing either excessively high, resulting in toxic/side effects, or too low, resulting in ineffectiveness. Furthermore, adherence to the recommended dosage interval affects a patient's plasma medication concentration at a specific time.

For increasing markets and indications, extending product life cycles, and creating opportunities, novel drug delivery systems are developed. The most common method for achieving systemic effects is oral administration because it is simple to consume, pain-free, adaptable, and most importantly, patient-compliant. Tablets are the preferred solid dosage form because to patient compliance, highly precise dosing, and efficient production. Because of the small cost of therapy, suitability of manufacturing, and high levels of patient compliance, the oral route remains the best way to administer therapeutic drugs. For a given therapeutic situation, many patients require an immediate commencement of effect, necessitating an instantaneous release of the medication.

Type 2 diabetes (T2DM) affects more than 380 million people worldwide, and it's predicted that figure will increase to more than 590 million by the year 2035. To address this global epidemic, numerous organizations both public and private have devoted a lot of time, effort, and money to treatment, prevention, and education. Despite greatest efforts, the prevalence of T2DM is still rising, particularly in light of the growing elderly population, rising obesity rates, and expanding numbers of high-risk ethnic groups.

However, in order to establish and sustain long-term glycemic control, diabetes' physiologic and progressive nature necessitates a combination of pharmaceutical therapy and lifestyle

changes. Excessive hepatic glucose synthesis, reduced peripheral glucose absorption by insulin-sensitive tissues, and insufficient insulin secretion are the main physiologic abnormalities of T2DM.

Imeglimin is the first medication in the "glimin" class of glucose-lowering medications. A novel drug for the treatment of type 2 diabetes mellitus. With type 2 diabetes, addressing abnormalities in both insulin secretion and sensitivity is a requirement for achieving optimal glucose management. Imeglimin's distinct mode of action targets the three pathophysiologic elements of type 2 diabetes – i) excessive hepatic glucose synthesis, ii) poor peripheral glucose uptake by insulin-sensitive tissues, iii) dysfunctional pancreatic beta-cells.

They consist of Imeglimin is a special medication due to its variety of effects, which appear to make it a potential novel antidiabetic agent.

Imeglimin primarily increases insulin action, including the capacity to reduce hepatic glucose production and enhance insulin signaling in both the liver and skeletal muscle. It also increases glucose-stimulated insulin secretion (GSIS) and preserves the mass of beta-cells. Imeglimin Hydrochloride is a better potential target for the treatment of diabetes because it also targets mitochondrial bioenergetics. Hypoglycemia is an extremely rare side effect of Imeglimin hydrochloride. Imeglimin is a superior and suitable option for the treatment of hyperglycemia in people who have become resistant to insulin therapy or who are unable to achieve the target HbA1c with other anti-diabetic medications because it has the ability to deal with insulin resistance and it also improves insulin secretion from the pancreas.

***DEFINITION*:**

Immediate release tablets are ones that dissolve quickly and disintegrate to release the medication. A suitable diluent or carrier that is acceptable from a pharmacological standpoint and does not significantly slow down the rate of drug release and/or absorption can be used to deliver an immediate release. This phrase does not apply to drug formulations that have been adjusted to provide for "controlled," "sustained," "prolonged," "extended," or "delayed" drug release.

The term "release" refers to the delivery (or presentation) of the drug from the formulation to the gastrointestinal tract, to body tissues, and/or into systemic circulation. For gastrointestinal

tract release, the release occurs in pH values such as pH=1 to 3, particularly at, or about, pH=1.

Imeglimin is the first drug in a new class of oral anti-diabetic medications known as "glimins" that include tetrahydrotriazine. Its identification was made possible via an in vivo phenotypic screen (based on rodent antihyperglycemic efficacy), followed by additional chemical modification of a lead compound (Figure 1 depicts the chemical structure).

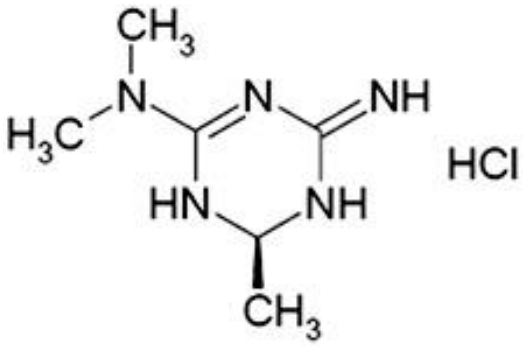

Figure 1

Imeglimin may have an effect on the three primary pathophysiologic factors that contribute to type 2 diabetes: decreased muscle glucose uptake, excessive hepatic gluconeogenesis, and increased beta-cell death. As compared to Metformin and Sitagliptin, Imeglimin improves hemoglobin A1c and fasting plasma glucose in a similar manner.

The fundamental mechanism of Imeglimin involves targeting mitochondrial bioenergetics and enhancing mitochondrial performance. The activity of the mitochondrial respiratory chain complex is modulated by Imeglimin, and the generation of reactive oxygen species is decreased. Imeglimin has been demonstrated to increase glucose-stimulated insulin production by enhancing P-cell glucose responsiveness in type 2 diabetes patients and to enhance insulin sensitivity in a mouse model of diabetes, allowing for the restoration of normal glucose tolerance. Imeglimin has recently been demonstrated to block the opening of the mitochondrial permeability transition pore, a recognized cause of cell death, in human endothelial cells without impairing mitochondrial respiration. This study raises the possibility of end organ protection (e.g., kidney or heart).

ENHANCED INSULIN ACTION BY IMEGLIMIN

Imeglimin can amplify insulin activity, according to a number of lines of evidence, in addition to its notable benefits in reversing -cell dysfunction.

Imeglimin improves the in vivo activity of insulin. There have also been reported direct actions that increase glucose absorption in skeletal muscle cells and decrease gluconeogenesis in hepatocytes.

Molecular Mechanisms

Improved mitochondrial function

Given Imeglimin's effects on several organs and cell types, it is not surprising that mitochondrial dysfunction which affects numerous tissues in T2D—might be responsible for the pleiotropic positive phenotypic changes brought about by Imeglimin treatment. Imeglimin has a number of known effects that have been shown to modulate mitochondrial function and produce potentially advantageous downstream sequelae, as shown in Figure 2.

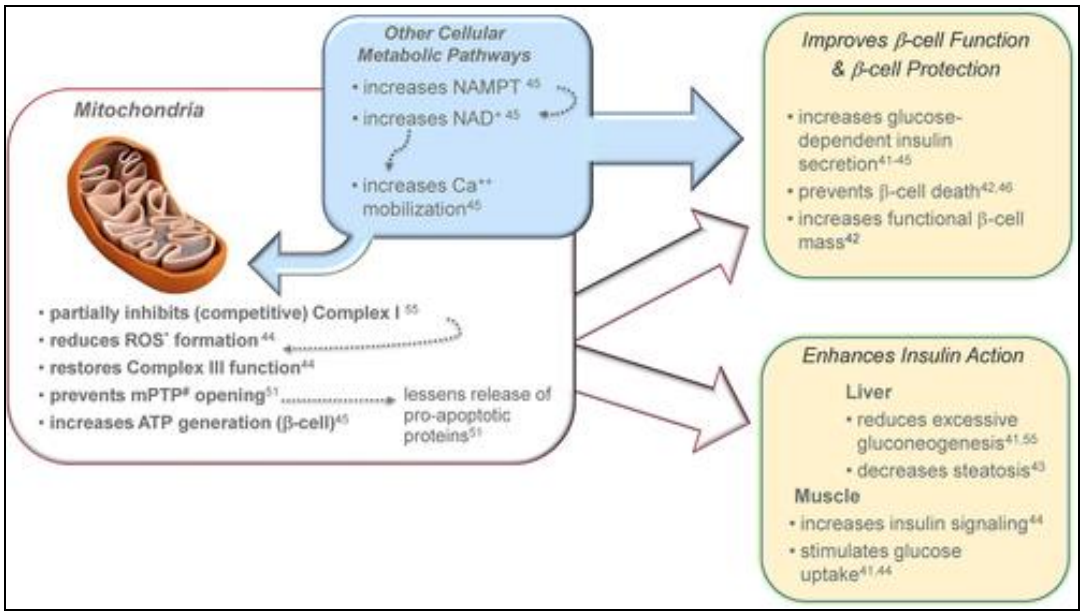

Figure 2

Imeglimin improves ATP production and raises the ATP/ADP ratio in sick pancreatic islets, suggesting a general improvement in mitochondrial function. However, when obligate mitochondrial fuels like leucine or succinate are used, Imeglimin's ability to boost GSIS is still present. Imeglimin also encourages the synthesis of NAD+ in diabetic GK rat islets, as will be discussed more below. Cellular NADH content remained unchanged in this situation, however the NAD/NADH ratio increased dramatically by 30%–31%. Although there was no net increase in total islet NADH, an increase in the NAD+ pool raises the possibility of a

greater supply of the reducing equivalents required to power oxidative phosphorylation along the mitochondrial electron transport chain.

Using mitochondria purified from animals with diet-induced diabetes who had liver tissue treated with Imeglimin, respiration improvements were assessed. More particular, Imeglimin partially inhibited Complex I while partially restoring inadequate Complex III activity. By measuring H2O2 production with succinate as a substrate, this rebalancing effect was linked to a significant decline in excessive disease-associated ROS generation. Together, these findings suggest a potential role for a reduction in ROS produced by reverse electron flow via Complex I. This study also identified possible positive effects of Imeglimin on cardiolipin content and other mitochondrial structure-related elements. Imeglimin's ability to inhibit ROS generation by reducing reverse electron transport through Complex I was duplicated using human endothelial cells (HMEC-1), although no discernible decrease in cellular oxygen consumption was seen.

FORMULATION ASPECTS IN DEVELOPING IRDDS:

The traditional methods for creating tablets with immediate release are listed below. The following describes the traditional method used to prepare immediate release tablets:

1. The method of moulding tablets

2. The mass extrusion method

3. Using stable dispersions

4. Using direct compression

5. The wet granulation method.

Criteria for immediate release drug delivery system:

If the dosage is solid, it should quickly dissolve or disintegrate in the stomach.

For liquid dose forms, compatibility with taste masking is required.

Be transportable without posing a fragility risk.

After being taken orally, it shouldn't leave much or any residue in the mouth.

Have little susceptibility to environmental factors like temperature and humidity.

Be inexpensively produced utilising standard processing and packaging machinery.

Quick medication breakdown and absorption, which could result in a quick start to action.

Merits of Immediate Release Drug Delivery System:

Increased convenience and better compliance.

The capacity to deliver liquid medication's benefits in the form of a solid formulation.

Adaptable and compatible with current packaging and processing equipment.

It is economical.

Increased pharmaceutical composition solubility.

Reduced disintegration and dissolving times for oral dosage formulations with instant release.

Challenges to Develop IRDDS

It ought to quickly dissolve or disintegrate in the stomach.

Be transportable without posing a fragility risk.

Feel good in the mouth.

After oral administration, there shouldn't be any, little, or no residue left in the mouth.

Should not be overly sensitive to changes in temperature and humidity.

Be inexpensively produced utilising standard processing and packaging machinery.

Quick medication breakdown and absorption, which could result in a quick start to action.

Tablet Excipients and their functionalities:

The quality and performance of the delivery system are greatly influenced by the excipients used in its design. Despite the fact that excipients are typically thought of as nontoxic, there are some known excipient-induced toxicities, such as renal failure and death from diethylene glycol, osmotic diarrhoea from ingesting mannitol, hypersensitivity reactions from lanolin, and cardiotoxicity from propylene glycol.

In dosage formulations for immediate release, excipients balance the qualities of the active ingredients. To avoid contact with the active ingredients, this necessitates a thorough

understanding of the chemistry of these excipients. Another concern that formulators must deal with is how much these substances will cost.

Tablets contain a number of inert substances known as additives or excipients in addition to the active ingredients.

Different excipients are:

1. Diluent
2. Adhesive and Binder
3. Disintegrants
4. Lubricants and glidants
5. Film forming material
6. Opacifier & Plasticizer
7. Film smoothening agent
8. Coating solvents

Evaluation of Post –compression parameter: [4], [6], [7]

Appearance:

The tablets were examined visually for capping, chipping, and lamination.

Tablet Dimensions/ Thickness:

Using a calibrated vernier calliper, thickness and diameter were measured. Tablets of each formulation were chosen at random, and each tablet's thickness was measured. The average values were computed using ten tablets of each formulation type. It is written in millimetres.

Hardness:

The hardness of a tablet determines how resistant it is to shipping, breakage, storage, transportation, and handling before use. We used the Monsanto hardness tester to measure the hardness of 20 tablets for each formulation. The tester's two jaws were placed around the tablet's oblong axis.

The measurement at this moment should be zero kg/cm2. The knob was then rotated while applying constant force until the tablet broke. At this moment, the value was noted.

Friability:

The strength of a tablet is measured by its friability. The following approach was done to test the friability using the Roche Friabilator. This test uses a plastic chamber that rotates at a speed of 25 rpm while dropping the tablets to a distance of 6 inches after each revolution to submit a number of tablets to the combined effects of shock and abrasion. Six pre-weighed tablets were used as a sample, which was placed in the Roche friabilator and run for 100 revolutions, or 4 minutes. Afterwards the tablets were reweighed and dusted. Most people consider a weight decrease of less than 1% to be acceptable.

Weight variation test:

20 tablets of each kind of formulation were individually weighed using an electronic balance to determine weight variation. The average weight was then determined, and the individual tablet weight was compared with the average value to determine the deviation in weight (IP/BP).

Table: 1 Specifications for Tablets as per IP/BP

Specifications for tablets as per IP/BP		
Sr No.	**Average Weight of Tablet**	**% Deviation**
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 or more	5

Drug Content Uniformity:

Each batch of 10 tablets was precisely weighed and pulverized. Weight the amount of powder equivalent to 100 mg of Imeglimin, and then mix it with 100 ml of phosphate buffer 7.5 in a volumetric flask. From this, 10 ml was pipetted out and then diluted to 100 ml with the standard solution. The resulting solution was filtered, and the amount of Imeglimin was determined using phosphate buffer as a blank in a 296nm assay.

In vitro disintegration time:

Disintegration is the term for the breaking down of a tablet into smaller pieces. Using disintegration test equipment in accordance with IP/BP regulations, the in-vitro disintegration time of a tablet was calculated.

In-Vitro dissolution Studies:

For the purpose of this study, in vitro dissolution tests were performed in phosphate buffer (PH 7.5) 0.1N HCl for 30 minutes to determine whether the formulation was capable of instantaneous drug delivery.

Evaluation Stability Study:

The stability of the active ingredient in the completed product must be a major consideration in any reasonable design and evaluation of dosage forms for medications in order to determine its approval or rejection. A medication is said to be stable if its chemical or biological activity does not fall below a set threshold of stated potency and its physical features have not changed noticeably or negatively during the time period after the formulation's manufacture and packaging.

CONCLUSION

The majority of patients want a drug's therapeutic activity to start working quickly, which is what these dosage forms provide. These tablets with quick release provide higher patient compliance and many more benefits than other dose forms. This review work was done with an aim to design an immediate release oral dosage forms and evaluation of the tablets, excipients used for immediate release tablets, mechanism of action and also various parameters.

Imeglimin is a unique oral drug that is first-of-its-kind and is intended to attack important pathophysiological elements of T2D. Its mode of action involves simultaneous enhancements of insulin activity in vital organs like the liver and skeletal muscle as well as improved pancreatic cell function. As shown in multiple different cell types, the molecule modifies mitochondrial activity at the cellular level, enhancing cellular energy metabolism and preventing cell death brought on by excessive ROS production or other insults. In islet β-cells, a further impact is being produced through increased NAD+ production and improved Ca++ mobilization.

Imeglimin Hydrochloride Immediate Release Tablet is discussed in general terms here, along with its mode of action and a number of other factors. As opposed to a systematic review, the purpose of this paper is to describe how Imeglimin Hydrochloride Immediate Release Tablet treats Type 2 diabetes (T2DM).

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