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FORMULATION DEVELOPMENT OF SAXAGLIPTINE MICROPARTICULATED DRUG DELIVERY SYSTEM FOR ENHANCING BIOAVAILABILITY AND STABILITY

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ABSTRACT
This study investigates the design, development, and evaluation of sustained-release Saxagliptin microparticles. This approach facilitated an assessment of the concentration of coating material influenced the drug release rate. The solvent evaporation method proved effective in producing discrete, spherical microparticles characterized by good flowability and minimal stickiness. a few formulation techniques and analytical methods for Saxagliptin have been reported[15-21], Therefore, this investigation seeks to design and develop novel microparticles of Saxagliptin aimed at treating diabetes[22]. This approach focuses on creating a controlled release formulation using a lower drug dose, thereby aiming to achieve consistent plasma drug concentrations. This may lead to enhanced patient compliance due to reduced dosing frequency, improved therapeutic efficacy, and minimized side effects resulting from a more controlled drug release profile. This study aims to develop a microparticle-based drug delivery system for Saxagliptin, its short biological half-life of approximately 3.1 hours necessitates frequent dosing (twice daily), which can contribute to non-adherence. Currently available in conventional tablet forms (2.5-5 mg/day), controlled release formulations present a promising solution. microparticles can encapsulate active ingredients, protecting them from degradation and facilitating their transport to specific sites within the body[13]. Their unique size and surface characteristics also allow for functionalization, enabling enhanced interaction with biological systems and improved efficacy in medical applications[14].

Keywords: Formulation, Microparticles, Saxagliptin, diabetes, therapeutic efficacy

1. INTRODUCTION
Oral drug administration is by far the most preferable route for taking medications. However, their short circulating half-life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. This results in pill burden and consequently, patient complains. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profile is to release the drug in a controlled manner and site specific manner (Vinodbhaiet al., 2011). Microparticles are a type of drug delivery systems where

the particle size ranges from one micron (one thousandth of a mm) to few mm. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Hence, they play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects (Lengyel et al., 2019).

Type 2 diabetes is a chronic condition that affects the way the body processes blood glucose[1]. It is characterized by insulin resistance, where the body's cells do not respond effectively to insulin, combined with a gradual decline in insulin production from the pancreas. This leads to elevated blood glucose levels, which can result in various health complications over time, such as heart disease, kidney damage, and neuropathy. Risk factors for developing type 2 diabetes include obesity, sedentary lifestyle, family history, and advanced age[2]. Management typically involves lifestyle changes, such as diet and exercise, along with medications when necessary to help regulate blood sugar levels and maintain overall health[3].

The increasing prevalence of type 2 diabetes, associated with modern lifestyles, has prompted intensified research into effective management strategies[4]. Millions of individuals grapple with this non-insulin-dependent form of diabetes, which necessitates long-term treatment often characterized by high rates of non-adherence. To address this challenge, sustained release drug delivery systems hold significant promise for improving healthcare quality. In the context of type 2 diabetes, maintaining consistent drug levels in the bloodstream is crucial. While novel drug development for type 2 diabetes is ongoing, equal emphasis is being placed on creating appropriate delivery systems that prolong drug action and enhance patient compliance by reducing dosing frequency[5].

Saxagliptin is a second-generation sulfonylurea, oral antihyperglycemic medication used to manage type 2 diabetes mellitus[6]. It belongs to the class of drugs known as DPP-4 inhibitors, which work by enhancing the body's incretin levels, leading to increased insulin secretion and decreased glucagon release in response to meals[7]. This dual action helps lower blood sugar levels while minimizing the risk of hypoglycemia[8]. Saxagliptin is often prescribed alongside diet and exercise and can be used alone or in combination with other diabetes medications to achieve better glycemic control[9,10].

1.1 DIABETES MELLITUS

There are two prominent forms of diabetes: -

Type 1 Diabetes Mellitus or Insulin Dependent Diabetes Mellitus (IDDM)

Although it can afflict individuals of any age, children and young adults are most affected. Environmental and genetic factors impact susceptibility to this autoimmune illness.

Type 2 Diabetes Mellitus or Non-Insulin Dependent Diabetes Mellitus (NIDDM)

Although it primarily affects adults, children and adolescents are increasingly experiencing it. Type 2 diabetes is characterized by an accumulation of glucose in the blood due to either insufficient insulin production or insulin resistance, which is the body's inability to respond to the effects of insulin (Whiting et al., 2011). Because type 2 diabetes symptoms can take years to manifest or be identified, many people with the disease go years without realizing they have it. In the meantime, the body is being harmed by high blood glucose levels. They are frequently only identified until diabetic problems have arisen (IDF, 2019).

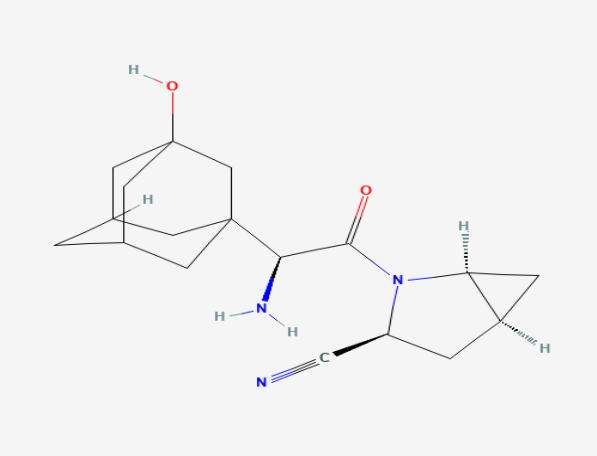
2. SAXAGLIPTIN SUMMURY

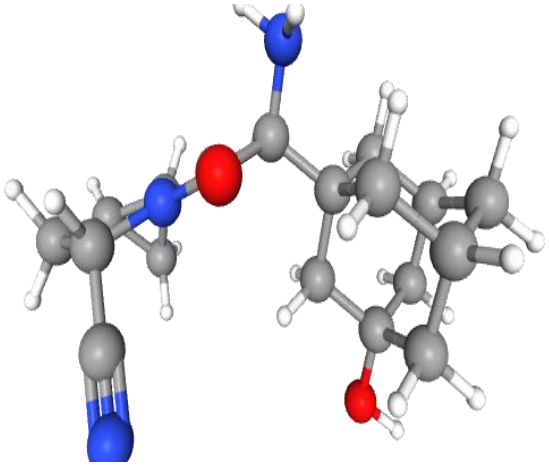
Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor which is used in combination with diet and exercise in the therapy of type 2 diabetes, either alone or in combination with other oral hypoglycemic agents. Saxagliptin is a relatively new medication and has yet to be implicated in causing clinically apparent liver injury.

Saxagliptin Anhydrous is the anhydrous form of saxagliptin, a potent, selective and competitive, cyanopyrrolidine-based, orally bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4), with

hypoglycemic activity. Saxagliptin is metabolized into an, although less potent, active mono-hydroxy metabolite.

2.1 Chemical Structure of Saxagliptin 2D AND 3D





2.3 IUPAC Name

(1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile.

2.4 Pharmacodynamics

Post-administration of saxagliptin, GLP-1 and GIP levels rise up to 2- to 3- fold. Because it is very selective of DPP-4 inhibition, there are fewer systemic side effects. Saxagliptin inhibits DPP-4 enzyme activity for a 24-hour period. It also decreased glucagon concentrations and increased glucose-dependent insulin secretion from pancreatic beta cells. The half maximal inhibitory concentration (IC50) is 0.5 nmol/L. Saxagliptin did not prolong the QTc interval to a clinically significant degree.

2.5 Saxagliptin Mechanism of action

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor antidiabetic for the treatment of type 2 diabetes. DPP-4 inhibitors are a class of compounds that work by affecting the action of natural hormones in the body called incretins. Incretins decrease blood sugar by increasing consumption of sugar by the body, mainly through increasing insulin production in the pancreas, and by reducing production of sugar by the liver. [Bristol-Myers Squibb Press Release] DPP-4 is a membrane associated peptidase which is found in many tissues, lymphocytes and plasma. DPP-4 has two main mechanisms of action, an enzymatic function and another mechanism where DPP-4 binds adenosine deaminase, which conveys intracellular signals via dimerization when activated. Saxagliptin forms a reversible, histidine-assisted covalent bond between its nitrile group and the S630 hydroxyl oxygen on DPP-4. The inhibition of DPP-4 increases levels active of glucagon like peptide 1 (GLP-1), which inhibits glucagon production from pancreatic alpha cells and increases production of insulin from pancreatic beta cells.

2.6 Toxicity

Adverse reactions reported in ≥5% of patients treated with saxagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, urinary tract infection, and headache.

3. MORPHOLOGY OF MICROPARTICLES

Microencapsulation is a technology used to entrap solids, liquids, or gases inside a polymeric matrix or shell (Khandbahaleet al., 2020). Microparticles are particulate dispersions or solid particles. Two

general micromorphologies of microparticles can be distinguished- microcapsules and microspheres. Microcapsule is a system in which drug containing core is completely surrounded by a polymer shell. The core can be solid, liquid or gas; the shell is a continuous, porous or non-porous polymeric layer (González et al., 2019). Microcapsules are classified into three basis categories as monocored, polycored and matrix type (Rani et al., 2021).Monocored microcapsules have a single hollow chamber within the capsule. Polycore microcapsules have a number of different sized chambers within the shell. Matrix type micro particle has the active ingredients integrated within the matrix of the shell. However, the morphology of the internal structure of a micro particle depends on the shell materials and the micro encapsulation methods that are employed.

3.1 IMPORTANT FEATURES OF MICROCAPSULES

The most significant feature of microcapsules is their microscopic size that allows for a huge surface area, for example the total surface area of 1µm has been reported to be about 60m. The total surface area is inversely proportional to the diameter. This large surface area is available for sites of adsorption and desorption, chemical reactions, light scattering etc (Timinet al., 2017).

3.2 ADVANTAGES

This type of drug delivery systems mainly provides the encapsulated material to reach the area of action without getting adversely affected by the environment through which it passes. Pharmaceutical and biomedical advantages of microparticle include:

- Taste and odor masking. Eg: Fish oils, sulfa drugs.
- Protection of drugs from environment.
- Particle size reduction for enhancing solubility of the poorly soluble drug.
- Sustained or controlled drug delivery Eg: KCl, Ibuprofen.
- Targeted release of encapsulated material.
- Live cell encapsulation. Eg: Resealed erythrocytes (figure: 5).
- Conversion of liquid to free flowing solids.
- Delay of volatilization.
- Separation of incompatible components Eg: Excipients, buffers and other drugs.
- Improvement of flow of powder.
- Safe handling of toxic substances.
- Aid in dispersion of water insoluble substance in aqueous media.

3.3 DISADVANTAGES

Although the advantages of microparticles are impressive there are certain limitations.
These include:

- The costs of the materials and processing of the controlled release preparation, which may be substantially higher than those of standard formulations.
- The fate of polymer matrix and its effect on the environment.
- The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
- Reproducibility is less.
- Process conditions like change in temperature, pH , solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
- The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents and the cost, time probability of success in securing government registration of the product, if required.

4. APPLICATIONS

Microparticulate drug delivery offers several applications for drugs having poor Bioavailability (Pulivendalaet al., 2020).A number of pharmaceutical encapsulated products are currently on the

market, Such as aspirin, theophylline and its derivatives, vitamins, antihypertensive, potassium chloride, progesterone and contraceptive hormone combinations.

- This technology is widely used in the design of controlled release and sustained release dosage forms.
- To mask the taste of bitter drugs.
- Reduction of Gastrointestinal irritations.
- These delivery system offers easy handling and storage of liquids by converting into pseudo-solids
- The hygroscopic nature of an active drug can be minimized.

CONCLUSION

Saxagliptinis an oral hypoglycemic (anti-diabetic drug) of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. Saxagliptin is used as monotherapy or in combination with other drugs for the treatment of type 2 diabetes. It does not appear to decrease the risk of heart attacks or strokes. It increases the risk of hospitalization for heart failure by about 27%. Like other DPP-4 inhibitors, it has relatively modest HbA1c lowering ability, is associated with a relatively low risk of hypoglycemia, and does not cause weight gain. Saxagliptin improved mean HbA1c levels (relative to placebo) in a 24-week trial in people with type 2 diabetes. Combination therapy with saxagliptin and metformin was more effective than saxagliptin or metformin monotherapy. When the relative benefits of increasing the dose of a sulfonylurea or adding saxagliptin were assessed in a study of 768 patients, combination treatments were shown to have a significantly greater impact on fasting blood glucose than increasing the tested glibenclamide dose alone.

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