Review Article

Nanoparticles formulations of insulin glargine: an overview

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Abstract

Insulin glargine, a long-acting insulin analog, is a cornerstone in the management of diabetes mellitus. However, its therapeutic efficacy is often hindered by limitations such as variable pharmacokinetics and suboptimal bioavailability. Nano-particle formulations have emerged as promising strategies to address these challenges, offering improved stability, prolonged action, and targeted delivery. This article provides an in-depth exploration of nano-particle formulation of insulin glargine, covering synthesis methods, physicochemical characterization, in vitro release kinetics, pharmacokinetic and pharmacodynamic evaluation, and long-term efficacy studies. Various types of nano-particles, including liposomes, polymeric nanoparticles, and lipid nanoparticles, are discussed in detail, along with their potential advantages and challenges. Furthermore, preclinical and clinical studies assessing the therapeutic potential of nano-particle encapsulated insulin glargine are reviewed, shedding light on the translational opportunities and future directions in this field

Keywords:nanoparticle,diabetes,controlled

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. It affects millions of people worldwide and poses significant challenges in terms of management and treatment. Insulin therapy remains the mainstay for controlling blood glucose levels in individuals with diabetes, particularly in those with type 1 diabetes and advanced type 2 diabetes. Among the various insulin analogs available, insulin glargine stands out as a long-acting basal insulin that provides consistent glycaemic control with a reduced risk of hypoglycaemia.[1,2] Despite its therapeutic efficacy, insulin glargine has limitations related to its pharmacokinetic profile, including variable absorption rates and prolonged duration of action, which may result in suboptimal glycaemic control and patient non-compliance. Addressing these limitations requires innovative approaches to improve the pharmacokinetic and pharmacodynamic properties of insulin glargine while maintaining its therapeutic efficacy and safety. In recent years, nano-particle formulation has emerged as a promising strategy to enhance the delivery of therapeutic agents, including insulin. Nano-particles, defined as particles with sizes ranging from 1 to 1000 nanometres, offer several advantages for drug delivery, such as increased drug stability, controlled release kinetics, targeted delivery to specific tissues, and improved bioavailability. These properties make nano-particles particularly well-suited for overcoming the challenges associated with conventional insulin formulations, including insulin glargine.[3]Nano-particle formulation of insulin glargine involves encapsulating the insulin molecule within nano-scale carriers, such as liposomes, polymeric nanoparticles, or lipid nanoparticles. These carriers protect the insulin from enzymatic degradation, facilitate its transport across biological barriers, and control its release kinetics, thereby improving its pharmacokinetic profile and therapeutic efficacy.[4]This introduction sets the stage for exploring the nano-particle formulation of insulin glargine in detail. Throughout this article, we will delve into the synthesis methods, physicochemical characterization, in vitro release kinetics, pharmacokinetic and pharmacodynamic evaluation, and long-term efficacy studies of nano-particle formulations of insulin glargine. By comprehensively examining the current state of research in this field, we aim to elucidate the potential of nano-particle formulation as a transformative approach for optimizing insulin therapy in diabetes management

1.Nano-particles synthesis and encapsulation techniques.

Synthesis Methods:

Nanoprecipitation: Nanoprecipitation involves the spontaneous precipitation of insulin glargine and polymer or lipid components from a solvent mixture into nano-scale particles. This method typically utilizes a water-miscible organic solvent, such as ethanol or acetone, to dissolve insulin glargine and polymers or lipids. The organic phase is then rapidly injected into an aqueous phase under stirring, leading to the formation of nano-particles through the diffusion-controlled precipitation of the drug and excipients. Nanoprecipitation is a simple and scalable technique suitable for

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producing polymeric or lipid-based nano-particles of insulin glargine with controlled size and drug encapsulation efficiency.[5]

Emulsion Techniques:

Solvent Evaporation: In this method, insulin glargine and polymer or lipid components are dissolved in a water-immiscible organic solvent, forming a primary oil phase. The oil phase is then emulsified into an aqueous phase containing surfactants or stabilizers to create a water-in-oil emulsion. Subsequent evaporation of the organic solvent under reduced pressure or gentle heating results in the formation of nano-particles encapsulating insulin glargine. Solvent evaporation is suitable for producing polymeric nano-particles with high drug loading and controlled release properties.[6]

Emulsion Solvent Diffusion: Emulsion solvent diffusion involves dispersing the oil phase containing insulin glargine and polymer or lipid components into an aqueous phase containing a stabilizer or surfactant. The organic solvent diffuses into the aqueous phase, leading to the formation of nano-particles through the precipitation of drug-loaded polymer or lipid material. Emulsion solvent diffusion allows for the encapsulation of insulin glargine in lipid or polymeric nano-particles with tenable size and drug release characteristics.

Encapsulation Techniques:

Direct Encapsulation: Direct encapsulation involves incorporating insulin glargine directly into the nano-particle matrix during synthesis. The drug is typically dissolved or dispersed in the solvent mixture along with polymer or lipid components before nano-particle formation. Direct encapsulation enables uniform distribution of insulin glargine within the nano-particle matrix and allows for precise control over drug loading and release kinetics.[7]

Remote Loading: Remote loading techniques are employed for hydrophilic drugs like insulin glargine, which may have low encapsulation efficiency using direct encapsulation methods. Remote loading involves encapsulating the drug into pre-formed nano-particles after their synthesis. This can be achieved by creating a pH gradient across the nano-particle membrane, facilitating the passive diffusion or active transport of the drug into the nano-particle core. Remote loading techniques offer improved drug loading efficiency and can be utilized to encapsulate hydrophilic drugs like insulin glargine in lipid or polymeric nano-particles.

Surface Modification: Surface modification techniques can be employed to functionalize the surface of nano-particles with targeting ligands, polymers, or stabilizers. Surface modification enhances the stability, biocompatibility, and targeting capabilities of nano-particles for insulin glargine delivery. Techniques such as covalent conjugation, adsorption, or layer-by-layer assembly can be used to modify the surface of nano-particles and tailor their properties for specific applications.[8] In summary, nano-particle synthesis and encapsulation techniques offer versatile approaches for formulating insulin glargine delivery systems with controlled release, enhanced stability, and targeted delivery capabilities. By optimizing synthesis parameters and encapsulation methods, researchers can develop nano-particle formulations that improve the therapeutic efficacy and patient compliance in insulin therapy for diabetes management.

Physicochemical characterization of nano particles.

The physicochemical properties of nano-particles play a crucial role in determining their behaviour, stability, and interactions within biological systems. Understanding these properties is essential for designing effective nano-particle formulations for drug delivery applications, including insulin glargine. Here, we will discuss some key physicochemical properties of nano-particles and their significance in the context of insulin delivery:

Particle Size: Nano-particles are characterized by their small size, typically ranging from 1 to 1000 nanometres. The particle size directly impacts various aspects of nano-particle behaviour, including surface area, drug loading capacity, and cellular uptake. For insulin delivery, smaller particle sizes are often preferred as they can enhance tissue penetration and improve bioavailability.

Surface Charge (Zeta Potential): The surface charge of nano-particles, represented by their zeta potential, influences their stability, dispersibility, and interactions with biological membranes. Positively or negatively charged nano-particles may exhibit different cellular uptake mechanisms and biodistribution profiles. Surface charge modification can be utilized to tailor the pharmacokinetics and tissue targeting of nano-particles loaded with insulin glargine.

Morphology: Nano-particle morphology refers to their shape, structure, and surface topology. Common nano-particle morphologies include spheres, rods, fibres, and vesicles. Morphological features can impact drug loading efficiency, release kinetics, and cellular uptake mechanisms. For insulin glargine delivery, nano-particles with high surface area and controlled morphology may offer improved encapsulation and release characteristics.

Surface Functionalization: Surface functionalization involves modifying the surface of nano-particles with various chemical groups or ligands to impart specific properties or functionalities. Functionalized nano-particles can enhance biocompatibility, target specific cell types or tissues, and facilitate controlled drug release. Surface functionalization strategies can be employed to optimize the pharmacokinetics and tissue specificity of nano-particle formulations of insulin glargine. [9]

Drug Loading Capacity: The drug loading capacity of nano-particles refers to the amount of drug that can be encapsulated or adsorbed onto the nano-particle surface. High drug loading capacity is desirable for maximizing therapeutic efficacy while minimizing the size and dose of nano-particle formulations. Optimization of drug loading parameters is essential to ensure efficient encapsulation of insulin glargine within nano-particles.
Stability: Nano-particle stability encompasses their physical, chemical, and colloidal stability under various storage and physiological conditions. Stability considerations include prevention of aggregation, degradation, and premature drug release. Stable nano-particle formulations are essential for

maintaining drug integrity and ensuring consistent therapeutic outcomes over time.

Overall, the physicochemical properties of nano-particles play a critical role in determining their suitability for drug delivery applications, including insulin glargine delivery. By understanding and optimizing these properties, researchers can develop nano-particle formulations that offer enhanced drug stability, controlled release kinetics, and targeted delivery for improved therapeutic efficacy in diabetes management

In vitro release kinetics.

In vitro release kinetics studies are essential for evaluating the drug release behaviour and kinetics of nano-particles encapsulating insulin glargine. These studies provide insights into the release profile, release mechanisms, and factors influencing drug release from the nano-particles.

1.Dissolution studies: Dissolution studies are fundamental for assessing the release behaviour of insulin glargine from nano-particle formulations. These studies provide valuable insights into the dissolution profile, dissolution kinetics, and factors influencing drug release from nano-particles.

Methods for Dissolution Studies:

Sample Preparation: Insulin glargine-loaded nano-particles are dispersed or suspended in a dissolution medium, typically aqueous buffers or simulated physiological fluids. The dispersion is then introduced into the dissolution apparatus, and drug release is monitored over time.

Sampling and Analysis: At predetermined time intervals, samples of the dissolution medium are withdrawn from the dissolution apparatus, filtered if necessary, and analysed for insulin glargine concentration using analytical techniques such as high-performance liquid chromatography (HPLC) or enzyme-linked immunosorbent assay (ELISA).

Validation and Quality Control: Dissolution studies should be performed under validated and reproducible conditions, with appropriate controls and quality assurance measures in place. Method validation includes assessment of linearity, accuracy, precision, and specificity of the analytical method used for drug quantification.

Release mechanism for nano particles of insulin glargine: Understanding the release mechanisms governing insulin glargine from nano-particles is crucial for optimizing drug delivery formulations and predicting their behaviour in physiological settings. Nano-particles release insulin glargine through various mechanisms, including diffusion, erosion, swelling, degradation, and combinations thereof. Here, we'll explore these release mechanisms in detail:

Diffusion-Controlled Release:

Fiskian Diffusion: In diffusion-controlled release, insulin glargine molecules diffuse passively through the polymeric matrix or lipid bilayers of the nano-particles driven by concentration gradients. Fick's law of diffusion governs the rate of drug release, with release kinetics following a square root of time dependency. [10]

Case II Transport: In some cases, the release of insulin glargine from nano-particles may deviate from Fiskian diffusion, exhibiting non-Fiskian or Case II transport behaviour. This occurs when polymer relaxation and erosion processes contribute significantly to drug release, leading to a linear release profile over time.

Erosion-Controlled Release:

Polymer Erosion: Erosion-controlled release occurs when the polymeric matrix of the nano-particles undergoes degradation or erosion in the dissolution medium, leading to the release of encapsulated insulin glargine. Polymer erosion can be influenced by factors such as polymer composition, molecular weight, crosslinking density, and environmental conditions.

Surface Erosion: Surface erosion occurs when the polymer matrix erodes primarily from the surface of the nano-particles, resulting in a gradual reduction in particle size and drug release. Surface erosion kinetics depend on the diffusion of water molecules into the polymer matrix and subsequent hydrolysis or enzymatic degradation of polymer chains. (11. Sah, H., & Chan, H.-K. (2023)

Swelling-Controlled Release:

Polymer Swelling: Swelling-controlled release occurs when the polymeric matrix of the nano-particles absorbs water from the dissolution medium, leading to swelling and expansion of the particles. Insulin glargine release is facilitated by the diffusion of drug molecules through the swollen polymer matrix, with release kinetics governed by polymer swelling and relaxation dynamics.

Diffusion through Swollen Matrix: Swelling of the polymeric matrix increases the mesh size and porosity, allowing insulin glargine molecules to diffuse more freely through the nano-particles. The extent of swelling and polymer-water interactions influence drug release kinetics and release profiles.

Degradation-Controlled Release:

Enzymatic Degradation: Degradation-controlled release occurs when enzymes present in the dissolution medium or biological environment catalyse the degradation of the polymeric matrix, leading to the release of insulin glargine. Enzymatic degradation kinetics depend on factors such as enzyme concentration, substrate specificity, and polymer susceptibility to enzymatic hydrolysis.

Hydrolytic Degradation: Hydrolysis of ester or amide bonds in the polymer backbone can trigger degradation-controlled release of insulin glargine from nano-particles. Hydrolytic degradation kinetics are influenced by factors such as pH, temperature, polymer composition, and hydrophilicity.

Combination of Mechanisms:

Many nano-particle formulations exhibit a combination of release mechanisms, with contributions from diffusion, erosion, swelling, and degradation processes. The relative importance of each mechanism depends on formulation parameters, polymer properties, drug loading, and environmental conditions. Understanding the interplay between different release mechanisms is essential for predicting drug release behaviour, optimizing formulation design, and tailoring release kinetics to achieve desired therapeutic outcomes.

5.Pharmacodynamic evaluation for nano particles of insulin glargine: Pharmacodynamic evaluation plays a crucial role in assessing the efficacy and therapeutic effects of nano-particles encapsulating insulin glargine. These evaluations provide insights into the biological activity, pharmacological profile, and glucose-lowering effects of nano-particle formulations in preclinical and clinical settings.

Bio-availability studies: Bioavailability studies for nano-particles of insulin glargine are essential for assessing the extent and rate of drug absorption following administration, comparing the systemic exposure to insulin glargine from nano-particle formulations with conventional insulin formulations. These studies provide critical insights into the pharmacokinetics, distribution, and bioavailability of insulin glargine encapsulated in nano-particles. Here, we'll explore the principles, methods, and significance of bioavailability studies for nano-particles of insulin glargine[12]

Principles of Bioavailability Evaluation:

Systemic Exposure: Bioavailability studies measure the systemic exposure of insulin glargine following administration of nano-particle formulations via various routes, such as subcutaneous, intramuscular, or intravenous injection. Systemic exposure reflects the fraction of the administered dose that reaches the systemic circulation and is available for pharmacological action. [13]

Pharmacokinetic Parameters: Bioavailability studies assess pharmacokinetic parameters, including maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), area under the plasma concentration-time curve (AUC), and half-life (t½), to characterize the absorption, distribution, metabolism, and elimination of insulin glargine from nano-particle formulations.

Comparative Analysis: Bioavailability studies compare the pharmacokinetic profiles of nano-particle formulations with conventional insulin formulations, such as insulin glargine solution or suspensions. Comparative analysis evaluates the relative bioavailability, absorption kinetics, and duration of action of nano-particle formulations, providing insights into their pharmacological performance and therapeutic equivalence.

Methods for Bioavailability Evaluation:

Animal Studies: Preclinical bioavailability studies are typically conducted in animal models, such as rats, mice, rabbits, or non-human primates, to assess the pharmacokinetics and bioavailability of nano-particle formulations. Animals are administered nano-particle formulations via the intended route of administration, and blood samples are collected at predetermined time points for analysis.

Blood Sampling and Analysis: Blood samples collected during bioavailability studies are analysed for insulin glargine concentration using analytical techniques such as enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or high-performance liquid chromatography (HPLC). Pharmacokinetic parameters are determined by fitting plasma concentration-time data to appropriate mathematical models.

Human Studies: Clinical bioavailability studies are conducted in human subjects to evaluate the pharmacokinetics and bioavailability of nano-particle formulations in vivo. Subjects are administered nano-particle formulations via the intended route of administration, and blood samples are collected for analysis. Clinical studies adhere to ethical guidelines and regulatory requirements for human research.

Significance and Interpretation:

Pharmacokinetic Profile: Bioavailability studies provide insights into the absorption, distribution, and elimination kinetics of insulin glargine from nano-particle formulations. Pharmacokinetic parameters derived from bioavailability studies help characterize the systemic exposure and duration of action of nano-particle formulations compared to conventional insulin formulations.

Formulation Optimization: Comparative analysis of bioavailability data facilitates formulation optimization and selection of optimal formulation parameters, such as particle size, surface properties, and excipient composition, to enhance drug absorption and bioavailability. Formulation modifications aimed at improving bioavailability can lead to enhanced therapeutic efficacy and patient compliance in insulin therapy. [14]

Regulatory Approval: Bioavailability studies are essential for regulatory approval of nano-particle formulations of insulin glargine for clinical use. Comparative bioavailability assessments provide scientific evidence of therapeutic equivalence or superiority of nano-particle formulations compared to conventional insulin formulations, supporting their registration and marketing authorization.

In summary, bioavailability studies are critical for assessing the pharmacokinetics, distribution, and bioavailability of nano-particle formulations encapsulating insulin glargine. By elucidating the systemic exposure and pharmacological profile of nano-particle formulations, these studies inform formulation optimization, regulatory approval, and clinical translation of novel insulin delivery systems for diabetes management.

Plasma concentration and time profile: The plasma concentration-time profile for nano-particles of insulin glargine provides valuable insights into the pharmacokinetics, distribution, and elimination kinetics of the drug following administration. This profile depicts the concentration of insulin glargine in the systemic circulation over time, reflecting its absorption, distribution, metabolism, and excretion from the body. Here, we'll explore the principles, methods, and significance of the plasma concentration-time profile for nano-particles of insulin glargine:

Principles of Plasma Concentration-Time Profile:

Absorption Phase: Following administration of nano-particles encapsulating insulin glargine, the drug is absorbed into the bloodstream via the subcutaneous or intramuscular route. The absorption phase is characterized by an increase in plasma concentration as insulin glargine is released from the nano-particles and enters the systemic circulation.

Distribution Phase: Once in the bloodstream, insulin glargine is distributed to target tissues and organs, such as muscle and adipose tissue, where it exerts its pharmacological effects. The distribution phase reflects the systemic distribution and tissue uptake of insulin glargine following absorption from the injection site.

Elimination Phase: Insulin glargine is metabolized and eliminated from the body primarily by enzymatic degradation and renal clearance. The elimination phase is characterized by a decrease in plasma concentration as insulin glargine is metabolized and excreted, eventually reaching undetectable levels.

Methods for Plasma Concentration-Time Profile Assessment:

Blood Sampling: Plasma concentration-time profiles for nano-particles of insulin glargine are determined by collecting serial blood samples at predetermined time points following administration. Blood samples are centrifuged to separate plasma, which is then stored and analysed for insulin glargine concentration using validated analytical methods, such as ELISA, RIA, or HPLC.

Pharmacokinetic Analysis: Pharmacokinetic parameters, including maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), area under the plasma concentration-time curve (AUC), and elimination half-life (t½), are calculated from the plasma concentration-time data using non-compartmental or compartmental analysis methods. These parameters provide quantitative information on the absorption, distribution, and elimination kinetics of insulin glargine from nano-particle formulations.

Significance and Interpretation:

Pharmacokinetic Profile: The plasma concentration-time profile for nano-particles of insulin glargine elucidates the pharmacokinetic profile and systemic exposure of the drug following administration. Pharmacokinetic parameters derived from the profile, such as Cmax, Tmax, AUC, and t½, provide insights into the absorption,

distribution, metabolism, and elimination of insulin glargine from nano-particle formulations.

Formulation Optimization: Analysis of the plasma concentration-time profile facilitates formulation optimization and selection of optimal formulation parameters, such as particle size, surface properties, and excipient composition, to enhance drug absorption, distribution, and bioavailability. Formulation modifications aimed at improving the plasma concentration-time profile can lead to enhanced therapeutic efficacy and patient compliance in insulin therapy. [15]

Clinical Translation: Plasma concentration-time profiles for nano-particles of insulin glargine are crucial for clinical translation and regulatory approval of novel insulin delivery systems. Comparative analysis of pharmacokinetic parameters with conventional insulin formulations provides scientific evidence of therapeutic equivalence or superiority, supporting their clinical development and commercialization.

Pharmacodynamic assessment: Pharmacodynamic assessment plays a pivotal role in evaluating the glucose-lowering effects, duration of action, and time profile of nano-particles encapsulating insulin glargine. These assessments provide critical insights into the therapeutic efficacy, pharmacological profile, and comparative performance of nano-particle formulations compared to conventional insulin formulations. Here, we'll explore the principles, methods, and significance of pharmacodynamic assessment and comparative studies for nano-particles of insulin glargine:

Pharmacodynamic Assessment:

Glucose-Lowering Effects: Pharmacodynamic studies assess the ability of nano-particles encapsulating insulin glargine to lower blood glucose levels in preclinical and clinical settings. Glucose-lowering effects are evaluated using validated methods such as glucose clamp techniques, continuous glucose monitoring (CGM), or glucose tolerance tests (GTT). These assessments quantify changes in blood glucose concentrations over time following administration of nano-particle formulations, providing insights into their therapeutic efficacy and duration of action.

Duration of Action: Pharmacodynamic assessments determine the duration of action of nano-particle formulations by analysing the time course of glucose-lowering effects relative to conventional insulin formulations. The duration of action reflects the sustained effect and prolonged therapeutic coverage of nano-particle formulations compared to rapid-acting or intermediate-acting insulin preparations.

Time Profile: Pharmacodynamic time profiles depict the onset, peak, and duration of glucose-lowering effects following administration of nano-particle formulations. Time-action profiles provide insights into the kinetics of insulin absorption, distribution, and metabolism, guiding optimal dosing regimens and administration schedules for nano-particle formulations.

Comparative Studies with Conventional Insulin Formulations:

Comparative Efficacy: Comparative pharmacodynamic studies assess the efficacy and glucose-lowering effects of nano-particle formulations relative to conventional insulin formulations, such as insulin glargine solution or suspensions. Comparative efficacy analysis evaluates the superiority, non-inferiority, or equivalence of nano-particle formulations in achieving glycaemic control and maintaining target blood glucose levels.

Duration of Action Comparison: Comparative studies compare the duration of action and sustained effect of nano-particle formulations with conventional insulin formulations using pharmacodynamic time profiles. Extended duration of action and prolonged therapeutic coverage of nano-particle formulations offer advantages in terms of dosing frequency, flexibility, and patient compliance in insulin therapy.

Time-Action Profile Comparison: Comparative pharmacodynamic analyses elucidate the time-course and onset of action of nano-particle formulations relative to conventional insulin formulations. Comparative time-action profiles provide insights into the kinetics of insulin absorption, distribution, and metabolism, facilitating dose optimization and individualized treatment regimens.

Significance and Interpretation:

Therapeutic Efficacy: Pharmacodynamic assessment and comparative studies provide critical data on the therapeutic efficacy, duration of action, and glucose-lowering effects of nano-particles encapsulating insulin glargine. Comparative efficacy analysis informs clinical decision-making and treatment selection, guiding the use of nano-particle formulations in diabetes management.

Formulation Optimization: Comparative pharmacodynamic studies facilitate formulation optimization and selection of optimal formulation parameters, such as particle size, surface properties, and excipient composition, to enhance therapeutic efficacy and duration of action. Formulation modifications aimed at improving pharmacodynamic performance contribute to enhanced glycaemic control and improved patient outcomes.

Clinical Translation: Pharmacodynamic assessments and comparative studies are essential for clinical translation and regulatory approval of nano-particle formulations of insulin glargine. Comparative pharmacodynamic data support the demonstration of therapeutic equivalence or superiority of nano-particle formulations compared to conventional insulin formulations, supporting their clinical development and commercialization.

In summary, pharmacodynamic assessment and comparative studies provide valuable insights into the glucose-lowering effects, duration of action, and time profile of nano-particles encapsulating insulin glargine. By elucidating the pharmacological profile and comparative performance of nano-particle formulations, these studies inform formulation optimization, clinical translation, and regulatory approval of novel insulin delivery systems for diabetes management.

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