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REVIEW

Recent Advances in Glimepiride Solubility Improvement: A Focus on Formulation Technologies – A Narrative Review

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Abstract: Glimepiride, a second-generation sulfonylurea used in the management of type 2 diabetes mellitus, is classified as a Biopharmaceutics Classification System (BCS) Class II drug. Its severely limited aqueous solubility (<0.004 mg/mL at pH <7) leads to erratic and insufficient oral bioavailability, preventing consistent attainment of therapeutic plasma levels. This narrative review analyzes literature published between 2015 and 2025 from databases including PubMed, Scopus, and ScienceDirect. This review critically examines advanced formulation strategies designed to enhance Glimepiride's dissolution rate and aqueous solubility. Approaches are grouped into two categories: (1) solid-state modifications—including solid dispersions, co-crystals, and inclusion complexes—which alter the drug's solid state properties, with co-crystals reported to improve in vivo absorption by up to 2.66-fold; and (2) nanoparticle-based systems such as nanosuspensions and self-nanoemulsifying drug delivery systems (SNEDDS), which increase surface area through particle size reduction, with nanosuspensions achieving up to a 6.58-fold solubility enhancement. The advantages and limitations of these technologies are evaluated to identify the most promising strategies for improving glimepiride's therapeutic performance and supporting better patient outcomes.

Keywords: glimepiride, solubility enhancement, BCS class II, solid-state modification, nanoparticle systems

Introduction

Diabetes mellitus (DM) is a common and complex metabolic disorder characterized by insufficient insulin production from pancreatic cells or diminished binding efficacy of insulin to cell surface receptors.[1] Consequently, diabetes mellitus is a chronic disease that poses a significant global health challenge, requiring effective therapeutic intervention.[2] The global diabetes epidemic, however continues to escalate, with projections indicating 643 million cases by 2030,[3] and of those, 90% of cases are type 2 diabetes mellitus.[4] Among the therapeutic options, sulfonylureas are a class of drugs used in the treatment of type 2 diabetes mellitus, one of which is glimepiride.[5] Glimepiride is a commonly prescribed second generation sulfonylurea utilized for the control of type II diabetes.[6] Its mechanism of action is as a stimulator of pancreatic β cells, with advantages including a single daily dose and effective HbA1c reduction (1.5–2.0%).[7,8] Additionally, glimepiride has several significant advantages over other sulfonylureas, such as a longer duration of effect and a lower tendency to cause hypoglycemia.[2]

However, glimepiride classified as a Biopharmaceutics Classification System (BCS) Class II medication, exhibits strong permeability yet possesses low water solubility, characterized by pH-dependent dissolution properties (<0.004 mg/mL at pH <7).[6,9,10] Solubility is a fundamental physicochemical feature that is crucial in the intricate realm of pharmaceutical development.[11] It is a pivotal factor that affects drug bioavailability and therapeutic efficacy.[12] These physicochemical qualities directly constrain the rate of medication absorption from the gastrointestinal system.[13]

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Consequently, glimepiride frequently has inadequate and inconsistent oral bioavailability, which may impede the attainment of stable therapeutic plasma levels and adversely affect patient clinical outcomes.[14]

This solubility limitation necessitates innovative formulation strategies to enhance drug performance while minimizing adverse effects.[15] To address these restrictions, several formulation modification procedures have been employed. These methodologies can be classified into two primary techniques: solid-state modification and nanoparticle-based delivery systems. This review seeks to provide a critical analysis and thorough comparison of recent advances in various methods designed to enhance the solubility of glimepiride, specifically addressing the advantages, disadvantages, and implementation challenges associated with each strategy to identify the most suitable formulation method.

Challenges of Glimepiride

Glimepiride is a sulfonylurea derivative,[16] with the chemical formula $C_{24}H_{34}N_4O_5S$ (Figure 1) and compound mass of 490.6 g/mol which presents as a crystalline material, white to yellowish white and odorless.[17] Glimepiride is an oral hypoglycemic drug from the third sulfonylurea drug generation that is commonly prescribed within the therapy in patients with type 2 diabetes.[18,19] Glimepiride primarily exerts its antihyperglycemic effect by enhancing insulin secretion from pancreatic β-cells.[20] The dose of glimepiride for type 2 diabetes mellitus therapy reaches 1 to 4 mg once a day.[8] Glimepiride is administered via the oral route, a route widely favored due to its longer half-life and efficacy as a monotherapy, capable of reducing 1.5–2.0% in HbA1c compared to other sulfonylureas. Commercial formulations of glimepiride provide rapid release, attaining peak serum concentrations 2–3 hours after oral administration, lead to a variable release profile. These oscillations may be alleviated by creating continuous and protracted delivery methods that can maintain a consistent medication level in plasma. Consequently, suitable dosage forms must be developed to improve solubility and therapeutic effectiveness.[21] According to the Biopharmaceutics Classification System, glimepiride belongs to Class II exhibiting strong membrane permeability but dissolve poorly in water,[9] and also a weak acid (pKa 6.2)[22] with a lipophilicity (LogP) value of 3.5 with a characteristic melting temperature of 207°C.[6] Furthermore, glimepiride has a pH dependent solubility, which is very low in acidic and neutral aqueous media. At these pH, the solubility of glimepiride is very low <0.004 mg/mL at 37 °C but increases slightly at pH >7 to 0.02 mg/mL. The low water solubility and slow dissolution of glimepiride lead to variable bioavailability and potential treatment failure caused by insufficient drug concentrations in the plasma.[23] Thus, a formulation strategy aimed at increasing the solubility of glimepiride is critically needed.

Formulation Approaches to Enhance the Solubility of Glimepiride

Glimepiride is classified as a Class II drug within the Biopharmaceutical Classification System (BCS), characterized by high permeability but very low aqueous solubility.[24] The poor solubility of Glimepiride in gastrointestinal fluids constitutes the primary obstacle in its oral administration, as it significantly limits both the rate and extent of drug absorption.[25] Consequently, formulation strategies primarily focus on enhancing Glimepiride's solubility. This solubility enhancement is crucial because it generates a higher concentration gradient across the intestinal membrane, thereby facilitating absorption, achieving improved systemic exposure, and ensuring the consistency of the therapeutic effect.

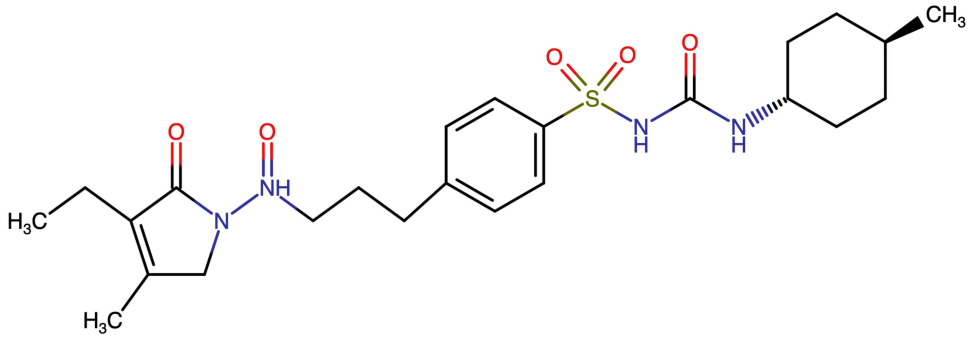

Figure 1 Chemical Structure of Glimepiride.

Contemporary formulation strategies for glimepiride can be conceptually divided into two principal categories: solid-state modification and nanoparticle-based delivery systems (Figure 2). Furthermore, a comprehensive summary of various formulation techniques, including their specific compositions, solubility enhancement results, and mechanisms of action, is presented in Table 1.

Solid Stated Modification

To overcome the solubility-limited bioavailability of glimepiride, solid modification strategies focus on engineering the drug's crystal lattice to create a more thermodynamically favorable state.[33] These strategies, which include the formation of solid dispersions, co-crystals, eutectic mixtures, and inclusion complexes, are designed to enhance apparent solubility and accelerate the dissolution rate. The preparation methods for various solid-state modifications of glimepiride are illustrated in Figure 3.

Solid Dispersion

A solid dispersion is a solid matrix composed of at least two components, namely a drug with low solubility and a carrier that is generally hydrophilic.[34] Multi-component solid dispersions can also be designed using more than two ingredients to improve formulation and therapeutic effectiveness simultaneously. Ternary solid dispersions containing surfactants

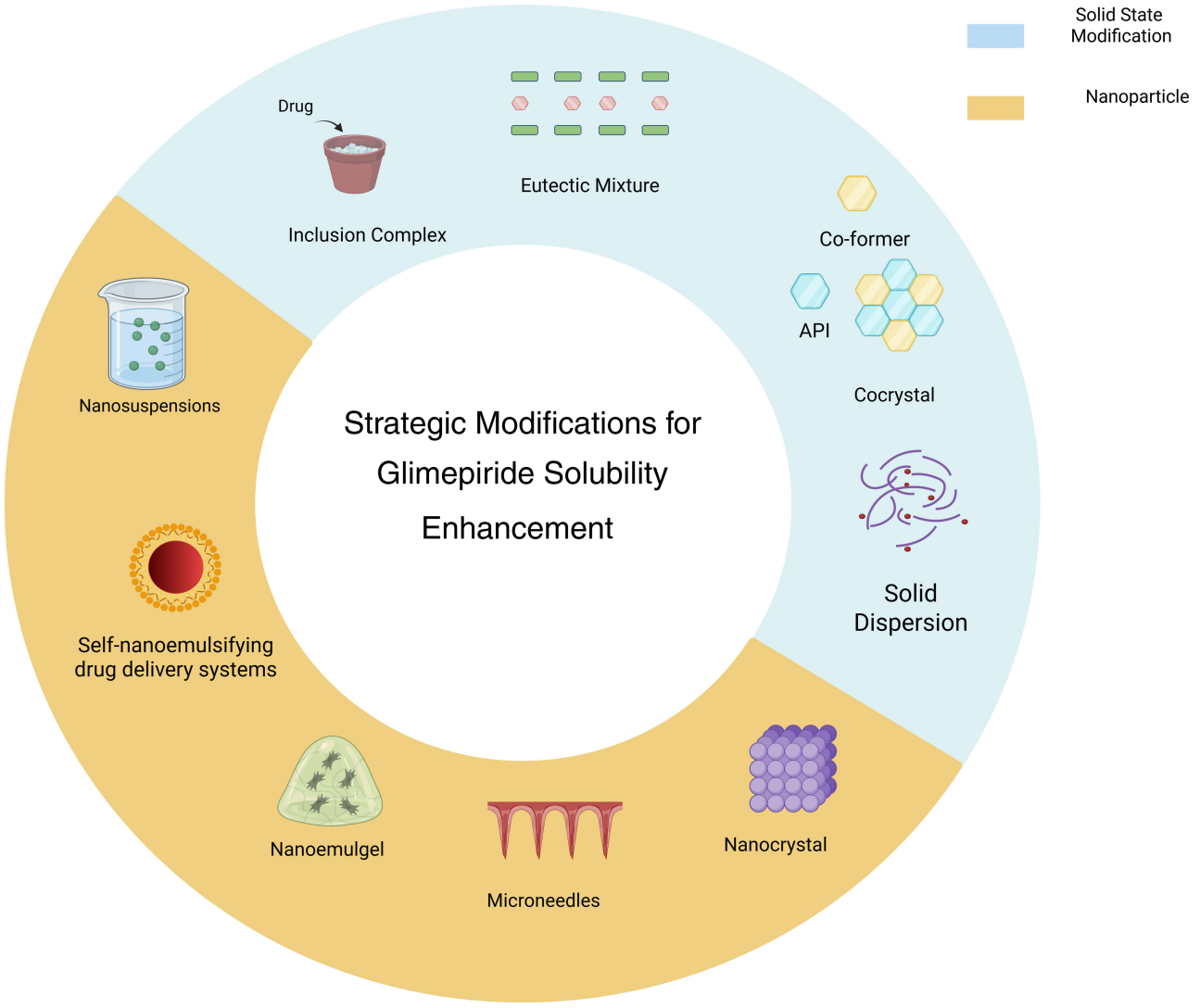

Figure 2 Strategic Modifications for Glimepiride Solubility Enhancement.

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Table 1 Strategies for Enhancing the Solubility of Glimepiride

Categories	Formulation strategy	Preparation Method	Results Solubility	Mechanism of Solubility Enhancement	Reference
Solid-state modifications	Co-crystallization	Ultrasound	60 µg/mL	Modification of the crystal lattice energy through intermolecular hydrogen bonding between the API and a co-former, enhancing thermodynamic stability and solvent affinity.	[23]
	Solid dispersion	Hydrotropy	8.56 µg/mL	Reduction of particle size to a molecular level and transformation of the drug from a crystalline state to a high-energy amorphous state, coupled with improved wettability by hydrophilic carriers.	[26]
		Kneading	192.285 ± 6.325 µg/mL,		[27]
		Solvent evaporation	0.9571 ± 0.005 µg/mL		[22]
		Kneading	16.12 ± 0.001 µg/mL		[28]
	Inclusion complex	Freeze-drying	1.94 µg/mL	Encapsulation of hydrophobic drug molecules within the non-polar cavity of a host (eg, cyclodextrin), while the hydrophilic exterior facilitates interaction with the aqueous medium.	[29]
	Eutectic mixture	Physical grinding	32.5 µg/mL	Reduction of the melting point below that of the individual components, leading to an increased dissolution rate due to simultaneous particle size reduction and crystalline lattice disruption.	[30]
Nanoparticle	Self-nanoemulsifying drug delivery system (SNEDDS)	Extrusion	25.00 ± 0.273 mg/mL	Spontaneous formation of fine oil-in-water (o/w) nanoemulsions in the gastrointestinal tract; the drug remains pre-solubilized in nano-droplets, bypassing the rate-limiting dissolution step.	[16]
		Spontaneous emulsification	40.07 ± 2.05 mg/mL		[16]
	Nanosuspension	Ultrasonication-assisted precipitation	179.26 ± 5.5 µg/mL	Drastic increase in specific surface area (following the Noyes-Whitney equation) through particle size reduction to the nanoscale, which significantly increases saturation solubility.	[31]
		Antisolvent precipitation	149.0 ±5.96 µg/mL		[10]
	Nanoemulgel	Spontaneous emulsification	22.96 ± 0.30 mg/mL	Integration of a nanoemulsion into a gel matrix to provide a high surface area for drug release and improved stability, facilitating better penetration through biological barriers.	[19]
			3.67 ± 0.13 mg/g		[32]
	Microneedles	Micromolding	0.4 g/mL	Mechanical creation of micro-channels in the stratum corneum, allowing the drug to bypass the primary diffusion barrier and reach the systemic circulation or dermal layers directly.	[17]

have been shown to significantly increase the dissolution rate of drugs.[35] Drugs can be dispersed in molecular form in carriers that are crystalline or amorphous to increase their solubility.[36] Solid dispersion is an effective approach for enhancing the solubility of poorly water soluble medicines, such as glimepiride, which has limited bioavailability due to its low solubility in water.[27]

Several researchers have reported successful applications in solid dispersion systems to improve the performance of glimepiride. Where dispersion was carried out using Polyethylene Glycol 4000 (PEG 4000) through kneading, it significantly improved the solubility behavior of glimepiride. Compared to the pure drug, the optimized film formulation showed accelerated in vitro drug dissolution within 10 minutes, with an average disintegration time of 31.33±0.471 minutes.[27] Solubility studies using PVP k40 (Polyvinylpyrrolidone) with the solvent evaporation method have also been shown to increase bioavailability with low water solubility. In this case, the solubility of glimepiride compared to the polymer shows that higher solubility is due to the formation of hydrogen bonds with water to form an amorphous structure, which increases drug release to 1 µg/mL and results in a disintegration time of 13 seconds and an in-vitro drug release profile of 96% at the end of 40 minutes.[22] Overall, this study shows that solid dispersion systems can significantly improve the solubility and release of oral glimepiride in a dosage form that is easy for patients to use. This strategy offers opportunities to improve patient compliance and maximize therapeutic outcomes.

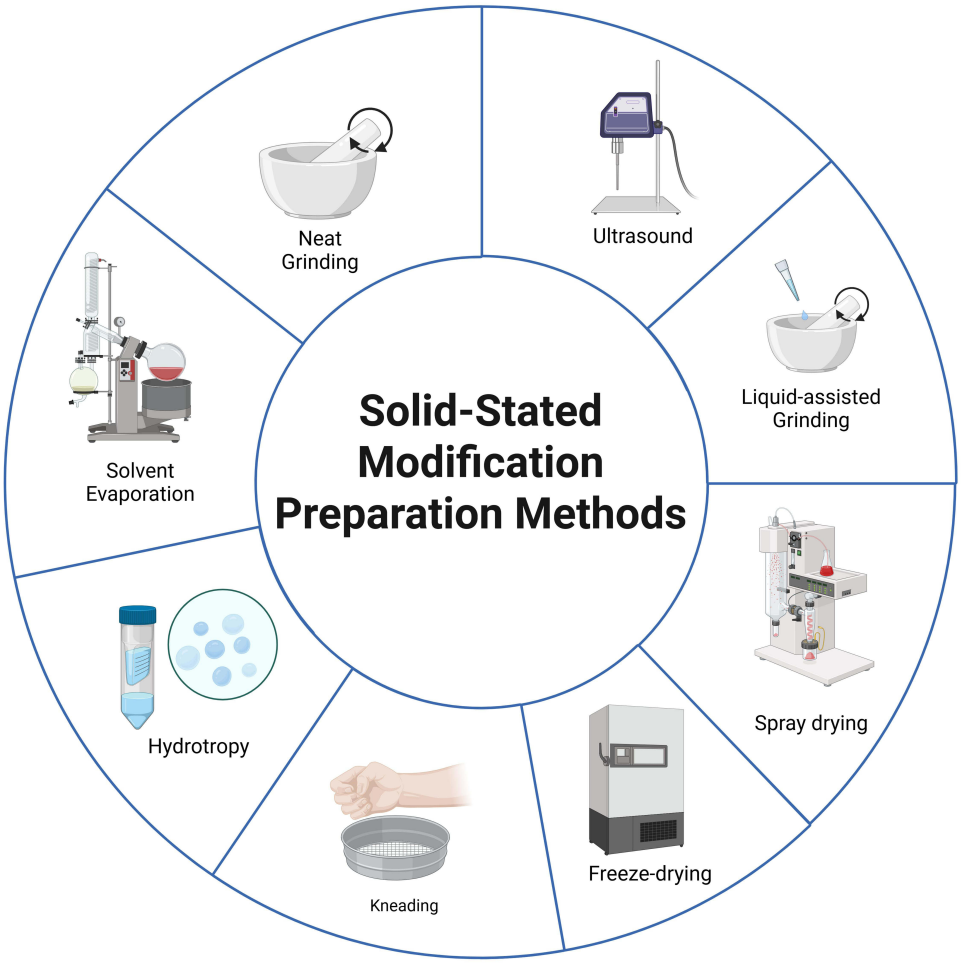

Figure 3 Solid State Modification Preparation Method.

Co-Crystal

Co-crystal technique is an approach in solid drug form design because it can improve physicochemical properties, such as dissolution speed, solubility, bioavailability, and physicochemical stability of an active substance, without any change in pharmacological activity.[37] Co-crystals comprise multiple molecular components that co-exist within a single crystalline structure. The formation process requires a coformer, which interacts with the active substance through hydrogen bonding, thereby improving solubility.[38] Co-crystals can be synthesized using multiple techniques, including supercritical fluid technology, slurry transformation, mechanical milling, antisolvent precipitation, thermal extrusion processing, ultrasound-assisted crystallization, spray dehydration, and evaporative solvent removal.[39] Various types of coformers used in the cocrystal formation process include ascorbic acid, citric acid, oxalic acid, benzoic acid, and succinic acid.[23]

The co-crystal formed with the oxalic acid co-former exhibited superior performance in the conducted research. This formulation showed a solubility increase of 65 µg/mL, and achieved a rapid dissolution rate reaching 71.93%, dissolution in 5 minutes and approximately 97.3% in 120 minutes for the glimepiride co-crystal. Critically, in vivo studies demonstrated a 2.66-fold enhancement in the area under the curve (AUC0-∞), confirming a significant boost in drug absorption.[23] The primary challenge in co-crystal development centers on the difficulty of selecting appropriate co-formers, which often leads to unexpected and undesirable outcomes. These complications include decreased solubility and dissolution rate, the manifestation of the spring and parachute effect, adverse microenvironmental pH changes, alterations in solid-state instability, and the occurrence of polymorphic transitions, all of which can severely compromise the intended benefits of co-crystallization.[40]

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Despite their significant advantages in enhancing solubility, co-crystals face critical stability challenges. They are often susceptible to dissociation or phase transformation back to the original crystalline form when exposed to high humidity or thermal stress during storage. Consequently, careful selection of co-formers and rigorous long-term thermodynamic stability testing are essential to ensure that the improved dissolution performance is maintained throughout the product's shelf life.[41]

Eutectic Mixtures

Eutectic mixtures, also referred to as eutectic solvents are formed through the combination of two or more substances, where at least one acts as a hydrogen-bond acceptor and another as a hydrogen-bond donor.[42] The eutectic mixture technique is applied to two molecules to lower the melting point of the mixture compared to the melting point of each molecule separately. The selected molecules should not undergo interaction to form a new chemical compound. Still, at a certain ratio, they may inhibit the crystallization of each other, thereby causing a decrease in the melting point.[43] The formation of eutectic mixtures follows a process analogous to the melting method used in solid dispersion preparation, involving the fusion of two components followed by controlled solidification. The advantages of eutectic mixtures include very easy to prepare with high purity and low toxicity.[44] The most commonly used technique for preparing eutectic mixtures is a classic and simple one, and very little effort has been made to propose new sophisticated methods.

For glimepiride itself, the formation of a eutectic system with L-arginine using a shared molar ratio was carried out using a grinding method with a mortar and pestle. The formulation of glimepiride and arginine forms an eutectic mixture with a ratio of 1:1 M and an eutectic temperature of 426.9 K, which significantly improves the solubility of glimepiride. This is due to intermolecular interactions, including hydrogen bonding and hydrophobic interactions between glimepiride and L-arginine. These results highlight the potential of eutectic mixtures as a simple yet effective strategy for improving solubility.[30] In addition, the eutectic mixture system of diacerein with 2,4-dihydroxybenzoate formulated as a coformer has been shown to increase solubility, compressibility, and bioavailability, where the manufacturing process uses acetone assisted grinding techniques. Solubility and dissolution studies show an increase of 2 and 1.8 times, respectively, compared to pure diacerein and the control batch. Pharmacokinetic studies prove that bioavailability is 2.1 times higher in the case of eutectics compared to diacerein and its stable properties. Therefore, eutectic mixture system can be a potential means of improving material characteristics.[45]

Inclusion Complex

Inclusion complexes are molecular structures in which hydrophobic drugs are partially or completely enclosed within the cavity of a parent molecule, commonly cyclodextrin.[46–48] The purpose of this encapsulation is to protect the drug from aqueous environments, increase its apparent solubility and dissolution rate without causing any changes.[49] One strategy for increasing the solubility and oral performance of glimepiride is the formation of inclusion complexes with captisol, which is a chemically modified β-cyclodextrin. The process of chemically modifying cyclodextrin aims to maximize solubility, stability, and bioavailability of the drug while minimizing systemic toxicity.[49] The structure of cyclodextrin is very important for drug solubility. Several researchers have found that glimepiride forms a more water-soluble complex with α- and β-cyclodextrin than with γ-cyclodextrin, indicating that structural and functional changes can optimize drug solubility.[50] In the ternary system, cyclodextrin forms both inclusion and non-inclusion complexes with glimepiride, resulting in enhanced solubility of the medication. Depending on the concentration of cyclodextrin in the system, aggregates of 1:1 or 1:2 glimepiride-cyclodextrin inclusion complexes are formed, which can further solubilize the drug by non-inclusion complexation or micelle-like structures.[51]

In studies conducted on the use of captisol with physical mixing or freeze-drying techniques, the solubility of glimepiride was significantly increased compared to unmodified compounds. The increase in solubility was more pronounced with captisol mass ratios of 1:1, 1:2 to 1:3, with inclusion complexes giving optimal results, especially at a ratio of 1:3, when solubility increased by 1.94 μg/mL or nearly tripled.[29] The results of this study are in line with previous reports showing that the use of captisol provides a significant advantage in increasing the water solubility of hydrophobic drugs such as ibuprofen.[52] Although the inclusion complex method offers several advantages, there are challenges that must be considered. The formation of inclusion complexes is often complex and requires high production

costs, particularly when employing specialized techniques such as freeze-drying or chemical modification of cyclodextrin. Additionally, the stability of inclusion complexes can be problematic, especially under various environmental conditions. As a result, not all types of drugs are suitable for this method, as not all hydrophobic drugs can effectively form inclusion complexes with cyclodextrin.[46,53]

Nanoparticles

Nanoparticles are colloidal carriers of submicron dimensions that can encapsulate pharmaceutical compounds, enhancing drug solubility, stability, and absorption in the gastrointestinal tract by augmenting surface area and contact with biological membranes.[54] Nanoparticle methods encompass nanocrystals, microneedles, nanoemulsions, self-nanoemulsifying drug delivery systems, and nanosuspensions, all aimed at enhancing solubility. The various nanoparticle preparation methods suitable for these delivery systems are summarized in Figure 4.

Nanocrystal

Nanocrystals are defined as submicron-sized colloidal drug delivery systems with an average size in the nanometer range (10–800 nm).[55] This approach increases surface area and dissolution rate. The most important factor of nanoparticles is the reduction of particle size to nanoscale dimensions, with an increase in the surface area of the particle in contact with the solvent medium to increase the solubility of the drugs, thereby increasing bioavailability.[56] Nanoparticles can be produced using top-down and bottom-up technologies. The top-down approach involves reducing large particles to the nanometer scale, such as grinding, while the bottom-up method produces nanoparticles from drug molecules in solution, for example through precipitation.[13] In a study conducted, the effect of using PEG 20000 and P90G on particle size reduction and nanocrystal stability was examined using precipitated (GLP-PEG) and complex (GLP-PEG-P90G) formulations with a drug: polymer ratio of 1:1 proved to be the most ideal in developing stable nanocrystals because

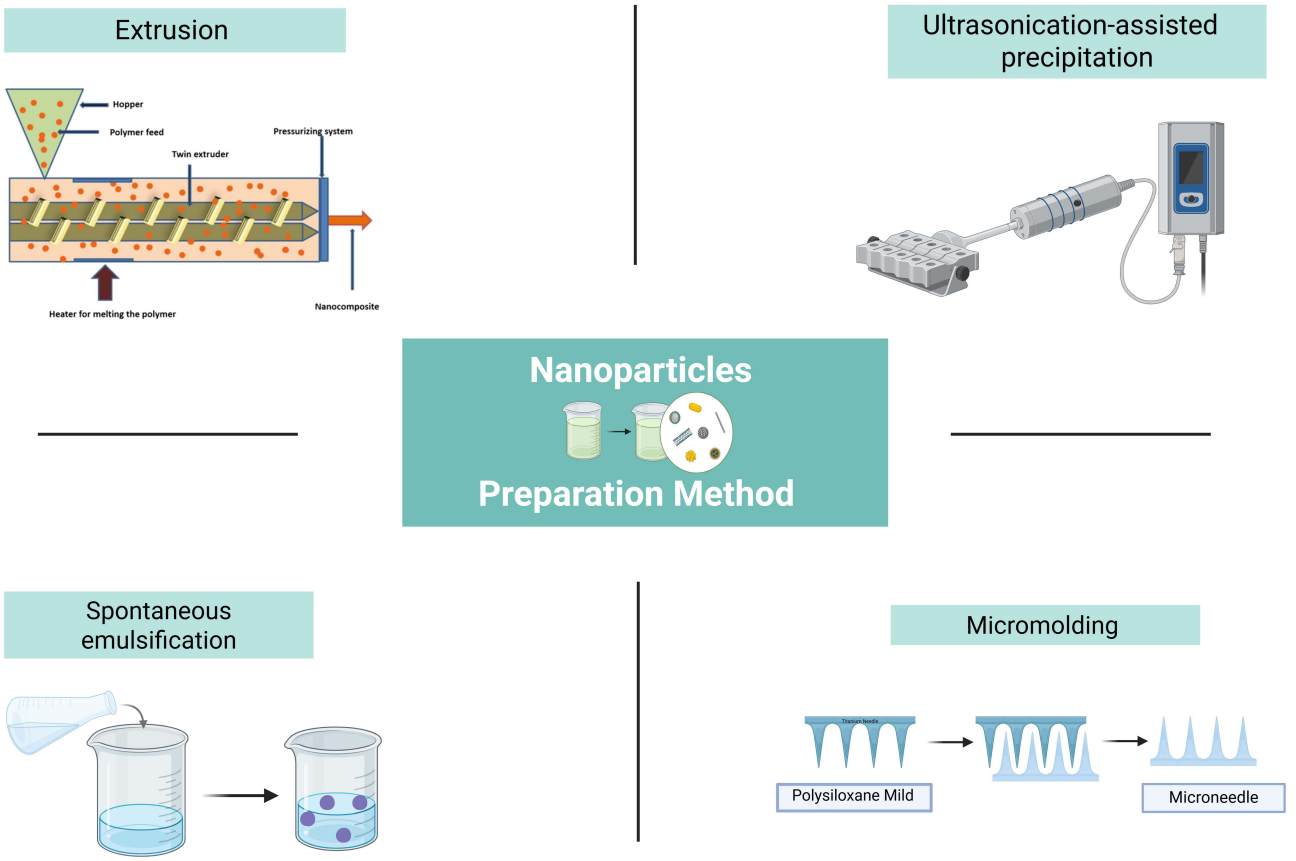

Figure 4 Nanoparticle Preparation Method.

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they exhibited smaller particle size and high stability.[57] In this case, it is stated that glimepiride nanocrystals are a promising carrier for drug delivery and can be used safely and effectively in the design of various formulations. Furthermore, PEG 20000 and P90G are excellent polymers and lipids for reducing particle size and stabilizing nanocrystals.[57]

Microneedles

Transdermal patches represent a pharmaceutical delivery approach where medicated systems are applied topically to administer drugs through the skin for systemic circulation.[58] Transdermal drug delivery systems in the form of patches can overcome the disadvantages associated with oral and parenteral routes. There are advantages offered such as ease and convenience of use in treatment, providing a certain dose significantly, and several aspects that can be controlled including first cross metabolism, toxicity, and variations in plasma drug concentrations.[59] Microneedles are microscopic, pointed structures that are less than one millimeter (sub-millimeter) long. It was originally developed as a transdermal system to enhance the penetration of drugs and vaccines through the skin layer (stratum corneum), facilitating efficient delivery of active substances without significantly damaging the tissue. Microneedles represent an innovative drug delivery platform comprising arrays of microscale projections.[60]

This system has garnered significant interest owing to its minimally invasive nature, user-friendly application, localized and sustained drug release capabilities, as well as versatile drug-loading potential. One of the things that must be considered in drug delivery through the stratum corneum (SC), as the outermost skin layer, serves as a hydrophobic physical barrier.[60] The permeability of active compounds through the stratum corneum is influenced by key physicochemical characteristics, including molecular weight below 500 Da, melting point under 200°C, and an optimal Log P range of 1–3.[61] Microneedles conventionally feature a microscopic protrusion ranging from 25–2000 μm in length, designed to correspond with epidermal and stratum corneum thickness (typically 10–15 μm). The needle tip usually has a radius of 1–25 μm to ensure efficient penetration. In order to penetrate the skin without breaking or warping, the needle must have sufficient strength and stiffness, which is affected by its material, geometry, and shaft width, which generally ranges from 10–300 μm.[62] Multiple microneedle variants exist, characterized by unique structural and functional attributes that enable their differentiation, including solid microneedles, hollow microneedles,[63] coated microneedles,[64] and dissolving microneedles.[65]

Microneedles can be made from a range of materials, including metals, silicon, glass, ceramic, and polymers, chosen based on the patch's design and composition. Typically, these materials must possess adequate mechanical strength to penetrate the skin effectively. Non-dissolving microneedles are designed to be biocompatible, chemically inert, and strong enough for skin insertion while avoiding immune reactions. On the other hand, coated and dissolving microneedles require water-soluble and biocompatible matrices that can safely break down in the body without causing toxicity. Another essential factor is the compatibility between the matrix materials and the incorporated drugs, which must be maintained during manufacturing, storage, and transportation.[66] Extensive clinical studies have repeatedly confirmed both the therapeutic effectiveness and safety profile of microneedle-based delivery systems. Current short-term safety data indicate no reported cases of either local dermal infections or systemic complications following microneedle application.[67] The microneedle delivery strategy using the nanomicelles method formulated with 10% soluplus® and 40% glimepiride has an average particle size of 82.6 ± 0.54 nm, PDI 0.1 ± 0.01, zeta potential 16.2 ± 0.18 mV, and achieves a 250 fold increase in solubility. This study demonstrates an alternative delivery system for glimepiride administration, resulting in improved bioavailability, enhanced patient compliance, reduced dosing frequency, and safety without adverse effects on the skin or health.[17] Microneedles, despite their potential in drug delivery, have several drawbacks such as silicone, glass, or certain polymers can be fragile. Manufacturing methods such as micro injection molding face challenges related to high initial costs and complexity. These issues highlight the need for continuous advancement in microneedle technology.[68]

Nanoemulgel

Nanoemulgels consist of nanoemulsions that can be nano sized emulsions with either aqueous or oleaginous continuous phases, consisting of a mixture between immiscible oil and water phases mediated by appropriate surfactants and co-

surfactants integrated into a gel based system.[69] Nanoemulgels convert nanoemulsions into higher viscosity systems with enhanced stability and reduced oiliness through the incorporation of gelling agents, which are used in the preparation of gel bases.[70] Nanoemulsions have low viscosity and spreadability, insufficient skin retention, and are not scalable, conventional gel matrices demonstrate limited capacity for effective hydrophobic compound incorporation.[71] While both systems present challenges, nanoemulgels provide superior characteristics including easy dispersion, prolonged drug release, water solubility, non-greasy texture, easy removal, and extended shelf stability.[72–74] The integration of nanoemulsions with gel systems results in nanoemulgel formulations that overcome the limitations of each system. The process of incorporating the drug into the nanoemulsion oil phase, which is then incorporated into the gel base, enables efficient delivery of hydrophobic compounds through the hydrogel medium.[75]

Additionally, this system avoids gastrointestinal side effects, is easy to use, and provides superior safety and therapeutic profiles, thereby enhancing patient compliance with therapy.[76] Nanoemulgel is a combination system consisting of two main components, namely an emulsion with nano-sized droplets and a gel matrix. The emulsion used can be either oil-in-water or water-in-oil, acting as a drug delivery medium and stabilized by an emulsifying agent. Meanwhile, the gel is formed from polymers that undergo volume expansion due to fluid absorption. The formulation of nanoemulgel includes several essential components that work synergistically to support the stability and efficacy of the drug delivery system, including aqueous solvents, oils, emulsifiers (surfactant and co-surfactant), gelling agents, preservatives, antioxidants, and humectants.[75] During the manufacturing process, critical points such as the preparation method of nanoemulsions must be strictly controlled to achieve uniform particle size. Environmental factors such as temperature and light exposure, especially if the active ingredient is thermolabile or photosensitive, must also be carefully managed. Nanoemulgel characterization includes zeta potential, droplet size, polydispersity index (PDI), rheological characterizations, spreading testing, in-vitro release testing, ex-vivo permeability bio-adhesive properties, and skin irritation.[77] In a study where nanoemulsions were developed using clove oil, Tween-80, and PEG-400, and gelled using 3% xanthan gum, w/w, the results showed that the combination of glimepiride with clove oil and GMP/βCD/GEL-44/16 increased in vitro skin permeation compared to pure glimepiride, so that glimepiride gel based on topical nanoemulsion and GMP/βCD/GEL-44/16 can be used as an alternative to oral therapy in the treatment of diabetes.[19]

Self-Nanoemulsifying Drug Delivery System (SNEDDS)

Self-nanoemulsifying drug Delivery System (SNEDDS), this nanoemulsion-based delivery platform enhances the solubilization and intestinal absorption of poorly water soluble drugs through nanoscale lipid dispersion.[78,79] Through nanoemulsification, this system enhances lipid digestion by increasing interfacial surface area and generating submicron oil droplets that readily incorporate into mixed micelles for efficient intestinal absorption. Self-nanoemulsifying drug delivery systems (SNEDDS) enhances drug bioavailability through multiple mechanisms: modulating enterocyte membrane fluidity to promote transcellular permeation, inhibiting efflux transporters, reducing cytochrome P450-mediated intestinal metabolism, and circumventing hepatic first-pass effects.[80] Self-nanoemulsifying drug delivery system (SNEDDS) is a nanoemulsion formulation in anhydrous form.[81] Which consists of a homogeneous mixture of surfactants, cosurfactants, oils, and active drug substances. The excipients are selected based on their ability to form oil-in-water (O/W) nanoemulsions.[82]

Self-nanoemulsifying drug delivery systems (SNEDDS) formulations are characterized by globule size less than 100 nm, optically clear appearance, surfactant HLB value greater than 12, as categorized under Type IIIB of the Lipid Formulation Classification System (LFCS), oil phase more than 20%, and surfactant concentration between 40%-80.[83] Self-nanoemulsifying drug delivery systems (SNEDDS) have advantages such as large surface area and prompt pharmacological response, ability to improve drug bioavailability, long-term stability, improved patient compliance, better taste, dose reduction, dissolving large amounts of lipophilic drugs, and protecting drugs from hydrolysis and enzyme degradation.[84] In addition, self-nanoemulsifying drug delivery systems (SNEDDS) can also increase the interfacial tension capacity of drugs with low interfacial tension, ease of formulation, and ease of large-scale production.[85] The limitations of self-nanoemulsifying drug delivery systems (SNEDDS) include high production costs, stability affected by temperature and pH, problems related to drug compatibility with other material components, and packaging preparations in hard or soft capsules so that at any time they can leak.[84] Nanoemulsions can be produced

through two main approaches.[86] First, the low-energy method, which utilizes the natural chemical energy of the system, requiring only a small amount of power and gentle stirring to produce nanoemulsion particles. This technique is more energy-efficient and includes spontaneous emulsification, temperature-induced phase inversion, and composition-induced phase inversion methods.[82] Key factors in this method include the hydrophilic-lipophilic balance of the oil, the combination of emulsifier and co-emulsifier, process temperature, and the distribution of the drug, oil, emulsifier, co-emulsifier or cosolvent, and aqueous phase. Second, high-energy methods, which rely on mechanical equipment to generate strong crushing forces to reduce particle size. Examples of equipment used include microfluidizers, homogenizers, and ultrasonicators. However, this method can generate heat during the process, making it unsuitable for drugs that are not heat-resistant.[87] Critical aspects in formulation include the selection of components (such as oil phase, surfactants, and co-surfactants), drug solubility, and cost of production. It is necessary to assess various physicochemical properties, such as droplet size, polydispersity index (PDI), zeta potential (ZP), morphology, drug encapsulation efficiency, formulation stability, DSC, FT-IR, as well as assessments along with both in vitro and in vivo release evaluations.[81,86] In self-nanoemulsifying drug delivery systems (SNEDDS) formulation, the solubility and absorption of glimepiride were significantly improved, with a particle size of 45.6 nm and solubility of 25.0 mg/mL. Then, three types of glimepiride tablets were developed in liquisolid preparations, direct compression tablets, and 3D printed tablets. Liquisolid and 3D-printed tablets showed better and more controlled in vitro drug release compared to direct compression tablets. Pharmacokinetic studies in rats showed that liquisolid and 3D-printed tablets had better bioavailability, with relative bioavailability of 121.68% and 113.86%, respectively, compared to commercial products.[88]

On the other hand, self-nanoemulsifying drug delivery systems (SNEDDS) provide superior spontaneous emulsification but involve higher production costs compared to conventional methods. This is primarily due to the requirement for high concentrations of high-purity surfactants and co-surfactants to ensure nano-droplet stability. Beyond cost concerns, the high surfactant load also necessitates careful toxicological evaluation, as excessive use may lead to gastrointestinal mucosal irritation during chronic administration.[80,88]

Nanosuspension

Solubility is related to particle size in that the smaller the particle size, the larger the surface area, thereby increasing the chance of particles being solubilized.[89] Reducing particle size to less than 1 μm is believed to increase solvation pressure and disrupt interactions between solute molecules, thereby accelerating the solubilization process of a substance.[90] Currently, there are many technological developments, one of which is nanosuspension technology, which aims to increase drug solubility by stabilizing microcrystal particles in pressurized water media.[91] Nanosuspensions have been shown to increase solubility, absorption, bioavailability, and area under the curve (AUC) and accelerate the time to reach the maximum concentration of the drug in the body.[91,92]

Nanosuspension technology offers multiple benefits, notably enhancing drug bioavailability through two primary mechanisms: elevation of saturation solubility and acceleration of dissolution kinetics for poorly soluble active compounds, as well as strengthening adhesion to cell surface membranes,[92] enabling passive targeting with particle sizes that are on the nanometer scale, simple, easy, and economical production process, and able to produce rapid and reproducible formulations.[93,94] The effective development of nanomicellar systems requires meticulous consideration of three essential factors: material selection, production methods, and thorough analysis. The core of this technique lies in the selection of amphiphilic polymers, such as Poloxamer, which can efficiently self-assemble into structures with appropriately balanced hydrophilic and hydrophobic domains for optimum drug encapsulation with lecithin.[95]

Nanosuspension production methods are typically categorized into three primary approaches: bottom-up nanoparticle assembly, top-down particle size reduction, and hybrid combination techniques.[96] The top-down approach involves initially reducing drug crystals to the micrometer scale, followed by further fragmentation to nanodimensions in a stabilizer solution.[93] Prevalent bottom-up techniques encompass antisolvent precipitation and precipitation through ultrasonication. Hybrid technologies generally combine a bottom-up process, such as precipitation, with a top-down technique, such as high-pressure homogenization.[90]

Several critical points that must be considered in the preparation of nanosuspensions, as in the bottom-up process, important formulation parameters are solvent ratio and solvent type, while process parameters include temperature,

stirring speed, stirring time, and droplet size.[97] For the top-down process, formulation parameters include stabilizer type and stabilizer ratio, while process parameters include temperature, stirring speed, stirring time, and chamber filling volume.[93] Characterization of nanosuspension based drug delivery systems generally includes chemical, physical, and biological testing. However, several important factors that must be evaluated include the average particle size and distribution, crystalline structure and particle morphology, nanosuspension charge, saturation solubility, dissolution rate, stability, and in vivo biological activity.[97] The research demonstrated a substantial enhancement in the solubility of glimepiride when formed as nanoparticles. The pure glimepiride exhibited a solubility of 27.25 ± 6.8 μg/mL in water. The glimepiride nanoparticles exhibited a 3.50 to 6.58-fold increase in in vitro saturation solubility.[31]

While nanosuspensions demonstrate promising results at the laboratory scale, transitioning to industrial-scale manufacturing presents substantial scalability challenges. High-energy processes, such as high-pressure homogenization, require specialized equipment and significant energy consumption. Furthermore, maintaining a uniform particle size distribution across large production batches remains technically difficult, which may lead to batch-to-batch variability in therapeutic efficacy.[90,94]

Challenges, Limitations, and Future Prospectives

Notwithstanding notable advancements in formulation technologies aimed at improving glimepiride's solubility, considerable obstacles and constraints remain, hindering large-scale manufacture and clinical application. Solid-state modification strategies face inherent challenges, including the intricate and empirical selection of appropriate co-formers for co-crystallization,[98] the significant physical instability and risk of recrystallization of amorphous solid dispersions over time,[99] and the elevated production costs and long-term stability issues linked to inclusion complexes.[19]

The main challenges of nanoparticle-based delivery systems are the intricate and energy-intensive manufacturing process,[1] the difficulty in maintaining the long-term physical stability of colloidal systems, and the reliance on specialized, frequently expensive, excipients and equipment.[100] Moreover, the overarching challenges of implementing manufacturing standardization, securing regulatory approval for new excipients, guaranteeing batch-to-batch consistency, and comprehensively assessing potential toxicity and the overall heightened production costs must be resolved to ensure the commercial feasibility of these innovative formulations.[96]

Looking forward, future research should prioritize more translational and scalable strategies such as the integration of multimodal formulation approaches (eg, combining co-crystals or amorphous solid dispersions with polymeric or lipid-based carriers) and the adoption of continuous or low-energy manufacturing platforms to reduce variability and cost. The incorporation of computational and machine-learning-based tools for rational excipient selection and process optimization represents a promising avenue to minimize empirical screening. In addition, stability-enhancement techniques, including surface engineering, polymeric stabilizers, and solidification of colloidal systems through spray-drying or lyophilization, are expected to play a key role in improving long-term physicochemical robustness. Establishing reliable in vitro–in vivo correlations, performing systematic toxicity assessments, and engaging early with regulatory agencies will further accelerate clinical translation. Collectively, these future-oriented strategies are anticipated to bridge existing gaps between laboratory development and real-world pharmaceutical implementation, ultimately facilitating the successful commercialization of solubility-enhanced glimepiride formulations.

Conclusion

The classification of glimepiride as a BCS Class II drug presents a significant challenge due to its poor aqueous solubility, which compromises oral bioavailability and therapeutic consistency. This review critically examined two principal formulation strategies to overcome these limitations: solid-state modification and nanoparticle-based delivery systems. Solid-state modification approaches, including solid dispersions, co-crystals, eutectic mixtures, and inclusion complexes, have proven effective in enhancing the apparent solubility and dissolution rate of glimepiride by altering its physicochemical and crystalline properties. In parallel, nanoparticle-based systems, such as nanosuspensions, SNEDDS, and nanoemulgels, improve solubility primarily through particle size reduction, increased surface area, and improved interaction with gastrointestinal fluids. Despite the promising in vitro and in vivo outcomes reported for these advanced formulations, several challenges remain, particularly with respect to physical stability, manufacturing complexity, cost,

and scalability for industrial production. Future research should therefore focus on optimizing these formulation strategies to ensure long-term stability, economic feasibility, and successful large-scale manufacturing. Overall, continued advances in formulation technology hold substantial potential to improve the therapeutic performance of glimepiride and, ultimately, clinical outcomes in patients with Type 2 Diabetes Mellitus.

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Disclosure

The author(s) report no conflicts of interest in this work.

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