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*Review*

# The solid-state modification for solubility enhancement of practically insoluble glimepiride: A systematic review

[Modificación del estado sólido para mejorar la solubilidad de la glimepirida prácticamente insoluble: Una revisión sistemática]

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**Abstract**

*Context*: Solubility is a crucial physicochemical property of pharmaceuticals that directly influences the absorption and bioavailability of drugs within the human body. Glimepiride, an oral anti-diabetic agent included in the Biopharmaceutics Classification System (BCS) class II, is practically insoluble in water. Various solid-state modification techniques have been implemented to improve the solubility of glimepiride, namely by the formation of co-crystals, co-amorphous, inclusion complexes, and solid dispersions.

*Aims*: To systematically review the enhancement of glimepiride solubility after solid-state modifications, including co-crystals, co-amorphous, inclusion complexes, and solid dispersions.

*Methods*: This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The citation searches for records published in the last ten years from reputable journals. The eligibility criteria of the identified study are as follows: Population (P): Glimepiride is practically insoluble in water; Intervention (I): Solid-state modification of glimepiride includes co-crystals, co-amorphous, inclusion complexes, and solid dispersions; (C): Glimepiride raw material before solid-state modification; and Outcome (O): Solubility and dissolution enhancement. ADA tool was used to assess the quality of the records.

*Results*: A total of 5,220 records were found. The duplicates and undesired articles were excluded. 14 relevant records were further identified through citation searching. The screening and exclusion of records based on the inclusion and exclusion criteria left 13 eligible studies. The studies show that solid-state modification, including co-crystals, amorphous, inclusion complexes, and solid dispersions, can enhance the solubility of practically insoluble glimepiride.

*Conclusions*: Solid-state modification could improve the solubility and dissolution of glimepiride.

*Keywords*: co-amorphous; co-crystals; dissolution; glimepiride; inclusion complexes; solid dispersions.

**Resumen**

*Contexto*: La solubilidad es una propiedad fisicoquímica crucial de los productos farmacéuticos que influye directamente en la absorción y biodisponibilidad de los fármacos en el cuerpo humano. La glimepirida, un agente antidiabético oral, está incluida en la clase II del Sistema de Clasificación Biofarmacéutica (BCS), y es prácticamente insoluble en agua. Se han implementado varias técnicas de modificación del estado sólido para mejorar la solubilidad de la glimepirida, a saber, mediante la formación de cocristales, coamorfos, complejos de inclusión y dispersiones sólidas.

*Objetivos*: Revisar sistemáticamente la mejora de la solubilidad de la glimepirida después de las modificaciones del estado sólido, incluidos los cocristales, los coamorfos, los complejos de inclusión y las dispersiones sólidas.

*Métodos:* Esta revisión siguió la declaración de Elementos de informe preferidos para revisiones sistemáticas y metaanálisis (PRISMA) 2020. Las búsquedas de citas incluyen registros publicados en los últimos diez años en revistas de renombre. Los criterios de elegibilidad del estudio identificado son los siguientes: Población (P): La glimepirida es prácticamente insoluble en agua; Intervención (I): La modificación en estado sólido de la glimepirida incluye cocristales, coamorfos, complejos de inclusión y dispersiones sólidas; (C): Materia prima de glimepirida antes de la modificación en estado sólido; y Resultado (O): Mejora de la solubilidad y la disolución. Se utilizó la herramienta ADA para evaluar la calidad de los registros.

*Resultados*: Se encontraron 5220 registros. Se excluyeron los artículos duplicados y no deseados. Se identificaron 14 registros relevantes mediante la búsqueda de citas. La selección y exclusión de registros según los criterios de inclusión y exclusión dejó 13 estudios elegibles. Los estudios muestran que la modificación en estado sólido, incluidos los cocristales, los amorfos, los complejos de inclusión y las dispersiones sólidas, pueden mejorar la solubilidad de la glimepirida prácticamente insoluble.

*Conclusiones*: Se demostró que la modificación en estado sólido podría mejorar la solubilidad y la disolución de la glimepirida.

*Palabras Clave*: coamorfo; cocristales; disolución; complejos de inclusión; dispersiones sólidas; glimepirida.

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## INTRODUCTION

The oral route of drug administration is the most commonly preferred method among the public due to its convenience and ease of use. However, this route is subject to various biopharmaceutical and pharmacokinetic processes within the body, often leading to low bioavailability. Low bioavailability is frequently attributed to the solubility of the drug (Ferdiansyah et al., 2021). Drugs with low solubility typically exhibit poor dissolution rate characteristics and, subsequently, low bioavailability. The solubility of a drug plays a critical role in its absorption in the gastrointestinal tract, influencing the desired therapeutic outcomes (Haeria et al., 2018; Krishna and Yu, 2008).

Glimepiride (Fig. 1), an oral anti-diabetic agent belonging to the sulfonylurea group, included in the Biopharmaceutics Classification System (BCS) class II drugs, is practically insoluble in water. One approach involves employing solid-state modification techniques to enhance the solubility of drugs such as glimepiride.

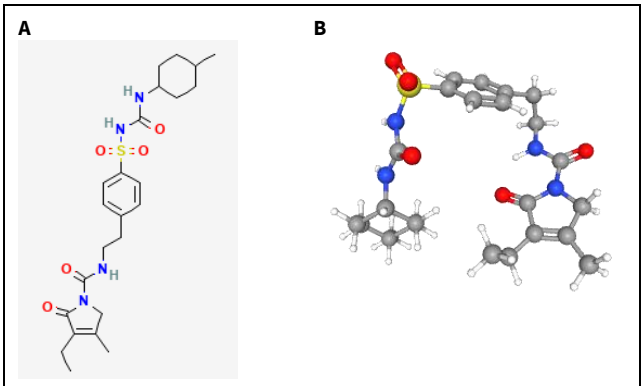


**Figure 1.** Structure of glimepiride in two-dimensional **(A)** and three-dimensional **(B)** format.

Glimepiride is a long-acting, third-generation sulfonylurea with hypoglycemic activity. Compared to other generations of sulfonylurea compounds, glimepiride is very potent and has a longer duration of action. This agent is metabolized by CYP2C9 and shows peroxisome proliferator-activated receptor gamma (PPARgamma) agonistic activity (National Center for Biotechnology Information, 2024).

Solid-state modification refers to methods that alter the supramolecular arrangement of the same components through the formation of polymorphs or amorphous solids, as well as methods that modify the molecular components of the crystal lattice by forming salts, co-crystals, or solvates (Hughey et al., 2016). Various solid-state modification approaches can be utilized to improve drug solubility, including co-crystals, co-amorphous, inclusion complexes, and solid dispersions (Fig. 2).

Previous reviews about solubility enhancement of all anti-diabetic drugs using a co-crystallization approach, not only on glimepiride (Batisai, 2021). Other previous reviews about efforts to increase the solubility and dissolution of active pharmaceutical ingredients in general did not focus on glimepiride (Sopyan et al., 2022). Therefore, this review aims to be the first systematic review investigating the solid-state modification for solubility enhancement of practically insoluble glimepiride, including co-crystallization, inclusion complexes, co-amorphous formulations, and solid dispersions. This review provides an overview of various solid-state modification techniques to improve the solubility and dissolution rate of BCS II drugs, such as glimepiride, which is practically insoluble in water. Finally, this increase in dissolution rate will impact the oral bioavailability of the drug.

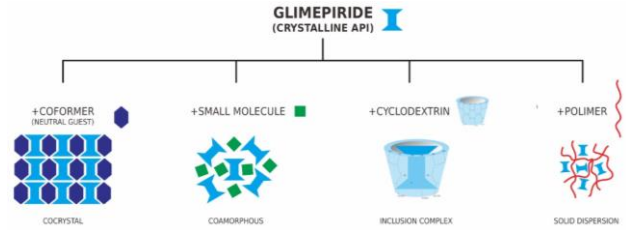


**Figure 2**. Illustration schematic of co-crystal, co-amorphous, solid dispersion, and inclusion complex formations in glimepiride.

## MATERIAL AND METHODS

The research was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The relevance of the study is determined by using the inclusion criteria formulated using Population, Intervention, Comparison, and Outcomes (PICO) (Table 1).

**Table 1**. PICO criteria for this review.

| | |
|---|---|
| Population | Glimepiride is practically insoluble in water |
| Intervention | Solid-state modification of glimepiride includes co-crystals, co-amorphous, inclusion complexes, and solid dispersions |
| Comparison | Glimepiride raw material before solid-state modification |
| Outcome | Solubility and dissolution enhancement |

The articles were screened and reviewed by two reviewers (RT and SI). The quality of the study and the risk of bias were assessed with the American Dietetic Association (ADA) tool (ADA, 2005). Any disagreements will be resolved by reevaluating the articles using the checklist and discussing them with other investigators (DF and AN). The final decision was made based on the agreement of all reviewers.

### Eligibility criteria

After obtaining the articles, a screening process was carried out using inclusion and exclusion criteria. The inclusion criteria used were research articles on solid-state modification of the pharmaceutical raw material glimepiride, including co-crystals, inclusion complexes, co-amorphous forms, and solid dispersions. The articles were published in the last 10 years (2014-2024), the research articles were accessible in full text, and the articles were written in Indonesian or English. The research articles that met the inclusion criteria were then further screened using the exclusion criteria. The exclusion criteria used were review articles, research articles that did not include solubility and dissolution rate data from the solid-state modification of the pharmaceutical raw material glimepiride, and research articles that were not indexed by Scopus. The research articles that met the exclusion criteria were used as data sources.

### Information sources

The search for research articles was conducted through reputable publishers, namely Google Scholar, Science Direct, MDPI, Taylor & Francis, American Chemistry Society, and Garuda. The search process used keywords such as "solid dispersion glimepiride" AND "dispersi padat glimepirid" AND "co-amorphous glimepiride" AND "inclusion complexes glimepiride" AND "kompleks inklusi glimepirid" AND "co-crystals glimepiride" AND "kokristal glimepirid" AND "enhancing dissolution glimepiride" AND "dissolution of glimepiride" AND "dissolution rate of glimepiride".

### Search strategy

Reviewers independently searched data in databases and identified literature through other sources using Harzing's Publish or Perish, an application that accelerates the initial screening process of abstracts and titles with a high level of usability. The search results from Harzing's Publish or Perish database were independently reviewed based on the specified criteria. Specifically, the population, type of intervention, and assessed outcomes will be evaluated during the selection process. Any disagreements were resolved through consensus among the other authors.

### Selection process

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist and flow diagram to ensure the quality of this study. The systematic literature search was carried out independently by authors, and any discrepancies were resolved through discussions with all authors. The selection process consisted of four main stages: identification, screening, inclusion, and exclusion. Initially, duplicate studies were removed during the identification stage, followed by screening based on titles and abstracts. Subsequently, each study was evaluated, and its full text was reviewed to determine whether it met the inclusion and exclusion criteria. Studies that met these criteria were included for further synthesis.

### Data collection process

If available, the following variables were extracted from all included RCTs: year of publication, solid-state modification techniques, solid-state modification characterization results, and solubility and/or dissolution test results of glimepiride. The author carried out data extraction, and any discrepancies between reviewers were discussed and consulted. Information from the selected articles was manually collected, organized into tables, and subjected to qualitative synthesis.

### Data items

The data extracted from the review include details such as the solid-state modification techniques used, methods of these solid-state modification techniques, characterization results of solid-state modification, and solubility and dissolution test data of glimepiride. The main objective of this systematic review is to compare the solubility and dissolution of glimepiride before and after solid-state modification.

### Study risk of bias assessment

The quality and risk of bias of the included studies were assessed using the ADA quality criteria checklist. Two reviewers independently conducted this assessment and discussed their findings with other reviewers before moving on to the next review phase. Research that met the criteria received a positive (+) value, indicating that the study adequately addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis. Studies were rated negatively (-) if they failed to address these issues and neutrally (Φ) if they were neither particularly strong nor weak in these areas (ADA, 2005).

### Effect measures, synthesis methods, reporting bias assessment

Online data processing tools, such as Google Sheets, will be employed to organize the data. This tool was selected due to its real-time collaboration feature, which allows all reviewers to simultaneously access and make corrections to the data synthesis results. This greatly minimizes the risk of errors in our collaborative data synthesis process.

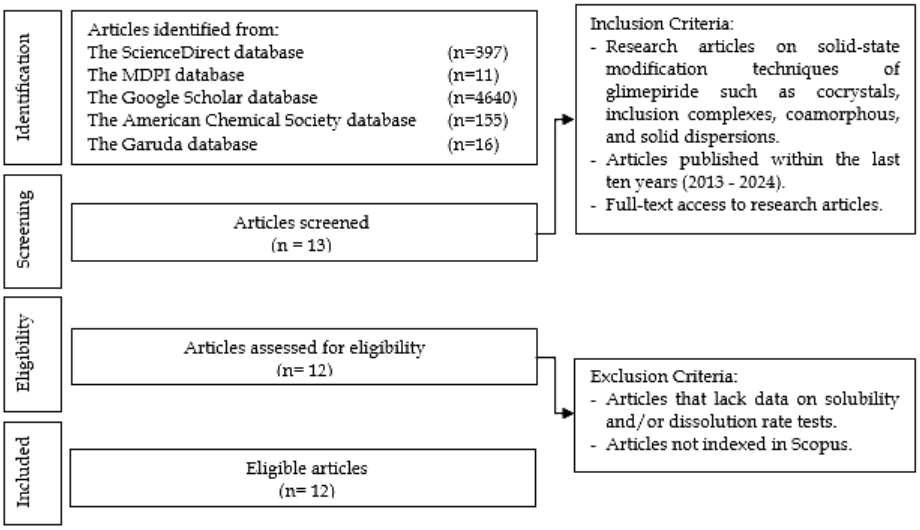


**Figure 3.** PRISMA flow diagram of article research.

## RESULTS

### Study selection

This systematic literature review search identified 5219 records from the searching process (Fig. 3). After the exclusion of irrelevant articles (n = 5169) not indexed on Scopus (n = 14), unavailable full text (n = 5), and there was no solubility and/or dissolution rate testing data (n = 16). There were 13 articles that met the inclusion criteria.

### Study characteristics

The overall characteristics of the 12 articles that meet the inclusion criteria are summarized in Table 2.

The outcomes were explained based on solubility and dissolution data to measure the solubility enhancement of glimepiride after solid-state modification. Solid-state modification is a method that changes the solid phase of a substance by altering its supramolecular arrangement. This can involve the formation of polymorphs or amorphous solids, as well as the modification of the molecular components of crystal lattice through the formation of salts, co-crystals, or solvates. The primary goal of solid-state modification is to improve the solubility, stability, or other characteristics of a solid substance (Hughey et al., 2016). Solid-state modification techniques used to enhance drug solubility include co-crystals, inclusion complexes, co-amorphous, and solid dispersions.

### Risk of bias in studies

Twelve eligible studies were evaluated for their quality and risk of bias. Quality assessment was carried out using the ADA quality checklist (ADA, 2005). No articles were excluded based on the assessment result. All of the 12 studies reviewed had positive ratings, according to Table 3.

### Results of individual studies

Solid-state modification is a method that changes the solid phase of a substance by altering its supramolecular arrangement. This can involve the formation of polymorphs or amorphous solids, as well as the modification of the molecular components of crystal lattice through the formation of salts, co-crystals, or solvates. The primary goal of solid-state modification is to improve the solubility, stability, or other characteristics of a solid substance (Hughey et al., 2016). Solid-state modification techniques used to enhance drug solubility include co-crystals, inclusion complexes, co-amorphous, and solid dispersions.

*Solubility*

Solubility refers to the ability of a substance to dissolve in another substance, forming a homogeneous solution in solid, liquid, or gas form. Several factors influence solubility, including the choice of solvent, temperature, and pressure. In pharmaceutical sciences, solubility is crucial for determining drug formulation and assessing the concentration that can reach systemic circulation to elicit pharmacological effects. Drugs with low solubility can face challenges such as poor absorption, reduced therapeutic efficacy, and the potential need for higher doses (Yoga and Hendriani, 2013).

*Dissolution*

Dissolution is the process by which a drug becomes available in the body through dissolution in

the gastrointestinal tract fluids. Factors that influence the dissolution rate can also impact the bioavailability of the drug. Dissolution testing is commonly performed on pharmaceutical dosage forms for oral administration, such as tablets, caplets, and capsules. This testing adheres to principles outlined in the Noyes-Whitney equation [1] (Krishna and Yu, 2008).

$$\frac{dc}{dt} = \frac{DA}{hv}(C_s - C) \quad [1]$$

In the given framework, D represents the diffusion coefficient, denoting the rate of diffusion of the drug molecules within the medium. h signifies the thickness of the diffusion boundary layer existing between the solid-liquid interface, A stands for the surface area of the drug that is exposed to the dissolution media, and v represents the volume of the dissolution medium. $C_s$ denotes the saturation concentration of the solute within the dissolution medium at the specified experimental temperature. C refers to the concentration of the drug in the solution at a given time, t. The dissolution rate, symbolized by dc/dt, quantifies the alteration in drug concentration concerning time. Within this conceptual framework, the dissolution rate is modulated by factors such as drug solubility, the process of diffusion that facilitates the movement of dissolved molecules from the solid surface through the thin solvent layer encompassing the drug particles, and the effective surface area in contact with the solvent (Krishna and Yu, 2008).

*Solid-state modification*

The enhancement of drug solubility and dissolution can be achieved through the manipulation of its physical properties, such as employing solid-state modification techniques. Solid-state modification involves altering the supramolecular arrangement of a substance's solid phase through the generation of polymorphs or amorphous solids, as well as modifying the molecular components of the crystal lattice via the formation of salts, co-crystals, or solvates. The primary objective of solid-state modification is to augment the solubility, stability, or other pertinent properties of a solid substance (Hughey et al., 2016). Techniques within solid-state modification that can be utilized to elevate drug solubility include the utilization of co-crystals, inclusion complexes, co-amorphous, and solid dispersions.

**Table 2.** Characteristic of study.

| Author | Solid-state modifications | Methods | Primary outcome | Secondary outcome |
|---|---|---|---|---|
| (Chhajed et al., 2020) | Co-crystals | Solvent drop grinding | Data on solubility and dissolution rate | Characterization of DSC, XRD, FTIR, and SEM |
| (Jaafar and Radhi, 2020) | Co-crystals | Solvent evaporation | Data on dissolution rate | Characterization of DSC, PXRD, and FTIR |
| (Zidan et al., 2023) | Co-crystals | Ultrasound-assisted co-crystallization | Data on solubility and dissolution rate | Characterization of DSC, PXRD, FTIR, and SEM. |
| (Das et al., 2020) | Co-crystals | Solvent evaporation | Data on solubility and dissolution rate | Characterization of DSC, XRD, and SEM |
| (Bian et al., 2019) | Co-crystals | Solvent evaporation | Data on dissolution rate | Characterization of DSC, PXRD, POM, and FTIR |
| (Cruz-Angeles et al., 2019) | Co-amorphous | Melt quenching | Data on dissolution rate | Characterization of DSC, FTIR, and PXRD |
| (Park et al., 2020) | Co-amorphous | Supercritical anti-solvent | Data on solubility and dissolution rate | Characterization of DSC, FTIR, and SEM |
| (Syukri et al., 2015) | Inclusion complexes | Freeze drying | Data on dissolution rate | Characterization of FTIR and SEM |
| (Pal et al., 2020) | Inclusion complexes | Freeze drying | Data on solubility and dissolution rate | Characterization of DSC, PXRD, FTIR, and SEM |
| (Bachir et al., 2013) | Inclusion complexes | Co-evaporation | Data on dissolution rate | Characterization of DSC, FTIR, and XRD |
| (Sakure et al., 2020) | Solid dispersion | Spray drying | Data on solubility and dissolution rate | Characterization of DSC and FTIR |
| (Surini et al., 2018) | Solid dispersion | Spray drying | Data on dissolution rate | Characterization of DSC, FTIR, and XRD. |

DSC: Differential scanning calorimetry; FTIR: Fourier transform infrared; XRD: X-ray diffraction; SEM: Scanning electron microscopy; PXRD: Powder X-ray diffraction.

**Table 3**. Risk of bias assessment using the ADA quality criteria checklist for review articles.

| Author and year | Relevance question | | | | Validity question | | | | | | | | | | Quality rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| (Chhajed et al., 2020) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Jaafar and Radhi, 2020) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Zidan et al., 2023) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Das et al., 2020) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Ye s | No | No | + |
| (Bian et al., 2019) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Cruz-Angeles et al., 2019) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Park et al., 2020) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Syukri et al., 2015) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Pal et al., 2020) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Bachir et al., 2013) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Sakure et al., 2020) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |
| (Surini et al., 2018) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | No | + |

| **Relevance question** | |
|---|---|
| 1. | Will the answer if true, have a direct bearing on the health of patients? |
| 2. | Is the outcome or topic something that patients/clients/population groups would care about? |
| 3. | Is the problem addressed in the review one that is relevant to dietetics practice? |
| 4. | Will the information, if true, require a change in practice? |
| **If the answers to all of the above relevant questions are "Yes", the report is eligible for designation with a plus (+) on the evidence Quality Worksheet, depending on answers to the following validity question.** | |
| **Validity question** | |
| 1. | Was the question for the review clearly focused and appropriate? |
| 2. | Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described? |
| 3. | Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased? |
| 4. | Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible? |
| 5. | Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined? |
| 6. | Was the outcome of interest clearly indicated? Were other potential harms and benefits considered? |
| 7. | Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described? |
| 8. | Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included? |
| 9. | Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed? |
| 10. | Was bias due to the review's funding or sponsorship unlikely? |
| **Minus/Negative (-)** | |
| If most (six or more) of the answers to the above validity questions are "No," the review should be designated with a minus (-) symbol on the Evidence Quality Worksheet | |
| **Neutral (Ø)** | |
| If the answer to any of the first four validity questions (1-4) is "No," but other criteria indicate strengths, the review should be designated with a neutral (Ø) symbol on the Evidence Quality Worksheet. | |
| **Plus/Positive (+)** | |
| If most of the answers to the above validity questions are "Yes" (must include criteria 1, 2, 3, and 4), the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet | |

*Co-crystals*

Co-crystal or co-crystallization is a physical modification process wherein a solid substance arises from the molecular interaction of two or more compounds, resulting in a distinct crystal lattice structure stabilized by intermolecular forces, including hydrogen bonding and Van der Waals interactions. Co-crystals exhibit the potential to ameliorate the bioavailability of poorly soluble pharmaceuticals by augmenting their solubility and dissolution kinetics. Typically, these co-crystalline formulations consist of an active pharmaceutical ingredient as the primary constituent, accompanied by a co-former agent, as documented in the works of Ferdiansyah et al. (2021) and Gracesella and Sopyan (2016).

A co-former serves as a non-ionically interacting agent during the co-crystallization process with active pharmaceutical ingredients within the crystal lattice.

These compounds typically exhibit high water solubility and low volatility. The precise selection of a co-former presents a considerable challenge in the fabrication of multi-component pharmaceutical crystals tailored for specific medicinal actives. The choice of co-former primarily hinges on its capacity to engage in hydrogen bonding with the pharmaceutical active ingredient, alongside adherence to generally recognized as safe (GRAS) standards to ensure safety and non-toxicity, as delineated by Wathoni et al. (2022).

The formation of co-crystals entails two distinct methods, namely thermodynamic approaches and kinetic strategies. Several of common methods in co-crystal formation are:

a. Solvent evaporation: The solvent evaporation technique stands out as the prevailing approach due to its simplicity and efficacy in enhancing pharmaceutical agents' stability and solubility. This method entails carefully selecting the drug and co-former in precise stoichiometric proportions, allowing them to dissolve homogeneously within a shared solvent. Subsequently, the solvent is evaporated, yielding the desired co-crystalline structure, as elucidated by Guo et al. (2021) and Thayyil et al. (2020).

b. Solvent drop grinding: Solvent drop grinding represents a co-crystal synthesis technique wherein grinding is coupled with the addition of a minimal solvent quantity. Employing the solvent drop grinding method facilitates the generation of higher purity co-crystals in contrast to dry grinding procedures. This methodology involves the amalgamation of glimepiride and the co-former in predetermined stoichiometric ratios within a mortar, followed by the introduction of a suitable solvent and subsequent grinding for a specified duration. The selection of solvent in this context demands precision, as the minute solvent volume must exhibit the capability to completely dissolve both the active ingredient and co-former, as discussed by Guo et al. (2021).

c. Ultrasound-assisted suspension co-crystallization: Ultrasound-assisted suspension co-crystallization represents a methodology akin to the slurry method, wherein the active ingredient and co-former are prepared within a suspension system or in a state of supersaturation. Subsequently, co-crystal formation is induced by ultrasound technology, which imparts mechanical energy to the system, facilitating co-crystal generation. Practically, the active ingredient and co-former, intended for co-crystal formation, are combined in predetermined ratios and suspended in a solvent. The resultant solution undergoes ultrasonic treatment within a glass vessel, following which the resulting solid is isolated via filtration and subsequent drying, as outlined by Aher et al. (2010).

The formation of intermolecular bonds within the co-crystal and the emergence of a new crystalline phase, crystal structure analysis employing X-ray diffraction (XRD), can be conducted. The diffraction pattern obtained via XRD analysis serves to identify the new crystalline phase of the co-crystal. Notably, the peak intensity observed in the diffraction pattern correlates with the degree of crystallinity, with heightened peak intensity indicative of increased crystallinity.

Thermal analysis of co-crystals utilizing differential scanning calorimetry (DSC) is imperative to assess the physical interactions between mixed substances. DSC facilitates the determination of substance melting points. In the context of co-crystals, hydrogen bonds induce a reduction in melting point, altering intermolecular bond strength and consequently diminishing the energy required for the melting phase transition Karagianni et al. (2018).

Fourier transform infrared (FTIR) analysis is a valuable tool for elucidating the structure and chemical characteristics of formed co-crystals. By scrutinizing spectral disparities between pure glimepiride and the co-crystal, FTIR enables the identification of co-crystal formation. This method discerns spectral deviations attributed to the presence of hydrogen bonds within the co-crystal, as discussed by Karagianni et al. (2018).

Scanning Electron Microscopy (SEM) analysis is a valuable technique for visually inspecting the formation of co-crystals. Microscopic examination reveals distinctive characteristics: particles of glimepiride present irregular shapes akin to small stones, possessing hardness and smooth surfaces devoid of pores or cracks. In contrast, caffeine exhibits elongated, fine needle-like crystals of varying sizes. However, the resultant co-crystal exhibits a distinct morphology, featuring dense irregularities reminiscent of small stone-like formations and an exceedingly rough surface. This observation corroborates the emergence of a novel co-crystal phase attributed to the establishment of hydrogen bonds between the drug and co-former, as detailed by Chhajed et al. (2020).

*Co-amorphous*

Co-amorphous systems represent a promising strategy for augmenting drug solubility. While the amorphous state inherently offers enhanced solubility compared to its crystalline counterpart, its instability predisposes it to re-crystallization. Hence, co-amorphous formulations not only enhance solubility but also bolster the stability of the amorphous form itself. This approach involves utilizing the drug in its solid amorphous state, forming a homogeneous mixture with one or more low molecular weight excipients and/or other drug molecules. Intermolecular interactions between the drug and co-formers, along with mixing effects, play pivotal roles in fortifying the stability of the amorphous phase and impeding crystallization, as articulated by Liu et al. (2021) and Silva et al. (2023). The selection of co-amorphous manufacturing methods assumes paramount importance in achieving optimal product performance. Key considerations include the thermal stability, melting point, and crystallization propensity of both the active ingredient and excipients, which collectively influence the choice of the appropriate manufacturing methodology.

a. Melt quenching: Melt quenching represents a technique utilized for fabricating co-amorphous materials, particularly applicable to substances exhibiting thermal stability during the molten state. In this approach, the co-amorphous blend undergoes initial heating until it reaches a molten state, followed by rapid cooling. This rapid cooling process is pivotal in minimizing the reversion of the drug to its crystalline form, as the drug solidifies in an irregular state, thereby circumventing crystallization phenomena and facilitating co-amorphous formation. Notably, the successful formation of a glimepiride-irbesartan co-amorphous system was achieved via the melt quenching method, yielding a dissolution rate at 180 minutes of 3.9 µg/mL, contrasting with pure glimepiride, which remained undetected (below the detection limit), as reported by Cruz-Angeles et al. (2019) and Soyata et al. (2022).

b. Supercritical anti-solvent (SAS): SAS technology represents an innovative approach for generating co-amorphous materials, employing supercritical carbon dioxide (SC-$CO_2$) as an anti-solvent. This method addresses limitations associated with conventional co-amorphous manufacturing techniques reliant on organic solvents, which often yield residual impurities in the final product. The SAS method mitigates the need for organic solvents, facilitating the production of finely dispersed particles with minimal dimensions, a feat challenging to achieve through traditional means.

In the SAS process, a solution comprising glimepiride and a co-former is initially prepared. Subsequently, $CO_2$ is pressurized and injected into a specialized chamber via a sprayer, concomitantly with the spraying of the drug solution. Following the completion of drug solution spraying, SC-$CO_2$ continues to flow to eliminate residual solvents. The resulting precipitated particles, in the form of amorphous solids, are then collected and stored in hermetic containers. This methodology has demonstrated efficacy in enhancing the dissolution rate of glimepiride-L-arginine to 4.25 µg/mL at 120 minutes, in contrast to pure glimepiride registering at 0.2 µg/mL, as evidenced by Franco and De Marco (2020) and Park et al. (2020).

Differentiating between co-amorphous systems and co-crystals can be achieved through powder X-ray diffraction (PXRD) analysis. In co-amorphous systems, observed peaks are characterized by broadness rather than sharpness. Broad peaks, as indicated in the PXRD results, are an anticipated outcome in co-amorphous system formation, where heightened peak area correlates with increased crystallinity degree.

Analysis using DSC is integral in comprehending the properties of co-amorphous mixtures. DSC analysis serves to validate the presence of a glass transition (Tg) phase, an expected characteristic of co-amorphous systems. The determination of Tg holds significance in co-amorphous system formation as it correlates with the stability of the mixture during storage, mitigating the risk of recrystallization. A higher Tg value signifies a greater likelihood of achieving a stable co-amorphous system resistant to crystallization during storage, as highlighted by Zhao et al. (2021).

*Inclusion complexes*

Inclusion complexation represents a particulate technique leveraging the mechanism of entrapping drug compounds within non-polar regions (guests) and embedding them into cavities (hosts). Interaction occurs between the non-polar segment of the guest molecule and the non-polar portion of the host molecule. Cyclodextrins stand out as one of the most frequently employed host molecules in this domain, as documented by Cheirsilp and Rakmai (2016).

The choice of method is tailored to accommodate the properties of both the drug and excipients intended for use. Available methods include:

a. Freeze drying: Freeze drying serves as a technique for fabricating inclusion complexes, particularly suited for thermolabile compounds. This method entails mixing host molecules with guest molecules in an aqueous medium under agitation. Subsequently, the solution undergoes freezing, and the resultant solid is subjected to drying by organic solvent washes followed by vacuum drying. Notably, freeze drying offers favorable outcomes and is amenable to large-scale production. Through this method, the successful formation of an inclusion complex between glimepiride and Captisol® has been achieved, resulting in a notable enhancement in glimepiride solubility from 0.56 µg/mL to 1.94 µg/mL, with the dissolution rate achieving 100% after 90 minutes, contrasting with pure glimepiride which exhibited a dissolution rate of 44%, as elucidated by Cheirsilp and Rakmai (2016) and Pal et al. (2020).

b. Co-evaporation: Co-evaporation stands as a technique employed for the production of inclusion complexes, which is particularly suitable for hydrophobic drugs. This method involves dissolving host molecules and guest molecules separately in distinct solvents until complete dissolution, followed by the mixing of the two solutions. Subsequently, an evaporator is utilized to remove the solvent, leaving behind the solid inclusion complex. Notably, co-evaporation has demonstrated efficacy in forming inclusion complexes, such as that between glimepiride and HPBCD, resulting in a significant enhancement in dissolution rate to 99.74% after 180 minutes, in contrast to pure glimepiride which exhibited a dissolution rate of 17%, as reported by Bachir et al. (2013) and Pandya et al. (2008).

DSC is also employed to assess the stability of inclusion complexes. Notably, the inclusion complex exhibits a higher temperature resulting from the molecular combination compared to the pure drug, indicative of the formation of a more stable complex than the pure drug, as elucidated by Bachir et al. (2013).

Analysis utilizing PXRD represents a valuable method for confirming the formation of inclusion complexes. The PXRD pattern of the inclusion complex exhibits broader and less defined peaks. This observation aligns with the formation of the inclusion complex, as reported by Pal et al. (2020).

Analysis employing SEM offers a visual means to observe the formation of inclusion complexes. In the inclusion complex, the absence of visible residues on its surface is noteworthy, likely attributed to the encapsulation process within the hydrophobic core. This observation underscores the successful formation of the inclusion complex, as documented by Pal et al. (2020).

*Solid dispersions*

Solid dispersion represents a technique employed to enhance the solubility and dissolution rate of water-insoluble drugs. It involves molecular blending of poorly water-soluble drugs with a carrier or hydrophilic matrix, where the drug release behavior is governed by the properties of the polymer carrier. This method aims to reduce the particle size of the drug to maximize surface area, thereby promoting faster dissolution in aqueous media. Upon entering the aqueous environment, the polymer and drug are released as fine colloidal particles, facilitating increased dissolution rates for water-insoluble drugs, as highlighted by Sakure et al. (2020), Vasconcelos et al. (2007), and Verma et al. (2011).

In solid dispersion, non-covalent bonding between the drug and polymer, typically through hydrogen bonds, is crucial. This interaction arises from changes in molecular arrangement during solid dispersion formation, leading to a transition from crystalline to amorphous states for the drug, as evidenced by Sakure et al. (2020).

The selection of the carrier polymer in solid dispersion formation is pivotal and must meet specific criteria. The polymer should be readily soluble, nontoxic, non-pharmacologically active, thermally stable with a low melting point, capable of enhancing drug solubility in water, and chemically compatible with the drug, as outlined by Verma et al. (2011).

Methods for producing solid dispersion commonly involve melting and dissolution. Spray drying, for instance, yields fine white powder by utilizing solvent evaporation to mix drug molecules with the carrier polymer, such as in the case of glimepiride-PEG using dichloromethane solvent. The resulting solution is dried via spray drying in a heated chamber to evaporate the solvent, leaving behind a fine powder. This technique effectively formed solid dispersion of glimepiride-gelucire 50/13, significantly enhancing solubility and dissolution rates, as reported by Sakure et al. (2020) and Surini et al. (2018).

In solid dispersion, the interaction between the drug and polymer involves the formation of non-covalent bonds, predominantly hydrogen bonds. This interaction leads to changes in the drug's molecular arrangement, transitioning from a crystalline to an amorphous state. DSC thermograms further elucidate

this transition, with a decrease in the area and a shift to lower temperatures of the drug's endothermic peak, indicating loss of crystallinity and increased amorphous properties, as observed by Sakure et al. (2020).

FTIR analysis serves as a valuable tool for observing interactions between drugs and excipients. Importantly, analysis of the obtained data reveals no discernible interference between the drug and polymer, as all major peaks of glimepiride remain unchanged in all solid mixtures, as elucidated by Sakure et al. (2020).

SEM analysis provides a visual means to observe the results of solid dispersion formation. Notably, solid dispersion formation via spray drying yields a finer powder compared to pure glimepiride. This outcome is attributed to the inclusion of excipients processed alongside glimepiride and subsequently dried using the spray drying method. The solid dispersion exhibits smaller particle sizes, as evidenced by SEM analysis, as reported by Surini et al. (2018).

## Result of syntheses

Down below are the solubility and dissolution results of the solid-state modification of glimepiride using co-crystals, co-amorphous, inclusion complexes, and solid dispersions.

*Co-crystals*

A co-former is used to form co-crystals. Co-formers must be inert, non-toxic, and compatible with active pharmaceutical ingredients, generally have high solubility in water, and can form hydrogen bonds. Table 4 shows the various co-formers used in glimepiride co-crystal formation and their dissolution results.

Oxalic acid (AO) exhibits co-former attributes, characterized by its pronounced water solubility of 108 g/L and a melting point of 183.5°C. The hydroxyl (-OH) moieties inherent in AO establish hydrogen bonds with glimepiride's carbonyl (C=O) functionalities, thereby precipitating hydrogen bonding interactions. These intermolecular associations markedly enhance the aqueous solubility of glimepiride, consequently amplifying its dissolution kinetics. The augmented dissolution profile, resulting from co-crystallizing AO with glimepiride, is discernible from dissolution assay outcomes. Moreover, employing the solvent evaporation approach yields a glimepiride-AO co-crystal (1:1) with a dissolution rate of 85% after 60 minutes, outperforming the 22% dissolution rate observed for glimepiride alone. Notably, the ultrasound-assisted suspension technique facilitates a significant enhancement in glimepiride solubility from 2 µg/mL to 60 µg/mL when forming the glimepiride-AO co-crystal. Subsequent dissolution testing reveals an impressive dissolution rate of 97.3% for the glimepiride-AO co-crystal after 120 minutes, as opposed to 22.06% for pure glimepiride (Jaafar and Radhi, 2020; Zidan et al., 2023).

**Table 4.** Co-crystals glimepiride (GMP) with solubility and dissolution test results.

| No | Co-former | Methods | Conclusions | References |
|---|---|---|---|---|
| 1 | Caffeine (CF) | Solvent drop grinding | The solubility of glimepiride increased from 05.116 mcg/ml to 2902.4 µg/mL.<br>After 150 minutes of dissolution, the GMP-CF co-crystal was 4.44% and GMP was 3.89%. | (Chhajed et al., 2020) |
| 2 | Citric acid (CA) | Solvent evaporation | After 60 minutes of dissolution, the GMP-CA (1:2) co-crystal was 58%, and GMP was 22%. | (Jaafar and Radhi, 2020) |
| 3 | Tartaric acid (TA) | Solvent evaporation | After 60 minutes of dissolution, the GMP-TA (1:2) co-crystal was 80%, and GMP was 22%. | (Jaafar and Radhi, 2020) |
| 4 | Oxalic acid (AO) | Solvent evaporation | After 60 minutes of dissolution, the GMP-AO (1:1) co-crystal was 85%, and GMP was 22%. | (Jaafar and Radhi, 2020) |
| 5 | Oxalic acid (AO) | Ultrasound-assisted suspension co-crystallization | The solubility of glimepiride increased from 2 µg/mL to 60 µg/mL. After 120 minutes of dissolution, the GMP-AO co-crystal reached 97.3%, while GMP reached 22.06%. | (Zidan et al., 2023) |
| 6 | Succinic acid (SA) | Solvent evaporation | The solubility of glimepiride increased to 80 µg/mL.<br>After 60 minutes of dissolution, the GMP-SA co-crystal was 89.96%, and GMP was 38%. | (Das et al., 2020) |
| 7 | Metformin (MET) | Solvent evaporation | After 90 minutes of dissolution, the GMP-MET co-crystal was 80%, and GMP was 15%. | (Bian et al., 2019) |

Caffeine (CF) serves as a co-former endowed with water solubility and a melting point of 236.08°C. Possessing keto amide and nitrogen functional groups, CF exhibits the capability to engage in hydrogen bonding interactions with the carboxyl groups of glimepiride. These intermolecular interactions significantly elevate the solubility and dissolution rate of glimepiride. The resultant glimepiride-CF co-crystal manifests a remarkable enhancement in glimepiride solubility from 5.116 µg/mL to 2902.4 µg/mL. Moreover, dissolution studies demonstrate a superior dissolution rate of 4.44% for the glimepiride-CF co-crystal, compared to 3.89% observed for pure glimepiride (Chhajed et al., 2020; Latif et al., 2018).

Citric acid (CA) functions as a co-former characterized by high water solubility and a melting point of 160.3°C. Facilitating the hydration process, CA promotes the wetting of glimepiride by water, thereby enhancing its dissolution in the aqueous medium. Through hydrogen bonding interactions, the hydroxyl functional groups (-OH) of CA interact with the carbonyl groups (S=O) of glimepiride. This molecular interaction results in the formation of hydrogen bonds between CA and glimepiride, consequently leading to an elevated dissolution rate of the glimepiride-CA co-crystal. The enhanced dissolution rate is evident, with the glimepiride-CA co-crystal achieving a dissolution rate of 58% after 60 minutes, as compared to 22% observed for pure glimepiride (Jaafar and Radhi, 2020; Rachmaniar et al., 2020).

Tartaric acid functions as a co-former characterized by high water solubility and has a melting point of 215.2°C. The carboxyl groups of TA bind with glimepiride, forming hydrogen bonds that facilitate the dissolution process of glimepiride in water. Tartaric acid (TA) possesses the ability to attract water, thereby facilitating increased contact between glimepiride and water molecules. Upon conducting dissolution tests spanning 60 minutes, the glimepiride-TA co-crystal exhibited a notable enhancement in dissolution rate, reaching 85%, as opposed to the 22% dissolution rate observed for pure glimepiride (Jaafar and Radhi, 2020; Ledianasari et al., 2022).

Succinic acid (SA) acts as a co-former with a solubility of 71 mg/mL and a melting point of 188°C. Through hydrogen bonding interactions, succinic acid binds with glimepiride, thereby augmenting the solubility and dissolution rate of glimepiride. The resultant glimepiride-SA co-crystal demonstrated an increased solubility of glimepiride to 80 µg/mL. Subsequent dissolution tests conducted over 60 minutes revealed a marked enhancement in the dissolution rate, reaching 89.86%, compared to the dissolution rate of pure glimepiride, which stood at 38% (Das et al., 2020).

Metformin (MET), an oral anti-diabetic drug akin to glimepiride, serves as a biguanide hypoglycemic agent, commonly employed as a first-line treatment for type 2 diabetes mellitus, often in conjunction with glimepiride, another primary therapy for long-term management. Both MET and glimepiride exhibit deficiencies in their physicochemical attributes. Thus, the amalgamation of these two drugs to form new crystalline entities aims to ameliorate their physicochemical characteristics. While MET demonstrates water solubility, glimepiride remains largely insoluble in water. Consequently, the creation of a novel crystal involving MET as a co-former endeavors to enhance the solubility of glimepiride. Hydrogen bond analysis reveals that all hydrogen bond donor and acceptor groups of MET engage in hydrogen bonding interactions with glimepiride. Notably, the bonds formed between MET and glimepiride encompass not only hydrogen bonds but also ionic bonds, involving the hydrogen atom (N-H) on nitrogen situated amid the sulfonyl and carbamide groups of glimepiride, which bind to the amine groups of MET. The coexistence of hydrogen bonds and ionic bonds in glimepiride-MET underscores robust stability and suggests MET's efficacy as a promising co-former in multidrug crystal formation. Moreover, dissolution tests conducted under acidic conditions (pH 1) consistently demonstrate a substantial augmentation in the dissolution rate of glimepiride-MET, reaching approximately 80% at the 90$^{th}$ minute (Bian et al., 2019).

*Co-amorphous*

Similar to co-crystals, an important component to consider in the formation of co-amorphous is the co-former. The co-former will determine the enhancement of solubility, dissolution rate, and stability of the co-amorphous system. The co-former used can be another drug with a similar effect or other components that are small molecules (Liu et al., 2021).

Table 5 shows the co-formers used to form glimepiride co-amorphous systems and their dissolution results.

Irbesartan (IBS), employed as a co-former in conjunction with glimepiride, facilitates the creation of a co-amorphous system. This system aims not only to enhance the solubility and stability of glimepiride but also to potentially serve as a combination therapy. Irbesartan, a drug utilized to block angiotensin II receptors for its antihypertensive properties, is intended to synergize with glimepiride in the co-amorphous system. Notably, irbesartan exhibits the ability to mitigate atherosclerosis, a condition associ-

ated with glimepiride. Hydrogen bonding interactions between glimepiride and IBS are established and facilitated by the presence of hydrogen donors and acceptors. Glimepiride offers three hydrogen bond donors and five functional groups serving as hydrogen bond acceptors, whereas IBS presents one hydrogen bond donor and five hydrogen bond acceptors. The amalgamation of these two drugs within the co-amorphous system effectively amplifies the dissolution rate of glimepiride. Specifically, at the 180$^{th}$ minute of dissolution, the dissolution rate of the glimepiride-IBS co-amorphous with a molar ratio of 0.01 measured 3.9 µg/mL, in contrast to pure glimepiride, which remained undetected (below the detection limit) (Cruz-Angeles et al., 2019; Liu et al., 2021).

L-arginine (ARG), an essential amino acid characterized by a high glass transition temperature (Tg), contributes to augmenting the stability of glimepiride within the co-amorphous system. Serving as a co-former, ARG inhibits the crystal growth of glimepiride through molecular interactions with glimepiride-ARG. These interactions involve the carbosamide group and aromatic ring of glimepiride interacting with the guanidinium group and propyl chain of L-arginine through hydrogen bonding. The formation of a co-amorphous system between glimepiride and ARG yields a substantial increase in glimepiride's solubility, rising from 0.6 µg/mL to 84.2 µg/mL, alongside an elevation in dissolution rate. Notably, at the 120$^{th}$ minute of dissolution, the rate measured was 4.25 µg/mL, compared to pure glimepiride, which stood at 0.2 µg/mL (Park et al., 2020).

*Inclusion complexes*

An important component in the formation of inclusion complexes is the host molecule, usually a derivative of cyclodextrin (Table 6), which can encapsulate a hydrophilic drug, such as glimepiride, within its hydrophobic cavity.

β-Cyclodextrin (BCD) represents one of the primary cyclodextrins utilized in pharmaceutical applications. Its prevalent use stems from its widespread availability, cost-effectiveness, favorable biocompatibility, and adequately sized cavity. While the three main cyclodextrin types exhibit negligible distinctions, BCD notably features a slightly larger hydrophobic cavity. Glimepiride, the target for modification, is accommodated within BCD's hydrophobic cavity, ensuring that only the hydrophilic portion of BCD, which interfaces with water, enhances the solubility and dissolution rate of glimepiride. The formation of an inclusion complex between glimepiride and BCD markedly elevates the dissolution rate of glimepiride, peaking at 99.74% at the 180$^{th}$ minute, contrasting with pure glimepiride's 17% dissolution rate (Bachir et al., 2013; Păduraru et al., 2022).

**Table 5.** Co-amorphous glimepiride (GMP) with solubility and dissolution test result.

| No. | Co-former | Method | Conclusions | Reference |
|---|---|---|---|---|
| 1 | Irbesartan (IBS) | Melt quenching | After 180 minutes of dissolution, the GMP-IBS co-amorphous with a molar ratio of 0.01 was 3.9 µg/mL compared to pure glimepiride, which was not detected (under the detection limit). | (Cruz-Angeles et al., 2019) |
| 2 | L-arginine (ARG) | Supercritical anti-solvent | The solubility of glimepiride increased from 0.6 µg/mL to 84.2 µg/mL. After 120 minutes of dissolution, the GMP-ARG co-amorphous with a molar ratio of 1:1 was 4.25 µg/mL compared to pure GMP, which was 0.2 µg/mL. | (Park et al., 2020) |

**Table 6.** Inclusion complexes glimepiride (GMP) with solubility and dissolution test result.

| No. | Complexing component | Method | Conclusions | Reference |
|---|---|---|---|---|
| 1 | β-cyclodextrin (BCD) | Freeze drying | The dissolution test was conducted after making tablets containing primogel and crospovidone. After 60 minutes of dissolution, the GMP-BCD inclusion complex reached 100%. | (Syukri et al., 2015) |
| 2 | Captisol® | Freeze drying | The solubility of glimepiride increased from 0.56 µg/mL to 1.94 µg/mL. After 90 minutes of dissolution, the GMP-Captisol® inclusion complex reached 100% compared to pure glimepiride, which was 44%. | (Pal et al., 2020) |
| 3 | β-cyclodextrin (BCD) | Co-evaporation | After 180 minutes of dissolution, the GMP-BCD inclusion complex reached 99.38% compared to pure glimepiride, which was 17%. | (Bachir et al., 2013) |
| 4 | Hydroxypropyl β-cyclodextrin (HPBCD) | Co-evaporation | After 180 minutes of dissolution, the GMP-HPBCD inclusion complex reached 99.74% compared to pure glimepiride, which was 17%. | (Bachir et al., 2013) |

Captisol®, chemically identified as sulfobutylether β-cyclodextrin, represents a chemically modified version of BCD. This modification is undertaken to optimize safety and enhance the solubility, stability, and bioavailability of drugs. Captisol® has undergone preclinical and clinical evaluations, exhibiting reduced toxicity relative to BCD and superior drug solubility enhancement interactions. Analogous to BCD, Captisol® encapsulates drug molecules within its hydrophobic cavity. The formation of an inclusion complex between glimepiride and Captisol® results in increased solubility, rising from 0.56 µg/mL to 1.94 µg/mL, and enhanced dissolution rate, achieving 100% at the 90$^{th}$ minute, compared to pure glimepiride at 44% (Pal et al., 2020).

Hydroxypropyl β-cyclodextrin (HPBCD) emerges as a derivative of BCD. HPBCD incorporates hydroxypropyl groups, exhibiting improved water solubility and heightened safety. The inclusion complex formation between glimepiride and HPBCD yields superior outcomes compared to employing BCD alone. At the 180$^{th}$ minute, the dissolution of the glimepiride-HPBCD inclusion complex attains 99.74%, whereas pure glimepiride achieves a mere 17% dissolution rate (Pal et al., 2020)

*Solid dispersions*

An important component in the formation of solid dispersions is the carrier polymer. The properties of the carrier polymer affect the solubilization of the drug dispersed within it, so its selection must meet specific criteria: it should be inert, easily soluble in water, non-toxic, compatible, and stable against heat (Verma et al., 2011). Table 7 presents the carrier polymers used in the formation of solid dispersions of glimepiride and their dissolution results.

Polyethyleneglycol (PEG), represents a polyether compound frequently employed in the creation of solid dispersions, characterized by a molecular weight spanning from 3000 to 300,000. The nomenclature of PEG, such as PEG 6000 and PEG 4000, denotes variations in their molecular weights, with PEG 6000 and PEG 4000 showcasing low melting points of 67.7 and 58.7°C, respectively. PEG plays a pivotal role in augmenting the solubility, dissolution, and bioavailability of poorly water-soluble drugs by facilitating hydrophobic drug dissolution in water by disrupting the robust water lattice structure. Solid dispersions formed with PEG effectively enhance the solubility and dissolution rate of glimepiride. In glimepiride-PEG 6000, the solubility escalated from 3.98 µg/mL to 70 µg/mL, with a dissolution rate of 85.94% at 30 minutes. Similarly, in glimepiride-PEG 4000 solid dispersion, solubility surged from 3.98 µg/mL to 65 µg/mL, with a dissolution rate of 75.96% at 30 minutes (D'Souza and Shegokar, 2016; Sakure et al., 2020; Verma et al., 2011).

PEG finds utility in combining with other polymers or excipients in forming solid dispersions, commonly termed co-processed excipients (CE). CE entails the amalgamation of two or more excipients via specialized techniques like drum-drying and spray drying, resulting in alterations solely in physical properties while preserving chemical structure. Integration of multiple excipients aims to synergize their properties to maximize drug dissolution rates. Solid dispersion formation utilizing CE (PVP:MD:PEG) notably elevated the dissolution rate of glimepiride, achieving 74.22% at 120 minutes in contrast to a mere 18.45% for pure glimepiride (Surini et al., 2018).

**Table 7.** Solid dispersion glimepiride (GMP) with solubility and dissolution test result.

| No. | Carrier | Method | Conclusions | Reference |
|---|---|---|---|---|
| 1 | PEG 6000 | Spray drying | The solubility of glimepiride increased from 3.98 µg/mL to 70 µg/mL. After 30 minutes of dissolution, the solid dispersion of GMP-PEG 6000 with a ratio of 1:03 reached 85.94%. | (Sakure et al., 2020) |
| 2 | PEG 4000 | Spray drying | The solubility of glimepiride increased from 3.98 µg/mL to 65 µg/mL. After 30 minutes of dissolution, the solid dispersion of GMP-PEG 4000 with a ratio of 1:03 reached 75.96%. | (Sakure et al., 2020) |
| 3 | Gelucire 50/13 | Spray drying | The solubility of glimepiride increased from 3.98 µg/mL to 73 µg/mL. After 30 minutes of dissolution, the solid dispersion of GMP-gelucire 50/13 with a ratio of 1:03 reached 93.73%. | (Sakure et al., 2020) |
| 4 | Polyvinylpyrrolidone (PVP), maltodextrin (MD), and polyethylene glycol (PEG) | Spray drying | After 120 minutes of dissolution, the solid dispersion of GMP-(PVP:MD:PEG) with a ratio of 2:1:1 reached 74.22%, while pure GMP only reached 18.45%. | (Surini et al., 2018) |

Gelucire 50/13, chemically denoted as stearoyl macrogol-32 glycerides, stands as a PEG ester comprising small glyceride fractions and unbound PEG, featuring an HLB value of 11 and a melting point of 50°C. Possessing exceptional surfactant properties, Gelucire 50/13 enhances the solubility and wetting of pharmaceutical active ingredients, capable of self-emulsification upon water contact, thereby forming fine dispersions like microemulsions. Additionally, Gelucire 50/13 augments drug solubility within the body, facilitating drug absorption. Gelucire 50/13 effectively forms solid dispersions with glimepiride, amplifying its solubility from 3.98 µg/mL to 73 µg/mL, with a dissolution rate reaching 93.73% at 30 minutes (Panigrahi et al., 2018; Surini et al., 2018).

## DISCUSSION

This is the first systematic literature review comparing several solid-state modification techniques in enhancing the solubility and dissolution rate of glimepiride. This systematic review indicates that glimepiride, which has practical insolubility in water (Depkes, 2020), can have its solubility improved using various solid-state modification techniques. Solid-state modification refers to a process that alters the solid-state arrangement of a substance at the supramolecular level of the same components (Hughey et al., 2016). This systematic review discusses four techniques that can be used: co-crystallization, co-amorphous, inclusion complexes, and solid dispersions. As seen in the results section, all four techniques successfully improved the solubility of glimepiride, though there are differences in their outcomes.

From the six articles obtained on co-crystals, the combination of co-crystals with oxalic acid using ultrasound-assisted suspension co-crystallization showed the highest solubility improvement, reaching 97.3% compared to pure glimepiride, which was only 22.06% (Zidan et al., 2023). Oxalic acid is highly soluble in water, making it an ideal co-former that plays a significant role in enhancing the solubility of glimepiride.

In the co-amorphous technique, only two articles with extractable data were found. Among the four techniques discussed, co-amorphous showed the lowest solubility improvement. The highest solubility improvement observed was the combination of glimepiride with L-arginine, reaching 4.25 µg/mL compared to pure glimepiride at 0.2 µg/mL.

In the inclusion complex technique, three articles with extractable data were found. Inclusion complexes require a host molecule with a hydrophobic interior, allowing glimepiride to be inserted into this hydrophobic site. Throughout the search, cyclodextrin is the host molecule frequently used in inclusion complexes, especially β-cyclodextrin. Among the four solid-state modification techniques, the inclusion complex modification showed the highest results, with the formation of an inclusion complex between glimepiride and Captisol® achieving a dissolution rate of 100% compared to 44% for pure glimepiride (Pal et al., 2020).

This study has implications for practice and future research. The positive findings from this study suggest that among the four solid-state modification techniques, all successfully improved the solubility of glimepiride, with the most significant improvement seen in the inclusion complex.

On the other hand, the positive results from this study may be encouraging for researchers, as there is now a systematic review comparing several methods, which can alleviate the difficulty of testing each method individually. Future studies could explore other solid-state modification techniques that have the potential to further enhance the solubility and dissolution rate of glimepiride.

### Strengths and limitation

This article is the first comprehensive systematic literature review on various solid-state modification techniques for enhancing the solubility and dissolution rate of glimepiride. To the authors' knowledge, they have only found one study on a systematic review of solid-state modification without mentioning the specific drug studied. In this review, not all articles included solubility and dissolution tests; some included only one of these tests, and some others included both.

## CONCLUSION

This systematic review comprehensively explores how solid-state modification techniques improve the solubility and dissolution of glimepiride. Specifically, discusses about co-crystals, co-amorphous, inclusion complexes, and solid dispersions. The study's findings suggest that while all four techniques successfully enhance glimepiride's solubility, the inclusion complexes method is the most effective. These results may benefit researchers by providing a comprehensive comparison of methods and guiding future research to explore additional techniques for enhancing glimepiride's solubility.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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| Design | x | | x | |
| Definition of intellectual content | x | x | | x |
| Literature search | x | | x | |
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