Global Health: Journal of Health Sciences, Public Health and Pharmacy

E-ISSN: 3062-8687
P-ISSN: 3063-7465

Research Article

Literature Review: Application of Particular Solvents in Injection Formulations: DMSO, PEG, and Pyrogen Free Water

Silvy Aldila [1*], Farah Destyana Nurainy [2], Ummi Kalsum [3], Akmalia Septi Haliza [4], Easter Kaniada Kristanti [5], Recta Syifa Dwimart [6], Muhammad Rayhan [7]

[1] Pharmacy Department, STIKES Telogorejo Semarang, Central Java, Indonesia
e-mail : silvy@stikestelogorejo.ac.id
[2] Pharmacy Department, STIKES Telogorejo Semarang, Central Java, Indonesia
[3] Pharmacy Department, STIKES Telogorejo Semarang, Central Java, Indonesia
[4] Pharmacy Department, STIKES Telogorejo Semarang, Central Java, Indonesia
[5] Pharmacy Department, STIKES Telogorejo Semarang, Central Java, Indonesia
[6] Pharmacy Department, STIKES Telogorejo Semarang, Central Java, Indonesia
[7] Pharmacy Department, STIKES Telogorejo Semarang, Central Java, Indonesia

* Corresponding Author : Silvy Aldila

Abstract: The selection of appropriate solvents in sterile injection formulations plays a pivotal role in determining the stability, efficacy, and safety of pharmaceutical products. Among the commonly utilized solvents, Dimethyl Sulfoxide (DMSO), Polyethylene Glycol (PEG), and pyrogen-free water exhibit distinct physicochemical properties and functional roles. This study aims to analyze the characteristics, functions, and implications of these three solvents within the context of sterile injectable preparations. The research methodology involves a comprehensive review of six peer-reviewed scientific articles published within the last five years, focusing on solvent performance, compatibility, and safety profiles. Findings reveal that DMSO is highly effective in dissolving lipophilic compounds due to its strong solvating capacity. However, its use at elevated concentrations may lead to irritation and cytotoxicity, necessitating careful dosage regulation. PEG, particularly in its flexible molecular weight variants, serves as a co-solvent and viscosity modifier, enhancing solubility and stability of active pharmaceutical ingredients. Pyrogen-free water, characterized by its inertness and biocompatibility, remains the gold standard for injection solvents, offering minimal risk and broad applicability across drug classes. The study underscores the importance of aligning solvent selection with the physicochemical nature of the drug, intended route of administration, and patient safety considerations. Furthermore, the potential for combining solvents to achieve optimized formulations is highlighted as a promising avenue for future pharmaceutical development. Such combinations may offer enhanced solubility, reduced toxicity, and improved delivery mechanisms, particularly for complex or poorly soluble compounds. In conclusion, understanding the nuanced roles of DMSO, PEG, and pyrogen-free water is essential for formulating safe and effective sterile injections. This research contributes to the growing body of knowledge supporting rational solvent selection and encourages further exploration into innovative solvent systems for advanced drug delivery.

Keywords: Injectable Solvent, DMSO, PEG, Pyrogen-Free Water, Sterile Formulation

Received: May 17,2025;
Revised: May 31,2025;
Accepted: June 16,2025;
Published: June 30,2025;
Curr. Ver.: June 30,2025;

1. Introduction

The manufacture of sterile injection formulations has become a major concern in the development of parenteral pharmaceuticals, due to the high demands for safety, stability, and bioavailability (Mishra et al., 2021). A crucial element in this formulation is the solvent, which not only serves as a medium for the active ingredient but also as a factor that affects the efficacy of biopharmaceuticals and sterilization of preparations (Rahmawati, 2022). The

solvent used must meet criteria such as non-toxicity, non-irritating, and compatibility with other active ingredients and excipients (EMA, 2020).

In recent decades, the use of specialty solvents such as dimethyl sulfoxide (DMSO), polyethylene glycol (PEG), and pyrogen-free water has increased in injection formulations, especially for active compounds that are difficult to dissolve in water. DMSO is known as an amphiphilic solvent that has a significant capacity to penetrate cells and dissolve polar and non-polar substances (López et al., 2023). However, PEG is used because of its wide compatibility with active substances, suitable viscosity for injection, and its harmless properties (Abdellatif et al., 2020). Meanwhile, due to its high purity and no endotoxins that can cause fever, pyrogen-free water has emerged as the industry standard for injectable solvents (Indonesian Pharmacope, 2021).

The use of these solvents still poses some problems that require further investigation. DMSO is an effective solvent; however, improper use can lead to systemic toxicity and dermatological side effects (Islam et al., 2022). DMSO is known for its ability to effectively penetrate cells and dissolve a variety of compounds, including hydrophilic and lipophilic substances. DMSO has the potential to inhibit mitochondrial function and cause disruption of cellular metabolism if used in excess. Common dermatological side effects include erythema, pruritus, and burning at the injection site. In certain cases, PEG can cause irritation or hypersensitivity reactions, especially at large-volume injections (Chen, 2020). Pyrogen-free water requires strict production and testing protocols due to the significant risk of microbiological contamination (Puta, 2023). The selection and use of certain solvents in injection formulations should be based on a thorough understanding of their pharmaceutical properties and toxicology. Recent studies highlight the importance of an evidence-based approach in the selection of injectable solvents, taking into account factors such as stability, solubility effectiveness, sterility, and patient safety (Nguyen, 2022). Recent developments in formulation technology and contemporary sterilization methods increase the optimization of this solvent in sterile injection (Suryadi, 2021).

2. Theoretical Studies

Solvent Selection Theory in Sterile Injection Formulation

The selection of solvents in sterile injection formulations is very important because it affects the stability of the drug, safety, patient comfort, and therapeutic effectiveness. The solvent used must meet the requirements of sterile, pyrogen-free, non-toxic, compatible with active substances and additives, and chemical-physically stable (Allen, 2020).

Solvent Selection Factors

The selection of solvents is influenced by the physicochemical properties of the drug (solubility, pKa, stability), the route of administration, the safety of the use of cosolvents, and compatibility with additives and containers. For example, intravenous injections are mandatory to use aqueous solvents, while intramuscular injections may use oils to prolong drug release (Allen, 2020; USP, 2021).

Ideal Solvent Criteria

The ideal injectable solvent should:

a. Sterile and pyrogen-free, due to the presence of endotoxins it can cause fever and serious toxic reactions (USP, 2021).
b. It is non-toxic and non-irritating, so it does not cause local or systemic reactions (Ministry of Health of the Republic of Indonesia, 2020).
c. It is compatible with drugs and excipients, so it does not cause precipitation, discoloration, or degradation (Rowe et al., 2009).
d. Chemically, physically, and microbiologically stable, including stable to light, oxidation, and hydrolysis (Aulton & Taylor, 2018).
e. It has a good dissolving capacity for therapeutic doses of drugs (Allen, 2020).
f. Physiological, that is, with pH and osmolality close to body fluids in order to be tolerated (Ansel et al., 2011).

Solvent Type

a. Aqueous Solvent (water-based)

Aqueous solvents are the top choice because they are safe, physiological, and compatible with many medications. Types include:

1) Water for Injection (WFI): pyrogen-free pure water, standard for injection manufacturing.
2) Sterile Water for Injection (SWFI): Sterilized WFI, used as a powder reconstruction solvent.
3) Saline (NaCl 0.9%): used to make isotonic solutions.
4) Dextrose 5%: as an alternative to maintain osmolality (USP, 2021).

Aqueous solvents have limitations for drugs that are highly lipophilic or unstable in water, so they need additional cosolven (Allen, 2020).

b. Non-Aqueous Solvents (oil-based/organic)

Used for lipophilic drugs or injection depots:

1) Pure vegetable oils (sesame, peanut, cotton, corn oil) that are free from drowsiness.
2) Organic cosolvents: ethanol, propylene glycol, polyethylene glycol (PEG 400), glycerin.
3) Cosolven–water mixtures, e.g. ethanol–water or PEG–water, are used to increase solubility (Rowe et al., 2009).

Oil solvents are suitable for intramuscular depot injection because they slow down absorption, but should not be used intravenously due to the risk of fatty embolism (Aulton & Taylor, 2018).

3. Research Methods

The purpose of this systematic literature review (SLR) was to investigate the use of specific solvents, including dimethyl sulfoxide (DMSO), polyethylene glycol (PEG), and pyrogen-free water, in the development of sterile injection preparations. This study aims to collect and synthesize information from various previous studies to achieve an in-depth understanding of the benefits, risks, and regulations related to the use of these three solvents.

Literature searches were conducted using several leading scientific databases, including PubMed, ScienceDirect, Google Scholar, and two national databases, Garuda and Neliti. Keywords used include 'DMSO injection formulations', 'PEG in parenteral treatment', 'pyrogen-free water for injection', and various Boolean combinations such as ('DMSO' AND 'sterile injection') or ('PEG' AND 'injection solvent'). The requirements for inclusion are that the publication must be written in English or Indonesian, published within the last five years (2019–2024), have the availability of the full text, and in particular address the use of one of the three solvents in sterile injection formulations. Articles that exclusively discuss non-parenteral forms of preparation, are duplicates, or are irrelevant will be excluded from the analysis.

The article selection process is carried out in stages, starting with identification (n=40), which includes search results from databases and other sources. Titles and abstracts are used to filter out 30 articles after duplicates are removed. Furthermore, 40 articles underwent additional analysis through full-text reading. However, 34 articles were removed because they did not meet the inclusion criteria substantially. Finally, six publications were selected for further examination.

4. Results and Discussion

The results of the analysis of six scientific articles show that the stability, safety, and efficacy of the final product are significantly affected by the use of specific solvents in the formulation of sterile injection preparations. Dimethyl sulfoxide (DMSO), polyethylene glycol (PEG), and water for injection (WFI) are the three most reviewed types of solvents. Each of these solvents has different characteristics and functions in parenteral formulations.

Based on six articles, DMSO was used in two studies, with the majority of these studies involving topical injection preparations, peptides, and anticancer formulations. DMSO is known for its ability to increase the solubility and penetration of active substances; however, DMSO can cause irritation and toxicity at concentrations above 20%. The use of DMSO at safe limits ≤10% v/v for direct injection is recommended in related articles, as written by Zhang et al. (2021).

Two of the six articles examined contained polyethylene glycol (PEG), specifically the PEG 400 type. PEG is used as a co-solvent and viscosity regulator in a variety of preparations, such as injection depots, antibiotics, and herbal preparations. PEG can improve the chemical and physical stability of preparations without causing harmful reactions at concentrations below 30% (Müller, 2020). The term "stability" refers to the ability to maintain the concentration of the active substance in a solution without undergoing physical changes or chemical degradation during storage. The condition of biological products is examined specifically in relation to other solvents, such as pyrogen-free water. This study underscores the high safety of pyrogen-free water as a primary solvent, especially for formulations that require high sterility and are free from endotoxin contamination.

DMSO is the most commonly used solvent for the penetration and solubility of lipophilic compounds, PEG is used as a viscosity and stability regulator, and pyrogen-free water is the primary pure solvent with the best safety profile, according to the literature review. This data has been carefully summarized in a Data Table that describes the process of selecting and screening literature based on inclusion and exclusion criteria. The use of solvents in sterile injection formulations is not a generalization; rather, it must be adjusted to the needs of the formulation, the type of active substance, and the route of administration. This combination of solvents has the potential to be a new formulation strategy that improves therapeutic efficacy and provides additional stability.

Table 1. Data Extraction

Yes	Author (Year)	Solvent	Types of Injection Preparations	Purpose of Research	Conclusions
1	Zhang et al. (2021)	DMSO	Anticancer IV	Increasing the solubility of lipophilic anticancer compounds for intravenous injection	DMSO enhances the solubility of anticancer drugs and preserves solution stability for six months at concentrations ≤ 10%
2	Lee et al. (2020)	PEG 400	NSAID injections	Stabilizing the chemical structure of NSAIDs to prevent deterioration during storage	PEG 400 preserves the chemical stability of NSAID active ingredients from oxidation and hydrolysis at a concentration of 20%
3	Ahmad et al. (2022)	DMSO	Injectable peptide formulation	Enhancing the stability of the tertiary structure of peptide proteins to prevent denaturation or aggregation	DMSO preserves the three-dimensional structure of peptide proteins in injections and inhibits denaturation
4	Jones et al. (2023)	Free pyrogenic water	Biologic Subcutaneous	Achieving a sterile solvent for subcutaneous biologics that maintains microbiological stability	Free pyrogen water ensures microbiological stability and prevents pyrogenic reactions in biological preparations for Caesarean Section (CS)

5	Müller et al. (2020)	PEG 400	Medications for neurodegenerative disorders	Enhancing the solubility of neuroactive compounds while maintaining low toxicity levels	PEG 400 serves as a co-solvent in the formulation of injections for neurodegenerative medications and exhibits no toxicity at concentrations reaching 30%
6	Ibrahim et al. (2024)	DMSO	Injection into the dermal	Enhancing the transdermal absorption of active compounds into the skin layers	DMSO is utilized for transdermal penetration in dermal injections; however, its application requires regulation to prevent systemic or local adverse effects

The use of special solvents in sterile injection formulations is essential in the development of parenteral preparations, especially for active substances characterized by low solubility, instability, or specific formulation environmental requirements. An analysis of six articles that have been reviewed shows that dimethyl sulfoxide (DMSO), polyethylene glycol (PEG), and free pyrogenic water play a distinct and significant role in improving the quality of sterile injection preparations.

Dimethyl sulfoxide (DMSO) serves as a co-solvent or primary solvent in injection formulations, facilitating the solubility of lipophilic drugs, including anticancer compounds, peptides, and topical injection therapy. DMSO is known for its ability to penetrate biological membranes and facilitate the delivery of active substances into target tissues (Zhang et al., 2021). DMSO has limitations in injection applications, mainly due to its impervious properties at concentrations exceeding 20% and the potential for systemic toxicity if not carefully regulated (Ibrahim, 2024). Therefore, it is recommended to use it at a concentration of ≤10% v/v to guarantee safety.

Polyethylene glycol (PEG), specifically PEG 400, serves as a joint solvent and viscosity-controlling agent in injection formulations. PEG is known for its high biocompatibility and its ability to improve the solubility and stability of formulations, especially in herbal medicines, antibacterial agents, and depot formulations. Chemical stability is related to the ability of a drug to maintain its molecular structure, thereby preventing degradation or transformation into potentially harmful substances. PEG effectively maintains the stability and sterility of the preparation for up to three months. PEG shows no toxic effects at concentrations of 30% or lower, making it a safe and versatile option for a variety of parenteral routes.

Free pyrogenic water, also known as Water for Injection (WFI), serves as the primary solvent in sterile injection formulations. Its main advantages are its microbiological purity and the absence of endotoxins, making it ideal for formulations of vaccines, vitamins and infusion solutions. Pyrogen-free water exhibits a high safety profile, effectively preventing pyrogenic reactions and local irritation. WFI can maintain sterility during medium to long-term storage at the national level. Microbiological stability refers to the maintenance of a solution that is free from the proliferation of bacteria, fungi, or other microorganisms during its storage life. Non-pyrogenic results showed that the solution did not cause an increase in body temperature (fever) in the patient.

The selection of these three solvents should be adjusted based on the specific active substance, formulation purpose, route of administration, and regulatory requirements. DMSO is preferred for injection formulations intended for tissue penetration or experimental applications, while PEG offers greater flexibility as a co-solvent or viscosity modifier. WFI solvents serve as the standard for primary solvents; However, these solvents have limitations in dissolving lipophilic substances. Solvent combinations such as PEG-WFI or DMSO-WFI offer innovative and balanced formulation solutions. (Wang, 2021)(Chen, 2022).

Advances in formulation technology and the increasing demand for stability and safety in injection products underscore the importance of the use of specialty solvents such as DMSO, PEG, and pyrogen-free water in the manufacture of contemporary parenteral formulations. Evaluation of physicochemical properties, toxicity profiles, and solvent stability is essential to optimize formulations.

5. Conclusions

Literature studies show that the use of specific solvents, including dimethyl sulfoxide (DMSO), polyethylene glycol (PEG), and water for injection (WFI), significantly improves the quality of sterile injection formulations. DMSO is effective in increasing the solubility of lipophilic active substances and facilitating tissue penetration; However, its use should be limited due to the risk of irritation and toxicity at concentrations above 10-20%. PEG, especially PEG 400, functions as a chemically stable co-solvent, is considered safe at concentrations up to 30%, and effectively modulates viscosity to facilitate controlled drug release in depot formulations. Water for injection is a safe and stable primary solvent, especially for vaccines, biologics, and vitamins, as it does not trigger pyrogenic reactions or microbiological contamination. Furthermore, the use of combination solvents has emerged to reduce the limitations inherent in individual solvents in more complex formulations, while still taking into account the properties of the active ingredients, routes of administration, and safe concentration thresholds to prevent side effects.

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