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Systematic review of the stability and compatibility of propofol injection

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Abstract

One ampoule of propofol is often divided into several syringes or is sometimes combined with other drugs that may lead to incompatibility and instability. A systematic review of literature (PubMed, Science Direct, and Google Scholar) identified 37 pieces of research which suggest that the data on propofol stability are limited. Results of all of the identified studies indicated that the stability of propofol is less than 24 hours. Additionally, the evidence shows that glass packaging as well as storing in cold and dark conditions promote stability. What is more, propofol was proved to be incompatible with 23 of the 36 drugs tested. In conclusion, there is a relatively small body of literature that measures the physical stability of propofol. The findings of this review recommend keeping propofol in glass and storing it no longer than 24 hours. Compatibility data must be considered in co-administrations with propofol.

Key words: stability, compatibility, propofol, intravenous.

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The most popular intravenous general anaesthesia for both induction and maintenance for almost every surgery is propofol [1]. Propofol has several advantages, such as a fast onset of 15–20 seconds, minimal post-operative nausea and vomiting, and a short recovery time of 2–10 minutes [2]. Propofol also has some side effects, such as soreness at the time of injection and hypotension [3].

Propofol is formulated as an emulsion that has a milky white colour and a rather thick texture; it has a pH of 7 to 8.5 and has high solubility in oil (i.e., lipophilic) [4]. Propofol is formulated as a macro-emulsion with soybean oil (100 mg mL^{-1}), lecithin (12 mg mL^{-1}), and glycerol (22.5 mg mL^{-1}) that can easily become unstable [5]. Propofol is available as 1% and 2% concentrations in emulsions. Propofol 1% in a vial consists of 200 mg of the drug (10 mg mL^{-1} in a volume of 20 mL) [6].

Meanwhile, the dosage of propofol needed for anaesthesia induction is 1.5–2.5 mg kg^{-1} of body mass; thus, in general, an adult patient only needs 75–125 mg, meaning that one vial can be used for 2–3 patients [7]. Therefore, in daily practice, propofol emulsion is often divided into preparations and is stored for more than 24 hours, which may alter the stability of the original formula. In addition, propofol is often administered along with other IV drugs through the same line, which can induce incompatibility.

Emulsions such as propofol do not dissolve in water, which often causes incompatibility when mixed with other IV drugs that are generally water soluble [8]. In longer admixture durations, the drug is at risk of becoming unstable. A macro-emulsion of propofol can undergo degradation caused by oxidation that results in the enlargement of droplet sizes, exceeding the limit required by the FDA of an average particle size of < 0.45 µm and a fat globule percentage (PFAT5) > 5 µm of < 0.05% [9]. Oversized particles can cause embolisms in patients [10].

The risk of instability can be prevented by choosing the proper additives, compatible solvents, a safe storage environment, and an optimum administration time. Moreover, incompatibility can be prevented by knowing which drugs are compatible and safe to be given together. Therefore, information about the stability and compatibility is crucial to formulate a safe propofol administration. To the best of the researchers' knowledge, no publication has yet reviewed data on the stability and compatibility of propofol injection.

METHODS

Search strategy

Data collection was started in January 2020 by searching for literature using electronic media or databases such as PubMed, Science Direct and Google Scholar. The literature search was conducted

by selecting English language-based articles. The keywords used in the article hunt were "propofol", "stability", "physicochemical stability", "compatibility" and any names and synonyms of propofol. The literature search technique used keyword combinations with the Boolean operators "OR" and/or "AND".

Selection criteria

The inclusion criteria were those articles that have been published in English language, available in full text, in vitro studies that discuss the compatibility of propofol injection with other drugs, studies on the physical stability of propofol including visual research on the colour, homogeneity, precipitation, gas-forming ability, particle size analysis, pH measurement and/or chemicals in certain conditions and storage. The exclusion criteria were those articles that did not state data for the drug, solvent, or storage environment and did not clearly provide the results of both compatibility and stability tests.

From 77 articles reviewed in this study, 37 articles were selected based on compliance with the inclusion and exclusion criteria. The other 40 articles were excluded because 16 articles did not examine propofol stability both physically and chemically, 9 articles were duplications, and the rest were not experimental studies but comments, letters or reviews. The selection process of the articles for this study is shown in the Figure 1.

RESULTS

The selected studies on the stability of propofol medium-/long-chain triglycerides (MCT/LCT) showed sufficient methods that used physical parameters such as microscopy or the percentage of fat globules > 5 μm of < 0.05% (PFAT5) or chemical parameters such as concentration level. All studies showed clear methodology with detailed information related to the kinds of drugs and solvents used and replications. There were 7 articles that studied propofol stability in various packages and environments. The review results of each article are summarized in Table 1.

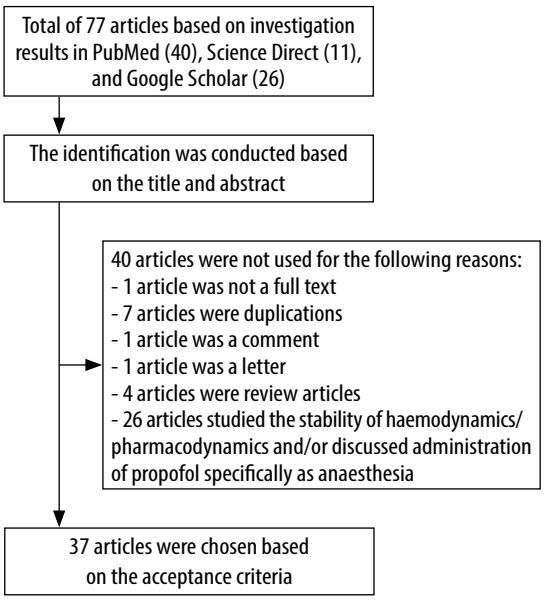

FIGURE 1. Diagram of retrieved studies

According to the criteria of compatibility studies, we evaluated the studies' quality, resulting in 11 articles that performed repetitions with a minimum of triplicate tests, 16 articles used a stimulated Y-site method, 13 articles used data for particle sizes or droplets for physical compatibility, and 12 articles provided data for chemical compatibility. Table 2 shows the results of propofol compatibility mixed with other drugs.

DISCUSSION

Propofol stability after being opened and packaged

Several studies have addressed the question of propofol stability: there are 7 reports on propofol stability, which employ various conditions. This review revealed that unopened propofol can maintain its stability, while it tends to quickly experience degradation resulting in instability after it is opened [10]. Propofol will undergo oxidative degradation after being exposed to oxygen. This review shows that the stability of propofol is associated with physical rather than chemical parameters. Propofol can preserve its chemical parameters for 30 days and can maintain its physical parameters for only 3 days under optimum conditions.

This review of stability included two typical propofols that are branded by three different manufacturers. The formulations contain different additives, such as long-chain triglycerides (LCT) from soybean oil with preservatives or a combination of medium- and long-chain triglycerides (MCT/LCT) with no preservatives. Two studies of propofol with LCT and preservatives showed longer physical stability than studies of propofol with preservative-free MCT/LCT [11–14]. These findings are correlated with the information from a brochure that states that Diprivan (LCT with preservatives) and Fresofol (propofol with MCT/LCT and preservative free) are stable for 12 and 6 hours, respectively. However, this is contradictory to the previous finding that the emulsion is less stable in LCT since there are longer triglyceride chains, which induce physicochemical stress and break the layer phase of the emulsifier [46]. Even though the preservatives do not directly affect the physical-chemical stability levels, microbial contamination

TABLE 1. Stability of propofol in various packages and environments

Reference	Solvent	Brand and content	Package	Storage environment (assay frame time)	Tested parameter	Stability result
Damitz *et al*., 2016 [10]	Unopened	Propofol, Fresenius-Kabi AG contains LCT with disodium edetate (EDTA)	Origin container	Room temperature and light (21 months)	Visual Microscopy HPLC (concentration level)	Stable for 21 months
Stewart, 2000 [11]	No added dilution (1% propofol)	Diprivan, AstraZeneca contains soybean oil (LCT) with disodium edetate (EDTA)	Polypropylene syringe	Room temperature (36 hours)	HPLC (concentration level)	Stable for 36 hours
Masaki, 2003 [12]	No added dilution (1% propofol)	Diprivan, AstraZeneca contains soybean oil (LCT) with disodium edetate (EDTA)	Glass vial	Room temperature	Visual microscopy	Stable for 24 hours
Rahmat, 2012 [13]	No added dilution (1% propofol)	Fresofol, Fresenius Kabi contains propofol 1% MCT/LCT, no preservative	Polypropylene syringe	Cold temperature (24 hours)	Visual microscopy PFAT5	Stable for 6 hours
Wei *et al*., 2013 [14]	Propofol ≥ 3 mg mL^{-1} in NaCl 0.9%	Propofol, Chi Sheng Chemical Corp contains 10% MCT/LCT, no preservatives	PVC Bag	Room temperature	Microscopy PFAT5	Stable for 6 hours
			Non-PVC bag (CRYOFAC)			Stable for 24 hours
			Glass container			Stable for 72 hours
	Propofol ≤ 2 mg mL^{-1} in NaCl 0.9%	Propofol, Chi Sheng Chemical Corp contains 10% MCT/LCT	PVC, non-PVC, and glass	Room temperature	Microscopy PFAT < 0.05%	Stable for 72 hours
Wei, 2013 [15]	Propofol in NaCl 0.9%	Propofol, Chi Sheng Chemical Corp contains 10% MCT/LCT	Non-PVC bag (CRYOFAC)	Room temperature and light	HPLC (propofol concentration)	Stable for 5 days
				Room temperature and dark		Stable for 8 days
				Cold temperature and dark		Stable for 15 days
Sautou-Miranda *et al*., 1996 [16]	Propofol 1% in glucose 5%	Diprivan, AstraZeneca contains soybean oil (LCT) with disodium edetate (EDTA)	PVC Bag	Room/cold temperature Light and dark	HPLC (propofol concentration)	Stable for 2 days
			Glass container			Stable for 30 days
			Polypropylene			Stable for 30 days

may change the pH, which can induce chemical reactions. However, those studies used divided doses in storage, which may introduce microbial contamination. In addition, when the preservatives combat microbial contamination, the number of particles < 0.5 µm as a physical parameter is reduced. Based on these limited data, additional confirmatory studies are needed to prove the stability of propofol in different compositions, including the type of emulsifier, lipids, and preservatives.

Regarding the packaging, propofol that has been opened and diluted with 5% glucose or 0.9% NaCl is more stable in a glass container than in a plastic one [14, 15]. Soutou-Miranda *et al*. showed that the level of propofol LCT with disodium edetate in 5% glucose solvent in a glass container can maintain its stability for up to 30 days, whereas it is only stable for up to two days if it is stored in a polyvinylchloride (PVC) plastic container [16]. Other studies support the results in which propofol MCT/LCT undergoes no physical changes for 72 hours in glass, which is longer than the maintenance in a polypropylene syringe and PVC [16]. Storing propofol in a plastic container causes abnormal globule size distribution of propofol. Propofol is a lipophilic chemical that can interact with ions that are present in plastic containers. This can occur because plastic containers are permeable to oxygen and contain plasticizers that dissolve in oil; therefore, it is better to avoid the utilization of plastic containers [46]. This interaction causes the formation of globules and active chemical absorption [16]. The results of this investigation show that propofol that has been opened and then repacked in a plastic container, such as a syringe injection, should not be stored for more than 24 hours [46, 48, 49].

TABLE 2. Study on compatibility of propofol with other drugs

References	Brand of propofol	Tested drugs	Mixing method	Sampling	Compatibility test method	Test result
Donnelly, 2008 [17]	Propofol 1%, Novopharm contains soybean oil (LCT)	Propofol-Ketamine	Mixed in polypropylene syringe in ratio 50 : 50 and 70 : 30	2 mL taken at 0, 1, and 3 hours	Visual, pH, HPLC (concentration level)	Compatible until 3 hours
Hanifah, 2020 [18]	Nupovel, Novell Pharmaceutical Laboratories contains soybean oil (LCT)	Propofol-Acetaminophen	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	1 mL taken at 0, 1, 4, and 24 hours	Visual, pH, microscopy	Incompatible starting from zero hours
Izgi *et al.*, 2018 [19]	Propofol 1%, Fresenius Kabi contains MCT/LCT	Propofol-Ketamine	Mixed in polypropylene syringe in ratio 5 : 1 and 6:7 : 1	1 mL taken at 0, 10, 30, 60, 90, 120, 180, 240, 300, and 360 minutes	Visual, HPLC (concentration level)	Compatible until 6 hours
Bedocs, 2019 [20]	Propofol, Hospira Inc contains soybean oil (LCT) with benzyl alcohol	Propofol-Ketamine	Mixed in polypropylene micro tube (10 mg of propofol +1 mg of ketamine)	1 mL taken at 6 and 24 hours	HPLC (concentration level)	Compatible from 6 to 24 hours
Zbytovská *et al.*, 2017 [21]	Propofol 1%, Fresenius Kabi contains MCT/LCT	Propofol-Sufentanil	Mix propofol 5 mL with 0.1, 0.2, and 0.5 mL of sufentanil	Taken at 1 and 24 hours	Visual, PSA (particle size/droplet)	Compatible until 24 hours
	Propofol-Lipuro, B. Braun contains LCT/MCT					
	Disoprivan, AstraZeneca contains soybean oil (LCT) with EDTA					
	Propofol-Anesia, UAB Norameda contains MCT					
	Propofol, Ratiopharm contains MCT					
Bennett *et al.*, 2001 [22]	Diprivan, AstraZeneca contains soybean oil (LCT) with disodium edetate (EDTA)	Propofol-Methohexital	Mixed in ratio 1 : 1	Taken at 0, 3, 6, 12, 24, and 48 hours	Particle size (particle size/droplet), HPLC (concentration level)	Compatible until 48 hours
Ortner *et al.*, 2009 [23]	Propofol 1%, Fresenius Kabi contains LCT/MCT	Propofol-Nimodipine	Mixed in ratio 1 : 1	10 µL taken at 0 hour and 20 hours	Visual, microscopy	Incompatible starting from zero hour
		Propofol-Remifentanil hydrochloride				Incompatible starting from zero hour
		Propofol-Fentanyl				Incompatible until 20 hours
Gersonde *et al.*, 2017 [24]	Propofol-Lipuro, B. Braun contains LCT/MCT	Propofol-Remifentanil hydrochloride	Mixed in ratio 10 : 1, 1 : 1, and 1 : 10	5 mL taken at 0, 15, 30 minutes, and 1, 2, 4, 8, 24, 96, and 168 hours	Visual, pH, DLS (particle size/droplet), HPLC (concentration level)	Incompatible starting from the first hour
Prankerd and Jones, 1996 [25]	Diprivan, ICI Pharmaceutical contains soybean oil with EDTA	Propofol-Thiopental sodium	Mixed in a vial in ratio 1 : 3, 3 : 5, 1 : 1, 5 : 3 and 3 : 1	2 mL taken at 0, 30 minutes, 3, 23, 26, and 47 hours	Visual, microscopy, HPLC (concentration level)	Compatible for no more than 48 hours
Chernin, 1996 [26]	Diprivan, AstraZeneca contains soybean oil (LCT) with disodium edetate (EDTA)	Propofol-Thiopental	Mixed in a polypropylene syringe until final concentration reaches 5 and 12.5 mg mL^{-1}	5 mL taken at 0, 4, 8, 24, 48, 72, 120, 168, 216, 240, and 264 hours (room temperature) and 0, 4, 8, 24, 48, 72, 120, 168, 216, and 312 hours (cold temperature)	Visual, pH, HPLC (concentration level)	Compatible for 1 to 13 days (temperature at 4°C) Compatible for 1 to 5 days (temperature at 23°C)

TABLE 2. Cont.

References	Brand of propofol	Tested drugs	Mixing method	Sampling	Compatibility test method	Test result
Szalai *et al.*, 2018 [27]	Diprivan, AstraZeneca contains soybean oil (LCT) with disodium edetate (EDTA)	Propofol-Magnesium sulphate, Potassium chloride	Mixed in polypropylene syringe (simulated Y-site) in ratio 1 : 1	2 mL taken at 15, 30, 60, and 120 minutes	Visual, pH, PSA (particle size/droplet)	Compatible until 2 hours
Lawrence *et al.*, 2009 [28]	Propofol, Bedford Laboratories contain soybean oil (LCT)	Propofol-palonosetron hydrochloride	Mixed in a polypropylene tube (stimulated Y-site) in ratio 1 : 1	Taken at 1 and 6 hours	Visual, HPLC (concentration level)	Compatible for 4 hours
Voirol *et al.*, 2015 [29]	Not mentioned	Propofol-Insulin	Mixed in a glass tube (stimulated Y-site) in ratio 1 : 1, 1 : 4, and 4 : 1	Taken at 24 hours	Visual	Compatible for 24 hours
Brammer *et al.*, 2008 [30]	Propofol, Bedford Laboratories contain soybean oil	Propofol-Doripenem	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	10 mL taken at 1 and 4 hours	Visual, turbidity	Incompatible starting from zero hours
Asempa *et al.*, 2018 [31]	Propofol, Sagent Pharmaceutical contains sodium metabisulfite	Propofol-Plazomicin	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	Taken at 0, 15, 30, and 60 minutes	Visual, pH, turbidity	Incompatible starting from zero hour
Kim *et al.*, 2017 [32]	Propofol 10 mg mL^{-1}, Premier Pro Rx	Propofol-Isavuconazonium sulphate	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	Taken at 0, 15, 60, and 120 minutes	Visual, pH, turbidity	Incompatible starting from zero hour
Avery *et al.*, 2019 [33]	Propofol 1%, Fresenius Kabi contains MCT/LCT	Propofol-Eravacycline	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	10 mL taken at 30 and 60 minutes	Visual, pH, turbidity	Incompatible starting from the first hour
Nilsson, 2019 [34]	Propofol-Lipuro, B. Braun contains soybean oil MCT	Propofol- Remifentanil hydrochloride	Mixed in a tube in ratio 10 : 1, 20 : 1, 1 : 1 and 1 : 20	Taken at 0 and 4 hours	pH, DLS and light obscuration (particle size/droplet)	Incompatible starting from zero hour
Chan *et al.*, 2008 [35]	Propofol, Bedford Laboratories contain soybean oil	Propofol-Ceftobiprole medocaril	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	10 mL of sample taken at quarter hour, 1, and 4 hours	Visual, turbidity, light obscuration (particle size/droplet)	Compatible for 4 hours
Singh *et al.*, 2011 [36]	Propofol, Hospira Inc contains benzyl alcohol	Propofol-Ceftaroline fosamil	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	10 mL of sample taken at quarter, 1, and 4 hours	Visual, turbidity, light obscuration (particle size/droplet)	Compatible until 4 hours
Monogue *et al.*, 2018 [37]	Propofol, Sagent Pharmaceutical contains sodium metabisulfite	Propofol-Fosfomycin	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	10 mL taken at 0, 15, 60, and 120 minutes	Visual turbidity	Incompatible starting from zero hour
Lee, 2019 [38]	Propofol 1%, Fresenius Kabi contains MCT/LCT	Propofol-Levetiracetam	Mixed in a vial (simulated Y-site) in ratio 1 : 1	5 mL taken at 0, 15, and 30 minutes	Visual, pH, turbidity	Compatible until 30 minutes
Housman *et al.*, 2011 [39]	Propofol, APP Formulation contains disodium edetate (EDTA)	Propofol-Telavansin	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	10 mL taken at 0, 15, 60, and 120 minutes	Visual, pH, turbidity	Incompatible starting from zero hour

TABLE 2. Cont.

References	Brand of propofol	Tested drugs	Mixing method	Sampling	Compatibility test method	Test result
Raverdy *et al*., 2013 [40]	Not mentioned	Propofol-Vancomycin	In one infusion line	Taken at 1 hour	Visual, HPLC (concentration level)	Incompatible starting from the first hour
Baririan, 2003 [41]	Not mentioned	Propofol-Cefepime	In one infusion line	Taken at 1 hour	Visual, pH, HPLC (concentration level)	Incompatible starting from the first hour
Thabit, 2017 [42]	Propofol, Fresenius Kabi contains MCT	Propofol-Tazobactam-Ceftolozan	Mixed in a glass tube (simulated Y-site) in ratio 1 : 1	10 mL taken at 0, 15, 60 and 120 minutes	Visual, pH, turbidity	Incompatible starting from zero hour
Trissel, 1997 [43]	Diprivan, AstraZeneca contains soybean oil with disodium edetate (EDTA)	Propofol-Calcium chloride	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from the first hour
		Propofol-Diazepam	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from zero hours
		Propofol-Methotrexate	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from the first hour
		Propofol-Amikacin sulphate	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from zero hours
		Propofol-Gentamicin sulphate	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from zero hours
		Propofol-Netilmicin sulphate	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from zero hours
		Propofol-Phenytoin	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from zero hours
		Propofol-Tobramycin sulphate	Mixed in polycarbonate tube in ratio 1 : 1 (simulated Y-site)	Taken at 15 minutes and 1 hour	Visual, HPLC (concentration level)	Incompatible starting from zero hours
Masaki, 2003 [12]	Diprivan, AstraZeneca contains soybean oil with disodium edetate	Propofol-Lidocaine	Mixed 20 mL of propofol with 5 mg, 10 mg, 20 mg, 40 mg of lidocaine in one vial	Taken at 0, 10, 20, 30 minutes, and 1, 3, 6, and 24 hours	Visual, SEM (diameter droplet)	Incompatible with addition of ≥ 20mg starting from the 3rd hour Compatible with addition of ≤ 10 mg until 24 hours
Park *et al*., 2003 [44]	Diprivan, AstraZeneca contains soybean oil with EDTA	Propofol-Lidocaine	Mixed propofol with lidocaine 0, 10, 20, 30, 40, 50 mL in a vial	Taken at 0, a half, 1, 2, 3, 4, and 6 hours	Microscopy laser diffraction (particle size/droplet)	Incompatible with addition of 50 mg starting from the second hour
Levadoux, 1996 [45]	Diprivan, AstraZeneca contains soybean oil with disodium edetate (EDTA)	Propofol, Alfentanil	Mixed in one bag	Taken at 0, 15, 30 minutes and 1, 2, 4, and 6 hours	HPLC (concentration level)	Incompatible starting from the sixth hour
Vallée *et al*., 2019 [46]	Propofol, Novopharm contains soybean oil	Propofol-Ringer lactate	Mixed in a glass tube (simulated Y-site)	1 mL taken at 0, 15 minutes, and 1, 2, 3, and 4 hours	Visual, light obscuration (particle size/droplet)	Incompatible starting from zero hours

Propofol stability is also affected by temperature and light. Propofol MCT/LCT maintains its concentration level up to 8 days at room temperature and 15 at a cold temperature [15]. In addition, at room temperature, propofol MCT/LCT is stable for 5 days in the light and 8 days in the dark [15]. In contrast, it can maintain its stability up to 15 days in a dark environment [15]. High temperature and light exposure may trigger hydrolysis and the production of free fatty acids, which can cause destabilization of the emulsion and a change in the pH.

The concentration of propofol is also critical. Wei reported that propofol ≤ 2 mg mL^{-1} was physically stable up to 72 hours in PVC, CRYOFAC, or a glass container. Meanwhile, at higher concentrations of ≥ 3 mg mL^{-1}, the stability can be maintained up to 72 hours only in a glass container. Propofol in PVC and CRYOFAC containers was stable up to 6 and 24 hours, respectively [15]. Interestingly, at low concentration (≤ 2 mg mL^{-1}), propofol preserves its stability up to 72 hours either in a glass, PVC, or non-PVC container.

While propofol chemically exhibits longer stability, its physical changes such as the enlargement of globules indicate damage to the state of the emulsion. Globules that are larger than 5 microns can become stuck in the microvasculature and can induce micro-emboli. Therefore, the stability of the emulsion is dependent on physical materials that may induce embolism. The findings of this review suggest that propofol either in LCT or MCT/LCT is better stored in glass containers and in cold, dark conditions, for no longer than 24 hours.

Compatibility of propofol with other drugs

The compatibility referred to in this study is a condition in which the mixture of one drug with other drugs does not cause undesired reactions, whereas incompatibility is a condition in which undesired reactions emerge and cause changes in the physical and chemical stability of propofol and its therapeutic effects [50, 51]. Thirty-one articles reviewed in this study presented findings related to the compatibility of propofol with other drugs. The results of the review are shown in Table 3.

Propofol is an injectable lipid emulsion administered to patients through an intravenous line as a single unit or co-administered with other drugs in a similar administration line. Combining propofol with other drugs can cause interactions among drugs that trigger both physical and chemical incompatibilities. Emulsion changes such as colour changes, pH, globule size enlargement, precipitation, emulsion degradation, and concentration degradation are indications that show the incompatibility of the combination. Table 3 shows the incompatibility of propofol combination with 23 drugs.

Phenytoin, tobramycin sulphate, gentamicin sulphate, amikacin sulphate, calcium chloride, netilmicin sulphate, doripenem sulphate, methotrexate, cefepime, vancomycin, and Ringer's lactate show the occurrence of precipitation after mixtures are created. Incompatibility in which precipitation occurs is generally caused by an acid-base reaction among the tested chemical compounds, which is indicated by the undiluted non-ionic complex [52].

The instability of propofol leads to the occurrence of emulsion damage as emulsion degradation in the form of flocculation and coalescence that can cause enlargement of droplet size. Flocculation is a condition in which droplets stick to each other as the result of weak electrostatic repulsive forces among the droplets. In the flocculated state, a film layer on the droplet's surface that sticks to itself will disintegrate, causing the droplets to group and enlarge in diameter. This process is termed coalescence [5].

Flocculation occurs in the mixing process of propofol with acetaminophen [18]. Flocculation occurs as a result of decreasing propofol solubility, which causes the enlargement of emulsion globules [18]. The addition of lidocaine ≥ 20 mg causes degradation in the form of coalescence [12]. This review shows that propofol dilutes and diffuses with water phases, which causes it to group, creating larger droplets and then forming a separated layer on the surface area that can be seen by the naked eye [12]. Lidocaine is compatible with propofol at concentrations ≤ 10 mg for 24 hours [25]. Nimodipine and remifentanil hydrochloride show the occurrence of coalescence after being mixed with propofol.

In addition, emulsion damage can occur in the form of cracking and an inversion phase. Cracking occurred when propofol was mixed with telavancin, fosfomycin, tazobactam, isavuconazonium sulphate and plazomicin. Cracking describes the formation of an oil-free layer on the surface of the emulsion. Moreover, the mixing of propofol with diazepam shows the occurrence of phase inversion [42]. Emulsion phase inversion is the phenomenon of dispersion of one liquid phase in another, such as that observed in the process of interconversion between two types of simple emulsions: water-in-oil and oil-in-water emulsions [53].

Emulsion degradation, such as flocculation, creaming, cracking, and coalescence, occurs due to the impact of mixing propofol with other drugs, which causes the occurrence of globule enlargement over time. Fat globules of sufficiently large size, usually droplets more than 5 μm in size, that are administered by intravenous administration could cause embolism in patients [11]. Therefore, the mixture of propofol with incompatible drugs should be avoided to ensure the greatest safety to the patient.

TABLE 3. Occurrence of incompatibility of propofol mixed with other drugs

Name of drugs	Incompatibility
Acetaminophen	Direct globule size enlargement and colour changing within one hour of mixing [18]
Alfentanil	Concentration degradation of the drug within six hours of mixing [45]
Amikacin sulphate	Precipitation indicated by formation of white sediment immediately after mixing and the occurrence of colour changing from white to yellow [43]
Calcium chloride	Precipitation indicated by formation of white sediment within one hour of mixing [43]
Cefepime	Precipitation indicated by formation of sediment within one hour of mixing [41]
Diazepam	Emulsion damage directly after mixing by the occurrence of oiling out [43]
Doripenem	Precipitation indicated by the formation of sediment directly after mixing [30]
Eravacycline	Direct colour changing immediately after mixing and decrease of pH value [33]
Fosfomycin	Formation of an oil-free layer above the emulsion surface after mixing [37]
Gentamicin sulphate	Precipitation indicated by formation of white sediment directly after mixing [43]
Isavuconazonium sulphate	Formation of an oil-free layer above the emulsion surface after mixing [32]
Methotrexate	Precipitation indicated by formation of white sediment within one hour of mixing [43]
Netilmicin sulphate	Precipitation indicated by formation of white sediment directly after mixing [43]
Nimodipine	Coalescence of oil droplets that causes emulsion phase separation after mixing [23]
Phenytoin	Precipitation indicated by formation of crystalline sediment immediately after mixing [43]
Plazomicin	Formation of an oil-free layer above the emulsion surface after mixing [31]
Remifentanil hydrochloride	Fatty globule size enlargement as the result of coalescence and colour changing from white to yellow within 24 hours [24] Formation of aggregate directly after mixing [23]
Ringer lactate	Precipitation indicated by formation of sediment immediately after mixing [46]
Tazobactam–Ceftolozane	Formation of an oil-free layer above the emulsion surface after mixing and change of pH value [42]
Telavancin	Formation of an oil-free layer above the emulsion surface after mixing [39]
Tobramycin sulphate	Precipitation indicated by formation of white sediment directly after mixing [43]
Vancomycin	Precipitation indicated by formation of sediment within one hour of mixing [40]

CONCLUSIONS

This review identified that opened propofol MCT/LCT can maintain its physical stability for up to 6 hours, whereas opened propofol LCT with EDTA can remain stable for up to 24 hours. Propofol ≥ 3 mg mL^{-1} is stable in a PVC, non-PVC (CRYOFAC), or glass container for up to 6 hours, 24 hours, and 72 hours, respectively. Propofol that is diluted in NaCl and 5% glucose is best kept in a glass container at low temperature and in a dark environment. Based on the compatibility test, propofol is compatible with fentanyl, insulin, potassium chloride, ketamine, levetiracetam, lidocaine ≤ 10 mg, magnesium sulphate, methohexital, palonosetron hydrochloride, ceftaroline fosamil, ceftobiprole medocaril, sufentanil, and thiopental. Meanwhile, propofol is incompatible with acetaminophen, alfentanil, amikacin sulphate, calcium chloride, cefepime, diazepam, doripenem, eravacycline, fosfomycin, gentamicin sulphate, isavuconazonium sulphate, lidocaine ≥ 20 mg, methotrexate, netilmicin sulphate, nimodipine, phenytoin, plazomicin, remifentanil, Ringer's lactate, tobramycin sulphate, telavancin, tazobactam–ceftolozan, and vancomycin. The findings of this study suggest that the use of combined drugs that show incompatibility should be avoided or should be administered directly after the mixture is created.

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