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(54) **Title:** PHARMACEUTICAL COMPOSITION OF PROPOFOL

(57) **Abstract:** The present invention relates to a stable injectable emulsion formulation of Propofol having uniform droplet size, which is obtained at a pH above 8.5 and by avoiding a rotary sterilizer.



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PHARMACEUTICAL COMPOSITION OF PROPOFOL

FIELD OF THE INVENTION

The present invention relates to pharmaceutical composition(s) containing a
5 lipophilic therapeutic agent. In particular, the invention provides pharmaceutical compositions containing the compound 2,6-diisopropylphenol (propofol) and methods of preparing the same.

BACKGROUND OF THE INVENTION

2,6-Diisopropylphenol, generically known as, Propofol, is an intravenous short-
10 acting anaesthetic agent, which since its introduction in the late 80s has gained wide acceptance for inducing and maintaining anesthesia, as well as for sedation. The drug exhibits many notable advantages such as minimal side effects, controllable anaesthetic state, quick onset and rapid emergence from general anesthesia.

15 Propofol is lipophilic in nature and helps in providing rapid anesthetic action. However, the lipophilicity of Propofol, which is a liquid at room temperature, renders it relatively insoluble in water. The molecule has a calculated partition coefficient (Log P_{calc}) of 3.83 and presents little opportunity for solubilization through salt formation. Therefore, it is formulated as an oil-in-water emulsion, in
20 which the disperse phase is soya-oil containing dissolved Propofol with emulsification using lecithin.

Such formulations, because of their lipid component are good substrates for bacterial growth. Further, the parenteral administration of large volumes of lipid emulsions and/or the administration of lipid emulsions over prolonged periods of
25 time may result in hyperlipidemia.

Despite these shortcomings of an oil-in-water emulsion, propofol has been a successful anesthetic and is commercially available for human administration.

Diprivan[®] injectable emulsion is a white, oil-in-water emulsion containing 10 milligrams propofol per milliliter of emulsion, 100 mg soybean oil per mL, 22.5 mg glycerol per mL, 12 mg egg lecithin per mL, 0.005% disodium edetate and sodium hydroxide. Diprivan[®] injectable emulsion is indicated as a single-use
5 parenteral product. The said formulation is the subject matter of US 5,714,520 filed by Jones et al.

PropoFlo[®], another oil-in water emulsion, contains 10 milligrams propofol per milliliter of emulsion, contains 100 mg soybean oil per mL, 22.5 mg glycerol per mL, 12 mg egg lecithin per mL, benzyl alcohol 20 mg per mL, oleic acid 0.6 mg
10 per mL and sodium hydroxide which is adequately disclosed in US 6,140,373 of May et al. Rapinovel[®] anesthetic injection is a white, oil-in-water emulsion containing 10 milligrams propofol per milliliter of emulsion, 100 mg soybean oil/mL, 22.5 mg glycerol/mL, 12 mg egg lecithin/mL, 0.25 mg sodium metabisulfite/mL, and sodium hydroxide. The said formulation was disclosed by
15 Mirejovsky et al in US 6,147,122.

Further, George et. al in US 6,028,108 disclosed use of pentetate (diethylenetriamine-pentaacetate, DTPA) to avoid microbial contamination in Propofol emulsion formulation. Similarly, Goyal et al in US 2009/0131538 discloses use of formaldehyde sulfoxylate to avoid microbial contamination in
20 Propofol emulsion formulation.

From the above, it would be evident that there is plethora of literature focusing on reduction of microbial contamination in the formulation by using a suitable antimicrobial agent in Propofol formulations.

However, another important factor of such emulsion formulation is the droplet
25 size of the emulsion. Emulsions intended for intravenous use should have an extremely small droplet size as this has a direct effect on both toxicity and stability. Any large droplet placed in the circulation may lodge in the pulmonary capillaries and could potentially lead to an embolism. The exact size at which this

phenomenon becomes important is widely debated and pharmacopoeial limits on particulates in parenterals are vague, although 5 μm is generally accepted as an upper limit. Emulsions containing droplets ranging in size from 0.5 to 1.0 μm are utilized more rapidly by the body than emulsions with 3–5 μm droplets.

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Emulsions are thermodynamically unstable and various processes lead to changes in the drop size-distribution and/or emulsion structure. The most common processes of emulsion destabilization are drop-drop coalescence, flocculation, creaming, and the Ostwald ripening. During flocculation and creaming, the emulsion structure changes, while drop-size distribution may remain unaltered. In contrast, the drop-drop coalescence and the Ostwald ripening lead to changes in the drop-size distribution with time.

Therefore, the formulator must pay special attention to these destabilization tendencies of emulsions. The process for preparation of injectable formulation needs to be carefully monitored to minimize the droplet size and also to control the size distribution for optimal stability of the final dosage form. Published reports reveal a significant proportion of fat particles greater than 5 microns (5000 nm) in the marketed Propofol formulations.

Generally, it is believed that the most essential parameters influencing the particle size are homogenization pressure and number of cycles. In addition, homogenization temperature, pH value and steam sterilization procedure could also affect the particle size of an emulsion.

The intravenous emulsions must be sterile and steam sterilization is the preferred sterilization method on commercial scale. The sterilization process supplies energy which can further destabilize the thermodynamically unstable emulsion system causing coalescence and flocculation. Thus, sterilization conditions must be selected carefully to ensure both the stability and particle size of the final product. The classical method for manufacture of Propofol emulsion employs a rotary autoclave. The rotary cycle ensures that the product is in constant motion

during the cycle, preventing separation of the two phases. The rotary sterilizer, during the sterilization cycle facilitates heat transfer and maintains emulsion integrity because of the continuous agitation of the product. There are two types of batch sterilizers that can be used for the sterilization of lipid emulsions, the shaking cycle and the rotary cycle. For the shaking cycle, the product must be agitated lying on its side providing oscillatory movement along the container centroidal axis. The agitation frequency maintained throughout the cycle must be, e.g., 70 rpm. For the rotary cycle, the product must be agitated throughout the sterilization process with the containers being horizontally positioned in rack(s) in a fixed manner and the rack(s) being rotated to result in an agitation.

Needless to mention, recourse to such special rotary sterilizers requires additional capital expenditure thereby rendering overall manufacturing process commercially unviable. Moreover, the stability of such sterilized product depends on critical vagaries of sterilization cycle, temperature, agitation frequency etc. Further, with a pressurized system such as autoclaving, the action of agitation inside the rotary autoclave might cause breaking of the vials and product spillage.

Hence, there is an ongoing need for formulations of propofol and, in particular, for injectable, aqueous formulations of propofol that are sterile and stable for indefinite periods under clinical conditions. At the same time, there is a need for a process for preparing aqueous formulations of propofol, which results in minimum destabilization of propofol formulation.

OBJECTS OF THE INVENTION:

An object of the present invention is to provide a stable injectable formulation of propofol.

Another object of the present invention is to provide a stable injectable formulation of propofol which will have uniform droplet size.

Still another object of the present invention is to provide a process for preparation of a stable injectable formulation of propofol.

A further object of the present invention is to provide a process for preparation of a stable injectable formulation of propofol, wherein the said process has minimal
5 destabilization effect on propofol formulation.

SUMMARY OF THE INVENTION

The present invention provides a stable injectable emulsion formulation of propofol having uniform droplet size. Typically, the present invention provides a simple, commercially viable process for manufacture of injectable emulsion
10 formulation.

Typically, the process used in production of injectable emulsion formulation of propofol involves formation of an aqueous phase and oil phase. Water soluble and oil-soluble ingredients are generally dissolved in the aqueous phase and oil phase, respectively. Emulsifiers, such as phosphatides, can be dispersed in either oil or
15 an aqueous phase. Both phases are adequately heated and stirred to disperse or dissolve the ingredients. The lipid phase is then generally added to the aqueous phase under controlled temperature and agitation (using high-shear mixers) to form a homogenously dispersed coarse emulsion. The coarse emulsion is then homogenized (using a microfluidizer or a high-pressure homogenizer) at
20 optimized pressure, temperature, and number of cycles to further reduce the droplet size and form fine emulsion. Factors such as type and concentration of oil phase and surfactants, operating temperature, pressure, number of cycles, etc. has influence on the mean droplet size during high-pressure homogenization and microfluidization, hence need to control critically. The pH of the resulting fine
25 emulsion is then adjusted to the desired value and the emulsion is filtered through 0.45 to 5 μm filters. The fine emulsions are usually packed in USP Type I glass containers. The packed vials are then sterilized terminally by autoclaving.

Thus, in the present process, the desired droplet size is not affected by exposure to the high temperature required for steam sterilization. Hence, unlike the prior art commercial formulation processes, the need for rotary sterilizers is avoided by the present process.

5 DETAILED DESCRIPTION OF THE INVENTION

Typically, one aspect of the present invention relates to a method for preparation of a stable injectable emulsion formulation of propofol having uniform droplet size. The main requirement of all injectable emulsions formulation is uniform droplet size. The present invention achieves this requirement by suitably
10 modifying the pH during the process of emulsification. Thus, in one aspect the present invention relates to a stable injectable formulation of propofol obtained from coarse propofol emulsion having alkaline pH, preferably above 8.

As used herein the term coarse emulsion means a crude mixture of the aqueous phase and oil phase. The main difference between coarse emulsions and the final
15 emulsion lies in the droplet size of the dispersed phase. Final emulsion has droplets

typically in the size range 100–300 nm whereas coarse emulsion has the particle size in the range of 300 to 3000 nm.

Emulsions are thermodynamically unstable systems and various processes lead to
20 changes in the drop size-distribution and/or emulsion structure. Generally, it is believed that the most essential parameters influencing the particle size are homogenization pressure, number of cycles, homogenization temperature, pH value and steam sterilization procedure could affect the particle size of an emulsion.

25 The classical method for manufacture of emulsions employ a rotary autoclave as it is believed that the rotary cycle ensures the constant motion of the product, preventing separation of the two phases. However, the present inventors have surprisingly found out that if the pH of the coarse emulsion is adjusted in the

alkaline range, preferably above 8, then stationary or normal conventional steam autoclave could be used for sterilization of the emulsion without affecting its stability.

Typically, the composition of the present invention comprises from 0.1 to 5%, by weight, of propofol. Preferably the composition comprises from 1 to 3 % by weight of propofol and, in particular, about 1% or about 2%.

In another aspect of the invention, propofol alone is emulsified with water by means of a surfactant. Alternatively, and preferably, the propofol is dissolved in a water-immiscible solvent prior to emulsification.

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The water-immiscible solvent is suitably present in an amount that is up to 30% by weight of the composition, more suitably 5-25%, preferably 10-20% and in particular about 10%. A wide range of water-immiscible solvents can be used in the compositions of the present invention. Typically, the water-immiscible solvent is a vegetable oil, for example soy bean, safflower, cottonseed, corn, sunflower, castor or olive oil. Preferably, the vegetable oil is soy bean oil. Alternatively, the water-immiscible solvent is an ester of a medium or long-chain fatty acid for example a mono-, di-, or triglyceride; or is a chemically modified or manufactured material such as ethyl oleate, isopropyl myristate, isopropyl palmitate, a glycerol ester or polyoxy hydrogenated castor oil. Furthermore, the compositions of the present invention may comprise a mixture of two or more of the above water-immiscible solvents.

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Propofol, either alone or dissolved in a water-immiscible solvent, is emulsified by means of a surfactant. Suitable surfactants include synthetic non-ionic surfactants, for example ethoxylated ethers and esters and polypropylene-polyethylene block co-polymers, and phosphatides for example naturally occurring phosphatides such as egg and soya phosphatides and modified or artificially manipulated phosphatides (for example prepared by physical fractionation and/or

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chromatography), or mixtures thereof. Preferred surfactants are egg and soya phosphatides.

5 Additives such as tonicity modifiers, antioxidants and preservatives are usually added to the aqueous phase (water for injection). Tonicity adjustment can be achieved with glycerin, sorbitol or xylitol. Antioxidants such as α -tocopherol, ascorbic acid, and deferoxamine mesylate are generally added to prevent oxidation of the oil and drug substance. Additionally, antimicrobial agents such as EDTA, sodium benzoate and benzyl alcohol, are added to the aqueous phase to
10 prevent microbial growth.

The oil-in-water emulsion of the present invention is prepared by homogenizing the oil and aqueous phases. The oil phase is prepared by dissolving propofol and other oil-soluble ingredients in a water-immiscible solvent whereas the aqueous
15 phase comprises of water-soluble ingredients. Emulsifiers, such as phosphatides, can be dispersed in either oil or aqueous phase. Both phases are adequately heated and stirred to disperse or dissolve the ingredients. The lipid phase is then generally added to the aqueous phase under controlled temperature and agitation (using high-shear mixers) to form a homogenously dispersed coarse emulsion.

20

Typically, the process of preparing emulsion is as follows:

- a) Preparing aqueous phase by mixing water soluble ingredients such as glycerine, egg lecithin, disodium EDTA in water ;
- b) Preparing oil phase by dissolving propofol in solvent for
25 propofol;
- c) Mixing and homogenizing the aqueous and the oil phase;
- d) Adjusting the pH of the coarse emulsion in the range of 8.5 to 11; and
- e) Preparing the final Propofol emulsion.

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The pH of the coarse emulsion is then adjusted to above 8.0, preferably in the range of 8.5 to 11.0. After pH adjustment, the solution is stirred and the final volume is adjusted with water for injection. The coarse emulsion is then homogenized (using a microfluidizer or a high-pressure homogenizer) at
5 optimized pressure, temperature, and number of cycles to further reduce the droplet size and form a fine emulsion. Typically, the obtained Emulsion has a globule size in the range of 100 to 300 nm.

The emulsion is then filtered through 0.45 to 5.0 μm filters and packed in suitable
10 containers such as USP type I glass containers. Siliconized containers could also be used. Additionally, teflon-coated vial plugs/stoppers are useful to prevent oxygen permeation and softening on contact with the oil phase. The entire process (filtration/ coarse and fine emulsion preparation) is preferably carried out under nitrogen atmosphere whenever possible and especially in cases where the
15 excipients and drugs are sensitive to oxidation.

The compositions of the present inventions are typically sterile aqueous formulations and are prepared according to conventional manufacturing techniques using for example aseptic manufacture or terminal sterilization by
20 conventional stationary autoclaving apparatus and procedure.

The present inventors have surprisingly found that if the pH of the coarse emulsion is adjusted well above 8, preferably in the pH range of 8.5 to 11.0, more preferably in the range of 10.0 to 11.0, then the terminal sterilization has very
25 minimal influence on droplet size of the emulsion. In other words, the droplet size is not at all affected by the temperature and time of the conventional steam sterilization methods (121°C for 45 minutes). Moreover, by adjusting the pH, recourse to rotary sterilizer is also avoided.

The principles, preferred embodiments, and modes of operation of the present
30 invention have been described in the foregoing specification. The invention which

is intended to be protected herein, however, is not to be construed limited to the particular forms disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art, without departing from the spirit of the invention.

- 5 The invention is further explained with the help of following illustrative examples, however, in no way these examples should be construed as limiting the scope of the invention.

EXAMPLES

Example – 1: Preparation of Propofol emulsion

10

Sr. No.	Ingredients	Qty per ml
1	Propofol USP	10 mg
2	Soybean oil USP	100 mg
3	Glycerin USP	22.5 mg
4	Lecithin NF(LIPOID E80)	12 mg
5	Edetate disodium USP	0.055 mg
6	Sodium Hydroxide	q.s. to adjust pH
7	Water for Injection	q.s.to 1 mL

The composition of the present invention is suitably formulated as follows:

- 15 **Preparation:** A sterile aqueous oil-in-water emulsion for parenteral administration was prepared as follows. All processing stages were carried out under nitrogen and weights, refer to weight in the final volume.

1. An aqueous phase was prepared by adding glycerin, edetate disodium and egg lecithin in water.

2. The oil phase was prepared by adding propofol to the soybean oil.
3. The oil phase was added to the aqueous phase at a temperature below 25°C and homogenized at high pressures to get a coarse emulsion.
4. The pH of the coarse emulsion was adjusted to pH in the range of 10.5 to 11.0 by using 0.2 N sodium hydroxide solution and the solution was brought to final volume with water and homogenized at high pressure.
5. After the final emulsion was formed, it was filtered through 1.0 µm filter.
6. It was then filled into containers under nitrogen and autoclaved.

10 **Example – 2: Preparation of Propofol emulsion with various pH**

Various Propofol formulations differing in pH of the coarse emulsion were prepared as given in below table. The particle size was evaluated before and after sterilization, using the results is summarized in the Table -1. The particle size was measured by Zetasizer Nano ZS90, which uses dynamic Light Scattering at a 90 degree angle to measure particle size

Table -1: Effect of pH on droplet size of emulsion sterilized by autoclaving

Sr. No.	Batch No.	Before Autoclave		After Autoclave	
		pH	Droplet Size	pH	Droplet Size
1	Batch -1	7.0	192	6.5	449
2	Batch -2	8.0	199.4	7	320
3	Batch -3	10.4	198	8.4	205
4	Batch -4	10.1	198	8.1	207

CLAIMS:

1. A stable injectable formulation of propofol obtained from coarse propofol emulsion having pH in the range of 8.5 to 11.
2. A coarse emulsion comprising propofol, an oil phase, and an aqueous phase wherein the coarse emulsion has pH in the range of 8.5 to 11.
3. The coarse propofol emulsion according to claim - 2 wherein the emulsion has the pH in the range of 10 to 11.
4. The coarse propofol emulsion according to claim - 2 wherein the emulsion has a mean globule size in the range of 300 to 3000 nm.
5. A process for preparation of stable oil in water emulsion of propofol comprising:
 - a) Preparing aqueous phase by mixing water soluble ingredients in water;
 - b) Preparing oil phase by dissolving propofol in solvent for propofol;
 - c) Mixing and homogenizing the aqueous and the oil phase;
 - d) Adjusting the pH of the coarse emulsion in the range of 8.5 to 11; and
 - e) Preparing the final Propofol emulsion.
6. A process for preparation of stable oil in water emulsion of propofol according to claim - 5, further comprising a step of terminal sterilization.
7. A process for preparation of stable oil in water emulsion of propofol according to claim - 6, wherein terminal sterilization is carried out by normal steam autoclaving.
8. A process for preparation of stable oil in water emulsion of propofol according to claim - 5, wherein the pH of the coarse emulsion is in the range of 10 to 11.

9. A process for preparation of stable oil in water emulsion of propofol according to claim – 5, wherein water soluble ingredients are selected from tonicity modifiers, antioxidants and preservatives.
10. A process for preparation of stable oil in water emulsion of propofol
5 according to claim – 5, wherein the final emulsion has a mean globule size in the range of 100 to 300 nm.