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SCIENTIFIC ARTICLE

Pharmacodynamic Evaluation and Physical/Chemical Analysis of Two Formulations of Propofol used in Target-Controlled Infusion

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Abstract

Background and objectives: There are several formulations of propofol available to the anesthesiologist for clinical use. The aim of this study was to analyze the physicochemical properties, pharmacodynamic effect, and pharmaceutical and clinical equivalence of the reference drug propofol as well as a similar formulation.

Method: Sixteen volunteers were enrolled in this randomized, double-blind, and paired study of Diprivan® and Propovan® formulations. Formulations were given as target-controlled infusion with target concentration of 3.0 $\mu g.mL^{-1}$ for 15 minutes. Variables studied were the area under the curve (AUC) of the bispectral index (BIS) graph regarding time, minimum BIS reached and time to reach it, and recovery time. The two formulations were sent to analysis of particle size of lipid emulsion, surface potential, and active principle quantification.

Results: There was no difference between the formulations when comparing AUC, minimum BIS reached and time to reach it. The similar formulation recovery time was lower compared to the reference formulation (eight and 10 min, respectively, p = 0.014). Mean particle size of lipid emulsion, surface potential, and active ingredient quantification were similar for both formulations.

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Conclusion: There was no clinically significant difference between the use of propofol, reference Diprivan®, and the similar Propovan® during infusion. However, the recovery time was longer with the reference drug. Although analysis of both formulations studied show similar results regarding its physicochemical characterization, further studies should be conducted to justify this difference.

Introduction

There are various formulations of propofol available for clinical use in Brazil. Despite strict regulations by the National Health Surveillance Agency (ANVISA) regarding inspection and quality control of drugs, many questions remain about the real clinical equivalence between brands of existing drugs.

In clinical practice, many anesthesiologists empirically evaluated differences between propofol presentations, as the desired pharmacodynamic effect is only achieved with different doses of commercially available presentations of the same content.

Propofol (2,6-diisopropylphenol, 178.27 $g.mol^{-1}$, CAS: 2078-54-8) (Figure 1) is an intravenous anesthetic with hypnotic properties. It is widely used in clinical practice for anesthesia induction and maintenance due to its rapid onset of action, short duration, and few adverse effects when given in therapeutic doses. Its rapid onset of action is due to its easy passage through the blood brain barrier and almost immediate action on the central nervous system, mainly because of its high lipophilicity. It is usually presented as a lipid emulsion due to its very low water solubility. Commercial formulations of propofol emulsions are isotonic and generally consist of 10 or 20 $mg.mL^{-1}$ of propofol, 100 $mg.mL^{-1}$ of soybean oil, 22.5 $mg.mL^{-1}$ of glycerol, 12 $mg.mL^{-1}$ of egg yolk lecithin, 0.005% of edetate disodium (EDTA), water and sodium hydroxide for pH adjustment (pH 7.0-8.5) [1]. The physicochemical properties of emulsions, such as lipid composition, type of emulsifier, size and level of particle organization, surface potential, and pH, are directly related to the formulation performance and pharmacokinetic and dynamic behavior of the embedded active substance.

The aim of this study was to systematic and comparatively analyze the physicochemical properties, pharmacodynamic effect (hypnosis), and pharmaceutical and clinical equivalence of the reference drug propofol (Diprivan® - AstraZeneca do Brasil Ltd) and a similar formulation (Propovan® - Cristália Produtos Químicos Farmacêuticos Ltd). The tested hypothesis is that Diprivan® may differ from Propovan® regarding the hypnotic effect and pharmacokinetic characteristics (i.e., the main physicochemical and clinical characteristics), and that such differences are related to the differences in the average size of particles and active ingredient concentration in the formulations studied.

Material and method

Clinical study

After approval by the Research Ethics Committee and obtaining signed informed consent from sixteen healthy adult male subjects were enrolled in the study. The selected volunteers were allocated into two groups (double-blind, paired) and presented themselves at a predetermined location, with 8 hours fasting.

All volunteers were monitored with electrocardiogram (in leads DII and V1), peripheral oxygen saturation, noninvasive mean arterial pressure, and bispectral index (BIS). Oxygen was administered using a nasal catheter (2.0 $L.min^{-1}$) and a right antecubital vein puncture performed, connecting a venous catheter filled with one of the propofol formulations. Saline infusion was not administered at any time to break the fast or replace insensible losses.

Diprivan® and Propovan® formulations were delivered by target-controlled infusion using Marsh pharmacokinetic model (Ke0 0.26 min^{-1}) and minimum washout of 72 hours.

Infusion management and clinical variables evaluation were performed using the program Anestfusor (University of Chile, Santiago, Chile) coupled to an infusion pump (Pilot II Anaesthesia, Fresenius Kabi, Germany) and BIS (version XP, Aspect Medical, USA).

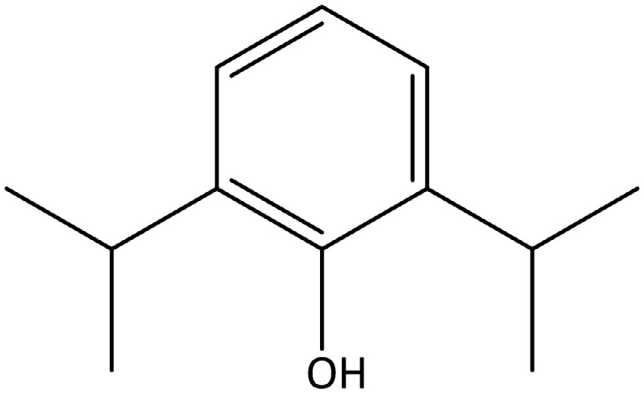

Figure 1 Propofol.

This was a randomized, double blind trial with two comparative periods between formulations (Diprivan® and Propovan®). To avoid biased behaviors, each syringe was filled and identified as formulation "A" or "B" and handed to the anesthesiologist responsible for the administration.

The samples of Diprivan® (Lot No. X09144B) and Propovan® (Lot No. 10075239) used in the study were stored according to manufacturer's recommendations.

Propofol was infused at target plasma concentration of 3.0 μg.mL^{-1}. After 15 minutes infusion, the target plasma concentration of propofol was reduced to zero.

The concentration values of propofol in the expected site of action (Ce) and BIS values were recorded at 60-second intervals during infusion and for 10 minutes after infusion.

For each subject, the degree of hypnosis was found by calculating the area under the curve (AUC) of the BIS graph regarding time by the sum of the trapezoid areas. We also assessed the minimum BIS reached during the experiment and the time required for its occurrence.

Recovery time was regarded as the period between the end of infusion and the time the patient had reached a BIS value of 70.

Statistical analysis of parametric attributes was performed using the paired Student's t-test and expressed as mean and standard deviation. The difference was considered statistically significant when $p < 0.05$.

The correlation between the predicted plasma concentration of propofol, site of action, and BIS for both reference propofol and similar was calculated using Pearson's correlation coefficient (ρ). We also calculated the coefficient of determination (R2) for the different correlations, which shows the proportion of variance (fluctuation) of one variable that is predictable from another variable. It represents the percentage of data closer to the line of best fit.

Physicochemical analysis

Both formulations of propofol were subjected to analysis of the mean particle size of lipid emulsion, Zeta potential (surface potential), pH, and quantification of active ingredient.

Analyses of mean particle size and zeta potential were performed using the dynamic light scattering equipment (Zetasizer Nano ZS - Malvern Instruments, U.K.), and pH measurements using the TA 350 pHmeter (Alfakit, Brasil) with universal glass electrode.

Microscopic image of the two lipid emulsion formulations of propofol was obtained by smear slide/coverslip and direct viewing under a light microscope (Olympus Optical IX70) amplified a thousand times and 30% obscuration.

Quantitative analysis of the active ingredient, propofol, in Diprivan® and Propovan® was performed by liquid chromatography coupled with mass spectrometry (LC-MS). Both formulations were diluted in isopropanol (IPA) to generate the respective stock solutions of 1.0 mg.mL^{-1}. Solutions were prepared by serial dilutions of stock solutions. The calibration curve was constructed with eight concentration levels doubled (1.0-1,000 ug.mL^{-1}). Formulations were studied twice (on different days) with batches of samples at a concentration of 100 ug.mL^{-1} in quintuplicate and injected volume of 1.0 uL. Chromatographic separation was performed over a Luna C18 column (150x2 mm, 3 u – Phenomenex, USA) eluted with acetonitrile and 10 mM ammonium acetate in water (45:55, respectively), in isocratic mode at a flow rate of 400 uL.min^{-1} and using an Agilent 1200 chromatograph. Analyte retention time was 4.6 minutes, in analytical run of 7.0 minutes. Mass detection was made using a spectrometer QTRAP 3200 (Sciex/Applied Bisystems, USA), with interface Turbo-V® (ESI-) in SIM mode (Single Ion Monitoring) and ion monitoring m/z = 177.2 (corresponds to deprotonated propofol [M-H] -).

Results

The mean age, weight, and height of the subjects were 30 years (25-43), 82 kg (71-94), and 177 cm (170-188), respectively.

Figure 2 shows the mean values of BIS regarding time during infusions of Diprivan® and Propovan®. Table 1 shows the pharmacodynamic variables. Figure 3 shows the values of plasma concentration (Cp) at the expected site of action (Ce) of propofol and BIS values obtained with Diprivan® and Propovan® infusions. Table 2 shows the correlation values between Ce, Cp, and BIS values obtained with Diprivan® and Propovan® infusions. Table 3 shows the results of quantitative analysis of drugs. The average particle size of lipid emulsion of Diprivan® and Propovan®, Zeta potential, and pH are shown in Table 4. Figures 5 and 6 show the particle size dispersion of propofol emulsion and Zeta potential distribution. Figures 7 and 8 show the images obtained by light microscopy with a magnifying power of 1,000x.

Discussion

The aim of this study was to perform a complete evaluation of the reference product (Diprivan®) and the product similar to propofol most used in Brazil (Propovan®), with the intention of demonstrating scientifically whether there is difference

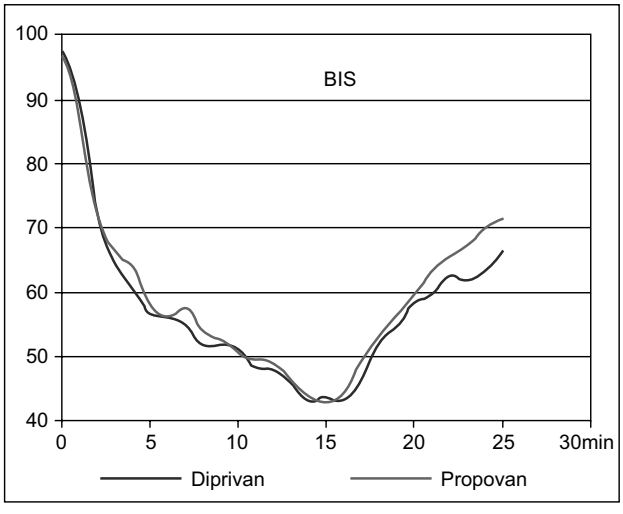

Figure 2 Mean Values of BIS regarding Time during Infusions with Diprivan® and Propovan®.

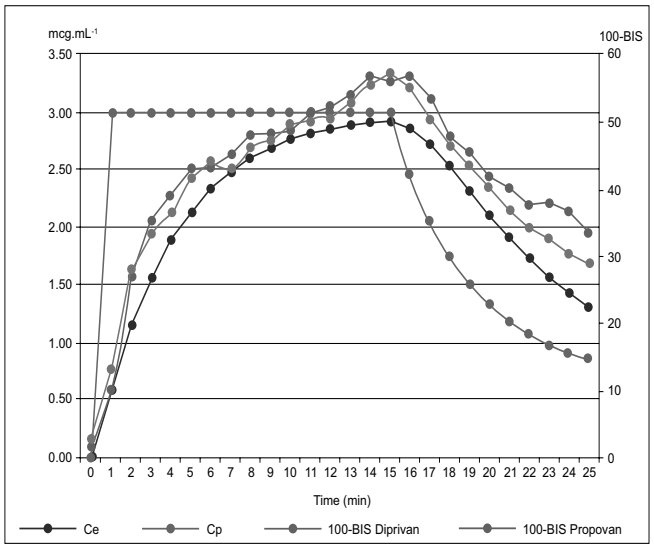

Figure 3 Plasma Concentration (Cp) Predicted Concentration of Propofol in Site ofAction (Ce), and Bispectral Index (BIS) Values with Infusion of Diprivan® and Propovan®.

Table 1 Pharmacodynamic Variables Expressed in Mean and Standard Deviation.

	Diprivan®	Propovan®	p
Total area	1,453.8 ± 205.9	1,498.7 ± 210.4	0.246
Area during infusion	886.7 ± 112.7	901.3 ± 134.3	0.535
Recovery area	545.6 ± 95.1	574.9 ± 81.8	0.100
Minimum BIS	37.9 ± 10.3	38.3 ± 9.8	0.742
Time to minimum BIS (min)	14.3 ± 2.8	13.7 ± 2.7	0.300
Recovery time (min)	10.0 ± 4.6	8.0 ± 3.5	0.014

Table 2 Correlation between Ce, Cp, and BIS values with Diprivan® and Propovan®.

	p	R^2
Ce and BIS – Diprivan	0.972	0.94
Ce and BIS – Propovan	0.988	0.97
Cp and BIS – Diprivan	0.437	0.19
Cp and BIS – Propovan	0.523	0.27

Ce: predicted concentration at the site of action of propofol; Cp: predicted plasma concentration of propofol; ρ: Pearson's coefficient, R^2: coefficient of determination; BIS: Bispectral Index.

between both formulations, especially regarding the hypnotic/anesthetic effect, active ingredient concentration, and characteristics of lipid emulsion.

First, we performed a clinical examination in healthy volunteers. Then, we proceeded to a thorough physicochemical evaluation of the presentations involved.

There was no difference in clinical examination regarding the degree and depth of hypnosis caused by both studied medications, as the area under the time curve of BIS mean values showed no significant difference (p = 0.246) (Table 1). There was also no significant difference between BIS minimum values (maximum effect achieved in volunteers) and time to reach this maximum effect (p = 0.742 and p = 0.3, respectively) (Table 1).

Studies conducted in other countries comparing the pharmacodynamic efficacy of Diprivan® and generic formulation of propofol show similar results [2-4]. However, the recovery time (BIS = 70) was 20% lower for Propovan® compared to Diprivan® (eight and 10 minutes, respectively). No difference that could explain this fact was found among the physicochemical variables tested. Perhaps further study of the lipid emulsion components may explain this difference.

Interestingly, a study comparing generic sevoflurane with Sevorane® showed that the time to spontaneous eye opening and handshake on verbal command was lower with the generic formulation [5].

According to other authors, there is a strong correlation between the predicted concentration at the site of action of propofol (Ce) and BIS [6,7]. In this study, the propofol Ce predicted by Marsh pharmacokinetic model (Ke0 0.26 min^{-1}) showed a strong correlation with BIS values for the two formulations used. However, the plasma concentration of propofol (Cp) predicted by the same model showed moderate correlation (0.3 < ρ < 0.7) with BIS values for both formulations, corroborating previously published data [6,8,9] (Table 2). This is basically caused by the delay in the balance between Cp and Ce in the central nervous system, called effector site [10].

Figure 3 shows the synchrony between pharmacokinetics and pharmacodynamics achieved by this pharmacokinetic model, both in the use of the reference and similar medications. The study shows that both formulations behave similarly even in target-controlled infusion. This fact was also seen in another study of propofol, which showed that the pharmacokinetic model predictability does not change with the use of generic formulation [11].

The quantification of propofol – active ingredient in both formulations – was similar. The technique of choice for drug quantitation by LC-MS [12,13] and the method used met the required criteria for accuracy and precision. The variation between the mean concentration of propofol in the analyzed formulations (0.98%) is within the content variation criteria recommended by ANVISA for drugs in bioequivalence studies or relative bioavailability (< 5%) [14] (Table 3 and Figure 4).

Factors related to lipid emulsion chemical and physical structure may also change its clinical efficacy, stability, and safety.

Chemically, benzene ring and isopropyl group make the propofol molecule highly lipophilic (octanol/water partition coefficient log p = 4.16) [15] and slightly soluble in water, therefore, its presentation in the form of salt is unlikely. Thus, propofol is usually found in emulsion formulation, such as a white emulsion, oil-water (discontinuous or dispersed phase/continuous phase), composed mainly of soybean oil, glycerol, and egg yolk lecithin [16]. Soybean oil has an important role in propofol solubility for preparing formulations. Because of its lipophilicity, propofol is found in high concentration in the dispersed phase and at low concentration in the continuous

Table 3 Results of Quantitative Analysis of Propofol by LC-MS in Diprivan® and Propovan® with Coefficients of Variation (CV%) and the Intra- and Inter-day Means.

Calibration Curve Data				
Calibration range	1.00 – 1,000 ug.mL^{-1}			
Regression type	Linear (y = ax + b) with weighting (1/x)			
Equation	y = 350x – 1.54			
Coefficient of determination	r = 0.9999			
Accuracy	93 – 105%			
Precision	± 1.5%			
Results				
Samples (100 ug.mL^{-1})	**Propovan (day 1)**	**Propovan (day 2)**	**Diprivan (day 1)**	**Diprivan (day 2)**
Intra-day average (ug.mL^{-1})	101	104	102	105
CV%	2.6	5.2	3.0	6.7
Inter-day average (ug.mL^{-1})	103		104	
CV%	4.3		5.0	
Variation Diprivan = reference Propovan = test	-0.98%			

LC-MS: Mass spectrometry.

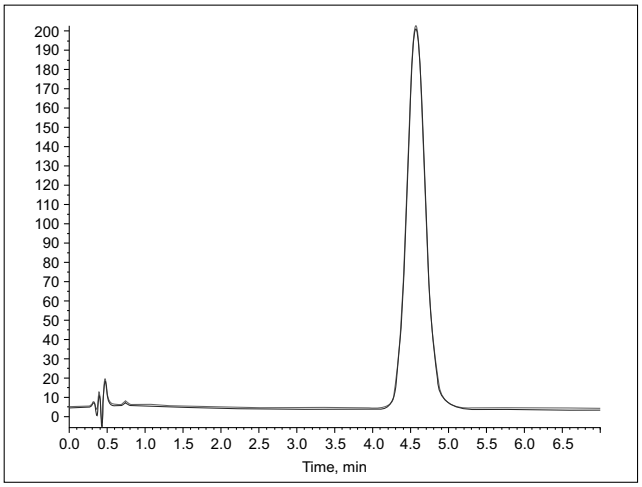

Figure 4 Chromatogram Overlay of Diprivan® and Propovan® regarding Active Ingredient Propofol.

phase [17]. Among the study drugs, Diprivan® contains in its formulation 0.005% EDTA, which has bacteriostatic properties. However, this agent does not affect the quality of anesthetic hypnosis [17].

According to the International Union of Pure and Applied Chemistry (IUPAC), emulsions are dispersions of immiscible liquids, oil in water (O/W) or water in oil (W/O). Preparations are thermodynamically unstable and do not form spontaneously. Thus, to maintain stability and homogeneity, energy is required for its formation and the use of combined emulsifying agents (surfactants) to increase the kinetic stability of preparation. Stability of emulsions is guaranteed by controlling the interfacial tension of the phases, obtaining a mechanically stable film, controlling the electrostatic or steric barrier and low volume of the dispersed phase, and obtaining uniform small particles.

In the formulations studied, the lecithin in egg yolk acts as an emulsifier, reduces surface tension between phases, and enables the formation of tiny disperse and stable oil droplets in the aqueous phase (continuous phase - larger volume of emulsion).

Only a limited number of emulsifiers are considered safe for use in parenteral and intravenous administrations. Compared with the synthetic options, lecithin is a good choice for this purpose because it is well tolerated, totally biodegradable and metabolized, as it is part of biological membranes.

Lecithins are mainly composed of phospholipids [66-76% phosphatidylcholine (FC); 15-24% phosphatidylethanolamine (PE), and 1% phosphatidylserine (PS)]. Because it is an amphiphilic lipid, it has a hydrophilic “head” (polar phosphates) and hydrophobic “tail” (nonpolar fatty acids). It is this feature that makes the link between oil and water in emulsion formation, which plays an important role in stabilizing the formulations. They act by promoting a negative electrostatic charge on the surface of the droplets, repelling them. The

magnitude of this surface potential (voltage) is quantified as Zeta potential. Emulsions are considered stable when Zeta potential varies between 50-40 mV [18,19].

In the present study, both propofol formulations showed very stable lipid emulsions, as Zeta potential was -54 and 48.4 mV (Diprivan® and Propovan®, respectively, Table 4). This emulsion stability results from the formation of a mechanical barrier between the oil droplets and aqueous phase and electrostatic repulsion forces between droplets. The breaking of one of these forces causes degradation of emulsion and separation of phases [17].

Important factors - such as pH - may change the Zeta potential making the emulsion unstable and, thus, decreasing the repulsive forces and results in coalescence and formation of large droplets. At acidic pH, Zeta potential may reach values close to zero, making the emulsion rather unstable [17].

Although the pH value found for Propovan® was equal to 6.92 (acid), it was not enough to alter the emulsion stability, as the Zeta potential values were within the recommended range (Table 4).

One study showed that in preparations of a generic propofol with pH between 4.0 and 5.0, the emulsion became unstable and with larger droplets of 5 mm after four hours of stirring (300 vibrations.min^{-1}). However, even with a stirring period of 16 hours, the emulsion of Diprivan® (pH 7.0-8.5) [20] remained stable.

The emulsion size of the oil particle is another key factor for the safety and stability of formulations. Emulsions containing droplets larger than 5-7 µm may cause thromboembolic events [21]. The average size of droplets acceptable for propofol formulations must be less than 1.0 µm (1,000 nm) [18,22]. Propofol emulsion formulations for commercial use have an average droplet size between 100 and 300 nm [20,23].

By the technique of dynamic light scattering, we found that the average emulsion droplet size between formulations was similar (Diprivan® 180.5 nm and Propovan® 177 nm, Table 4). However, the lipid emulsion of Diprivan® was more homogenous than the Propovan®, as the average dispersion was lower with Diprivan® (Figures 5, 7, 8).

When in contact with the bloodstream, the propofol dissolved in oily medium (within droplet) is rapidly diffused in the plasma. Consequently, the smaller the emulsion particle, the greater the surface area of contact with blood, the greater the release rate of the active ingredient, and the lower the latency [17].

Because the average droplet size of emulsions was similar, there was no difference in latency between both formulations. According to the clinical study performed, there was no significant difference in maximum effect reached (similar minimum values of BIS) and time required to reach this maximum effect.

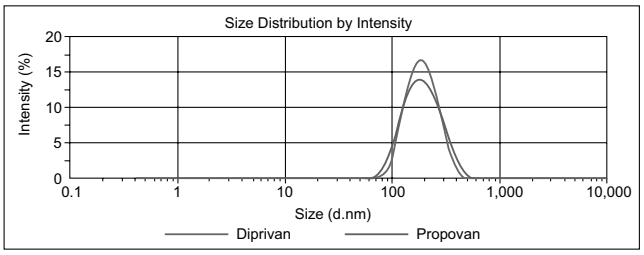

Figure 5 Size Distribution by Intensity.

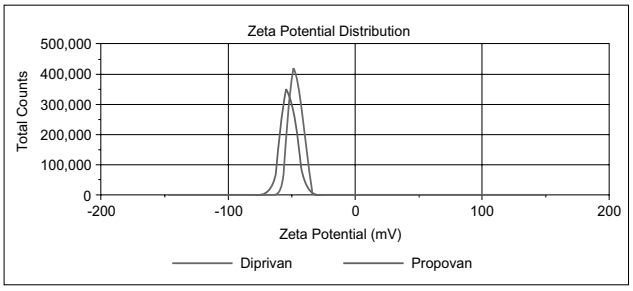

Figure 6 Zeta Potential Distribution.

Other authors have shown that clinical observations of propofol inconsistent activity may be related to individual differences in lipoprotein profile, enzyme activity or genetic diseases, instead of problems related to the pharmaceutical preparation itself [24].

A strong correlation was also found between the concentration of propofol in the site of action predicted by the Marsh pharmacokinetic model and bispectral index with both formulations. Qualitative analysis showed that both formulations present the same amount of active ingredient (propofol). The lipid emulsions of the formulations studied were stable, with similar average droplet size and surface potential and within the safe range.

In conclusion, with the dose used, there were no clinically significant differences between propofol (reference drug, Diprivan®) and generic drug Propovan® during infusion. However, the recovery time is longer with the reference drug. Although the physicochemical analysis of both formulations show similar results, perhaps further studies of other lipid emulsion components may justify this difference.

Table 4 Average Particle Size of Emulsions, Zeta Potential, and pH of Propofol Emulsion.

	Diprivan®	Propovan®
Average particle size (nm)	180.5 (78.8 – 458.7)	177.0 (68.06 – 615.1)
Zeta Potential (mV)	-54.0	-48.4
pH	7.35	6.92

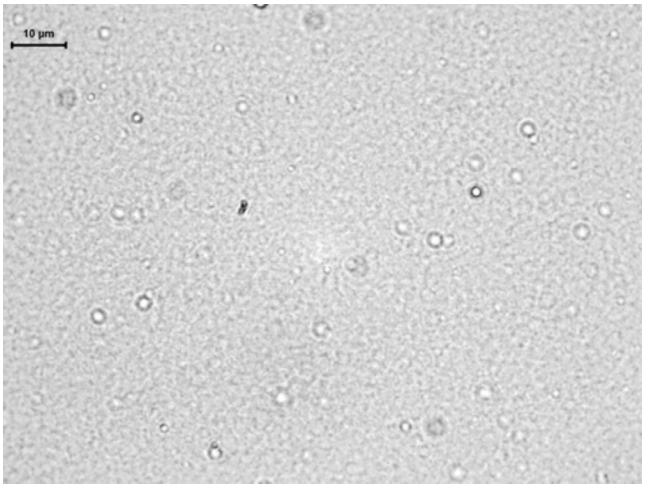

Figure 7 Image obtained by light microscopy with a magnifying power of 1,000 x.

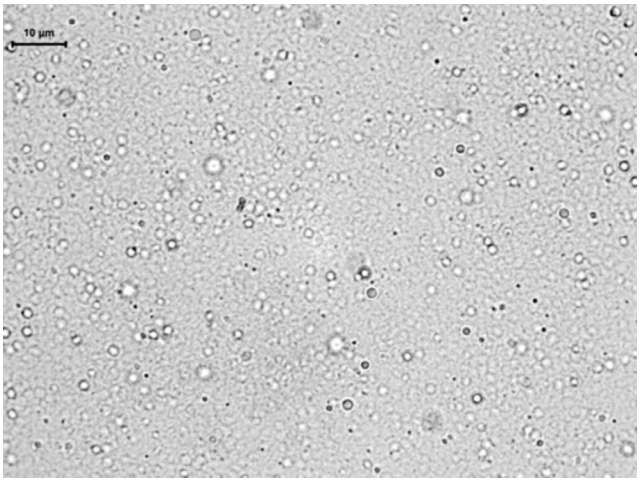

Figure 8 Image obtained by light microscopy with a magnifying power of 1,000 x.

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