Pharmaceutical Research, Vol. 25, No. 2, February 2008 (© 2007)
DOI: 10.1007/s11095-007-9471-5

Research Paper

Novel Lipid and Preservative-free Propofol Formulation: Properties and Pharmacodynamics

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Received May 2, 2007; accepted October 4, 2007; published online November 21, 2007

Purpose. Propofol is a water-insoluble intravenous anesthetic agent that is actually formulated as a water-in-oil emulsion with known drawbacks such as pain on injection, microorganism growth support and stability. We report on the properties of formulations of propofol in poly (*N*-vinyl-2-pyrrolidone)-block-poly(D,L-lactide), PVP–PLA, polymeric micelles (Propofol-PM).
Methods. Microbial growth in these formulations was evaluated with *Pseudomonas aeruginosa* (ATCC 9027), *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 25922) and *Candida albicans* (ATCC 10231). Sleep-recovery studies in female Sprague–Dawley rats, at a dose of 10mg/kg were performed to compare pharmacodynamic profiles of the new Propofol-PM formulations with those of Diprivan®, a commercially available lipid based propofol formulation.
Results. Growth of microorganisms was not supported in the Propofol-PM formulations tested. No significant differences in times to unconsciousness, awakening, recovery of righting reflex and full recovery were observed between Propofol-PM formulations and Diprivan®.
Conclusions. Propofol loaded in PVP–PLA micelles (Propofol-PM) is not significantly different in terms of pharmacodynamic but demonstrates no microorganism growth support and improved stability that opens up the door to pain on injection reduction strategy.

KEY WORDS: anesthesia; micelle; microbial growth; propofol; PVP–PLA.

INTRODUCTION

Propofol is the most widely used intravenous anaesthetic agent in the world. Rapid onset and short half-life permit both induction and maintenance of anaesthesia with, rapid clear-headed recovery and a low incidence of Post Operative Nausea and Vomiting (PONV). Pure propofol is a lipophilic, water-immiscible liquid unsuitable for intravenous administration. Early pre-clinical and human administrations were formulated in Cremophor EL; however, this provoked allergic responses and was superseded by an oil-in-water microemulsion of soybean oil and egg lecithin (1).

Limitations of emulsion presentations of propofol include pain on injection, risk of hyperlipidaemia, support for bacterial growth, and instability *versus* dilution, filtration and miscibility with other drug solutions (2,3). These drawbacks have fueled research and development efforts to reformulate propofol with reduced lipid contents or using lipid-free drug carriers. Examples include new formulations utilizing lower lipid contents (4–6) and/or mixtures of shorter and longer triglyceride chain length (4,7), various polymeric systems such as poloxamers (8,9), cyclodextrins (10,11), and other types of solvents (12). With the exception of Propofol Lipuro® (7), all new formulations have shown to be more painful on injection than the original emulsion. Baker *et al.*, have recently reviewed the formulation challenge (13). Water-soluble prodrugs of propofol are also in development (13–16). Their slower onset of action, lower potency and longer elimination time are counterintuitive for application to anaesthesia (3). However, these compounds may prove useful for sedation.

The objectives of this study were to incorporate propofol in polymeric micelles (Propofol-PM) made from amphiphilic block copolymers of poly-(*N*-vinyl-2-pyrrolidone) and poly-(D,L-lactide), PVP–PLA (Fig. 1), whilst maintaining its attractive clinical characteristics. PVP–PLA was first introduced as a polymeric micelle composition that successfully ameliorated the safety profile of existing paclitaxel and docetaxel formulations (17,18). Propofol-PM is presented as a lyophilized solid that instantaneously reconstitutes to form a clear solution of propofol 1%w/v (Fig. 2). We compared the potential for microbial growth support of three reformulated Propofol-PM formulations over a 24-h period with that of commercially available Diprivan® (containing EDTA as microbial growth retardant). We also conducted preliminary sleep/recovery studies to compare pharmacodynamic characteristics of these formulations to that of Diprivan®.

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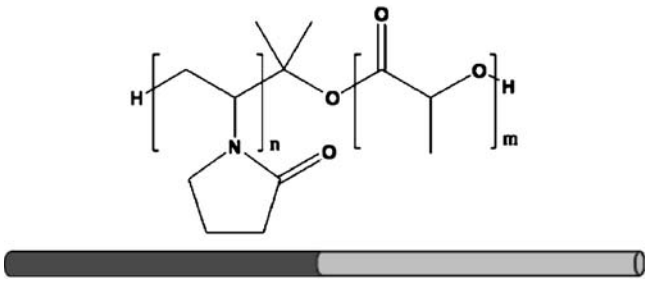

Fig. 1. (*Top*) Chemical structure and schematic representation of a poly(*N*-vinyl-2-pyrrolidone-*block*-poly(D,L-lactide), PVP–PLA, copolymer. Number of repeating units are distributions with number average values where $n \approx 22$ and $m \approx 20$. (*Bottom*) The *dark grey* segment represents the water-soluble PVP moiety and the *light gray* segment represents the lipophilic PLA moiety.

MATERIALS AND METHODS

Block Copolymer Synthesis

Poly (*N*-vinyl-2-pyrrolidone)-*block*-poly (D,L-lactide) copolymers (Fig. 1) were prepared as previously described (19). Briefly, *N*-vinyl-2-pyrrolidone is polymerized using a radical initiator in isopropyl alcohol and mercaptoethanol as a chain transfer agent. This procedure yields poly (*N*-vinyl-2-pyrrolidone), PVP, with one hydroxyl group (PVP–OH) of narrow poyldispersity (M_w/M_n = 1.3–1.5) and low molecular weight (M_n = 2,000–2,600 Da). Sodium hydride activates PVP–OH to anionically polymerize D,L-lactide in THF. Block copolymers used in the present studies had the following characteristics: 36.7% weight of poly (D,L-lactide), PLA, as determined by elemental analysis; average number molecular weights (M_n) ranging from 3,500 Da for Propofol-PM A series to 4,000 Da for Propofol-PM B series; $M_w/M_n \leq 1.2$. Absolute molecular weights of block copolymer samples were determined by a Precision Detectors (USA) PD light scattering detector coupled to a size exclusion chromatography (SEC) system using Waters Styragel® HT2, HT3 and HT4 columns at 40°C and 10 mM lithium bromide in dimethyl formamide (DMF) as the eluant. Refractive index and light scattering detectors were kept at 40°C, and the system was calibrated with a polystyrene standard.

Propofol-PM Formulations

Propofol (99.9%) was provided by Albemarle Corporation (USA). Propofol-PM formulations were prepared at different drug loading levels (DLL) according to the following Equation:

$$\%\mathrm{DLL} = \frac{\mathrm{Wt_{PPF}}}{(\mathrm{Wt_{PPF}} + \mathrm{Wt_{Polymer}})} \times 100\%$$

where $\mathrm{Wt_{PPF}}$ is the weight of propofol and $\mathrm{Wt_{Polymer}}$ is the weight of PVP–PLA in the formulation. Solutions of 7%, 10% and 12% DLL were prepared to assess the effect of propofol to polymer ratios. As presented in Fig. 2, PVP–PLA copolymer was first dissolved in water for injection (WFI) to form a micellar solution of PVP–PLA. Propofol was then added to the polymer solution and shaken vigorously until a clear, homogenous, solution was obtained. Typically, 30 to 60 min were required. The solution was then filtered sterile through a 0.2 μm filter and lyophilized. After lyophilization, vials were sealed with a rubber septum and aluminum cap to be stored in a closed box, at room temperature, until use. HPLC Assay of the solution before and after filtration and following lyophilization were performed to ensure propofol content was unchanged. Reconstitution in any of WFI, dextrose 5% (dextrose) or 0.9% saline (saline) yielded a clear, 1%w/v (10 mg/mL) propofol solution (Propofol-PM). All reconstitution media used in this study (WFI, dextrose and saline) were purchased from Abbott Laboratories. Propofol-PM B-series formulations involved polymer solubilization in sodium phosphate buffer (pH 7.4) instead of water prior to propofol addition and lyophilization. Lidocaine-containing formulations were prepared by directly reconstituting Propofol-PM B-series solid form using 0.2, 1 and 2% w/v Lidocaine solutions prepared from a 2%w/v lidocaine hydrochloride solution purchased from AstraZeneca and

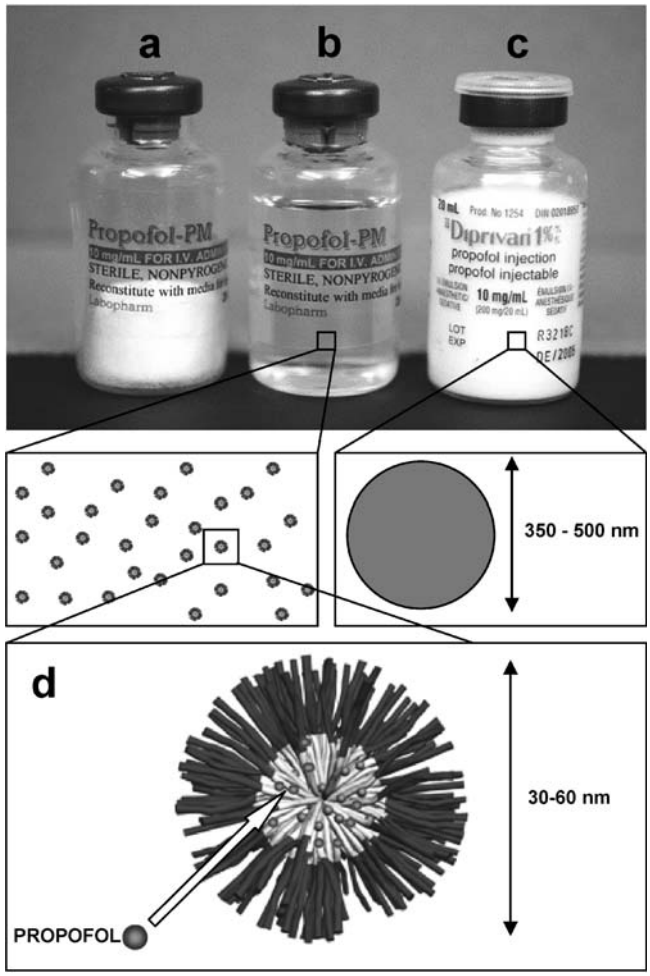

Fig. 2. Photograph and schematic representation of Propofol-PM and currently available propofol emulsion, Diprivan®. (**a**) Propofol-PM lyophilized cake. (**b**) Reconstituted Propofol-PM 1% (10 mg/mL) and (**c**) Diprivan®. Schematic representation of the relative particle size between Propofol-PM and an emulsion droplet. (**d**) Magnified view of a cross section of a propofol-loaded PVP–PLA micelle where PLA blocks (*light grey*) form the hydrophobic core of the micelle, able to dissolve propofol, and the PVP blocks (*dark grey*) form a corona which stabilizes the self-assembled nanocarrier in an aqueous environment.

diluted with WFI when required. All Propofol-PM used in the present paper, and reconstituted in either WFI, saline or dextrose, had a propofol concentration of 10 mg/mL ± 10%, unless otherwise specified.

High-performance Liquid Chromatography

Propofol concentrations of reconstituted Propofol-PM formulations were determined with a validated HPLC method based on European Pharmacopeia 01/2002:1558. A Hewlett Packard HPLC, model 1100 with a variable wavelength detector or diode array detector (275 nm), a normal phase column (Inertsil SIL-150A, 250 × 4.6mm, 5μm) and a hexane:acetonitrile:ethanol (990:7.5:1) mobile phase at 25°C. System suitability tests performed for each analytical run showed a percent recovery of 99–101%. Relative standard deviation of standards and quality control standards assay were below 2.5%. All assays were performed in triplicate.

Particle Size

Average micelle particle size and distribution were measured with a Malvern ZetaSizer Nano series dynamic light scattering instrument. Micelle size and distribution are reported as *z*-average and polydispersity index (PDI). Low volume polystyrene disposable cuvettes (12 mm) were used for sample handling and measurements at room temperature. CONTIN, a regularized Laplace inversion (20) analysis of dynamic single-angle laser light scattering data was performed to extract the hydrodynamic radius (R_h) from the correlation function. Average diameters in WFI, dextrose, and saline or in 0.1%, 0.2% and 2%w/v Lidocaine at 25°C were also determined and reported when appropriate.

Microbial Growth

We evaluated the potential for bacterial growth in injectable 1% propofol formulations reconstituted from Propofol-PM following inoculation with viable microorganisms; *P. aeruginosa* (ATCC 6538), *S. aureus* (ATCC 9027), *E. coli* (ATCC 25922) and *C. albicans* (ATCC 10231). Propofol-PM with a 10% Drug loading level was reconstituted using water for injection, 5% dextrose or 0.9% saline. Controls included PVP–PLA copolymer reconstituted in water for injection, 5% dextrose or 0.9% saline alone and the three reconstitution solvents without polymer. No preservatives, bacteriostatic or antimicrobial agents were added to any of the formulations. Diprivan® (AstraZeneca), containing EDTA as a microbial growth retardant, was used according to the manufacturer's instructions including aseptic techniques. Table 1 presents the ten different milieus that were tested for microbial growth support.

Using a nephelometer, a McFarland 0.5 suspension (ca. 10^8 cfu/mL) was prepared for each microorganism. The suspension was then diluted 1:100 and then 1:10 in non-bacteriostatic 0.85% saline to 10^5 cfu/mL. To ensure sterility, milieus #1–6 were filtered sterile on the day of the study using 0.2 μm filters after reconstitution, prior to inoculation. After filtration, one aliquot of 100 μL was withdrawn from each reconstituted formulation and tested for sterility at time 0 and 24 h without inoculation.

Table 1. Solutions Tested for Microbial Growth

#	Formulation/test Samples	Reconstitution Medium
1	Propofol-PM 1%w/v (10 mg/mL)	Water for injection
2	Propofol-PM 1%w/v (10 mg/mL)	Dextrose 5%
3	Propofol-PM 1%w/v (10 mg/mL)	Saline 0.9%
4	PVP–PLA solution (9%w/v)	Water for injection
5	PVP–PLA solution (9%w/v)	Dextrose 5%
6	PVP–PLA solution (9%w/v)	Saline 0.9%
7	Diprivan® (Astra Zeneca)	NA
8	Water for injection	NA
9	Dextrose 5%	NA
10	Saline 0.9%	NA

Propofol-PM stands for Propofol Polymeric Micelle. PVP–PLA stands for poly(*N*-vinyl-2-pyrrolidone)-*block*-poly(D,L-lactide) solutions at 9%w/v representing a placebo version of Propofol-PM.

Twelve aliquots of 270 μL were prepared for each milieu studied (four microorganisms and $n = 3$). 30 μL of each microbe strain suspensions prepared above were added to the 270 μL aliquot (10^4 cfu/mL) of the test milieus ($n = 3$) and left at 20°C for 24 h. At predetermined sampling times, 1 μL of suspension was inoculated onto blood agar plate (for *P. aeruginosa*, *S. aureus* and *E. coli*) or Sabouraud agar (for *C. albicans*) using a calibrated loop. Sampling times were 0 h, 2 h, 4 h, 6 h, 12 h and 24 h. For each microorganism strain tested, three replicates were performed and for each replicate, counts were done in duplicate. The plates were then incubated at 35°C for 20–22 h and the colonies forming units (cfu) were counted.

Sleep/recovery Studies

We evaluated recovery from anaesthesia after a single intravenous injection of propofol 10 mg/kg in rats ($n = 5$). In Study A, 1% propofol injections were prepared from Propofol-PM formulations (A-series) with Drug Loading Levels of 7%, 10% and 12% using dextrose 5% as solvent and compared to Diprivan®. In Study B, 1% propofol injections were prepared from Propofol-PM formulations (B-series) with drug loading levels of 7%, 10% and 12% using water for injection as solvent and compared to Diprivan®. Propofol 10 mg/kg was administered as a single bolus injection in the caudal vein approximately 5 cm from the distal end of the tail over 30 s. In order to effectively deliver 10 mg/kg, injection volumes were corrected for variation in individual rat weights and for exact propofol concentration in Propofol-PM as obtained from HPLC assay, except for Diprivan® which was considered to be 10 mg/mL exactly.

Female Sprague–Dawley rats were used in both studies. In study A, 20 female Sprague–Dawley rats weighing 251 ± 8 g (mean ± SD) were randomly allocated in four groups ($n = 5$). In study B, 20 female Sprague–Dawley rats weighing 214 ± 8 g (mean ± SD) were randomly allocated in four groups ($n = 5$). For both studies, each group received 10 mg/kg of one of the four 1% propofol formulations: respectively, Diprivan®, or reconstituted Propofol-PM 7%, 10% or 12%. The research adhered to the Principles of Laboratory Animal Care (NIH publication #85-23, revised in 1985) and all experiments followed a protocol approved by an in-house ethics

committee in accordance with Canadian Council on Animal Care guidelines.

Pharmacodynamic Parameters

Each rat was observed during and after injection and recovery times were recorded. Each rat had two observers at all time evaluating the time to first movement, righting reflex and full recovery. The time to first movement was considered as the time at which the rat opened its eyes. The time for righting reflex recovery was indicated by a spontaneous attempt to get back up on four legs. Full recovery was considered to be the time at which the rat had full control of its balance upon walking and/or being slightly pushed on the side. Animals were observed for overt toxic effects for 3days following administration.

RESULTS AND DISCUSSION

Formulation Properties and Stability

Propofol was successfully loaded to clear aqueous solutions by direct mixing of polymer, water and drug. The solid form obtained from lyophilizing the solution retained the propofol load as indicated by HPLC assays, i.e. comparison assay prior to filtration and following lyophilization are within the system suitability tests owning a relative standard deviation of less than 2.5%. This indicates thorough loading of the drug in the core of the solid micelle array and predictable dose. Particle size and osmolality of reconstituted Propofol-PM formulations are presented in Table 2. Propofol-PM 3A formulation, at 12% DLL, had a relatively larger micelle size at 64.6 nm when compared to an overall average of 28 ± 3 nm calculated for all other formulations. This increase in size suggests that the lower number and smaller volume of PVP–PLA micelles, due respectively to lower concentration and lower molecular weight of PVP–PLA used in the A-series, requires individual micelles to dissolve more propofol in comparison to other batches where the number and/or volume of available micelles is sufficient. This results in swelling of the PLA core were observed by DLS. Propofol-PM B3 (12% DLL) in which PVP–PLA has a slightly higher average molecular weight supports this hypothesis since it does not show a micelle size increase to the same extent.

One percent propofol injections reformulated from Propofol-PM (propofol 10 mg/mL) were stable over a period of more than 2 weeks following reconstitution. Stability was assessed in terms of propofol content, visual clarity and particle size distribution. Stability in presence of lidocaine, a local anesthetic agent often injected to patients prior to propofol to reduce pain on injection, was also evaluated. Park *et al.* (21) have demonstrated that the popular practice of premixing lidocaine solutions in propofol emulsions results in progressive emulsion breakdown where particle aggregation reaches sizes larger than 5 μm within 2 h when 30 mg of lidocaine (1.5 ml of 2%w/v lidocaine solution) is added to 20 mL of Diprivan® (lidocaine concentration of less than 1.4 mg/mL). Whilst immediate administration of propofol–lidocaine mixtures is clinically acceptable their unstable nature precludes use after storage. Lipid droplets in emulsions such as Diprivan® are stabilized by electrostatic repulsion. Addition of lidocaine hydrochloride increases the ionic strength of the aqueous phase thus diminishing the repulsive effect between droplets, allowing them to aggregate. In the present study, we directly reconstituted lyophilized Propofol-PM formulations (B-series) using lidocaine solutions of three different concentrations: 0.2, 1 and 2%w/v. Results indicate that micelle size distribution is stable over a period of at least 4 days (Table 3). Change in lidocaine concentration and thus ionic strength does not significantly affect the micelle stability because PVP–PLA is a non-ionic copolymer and is not stabilized by electrostatic repulsion, but mainly by steric stabilization.

Free propofol present in the aqueous phase (outside emulsion droplets and/or micelles) may be an important element causing pain on injection (22–24). Accordingly, a possible strategy to reduce this free propofol fraction would be to increase the ionic strength of the aqueous phase as to limit soluble propofol fractions by a simple "salting out" effect. This pain reduction strategy is not possible with emulsions and other ionic strength sensitive systems.

Microbial Growth Study

Propofol-PM A-series formulation of 10% DLL reconstituted in different injection media (WFI, dextrose and saline) yielded similar particle size distributions as those presented in Table 2 and had propofol concentrations of 10 mg/mL ± 5%. Fig. 3 presents the 24-h growth profile of the four microorganisms tested in Propofol-PM and PVP–PLA reconstituted in water for injection, and Diprivan®. Growth in water for injection (control) is also presented. Results obtained in dextrose and saline follow roughly the same trend (data not shown).

Microbial growth support in emulsion formulations of propofol is a well documented problem (25). Bennett *et al.*, have shown that extrinsic contamination caused by failure to use strict aseptic techniques during handling of propofol emulsions can lead to postoperative infections and major complications for patients (26). A recent alert was issued by the FDA to inform healthcare professionals about several

Table 2. Properties of 1% Propofol-PM Formulations after Reconstitution in Dextrose and Water for Injection (WFI)

Formulation	% DLL	Reconstitution Media	*z*-average (nm) Size (PDI)	Osmolality (mOsm)
Propofol-PM A1	7	Dextrose	25.1 (0.38)	438
Propofol-PM A2	10	Dextrose	25.5 (0.34)	355
Propofol-PM A3	12	Dextrose	64.6 (0.58)	342
Propofol-PM B1	7	WFI	28.4 (0.15)	284
Propofol-PM B2	10	WFI	29.9 (0.11)	240
Propofol-PM B3	12	WFI	33.1 (0.20)	224

Table 3. Particle Size Distribution and Polydispersity Index (PDI) of 1% Propofol-PM B2 Up to 4 days following Reconstitution in Lidocaine Solutions of Different Concentrations

	z-average Size (nm) and Polydispersity				
Lidocaine conc.	At Reconstitution	Day 1	Day 2 Size (PDI)	Day 3	Day 4
0.2% (2 mg/mL)	33.9 (0.23)	31.7 (0.22)	33.2 (0.18)	35.4 (0.28)	57.9 (0.15)
1% (10 mg/mL)	40.4 (0.30)	49.4 (0.16)	44.0 (0.27)	41.2 (0.30)	40.6 (0.24)
2% (20 mg/mL)	43.2 (0.29)	43.5 (0.30)	59.4 (0.30)	42.4 (0.30)	44.3 (0.32)

clusters of patients who have experienced chills, fever, and body aches shortly after receiving propofol for sedation or general anesthesia (27). In the present study, Diprivan® supported microorganism growth the most over the 24-h period. EDTA, a microbial growth retardant present in Diprivan®, efficiently controlled microorganism proliferation over the first hours, but was then followed by a period of significant growth. Similar results for *C. albicans* were reported by Fukada *et al.*, EDTA-containing propofol emulsions had slower growth rates than propofol emulsions containing no EDTA (28). *P. Aerigunosa* is not affected as much by EDTA as the microorganism rapidly grew after inoculation in Diprivan®, as measured after 2 h (Fig. 3c). Despite addition of preservatives such as EDTA, propofol emulsions have a limited shelf-life of 6 h once the bottle is punctured (29). Reconstituted Propofol-PM formulations, in any media, showed an immediate reduction and/or rapid elimination of microorganisms. Fig. 4 presents bacterial counts at 24 h after inoculation for Diprivan®, polymer solution (placebo) and Propofol-PM (10% DLL, 1%w/v propofol concentration, A-series) in all three different reconstitution media: (A) WFI, (B) saline and (C) dextrose. Also included are the bacterial counts at 24 h for the inoculated reconstitution media alone (control). Injection media controls (WFI, dextrose and saline) showed similar

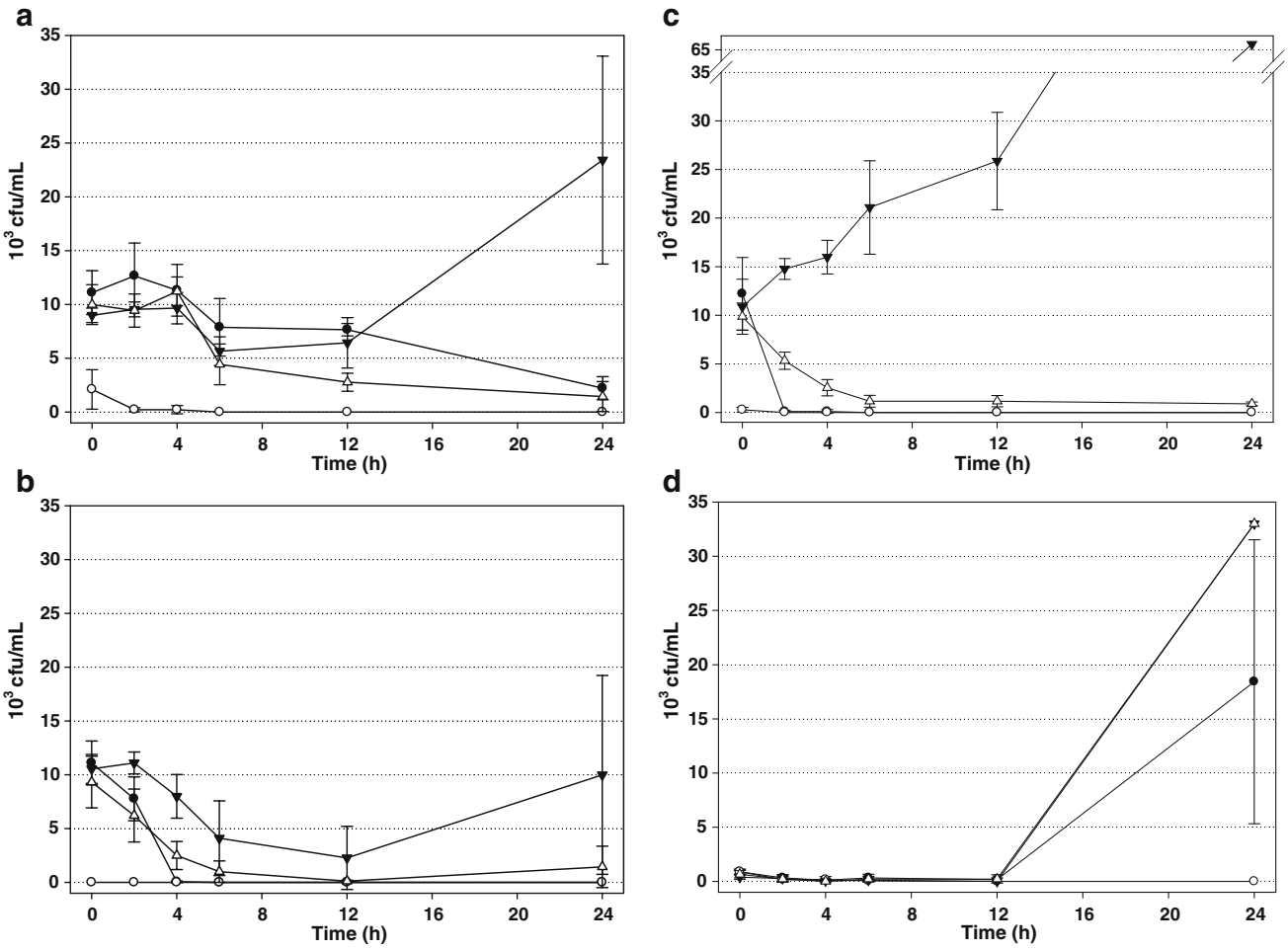

Fig. 3. Twenty-four-hour microorganism growth profiles at 20°C following inoculation of ca. 10^4 cfu/mL of (**a**) *S. aureus,* (**b**) *E. coli*, (**c**) *P. aeruginosa* and (**d**) *C. albicans* in WFI (r), PVP–PLA in WFI (●), Propofol-PM in WFI (○) and Diprivan® (▼). Diprivan and reconstituted Propofol-PM formulations all had 1%w/v of propofol.

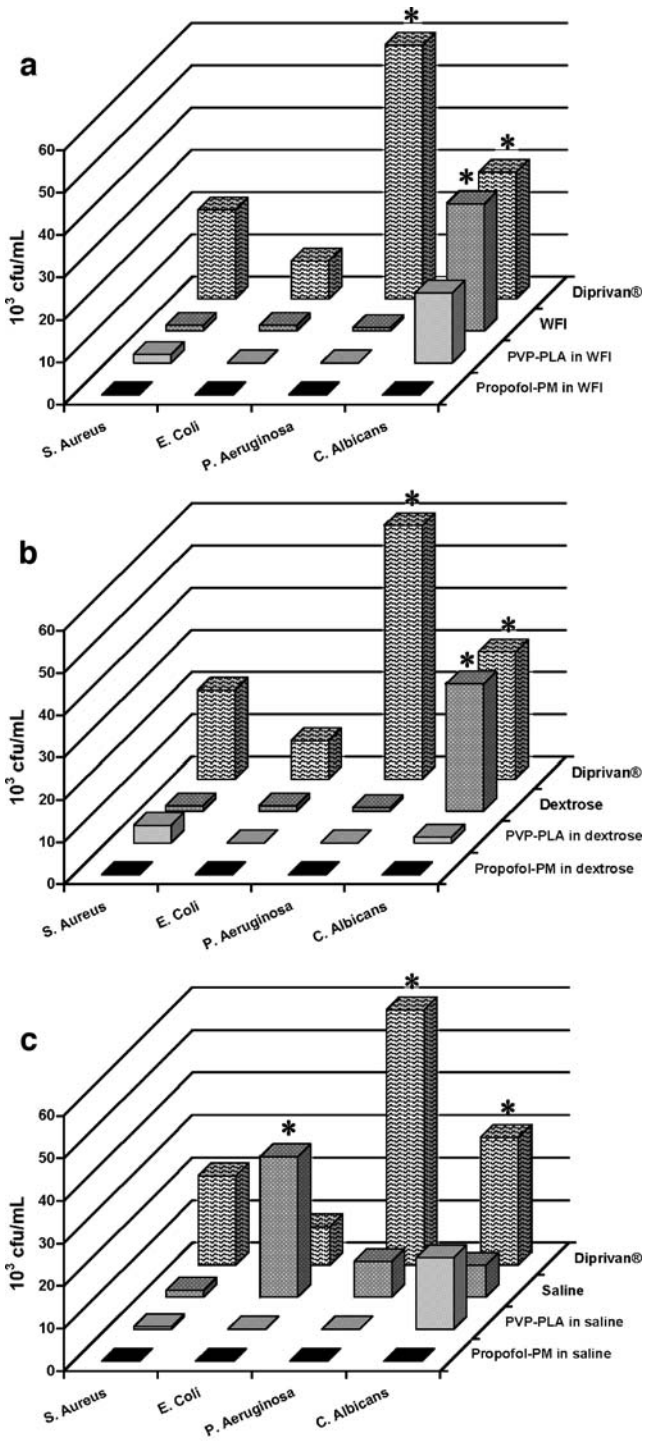

Fig. 4. Microorganism counts (cfu/mL) after 24 h at 20°C following inoculation of ca. 10^4 cfu/mL in (**a**) water for injection, (**b**) dextrose and (**c**) saline. Diprivan and reconstituted Propofol-PM both had a 1%w/v concentration of propofol. *Counts were actually evaluated to be "above" plotted value, i.e. plotted value represents the minimum number of counts visually assessable on said plate.

growth profiles to those of PVP–PLA solutions in the same respective media suggesting the polymer is not toxic for microorganisms. Pure propofol has been shown to have bactericidal effects for certain strains of bacteria and microorganisms like many other phenolic compounds (30). The failure of bacteria to proliferate in the reconstituted Propofol-PM formulation is thus thought to be due in part to this characteristic which takes over in the absence of nutritional supplies such as lipids.

Overall, results indicate that Propofol-PM does not support growth of the four microorganism tested in either reconstitution media. Microorganism counts at 24 h in all reconstitution media indicate that no living microorganism were detected in all reconstituted Propofol-PM formulations (Fig. 4). Diprivan® was able to support the growth of the greatest number of microorganisms tested over the 24-h period at room temperature. Only *E. coli* in saline and *C. albicans* in water and dextrose showed equal or more abundant proliferation than Diprivan® (Fig. 4).

Sleep/recovery Studies

Results of preliminary sleep/recovery studies indicate that pharmacodynamic profiles for the three Propofol-PM A-series formulations (reconstituted in dextrose) were similar to that of the commercially available oil-in-water formulation, Diprivan® (Fig. 5). There were no significant differences in time to lose consciousness, regain consciousness, recovery of righting reflex and full recovery. In the second study we tested a different polymer batch and modified the formulation to include a phosphate buffer before lyophilization. These modifications allowed testing both the polymer molecular weight effect and to produce an isotonic formulation upon reconstitution using WFI. These changes had no effect on time of righting reflex recovery in the range studied. Time for rig hting reflex recovery in the second study were 10.4 ± 3.3, 11.6 ± 1.7, 10.4 ± 2.9 and 10.3 ± 1.3 min (mean ± SD), for Diprivan®, and 1% propofol injections reconstituted from Propofol-PM at 7, 10 and 12% DLL, respectively.

Overall, the six Propofol-PM formulations tested in sleep/recovery studies proved to not be significantly different to each other or to Diprivan® in Sprague–Dawley rats at a fixed dose of 10 mg/kg. In all, four animals died during, or shortly after injection: two in study A (Diprivan® group), two in study B (7% DLL Propofol-PM group). It is believed that respiratory apnea lead to these deaths during injection in the tightly confined cylinders used to control the animals. No other animals sustained any observable toxic effects from use of neither Propofol-PM formulations nor Diprivan®.

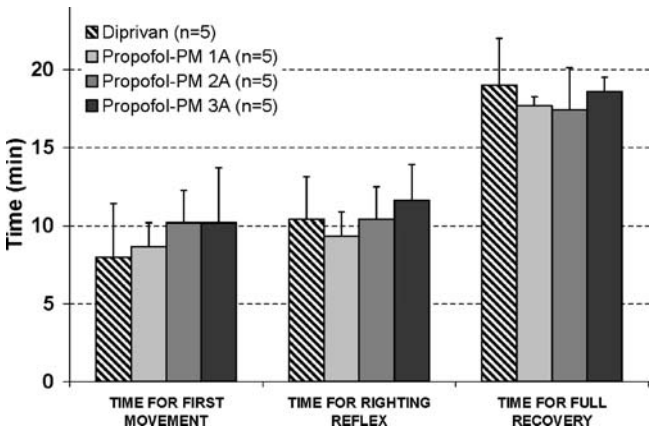

Fig. 5. Sleep-recovery study A results. Ten milligrams per kilogram, female Sprague–Dawley rats. (Onset of sleep is less than 1 min).

CONCLUSION

Propofol-PM is a new lipid-free propofol formulation that has demonstrated bacteriostatic/bactericidal properties which increase the safety profile of the formulation. This property is thought to come from the intrinsic bactericidal properties of propofol itself and the absence of nutrients such as lipids found in commercial emulsions. Propofol-PM has demonstrated stability in the presence of Lidocaine for over 4 days without any change in its particle size distribution, clarity or propofol content. Pharmacodynamic profiles of the drug in Propofol-PM formulations is not significantly different than that of Diprivan® over a range of drug loading levels of 7–12% and polymer average number molecular weight of 3,500–4,000 Da. This stability *versus* ionic strength variation indicates that it is potentially possible to reduce the water-soluble fraction of propofol in the formulation as a pain on injection reduction strategy. This approach is not possible with original commercial formulation and may prove to be the solution to this major drawback. Pharmacokinetic study should better define the formulation profile described in this study.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Serge Messier for his expertise in reviewing and performing the microbial study protocol.

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