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Stability of Propofol Medium Chain Triglyceride/Long Chain Triglyceride (MCT/LCT) in 0.9% NaCl Solution with CRYOVAC® Non-PVC Soft Bag Containers

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ABSTRACT

The compatibility of propofol MCT/LCT with non-PVC soft bag was investigated in this study. Solutions of 2.0 and 2.5 mg/mL propofol MCT/LCT in 0.9% NaCl solution were filled into CRYOVAC® containers. The studied samples were grouped and stored at ambient temperature (25 ± 2°C) in the light, at ambient temperature in the dark, and at 2-8°C in the dark for 5 days. At indicated sampling time, propofol was assayed by high-performance liquid chromatography. For long-term study, propofol samples were analyzed at day 8 and at day 15. The results showed that all studied samples were stable for 5 days. Propofol contents decreased by 8-12% and 15-23% when stored in the non-PVC bag at ambient temperature in the light for 8 days and 15 days, respectively. Studied samples in non-PVC bag stored at ambient temperature in the dark showed 3-9% decrease when stored for 8 days, whereas 10-13% decrease for 15 days. Propofol concentration in non-PVC bag stored at 2-8°C in the dark showed approximately 2-8% decrease at both day 8 and day 15. In conclusion, the 2.0 and 2.5 mg/mL propofol MCT/LCT in 0.9% NaCl solution with CRYOVAC® container stored at all conditions were stable for 5 days. It is found that samples stored at ambient temperature were more labile as compared to those at 2-8°C; moreover, propofol sample was vulnerable to light exposure. In addition, DEHP additive was not detected in the CRYOVAC® soft bag container by HPLC with a quantitation limit at 5 ppm. Therefore, CRYOVAC® non-PVC soft bag is a suitable container system for propofol MCT/LCT emulsion.

Key words: compatibility, propofol MCT/LCT, non-PVC soft bag containers

INTRODUCTION

As a common and safe anesthetic agent, propofol provides fast onset, deep sedation, rapid cognition and functional recovery. However, pain on injection is a major disadvantage with approximately 70% reported incidence when a standard emulsion formulation of propofol is administered with no intervention to reduce pain[(1)]. In addition to opioids or metoclopromide, one of the most frequently used method for pain management is the administration of lignocaine, a kinin cascade stabilizer[(2)], either before propofol injection, with or without a tourniquet[(3)] or added to the propofol emulsion as a premixture[(1,4,5)].

It is found that the amount of free propofol would result in injection pain in the aqueous phase of the emulsion. Efforts have been made to reduce propofol content in the aqueous phase. A new formulation of propofol has been demonstrated to ease the incidence of mild pain in 1997[(6)]. The new formulation of propofol contains equal proportions (50 : 50) of medium chain triglycerides (MCT) and long chain triglycerides (LCT), which was found to cause less pain on injection compared with standard propofol LCT.

Despite the successful development of emulsion formulation, propofol MCT/LCT is incompatible with PVC bags. The plastic additive, di-(2-ethylhexyl)phthalate (DEHP), was extractable in MCT/LCT formulation. Accordingly, glass vial, polypropylene bottles, and polyolefin bags were recommended[(7,8,9)]. To explore other container system, multi-layer structure plastic containers are attractive because plastic is flexible, and will collapse when the contents are drawn off, which means less space required and lower waste disposal costs.

CRYOVAC® containers are hot-formed by the blow-fill-seal process; no additive is used during the manufacturing. Moreover, the material contains little particulate contamination than glass or PVC, and does not contain any

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additives that are liable to migrate into the drug solutions. Risk of leachables and particulate issues are low. Therefore, we aimed to study the feasibility to use CRYOVAC® as a container closure system for propofol MCT/LCT emulsion.

For clinical dosing purpose, solutions containing 2.0 - 2.5 mg/mL of propofol MCT/LCT (in 5% glucose solution) are generally prepared and proven chemically and physically stable for 24 h at 25°C. In the present study, we investigated the compatibility of propofol MCT/LCT in 0.9% NaCl solution with the non-PVC CRYOVAC® containers. We studied the stability of the solutions stored under three different light and temperature conditions to evaluate whether solutions of 2.0 and 2.5 mg/mL propofol MCT/LCT in 0.9% NaCl solution could be prepared in advance.

MATERIALS AND METHODS

I. *Study Drug*

Propofol MCT/LCT was supplied by Chi Sheng Chemical Corporation (CSCC) as an injectable solution in 20 mL Ampule (10 mg/mL).

II. *Solvent for Dilution and Containers*

The 0.9% NaCl solution (Chi Sheng Chemical Corporation Medical) used to dilute the propofol MCT/LCT was supplied in CRYOVAC® polyolefins soft bag container (Sealed Air) and in glass bottle (Chi Sheng Chemical Corporation Medical).

III. *Study Design*

Two concentrations of propofol, i.e. 2.0 and 2.5 mg/mL, in MCT/LCT emulsion, which is commonly used in clinical practice, were prepared in this study. To prepare the 2.0 mg/mL solution, a total of 5 Ampule bottles, or 100 mL propofol MCT/LCT, were added to 400 mL 0.9% NaCl solution; for the preparation of the 2.5 mg/mL solution, 5 Ampule bottles (100 mL) of propofol MCT/LCT were added to 300 mL 0.9% NaCl solution. The dilutions were conducted under a laminar flow hood. Besides, the glass vial served as a control, since the compatibility of propofol MCT/LCT with glass has been established[10].

The solutions of propofol MCT/LCT in glass or CRYOVAC® non-PVC soft bag containers were stored under three different conditions: (I) at ambient temperature (25 ± 2°C) and in ambient light (daylight, out of direct sunlight, on a bench in the middle of the laboratory); (II) at ambient temperature in the dark (wrapped in aluminum foil); and (III) at 2-8°C in the dark (in a refrigerator). These conditions are those any diluted drug solution is liable to encounter in clinical practice before administrated to a patient. For each storage condition the study samples in CRYOVAC® were made in triplicate. A single glass control was prepared. The study design is listed in Table 1. The supplier recommends that diluted solutions of propofol MCT/LCT should not be frozen because of an increased risk of the emulsion liable to break up at low temperatures.

For each preparation, the first sample was taken immediately after dilution and bottling (sampling time T0), which served as the baseline. Subsequent samples were taken at the following times; on day 1 after 1-, 2-, 4-, 6-h storage, and then every day for 4 days (i.e. day-2, day-3, day-4, and day-5). For long term stability study, propofol MCT/LCT emulsion in 0.9% NaCl solution was sampled on day 8 and day 15.

IV. *Analytical Methods*

At each sampling time, the apperance was examined by visual inspection and the samples were analyzed by HPLC. First, the studied sample was transferred to a clear glass tube for visual inspection. The samples were examined against a white background and a black background under unpolarized light. The appearance of sample should be clear, contain no yellow oil drop and conform with a uniform phase.

For HPLC assay, sample was diluted with isopropanol (Macron, USA) and filtered using a 25 mm syringe filter with 0.45 μm PVDF membrance (Pall Corporation, USA). If any yellow oil drops were observed in visual inspection, the sample was shaked vigorously before diluted with isopropanol.

Propofol sample was loaded on a pentafluorophenyl-type stationary column (Interchim, 250 × 4.6 mm i.d., 5 μm). The mobile phase was a mixture (75/25, v/v) of acetonitrile (Panreac, SPAIN) and purified water (CSCC, Taiwan). The isocratic flow rate was 1 mL/min. The detection wavelength was set at 275 nm. An HPLC system (Alliance 2695, Waters) equipped with a photodiode detector (PDA 2996, Waters) was used in this study. Chromatograms were processed using Empower 2.

The standard solutions were prepared by dilution of 2 mg/mL propofol (U.S. Pharmacopeia reference standard, ROCKVILLE, MD, USA.) in isopropanolol (v/v). The concentrations of propofol standard are 0, 0.4, 0.6, 0.8, 1.0, and 1.2 mg/mL. These solutions were used to plot a calibration line with regression equation $y = ax + b$ (where x is the propofol concentration and y is the area under the propofol peak).

The propofol assay method, we used 0.8 mg/mL of USP propofol to confirm chromatographic system suitability including column efficiency: more than 1000 theoretical plates; tailing factor less than 1.5 for the propofol peak and relative standard deviation not more than 2% for the replicate injection. Precision, expressed as a relative standard deviation, was 0.24 and 0.5% for intra-day assay variability (n = 6) and for inter-day variability (n = 6), respectively. Method linearity was in the range from 0.4 to 1.2 mg/mL with a correlation coefficient $r^2 = 0.9999$. The equation for the mean calibration was $y = 5.4467 \cdot 10^6 x + 8.8397 \cdot 10^4$. The recovery of propofol from propofol MCT/LCT was 98.53 ± 0.11%[11]. The chromatographic method was able to detect and separate propofol from any degradation products such as

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3,3'-5,5'- tetraisopropyldiphenol and 2,6-diisopropylbenzoquinone. The HPLC method was validated as a stability-indicating method for propofol MCT/LCT emulsion. It provided specific quantitation of the drug itself without interference by any of its breakdown products and its formulation[11].

The average concentrations of propofol in study samples stored in CRYOVAC® were calculated from triplicate tests. The results are expressed in percentages relative to the initial concentration at T0 (value taken as 100%). Drug solutions are considered acceptable for use if the content is not less than 90% of the label claim[9].

V. *Chromatographic Analysis of DEHP*

Solutions of 2.0 and 2.5 mg/mL propofol MCT/LCT were filled into CRYOVAC® containers in three storage conditions for 15 days. Ten milliliter of the samples were extracted once with 10 mL of hexane. Then, direct injection of 20 μL the solvent extract was performed. All the measurements were performed in triplicate[12]. The column was a LICHROSPHER 100 RP18 endcapped (Merck). The mobile phase was a mixture of acetonitrile-water (95/5, v/v). The flow was isocratic at a flow rate of 1 mL/min. The detection wavelength was 224 nm. The standard DEHP was supplied by Chem Service, Inc. (Pennsylvania, USA).

RESULTS AND DISCUSSION

I. *Appearance of Study Samples*

The CRYOVAC® soft bags contained propofol samples, either 2.0 or 2.5 mg/mL, were stored at conditions listed in Table 1. All samples stored for 5 days showed no yellow oil drop and remained uniform phases as shown in Table 2 and 3. This result suggested the physical property of propofol MCT/LCT in 0.9% NaCl emulsion is stable for 5 days when stored at CRYOVAC® non-PVC soft bag.

II. *Concentration Changes of Propofol in Study Samples*

The propofol content was assayed by HPLC method. At each sampling time, three studied samples in soft bags and one control sample in glass vial were assayed. Table 2 showed that control propofol samples diluted to 2.5 mg/mL in 0.9% NaCl solution stored under all conditions were stable for 5 days in glass vial. For studied samples stored at ambient temperature and light condition, propofol content showed an 8% decrease, i.e. from 99 to 92%. When studied sample stored in the dark and at ambient temperature, propofol content changed from 100 to 94%. The same 6% decrease was observed when samples were stored in the dark and at 2-8°C, indicating that light exposure had little impact on propofol content. Of particularly noteworthy is the propofol contents for all study samples stored in CRYOVAC® non-PVC soft bags for 6 h did not change. The contents of studied samples started to decrease slowly from day 2.

The content analysis of propofol at 2.0 mg/mL was listed in Table 3. The control group showed the determined content was in the range from 96 to 98%. For studied samples stored at ambient temperature and light condition, propofol contents decreased from 100 to 92%, whereas 100 to 95% for study sample in the dark and at ambient temperature. When samples were stored in the dark and at 2-8°C, the determined contents were in the range from 100 to 97%. It was observed that all studied samples in this group were very stable for 6 hours, as indicated for 2.5 mg/mL studied group. An obvious decrease was detected when propofol was sampled at day 2, especially for samples stored at ambient temperature and light condition. The most striking changes were samples stored at ambient temperature and light condition, and both 2.5 and 2.0 mg/mL of propofol content decreased by 8%. For other groups as

Table 1. Experimental conditions

Container	Concentration of propofol MCT/LCT	Condition of storage	Number of preparations
CRYOVAC®	2.0 mg/mL	Ambient light and temperature	3
		Dark and ambient temperature	3
		Dark and at 2-8°C	3
	2.5 mg/mL	Ambient light and temperature	3
		Dark and ambient temperature	3
		Dark and at 2-8°C	3
Glass	2.0 mg/mL	Ambient light and temperature	1
		Dark and ambient temperature	1
		Dark and at 2-8°C	1
	2.5 mg/mL	Ambient light and temperature	1
		Dark and ambient temperature	1
		Dark and at 2-8°C	1

Table 2. Stability of solution of 2.5 mg/mL of propofol MCT/LCT in 0.9% NaCl solution

	Ambient light and temperature		Dark and ambient temperature		Dark and at 2-8°C	
	Glass (n = 1)	CRYOVAC® (n = 3)	Glass (n = 1)	CRYOVAC® (n = 3)	Glass (n = 1)	CRYOVAC® (n = 3)
Initial concentration (mg/mL)	0.90	0.921 ± 0.001	0.90	0.922 ± 0.002	0.898	0.922 ± 0.001
Percent initial concentration remaining after storage (mean ± S.D.)						
D1(1h)	99.33	99.89 ± 0.06	99.33	100.00 ± 0.11	99.44	99.78 ± 0.06
D1(2h)	100.44	99.68 ± 0.22	99.89	100.00 ± 0.17	100.00	99.35 ± 0.17
D1(4h)	99.67	98.59 ± 0.13	99.78	99.35 ± 0.06	99.55	99.13 ± 0.19
D1(6h)	98.67	98.37 ± 0.17	99.67	98.59 ± 0.17	98.66	98.92 ± 0.23
D2	99.78	96.10 ± 0.00	99.89	96.74 ± 0.06	99.11	97.61 ± 0.00
D3	99.89	94.79 ± 0.63	95.89	96.63 ± 0.11	96.44	96.42 ± 0.11
D4	99.22	92.52 ± 0.11	99.00	94.25 ± 0.06	100.00	95.66 ± 0.00
D5	99.89	92.08 ± 0.17	99.00	94.35 ± 0.11	100.22	94.25 ± 0.06
Appearance (D5)	White uniform	White uniform	White uniform	White uniform	White uniform	White uniform

Table 3. Stability of solution of 2.0 mg/mL of propofol MCT/LCT in 0.9% NaCl solution

	Ambient light and temperature		Dark and ambient temperature		Dark and at 2-8°C	
	Glass (n = 1)	CRYOVAC® (n = 3)	Glass (n = 1)	CRYOVAC® (n = 3)	Glass (n = 1)	CRYOVAC® (n = 3)
Initial concentration (mg/mL)	0.758	0.76 ± 0.01	0.759	0.76 ± 0.01	0.758	0.759 ± 0.01
Percent initial concentration remaining after storage (mean ± SD)						
D1(1h)	98.02	100.26 ± 0.08	96.97	99.87 ± 0.26	96.70	100.00 ± 0.13
D1(2h)	96.83	99.47 ± 0.20	96.31	99.87 ± 0.13	96.83	99.34 ± 0.08
D1(4h)	97.23	99.08 ± 0.08	96.05	99.21 ± 0.20	96.70	99.21 ± 0.08
D1(6h)	97.63	98.56 ± 0.02	96.71	98.55 ± 0.22	96.97	99.74 ± 0.15
D2	96.44	96.58 ± 0.08	96.18	97.50 ± 0.50	97.89	98.68 ± 0.08
D3	95.78	96.18 ± 0.13	95.52	97.37 ± 0.08	97.10	97.76 ± 0.00
D4	96.31	95.79 ± 0.35	97.10	97.24 ± 0.08	97.49	97.37 ± 0.26
D5	96.04	92.63 ± 0.20	96.84	95.00 ± 0.53	97.89	96.97 ± 0.13
Appearance (D5)	White uniform	White uniform	White uniform	White uniform	White uniform	White uniform

well as control groups, the changes were insignificant. The specification set for propofol drug content is not less than 90%. Accordingly, both 2.5 and 2.0 mg/mL of propofol in 0.9% NaCl solution were stable for 5 days.

III. *Long Term Stability of Propofol Emulsion in 0.9% NaCl Solution*

To understand the long term stability of propofol MCT/LCT emulsion in 0.9% NaCl, samples were analyzed at 8th day and at 15th day. Table 4 summarized the studied results. The control group in glass vial exhibited uniform solution phase and contained no yellow oil drop as shown in Table 4. The determined contents were in the range from 95 to 100%. This result indicated that the propofol MCT/LCT emulsion in 0.9% NaCl was very stable in glass vial for 2 weeks. For studied samples stored within CRYOVAC® at ambient temperature and under light condition for 8 days, the samples went opalenscence and developed small oil drop. After shaking to remix, about 10% decrease in content was detected by HPLC for both 2.5 and 2.0 mg/mL groups. For samples under condtion II and III, neither turbid solution nor oil drop was observed. Sample appearance was normal and the propofol contents was still greater than or equal to 90% (≧90%).

For studied samples stored within CRYOVAC® non-PVC bags at ambient temperature and under light condition for 15 days, propofol samples went turbid and developed a pale-yellow color as shown in Table 4. In addition, it was easy to observe small oil drops in sample solution. After remixing by shaking, the propofol content was less than 90%. For samples under condition II (in the dark and at ambient

Table 4. Propofol (%) in different solution after 8 and 15 days storage

	Day8		Day15	
	Glass	CRYOVAC®	glass	CRYOVAC®
Propofol MCT/LCT 2 mg/mL				
Ambient light and	95.29[a]	92.27[b]	94.99[a]	80.61[c]
temperature		92.27[b]		80.61[c]
		90.11[b]		77.69[c]
Dark and ambient	96.31[a]	97.73[a]	96.80[a]	90.79[a]
temperature		95.96[a]		89.79[c]
		96.22[a]		87.01[c]
Dark and at 2-8°C	96.17[a]	95.92[a]	96.74[a]	95.29[a]
		98.09[a]		102.17[a]
		95.41[a]		96.31[a]
Propofol MCT/LCT 2.5 mg/mL				
Ambient light and	98.55[a]	90.70[b]	100.71[a]	83.59[c]
temperature		88.19[b]		81.30[c]
		93.73[b]		85.16[c]
Dark and ambient	99.78[a]	95.40[a]	98.67[a]	89.97[c]
temperature		96.24[a]		90.07[a]
		91.33[a]		17.16[d]
Dark and at 2-8°C	99.78[a]	94.57[a]	96.17[a]	94.05[a]
		93.53[a]		94.68[a]
		94.57[a]		91.23[a]

[a] The sample solution shows white uniform solution phase and contained no yellow oil drop. The propofol content is greater than or equal to 90% (≧ 90%).
[b] The sample solution shows white cloudy accompany with some oil droplets. After shaking, the oil droplets will disappear. The propofol content is greater than or equal to 90% (≧ 90%).
[c] The sample solution shows light-yellow cloudy accompany with many oil droplets. The propofol content is less than 90% (< 90%).
[d] The sample solution is emulsified and layered seriously. The propofol content is less than detection limit.

temperature), similar results were obtained. One sample showed an extremely low propofol content, i.e. 17%, due to phase separation and very poor recovery after remixing. Interestingly, for samples stored and in the dark and at 2-8°C for 15 days, neither appearance change nor significant content change was observed, indicating that propofol emulsion in CRYOVAC® non-PVC bags was stable when stored at 2-8°C and in the dark for 15 days.

It was found the propofol samples went turbid at day 8 and worse at day 15. This phenomenon was alleviated by placing the samples in the dark. This suggested that propofol sample is sensitive to light exposure. It is likely that light exposure in the presence of residual oxygen is the major factor that resulted in the decrease of propofol content. In addition, propofol contents were different between solutions stored at room temperature and at 2-8°C after 15 days storage, suggesting temperature is another factor for the propofol stability. High temperature may accelerate permeability to water vapor and O_2, thus inducing instability of propofol emulsions. CRYOVAC® non-PVC bag compared to glass may slightly accelerate permeability to water vapor and O_2, especially at high temperature. This could be one reason using glass bottle as the container for a better stability since glass bottle was more impermeable than non-PVC bag. However, the variations in concentration were too slight for them to have any clinical impact. In this study, the decrease in propofol concentration started to occur only after 15 days storage at room temperature in non-PVC bag, well beyond the usual storage time in clinical practice. By avoiding light exposure and stored at 2-8°C, it is possible to place the propofol emulsion in non-PVC soft bag over 2 weeks.

Intravenously administered fat droplets exceeding 5 μm in diameter are believed to cause adverse reactions, in particular emboli in the lungs. Now that new particle detection techniques have emerged, new requirements for the limitation of particle sizes in intravenous fat emulsions have to be established. It would seem logical that next to the mean particle size requirement, also limitations be specified for the particle size distribution. Special attention should be paid to the number of large particles and the upper size limit. Each requirement should include the techniques and methods to be used.

IV. *Analysis of DEHP in the Propofol MCT/LCT Solution*

Non-PVC products may contain much smaller amounts of DEHP. Flexible PVC-free products still must be tested to ascertain whether they are in fact DEHP-free. No DEHP was detected in each solution of propofol MCT/LCT in CRYOVAC® after 15 days storage under any of the temperature and light conditions tested. The limit of quantification for DEHP by this chromatography method was ≦ 5 ppm of solution of propofol MCT/LCT in 0.9% NaCl solution.

CONCLUSIONS

In the present study, propofol MCT/LCT emulsion in 0.9% NaCl solutions were stored at three different conditions for 5 days and up to two weeks. Appearance of solution and propofol content were assayed to determine the stability of studied samples. According to the analytical results listed in Table 2 and Table 3, the propofol emulsion in non-PVC soft bag was stable for 5 days when stored at ambient tempearture and in the light, at ambient tempearture and in the dark, and at 2-8°C in the dark. For long term storage, propofol emulsion in CRYOVAC® non-PVC soft bag was stable for 15 days when stored at 2-8°C in the dark.

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