Artikel Asli/*Original Article*

Preparation and Physical Stability Evaluation of Palm Oil-Based Nanoemulsion as a Drug Delivery System for Propofol
(Pembangunan dan Pemeriksaan Kestabilan Fizikal terhadap Formulasi Nanoemulsi Berasaskan Minyak Sawit sebagai Sistem Penghantar Ubat Propofol)

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ABSTRACT

The objective of this study was to develop a formulation for propofol injection at various concentrations (1 and 2%) using palm oil-based nanoemulsion as the carrier. The nanoemulsions were characterised by globule size distribution (Dv 90 value), zeta potential, pH and viscosity determination. The physicochemical stability and accelerated stability of the formulations were also evaluated. Stability studies were performed for 6 months at 4, 16, 25 and 40ºC storage temperatures. The propofol content was analysed by HPLC study. The characterisation result of propofol nanoemulsion 1 and 2% showed good globule size distributions in Dv 90 values of 284 ± 1.15 nm and 304 ± 1.20 nm and also stable zeta potential values of-43.37 ± 0.96 mV and -40.97 ± 1.36 mV, respectively. Accelerated test showed that the formulations have excellent stability with no physical changes observed after centrifugation, autoclaving at 121ºC for 15 mins, shaking for 12 hours and thermal cycling test. The stability studies indicated that propofol emulsion show good stability for 6 months when stored at 4 ± 1ºC and 16 ± 1ºC based on Dv 90 values, zeta potential, and pH readings. No changes in propofol concentrations were observed after 6 months storage. Overall, propofol in palm oil-based nanoemulsions as carrier was found to be stable and can be used as an alternative anaesthetic injection.

Keywords: Nanoemulsion; propofol; palm oil; medium chain triglyceride; stability

ABSTRAK

Penyelidikan ini bertujuan untuk membangun satu formulasi suntikan Propofol dengan mengguna nanoemulsi berasas minyak sawit pada berbagai kepekatan (1 dan 2%) sebagai pembawa. Evaluasi ke atas size globul, potensial zeta, pH dan kelikatan dilakukan kepada formulasi nanoemulsi. Profil kestabilan fizikokimia dan kestabilan dipercepatkan juga ditentukan. Kajian kestabilan dilakukan selama 6 bulan pada suhu 4, 16, 25 dan 40ºC. Pemeriksaan kandungan propofol dilakukan dengan menggunakan kajian kromatografi cecair prestasi tinggi. Hasil evaluasi terhadap nanoemulsi propofol (1 dan 2%) menunjukkan sebaran globul saiz Dv 90 masing-masing ialah 284 ± 1.15 nm dan 304 ± 1.20 nm dan nilai potensial zeta yang stabil (-43.37 ± 0.96 mV dan -40.97 ± 1.36 mV). Ujian dipercepatkan seperti kajian penggoncangan selama 12 jam, proses autoklaf pada suhu 121ºC selama 15 minit, proses pengemparan dan juga proses kajian penyimpanan pada suhu berbeza menunjukkan formulasi nanoemulsi yang stabil tanpa perubahan sifat fizikal. Kajian kestabilan juga menunjukkan formulasi nanoemulsi yang stabil berdasarkan nilai Dv 90, potensi zeta, dan pH apabila ianya disimpan pada suhu 4 dan 16ºC selama 6 bulan. Formulasi nanoemulsi juga menunjukkan kestabilan ke atas kandungan propofol selepas disimpan selama 6 bulan. Keseluruhan, nanoemulsi berasas minyak sawit menunjukkan formula yang stabil dan boleh dijadikan sebagai medium penghantar alternatif bagi propofol.

Kata kunci: Nanoemulsi; propofol; minyak sawit; trigliserida rantai sederhana; kestabilan

INTRODUCTION

Determination of an appropriate drug carrier is one of the main problems in pharmaceutical development especially for a drug which is slightly soluble in water. The ideal criteria for an appropriate carrier should be that it is non-toxic and able to increase the efficacy of the active compound which it is carrying. Lipid emulsion is one of the popular and potential carriers for drugs which are slightly soluble in water (Kawakami et al. 2000). Lipid emulsion are used as a source of calories for non-ambulatory patients due to its stability and non-toxic nature. Its potential to be used as vehicle for drug delivery was realised in the late nineties (Floyd 1999).

Nanoemulsions have various advantages as a drug delivery system since they are found to be non-toxic, non-irritant and are not harmful towards human and animal cells (Shah et al. 2010; Aboofazeli 2010). The use of nanoemulsions can eliminate the bad taste from the drug, reduce drug toxicity and increase stability of light sensitive

drugs (Sukanya et al. 2013). Nanoemulsion has been successfully used in cosmetic products and food technology as well as a drug carrier system (Gutierrez et al. 2007).

Propofol (2, 6-diisopropylphenol) is a drug which is commonly used to induce or maintain anaesthesia in the intensive care unit and in procedures involving outpatient care (Peterson et al. 2003; Baker and Mohamed 2005). Its positive characteristics include rapid onset, short duration of action and minimal side effects. In the current market, soybean oil is used as the oil source in the production of propofol emulsion (Date & Nagarsenker 2008).

Palm oil is one of the sources of long chain triglycerides (LCT) similar to soybean oil. Palm oil is obtained from the mesocarp of *Elaeis guineensis*. Malaysia and Indonesia account for 83 percent of palm oil production and 89 percent of global exports (Imoisi et al. 2015). Utilisation of palm oil in pharmaceutical preparations is still not fully explored (Zainol et al. 2012). Although a number of researchers have developed propofol formulations, there is no report about any development of a propofol injection using palm oil as one of the major ingredients. This study was conducted with the aim of developing a propofol injection using palm oil-based nanoemulsion or NEMS™ (Nanoemulsion Minyak Sawit) as the carrier.

Palm oil is relatively stable to free radical oxidation as compared to soybean oil. Natural antioxidants and high contents of monounsaturated fatty acids (such as oleic acid) as well as saturated fatty acids which are found in palm oil are the main contributing factors to its stability against free radical oxidation. Polyunsaturated oils such as soybean shows a relatively poor stability since it is easily oxidised, isomerised and polymerised (Ong 2002). Palm oil contains vitamin E, especially tocopherols and tocotrienol (Maarasyid et al. 2014). These natural antioxidants can delay the oxidation of the palm oil-based emulsions (Edem 2002), thus it may increase the stability of the propofol formulation under high temperature especially during the sterilisation process. The addition of middle chain triglyceride (MCT) (from coconut oil) to the formulation increases the metabolism of the fatty acids and reduces the toxicity of long chain triglyceride (LCT) found in palm oil (Jumaa & Muller 2001).

The present study focused on the evaluation of the physical characterisation and stability of propofol in palm oil-based nanoemulsion. Parameters of stability measured were globule size distribution, pH, and zeta potential value in normal storage condition and in various temperatures for 6 months. Stability profile in accelerated test conditions was also determined. The analysis of propofol content in the nanoemulsion was also conducted.

MATERIALS AND METHODS

MATERIALS

Palm Oil (refined palm olein) was obtained from local cooking oil (Seri Murni, FFM Sdn Bhd, Malaysia). Palm olein is one of the fractionation products from palm oil which has been refined, bleached and deodorized (RBD). MCT oil was purchased from Enersos (Pharma Sdn Bhd, Malaysia). Pure propofol, sodium hydroxide, glycerol and sodium oleic were purchased from Sigma-Aldrich Germany. Lipoid E-80® (egg lecithin) was purchased from GmbH, Germany. Diprivan®, a soybean-based propofol injection was supplied by Astra Zeneca Macclesfield, UK. Double distilled water was used for all preparations. Chemicals for high-pressure liquid chromatography (HPLC) were of HPLC grade and all other chemicals were of analytical grade.

PREPARATION OF PROPOFOL NANOEMULSIONS

The coarse emulsion was prepared by mixing propofol and an emulsifier (Lipoid E-80®) in an oil mixture consisting of palm oil and MCT oil. The mixture was then heated at 70°C to obtain a clear oil phase. The aqueous phase consisting of glycerol as a co-surfactant and sodium oleate as stabilizer were heated to 70°C and agitated until uniformly dissolved. The oil phase was then gently added to the aqueous phase with high speed shear mixing initiated using a homogeniser (Ultra Turrax® IKA) at 10,000 rpm for 6 mins to obtain the coarse emulsion. The propofol nanoemulsion was subsequently prepared by passing the coarse emulsion through a high-pressure homogenizer (APV 2000, Denmark) at 600 bar for eight cycles to get the final emulsion. The pH was adjusted to 8.7 ± 0.1 with NaOH 0.1 N. Finally, the nanoemulsion was transferred to vials which were then purged with nitrogen gas, sealed and sterilized by autoclaving (Hirayama, Japan) at 121°C for 15 minutes. The composition of different formulations of propofol nanoemulsion is shown in Table 1.

TABLE 1. Composition of different formulation of propofol nanoemulsion

Ingredients	Propofol 1% in NEMS™/g	Propofol 2% in NEMS™/g
Propofol	1	2
Oil Phase (Palm oil and MCT)	10	10
Lipoid E-80®	1.2	1.2
Glycerol	2.5	2.5
Sodium oleate	0.01	0.01
Water for injection until	100	100

CHARACTERISATION OF PROPOFOL NANOEMULSIONS

The globule size distribution of the propofol nanoemulsion was measured by laser diffraction using Mastersizer 2000 (Malvern Instruments Ltd., UK). Prior to measurement, samples (± 2 mL) were diluted with water to ± 800 mL. Measurements were made in triplicate. Zeta potential of propofol nanoemulsion droplets was measured using

the Zetasizer Nano-ZS (Malvern Instruments Ltd., UK). Samples were first diluted (1:150) with water and transferred to disposable cuvettes. Results used were the average of three measurements. Determination of pH was made using a pH meter (Mettler-Toledo GmbH, Switzerland). The electrode was thoroughly rinsed after every individual sample in order to avoid errors due to oil contamination of the electrode. The viscosity of propofol nanoemulsions (6.7 mL sample) was determined undiluted at 25°C using Brookfield Digital Rheomter (Model DVIII, Brookfield Engineering Laboratories Inc., USA) utilising the SC4-18 spindle. Viscosity values were analysed using Rheocalc V3.1-1 software.

ACCELERATED STABILITY TESTS

Centrifugation was performed at 3800 rpm/60 min in ambient temperature using the Hettich Zentrifugen Universal 32R (Germany) centrifuge. Autoclaving process was conducted using an autoclave (Hirayama, Japan) set at 121°C for 15 min.

Shaking test and thermal cycling test were performed as previously described (Han et al. 2001). Shaking test was done by using samples in unopened containers which were shaken using Unitronic OR (Spain) at 100 strokes per minutes in room temperature for 2, 4, 6, 8, 10, and 12 hours.

Thermal cycling test was conducted by incubating the nanoemulsion in a Pro-tech incubator (Malaysia) at 30°C for 8 hours and followed by cooling at 4–8°C for 16 hours. This cycle was repeated daily and samples were withdrawn at 7, 14, and 21 days. Globule size was determined using the Mastersizer 2000 (Malvern Instruments Ltd., UK). All experiments were performed in triplicate.

STABILITY TEST

Stability of the nanoemulsion was assessed by monitoring the changes in globule size, zeta potential and pH of the nanoemulsion at normal storage condition (4°C). Data was taken every week for 24 weeks. Stability tests were conducted on samples stored at various temperatures (i.e. 16, 25 and 40°C). Tests were conducted at time intervals of 0 h, 1, 3 and 6 months.

APPARATUS AND CHROMATOGRAPHIC CONDITION

The HPLC analysis was performed using the Waters Associates (Waters Corp., Milford, MA) HPLC system. The system consisted of a controller (Waters 600), in-line degasser, an auto sampler (Waters 2707) and a photodiode array detector (Waters 2998). Separation was achieved with a reversed phase ODS symmetry C18 (15 cm × 4.6 mm; 5 μm globules) column. Mixture of methanol and deionised water (80:20) was used as the mobile phase. Flow rate of 1 mL/min was maintained and the wavelength for detection was 276 nm.

ANALYSIS OF TOTAL PROPOFOL CONTENT

The concentration of propofol in each sample was determined with a constructed calibration curve with the concentration range between 100 to 500 μg/mL. The propofol standard was dissolved with methanol and filtered through a 0.45 μm membrane and transferred to the HPLC vials. The method on sample preparation was adapted from a previous study by Babl (1995). An amount of 100 μL of nanoemulsion was diluted to 5 mL using methanol as diluent and filtered through a 0.45 μm membrane. The filtrates (10 μL) were then subjected to HPLC analysis to estimate the amount of propofol in nanoemulsion.

STATISTICAL ANALYSIS

All the data were analysed using Statistically Package for Social Sciences (SPSS) version 16.0. Data were analyzed using independent group t-test to compare the value of sample with standard. Data were presented as average value and standard deviation (SD). All experiments were done in triplicate. The differences were considered to be significant at level of $p \leq 0.05$.

RESULTS AND DISCUSSION

In this study, the mixture of palm oil and MCT (from coconut oil) was used as the oil phase for the nanoemulsion. This mixture exhibited a very good physical parameters such as globule size distribution, pH and zeta potential value as compared to the commercially available Diprivan® 1% (Astra-Zeneca, United Kingdom). Palm oil is commonly used as cooking oil (Ahmad et al. 1996) and as an adjuvant for food preparations (Mukherjee & Analava 2009). Intravenous administration of palm oil-based nanoemulsion in combination with MCT from coconut oil has been shown to be non-toxic in rabbits (Jufri et al. 2012). Palm oil can be considered as one of the most versatile vegetable oils (Ahmad et al. 1996) and it has a great potencial to be used pharmaceutical product development. Egg lecithin was chosen for development of propofol nanoemulsion as they are shown to be non-toxic (Wabel 1998), natural and has been used in parenteral products. This surfactant could form a stable emulsion without any separation even after the autoclaving process (Yamaguchi et al. 1995).

In this study, Diprivan® 1% was chosen as a standard and compared with propofol formulation that consists of palm oil and MCT oil. Diprivan® 1% contains propofol and is known as the original formulation. This formula is composed of a fat emulsion consisting of 10% soybean oil containing long-chain triglycerides (LCTs) (Le Guen et al. 2014).

CHARACTERISATION OF THE PROPOFOL NANOEMULSION

The globule size measurements of propofol nanoemulsion showed slightly higher values when compared to Diprivan®, as shown in Table 2. Size measurements established are acceptable for a parenteral product. The acceptable droplet diameter range for a nanoemulsion is between 50-1000 nm, but the common size range targeted is usually between 100-500 nm (Shah et al. 2010). In this study, laser diffractometry method was used to analyse globule size distribution of the nanoemulsion. This method provides information on the percentage of globule size distribution of the nanoemulsions. The Dv 50 value describes the particle size below which 50% of the volume of droplets exists and the Dv 90 shows particle size below which 90% of the volume of droplets exists.

potential in the range of between -30 to -50 mV and with pH range of 6–9 represents a stable value for an emulsion (Luk & Tian 2007; Driscol et al. 2001). The pH readings for all propofol nanoemulsions in this study were more than 7 (Table 3). It is within the requirement for intravenous formulation in which it should ideally be neutral, but can reside within the range of 4–9 (Liu 2008). It has been reported that emulsions with pH in this range will reduce the possibility of hydrolysis to the emulsifying agent in the emulsion (Floyd 1999). Emulsion with phospholipids will be stable in an alkaline medium (Peeters et al. 2004). The viscosity value showed that there were no significant different on viscosity value between propofol 1% and 2% when compared to Diprivan® 1% (Table 4). All of data showed that the rheology of the emulsion followed Newtonian principle.

TABLE 2. Globule size distribution of propofol in NEMS™ compared with Diprivan® 1% ($n = 3$)

| Formulations | Laser Difractometry | | |
| | Globule Size Distribution/nm | | |
	Dv 50	Dv 90	Uniformity
Propofol 1% in NEMS™	193±0.60	284±1.15	0.24±0.01
Propofol 2% in NEMS™	198±1.00	304±1.20	0.26±0.01
Diprivan® 1%	188±0.60	269±1.00	0.24±0.01

Zeta potential of 1 and 2% propofol nanoemulsions measured were -43.37 ± 0.96 mV and -40.97 ± 1.36 mV, respectively (Table 3). The result showed that the propofol nanoemulsions were stable and in agreement with previous work. Floyd (1999) reported that the emulsion with pH more than 7 would usually have a zeta potential value between -40 to -50 mV. It has been reported that the zeta

TABLE 3. Zeta potential and pH value of propofol in NEMS™ compared with Diprivan® 1% ($n = 3$)

Formulations	Zeta Potential/mV	pH
Propofol 1% in NEMS™	-43.37±0.96	7.32±0.02
Propofol 2% in NEMS™	-40.97±1.36	7.52±0.02
Diprivan® 1%	-43.30±1.93	7.66±0.02

TABLE 4. Viscosity of propofol in NEMS™ compared with Diprivan® 1% ($n = 3$)

Formulations	Viscosity/cps
Propofol 1% in NEMS™	1.61±0.07
Propofol 2% in NEMS™	1.73±0.11
Diprivan® 1%	1.69±0.06

TABLE 5. Effect of storage time at various temperature for 6 months on Dv 90 (nm), zeta potential (mV), and pH value ($n = 3$)

| | Time | Dv 90/nm | | | Potential Zeta/mV | | | pH | | |
		16ºC	25ºC	40ºC	16ºC	25ºC	40ºC	16ºC	25ºC	40ºC
Propofol 1% in NEMS™	0 month	284.3±1.0	284.3±1.0	284.3±1.0	-43.4±0.96	-43.4±0.96	-43.4±0.96	7.32±0.02	7.32±0.02	7.32±0.02
	1 month	285.6±0.6	283.0±1.2	288.0±1.0	-44.3±0.49	-49.2±1.25	-42.4±0.30	7.31±0.01	7.29±0.01	7.09±0.01
	2 month	288.0±1.7	293.0±2.4	297.6±1.5	-43.5±0.72	-38.2±0.96	-48.3±0.44	7.30±0.01	7.24±0.01	6.93±0.01
	3 month	289.3±0.6	292.0±1.0	299.3±1.5	-43.3±0.36	-47.0±2.11	-39.6±1.36	7.30±0.02	7.18±0.01	6.69±0.02
	6 month	285.3±1.0	289.0±2.6	295.0±4.3	-41.4±1.76	-39.7±3.11	-39.5±0.67	7.26±0.01	6.91±0.01	6.36±0.01
Propofol 2% in NEMS™	0 month	304.3±0.6	304.3±0.6	304.3±0.6	-40.9±1.36	-40.9±1.36	-40.9±1.36	7.52±0.02	7.52±0.02	7.52±0.02
	1 month	303.3±0.6	297.7±1.0	299.6±1.5	-40.9±0.60	-38.3±0.84	-56.7±0.35	7.50±0.01	7.49±0.01	7.17±0.01
	2 month	306.6±1.2	305.3±0.6	309.3±1.5	-44.4±0.55	-37.9±0.24	-40.9±1.94	7.47±0.01	7.31±0.01	6.99±0.01
	3 month	308.0±1.0	308.3±1.0	318±2.2	-43.7±0.42	-42.8±1.48	-51.8±1.80	7.44±0.02	7.02±0.01	6.80±0.02
	6 month	304.6±2.5	310.3±1.5	309±1.0	-42.8±1.48	-47.4±1.22	-54.7±0.96	7.42±0.01	6.84±0.01	6.45±0.01

TABLE 6. Propofol content of propofol in NEMS™ compared with Diprivan® 1% ($n = 3$)

Formulations	Concentration of propofol/mgmL-1	% Recovery
Propofol 1% in NEMS™	10.09±0.04	100.90
Propofol 2% in NEMS™	20.05±0.15	100.24
Diprivan® 1%	10.08±0.05	100.08

ACCELERATED TEST

The results showed that there were no physical changes observed after centrifugation and autoclaving (Figure 1). The formula had good stability over 12 hours for the shaking test and over 21 days for thermal cycling test without any significant changes in globule size ($p > 0.05$) as shown in Figure 2 and 3.

The accelerated test was performed in order to ensure and evaluate the stability of freshly prepared propofol emulsions when stored in extreme conditions. The purpose of centrifugation was to compare the globule size before and after pressure was added to the system in which centrifugation can lead to phase separation in unstable emulsion system (Restu et al. 2015). Autoclaving test was conducted to evaluate the influence of high temperature on the formulations especially for products which require sterilization. It is important for an intravenous emulsion to be stable after the standard sterility process (Jumaa & Muller 1999). There was no significant difference in globule size of the formulations, while the pH value decreased. This can be due to the release of the free fatty acid in emulsion from oil phase or emulsifying agent. But the product still fulfilled the requirement for pH limits. Shaking test was done to enhance the interaction of each globule in emulsion and to investigate the stability of emulsion (Han et al. 2001). Whereas thermal cycling test was done to determine the stability of emulsions when stored in a place with fluctuating temperatures.
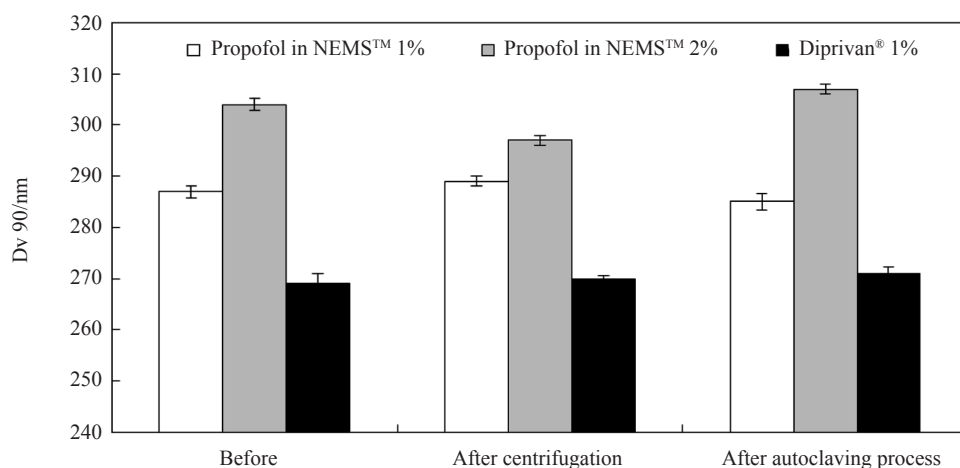

FIGURE 1. Dv 90 (nm) of the emulsions by laser diffractometry after centrifugation and autoclaving process ($n = 3$)
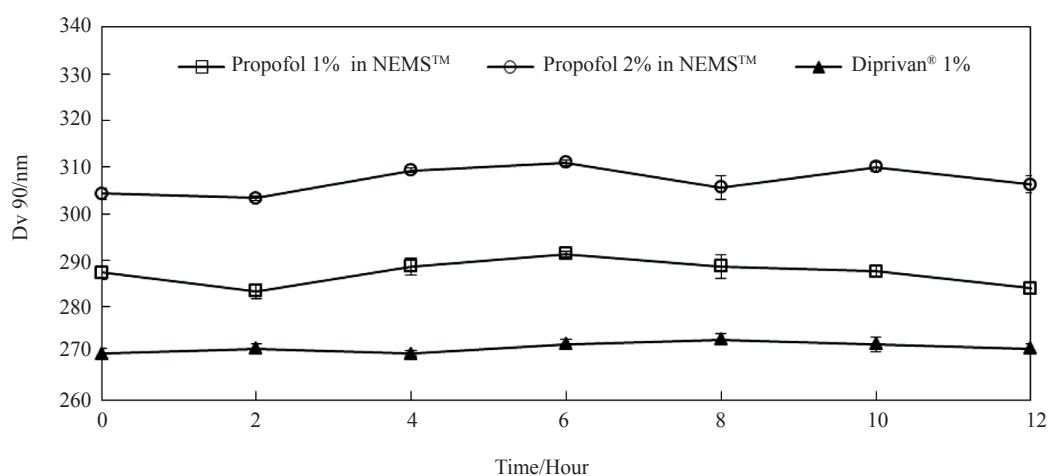

FIGURE 2. Dv 90 (nm) diameter of emulsions by laser diffractometry as a function of shaking time ($n = 3$)
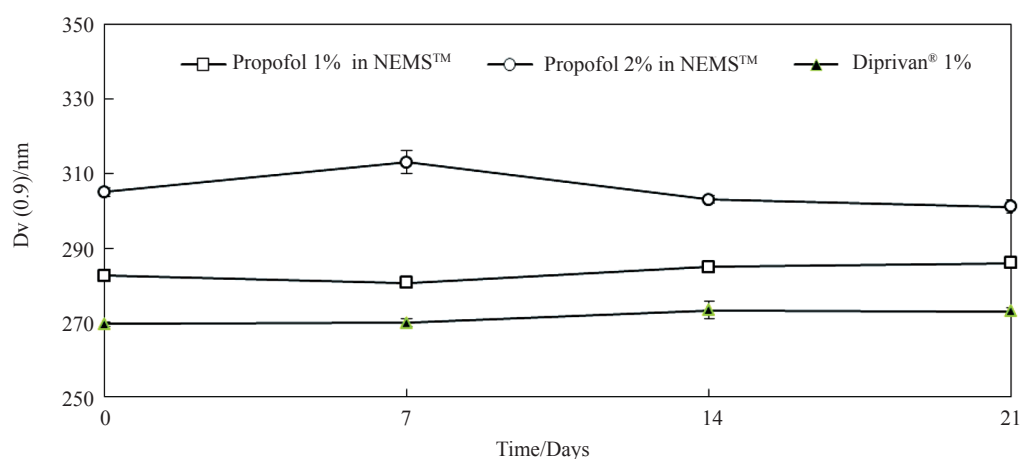
9

FIGURE 3. Dv 90 diameter of emulsions by laser diffractometry as a function of thermal cycling time ($n = 3$)

STABILITY TEST

In this study, formulations were stored at 4°C (refrigerated) for 6 months as intravenous emulsions are commonly stored at this temperature. The stability data established in this study showed that the propofol nanoemulsions developed were stable when stored at 4°C (Figure 4, 5 and 6). There were no significant difference ($p > 0.05$) for globule size, zeta potential and pH values of propofol nanoemulsions over a storage period of 6 months. Stability of the nanoemulsions when stored at various temperatures showed there were no significant difference on globule size, zeta potential and pH values when stored at 16°C. However, pH was reduced when stored at 25°C and 40°C (Table 5).

Stability of the dosage form is an important issue when nanoemulsions are to be used as drug carriers. The stability of the nanoemulsion during storage will ensure the content of the pharmaceutical active ingredient (i.e. propofol) in the dosage form is not compromised. The presence of natural antioxidants in palm oil may be the factor that enhances the stability of this vegetable oil-based nanoemulsion. Interestingly, palm oil has a high content of vitamin E in the forms of both tocopherol and tocotrienol with an unsaturated side chain that is not commonly found in other vegetable oils. Tocopherol is also less volatile such that it is able to persistently delay oxidation even in high temperatures (Imoisi 2015). Changes in globule size distribution and the zeta potential value when an emulsion is exposed to various conditions such as temperature will give a reliable picture of the stability profile of the emulsion.

The evaluation of the stability data showed that the physical character of the propofol nanoemulsions did not undergo any significant change during storage for 6 months in different storage conditions. However, there was a change in pH of the emulsion when stored at 25°C and 40°C. It might be due to hidrolysis process of egg lecithine and oil from the emulsions.when exposed to temperatures
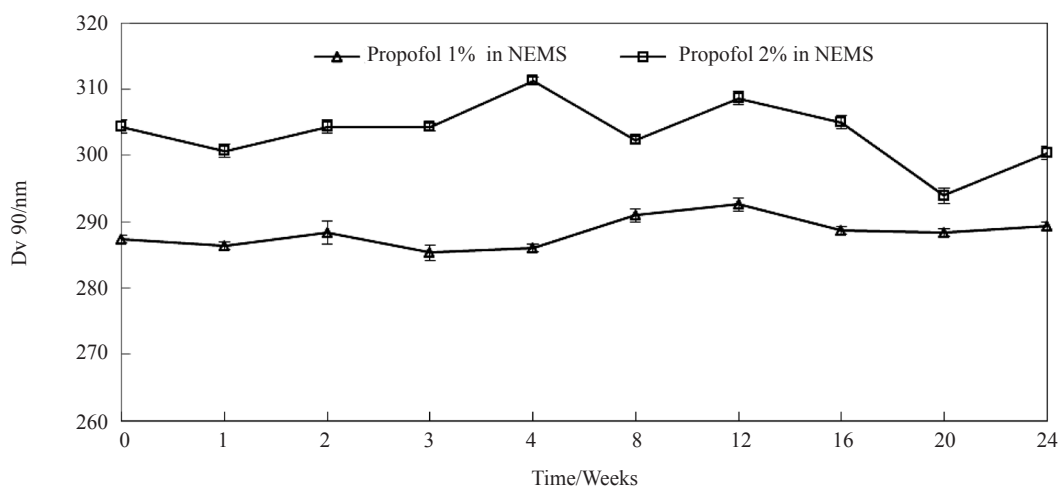

FIGURE 4. Effect of storage time (4°C) for 24 weeks on Dv 90 (nm) of propofol 1% and 2% in NEMS™ ($n = 3$)
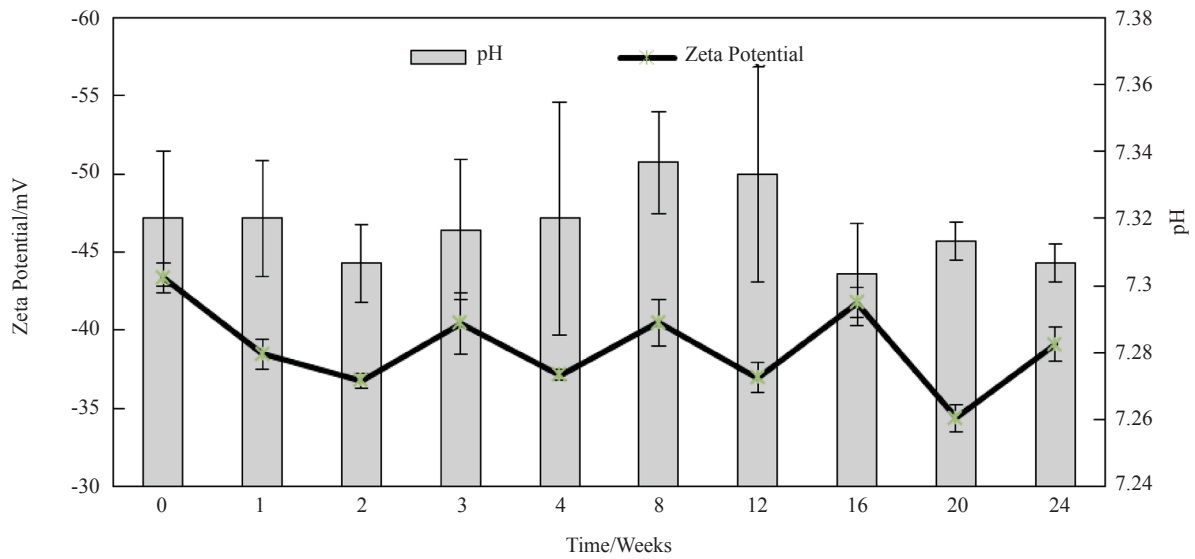
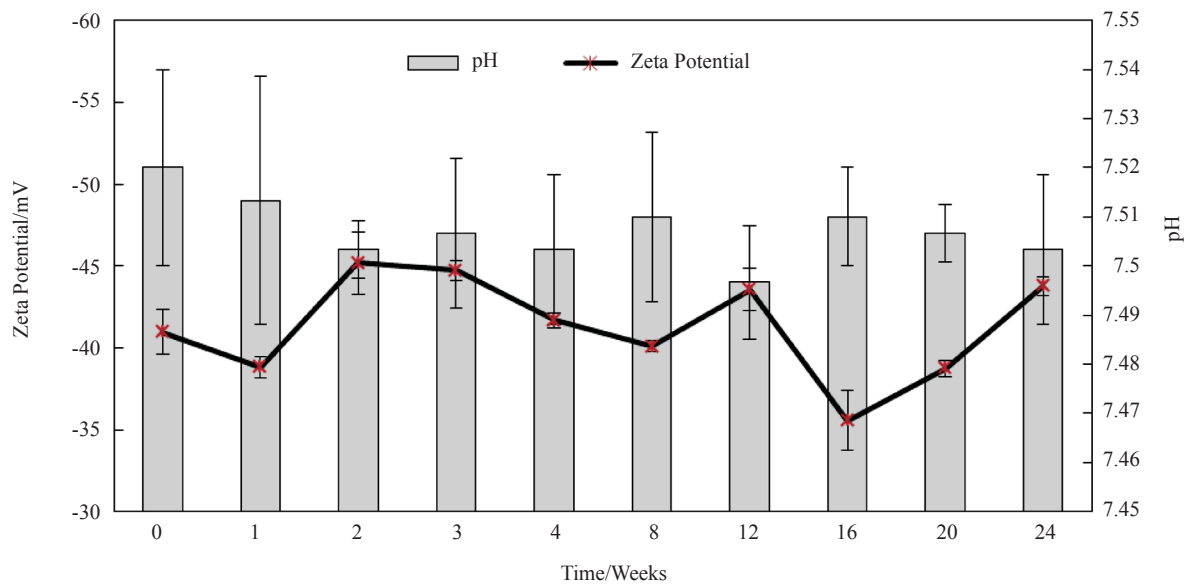FIGURE 5. Effect of storage time (4°C) for 24 weeks on zeta potential and pH value of Propofol 1% in NEMS™ ($n = 3$)

FIGURE 6. Effect of storage time (4°C) for 24 weeks on zeta potential and pH value of Propofol 2% in NEMS™ ($n = 3$)

above room temperature. High temperatures will change the phospatydil choline and phospatidyl ethanol amine into the lyso form and thus reduces the pH of the emulsions (Jiao & Diane 2005).

DRUG ANALYSIS

The aim of this test was to detemine the total propofol content in the nanoemulsion. The results showed that all of the propofol in NEMS™ formulations showed good recovery (Table 6). It is recommended that the content of propofol in an emulsion should be in the range of 98% to 102% (The United States Pharmacopeia 30, 2007). This

is very important to ensure that the dose is not clinically compromised and the propofol injection would give a maximal effect to patients.

CONCLUSION

The propofol nanoemulsions developed in this study demonstrated no change in physical stability when stored at room temperature for more than 6 months. The nanoemulsions were also stable after exposure to autoclaving process at 121°C for 15 min, centrifugation and shaking test for 12 hours. No changes in propofol

content of the nanoemulsions were found when kept at 4 and 16°C for 6 months. In conclusion, the intravenous propofol nanoemusion of 1 and 2% in palm oil-based nanoemulsin in combination with MCT oil (NEMS™) are stable and can be considered to be used as an alternative anaesthetic injection.

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13