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RESEARCH ARTICLE

Development of technology for producing submicron emulsion of propofol using a high-pressure homogenizer

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Abstract

Objectives. Currently, propofol emulsions are widely used in clinical practice due to their rapid action, low toxicity, and ease of administration, including control of anesthetic depth and rapid recovery of the patient following anesthesia. The market offers drugs from both foreign and domestic manufacturers containing imported pharmaceutical substances. The study set out to develop a technology for obtaining a fat emulsion of propofol for parenteral purposes using a high-pressure homogenizer based on pharmaceutical propofol obtained by alkylation and subsequent decarboxylation of 4-hydroxybenzoic acid, as well as to study the physicochemical properties of the obtained submicron emulsions.

Methods. A submicron propofol emulsion was prepared using a high-pressure homogenizer. pH was determined using a pH meter equipped with a combined glass electrode. Particle size and zeta potential of the submicron emulsion were determined on a laser particle analyzer using the dynamic and electrophoretic light-scattering methods, respectively. Quantitative propofol content in the resulting emulsion was determined using high-performance liquid chromatography.

Results. Optimal technological parameters of the high-pressure homogenization process were selected. The method of adding the oil phase directly into the high-pressure homogenizer is shown to entail lower time and energy costs as compared to the homogenization method involving a preliminary stage of obtaining a pre-emulsion. The physicochemical characteristics of the obtained submicron emulsions were subsequently determined to correspond to the characteristics required for the original drug Propofol-Lipuro®.

Conclusions. The proposed technology for obtaining a submicron propofol emulsion for parenteral use is based on dispersion of the aqueous and oil phases using a high-pressure homogenizer. As a result of the study, it was found that adding the oil phase directly into the high-pressure homogenizer at 20 MPa, including further dispersion at 60 MPa for 8 cycles, is optimal for obtaining a submicron propofol emulsion with the required characteristics.

Keywords

propofol, Propofol-Lipuro®, pre-emulsion, submicron emulsion, high-pressure homogenizer

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НАУЧНАЯ СТАТЬЯ

Разработка технологии получения субмикронной эмульсии пропофола с помощью гомогенизатора высокого давления

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Аннотация

Цели. В настоящее время в клинической практике активно используются эмульсии пропофола, обладающие быстрым действием, низкой токсичностью, легкостью введения, контролем глубины анестезии и быстрым восстановлением пациента после наркоза. На рынке представлены лекарственные препараты как иностранных, так и российских производителей, содержащие импортные фармацевтические субстанции. Целью данной работы являлась разработка технологии получения жировой эмульсии пропофола для парентерального применения с помощью гомогенизатора высокого давления на основе фармацевтической субстанции пропофола, полученной по методу алкилирования и последующего декарбоксилирования 4-гидроксибензойной кислоты, а также изучение физико-химических свойств полученных субмикронных эмульсий.

Методы. Субмикронную эмульсию пропофола получали с помощью гомогенизатора высокого давления. Значения pH определяли с использованием pH-метра, оснащенного комбинированным стеклянным электродом. Определение размера частиц и дзета-потенциала субмикронной эмульсии проводили на лазерном анализаторе частиц методом динамического светорассеивания и методом электрофоретического светорассеивания соответственно. Количественное содержания пропофола в полученной эмульсии определяли с помощью высоко эффективной жидкостной хроматографии.

Результаты. Подобраны оптимальные технологические параметры процесса гомогенизации высокого давления. Установлено, что методика введения масляной фазы напрямую в гомогенизатор высокого давления осуществляется с меньшими временными и энергетическими затратами по сравнению с методикой гомогенизации с предварительной стадией получения предэмульсии. Определено, что физико-химические характеристики полученных субмикронных эмульсий соответствуют характеристикам, предъявляемых оригинальному препарату Пропофол-Липуро®.

Выводы. Предложена технология получения субмикронной эмульсии пропофола для парентерального применения, основанная на диспергировании водной и масляной фазы с помощью гомогенизатора высокого давления. В результате проведенного исследования было установлено, что введение масляной фазы напрямую в гомогенизатор высокого давления при 20 МПа, а также дальнейшее проведение процесса диспергирования при 60 МПа в течение 8 циклов является оптимальным для получения субмикронной эмульсии пропофола с требуемыми характеристиками.

Ключевые слова

пропофол, Пропофол-Липуро®, предэмульсия, субмикронная эмульсия, гомогенизатор высокого давления

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INTRODUCTION

Propofol (2,6-diisopropylphenol) is a potent intravenous anesthetic widely used for administration and maintenance of anesthesia and for sedation in intensive care units [1–3].

2,6-Diisopropylphenol is an oily liquid at room temperature. The log*P* value for the 2,6-diisopropylphenol molecule, reflecting its hydrophobic properties, is 4.0; the distribution coefficient between octanol and water is 6761. These indices indicate the near complete insolubility of the molecule in aqueous solutions; consequently, it is necessary to use different carriers to administer propofol in the human body [4].

Among the significant pharmacological effects of Propofol are its ability to reduce cerebral blood flow, cerebral metabolic rate, and intracranial pressure. In addition, it acts as an antioxidant to remove free radicals and reduce lipid peroxidation, as well as activating gamma-aminobutyric acid (GABA) receptors [2, 3].

Clinical trials of a drug product in the form of an emulsion containing propofol were first conducted in 1977. However, due to the occurrence of anaphylactic reactions to polyethoxylated castor oil (Cremophor EL®), which was used as a solvent for the pharmaceutical substance, the product was withdrawn from the market. Nevertheless, research into the development of a drug based on 2,6-diisopropylphenol continued. In 1983 in Europe and later in 1986 in the United States, an oil-in-water emulsion was demonstrated to offer an anesthetic effect similar to that of a drug containing polyethoxylated castor oil, but without any anaphylactic reactions [5]. In 1989, Diprivan®, comprising a propofol-containing phospholipid emulsion for the intravenous induction and maintenance of general anesthesia in adult patients was brought to market in the United States. This drug product was the initial model for this type of medication [6].

Currently, there are various types of propofol-based emulsion drugs on the market, including Propofol-Lipuro® (Germany), Propofol-Egen® (Russia), Propofol-Binergy® (Russia), Propofol® (Korea), Propofol Fresenius® (Austria), Diprivan® (Italy). These drugs are produced in the form of 1–2% lipid emulsions for parenteral use[1],[2], which include soybean oil (5–10%), medium-chain triglycerides (0–5%), glycerol (2.25–2.5%), egg lecithin (1.2%). The surfactants used in these products are either 0.03% sodium oleate or the combination of 0.04–0.08% oleic acid and 0.005–0.011% sodium hydroxide [6–8].

In Russia, the production of drugs containing propofol as an active ingredient is based on the use of imported pharmaceutical substances. In the present study, we used a pharmaceutical substance of propofol obtained by the method of alkylation and subsequent decarboxylation of 4-hydroxybenzoic acid[3]. The structure of the obtained propofol substance was confirmed by ^{1}H nuclear magnetic resonance (NMR) spectroscopy [9].

The obtained submicron emulsions should meet the requirements in accordance with GPA.1.4.1.0007 of the 15th edition of the State Pharmacopoeia of the Russian Federation (SP RF XV)[4]: the average particle size should be less than 500 nm in accordance with GPA.1.4.2.0028 of the SP RF XV, while the zeta potential should be more than ±30 mV [10, 11].

The importance of maintaining a constant emulsion particle size is due to the necessity of ensuring the stability of the final dosage form [12]. Oils in the form of emulsions are better absorbed in the body because the absorption of oils into the gastrointestinal tract occurs only in the presence of surfactants [13]. However, particles larger than 300 nm may increase the risk of fat embolism. The stability of the emulsion is determined by the zeta potential. A decrease in the modulus of the electric charge value at the interface between the electric double layer and the dispersion medium can increase the rate of aggregation and coalescence [14].

Submicron emulsions can be produced using both high-energy and low-energy methods. High-energy methods generally involve the use of mechanical devices that generate high disruptive forces. Conversely, low-energy methods rely on changes in internal parameters that affect the hydrophilic-lipophilic balance of the systems. Although low-energy approaches are generally more effective and do not cause disruption or damage to encapsulated molecules, they have certain limitations related to the components used. In such cases, high concentrations of synthetic surfactants are required to achieve stable emulsions, which limits the scope of their application. In the context of obtaining emulsions for parenteral use, high-energy methods are favored, where mechanical dispersion is performed using high-pressure homogenizers, high-speed agitation, and

[1] Products. Binergia.ru. 2024. URL: https://binergia.ru/en/catalog/products.php. Accessed November 01, 2024.

[2] Propofol-Egen®. Armbio.bio. 2017. URL: https://armbio.bio/catalog/medications_contracts/non-inhalation_general_anesthetic_contract/propofol_egen. Accessed November 01, 2024.

[3] CN 106565424 A. Preparation method for high-purity propofol. Date of publication: 04.19.2017. URL: https://patentimages.storage.googleapis.com/36/be/e3/540d7228956dba/CN106565424A.pdf. Accessed September 12, 2024.

[4] The State Pharmacopoeia of the Russian Federation. 15th Ed. Moscow: 2023. URL: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/. Accessed December 12, 2024.

ultrasonic generators. The external load applied to the system (ultrasonic waves and pressure rise) breaks down droplets to the nanoscale to form stable thermokinetic stable emulsions [15–16].

Therefore, the present study sets out to develop a technology for obtaining a submicron emulsion of propofol for parenteral use using a high-pressure homogenizer, as well as to investigate the physicochemical properties of the obtained submicron emulsions.

MATERIALS AND METHODS

The following substances were used in the study: propofol substance obtained by alkylation and subsequent decarboxylation of 4-hydroxybenzoic acid (*Acros Organics*, Belgium); LIPOID Purified Soybean Oil (*LIPOID*, Germany); egg yolk phospholipid LIPOID E80 (*LIPOID*, Germany); LIPOID Sodium Oleate B (*LIPOID*, Germany); medium-chain triglyceride Lipoid MCT (*LIPOID*, Germany); glycerin (*ChemMed*, Russia); water for injection (SP RF XV, PA.2.2.0019).

The percentage of components (Table 1) in the submicron emulsion was chosen based on the original Propofol-Lipuro® 1% formulation[5].

In order to confirm the structure of the pharmaceutical substance propofol (Fig. 1) obtained by alkylation and subsequent decarboxylation of 4-hydroxybenzoic acid, ^{1}H NMR spectroscopy was used. Figure 2 summarizes the results of the analysis.

The ^{1}H NMR spectra of propofol measured in dimethyl sulfoxide DMSO-d_6 and deuterated chloroform $CDCl_3$ are consistent with the structure of 2,6-diisopropylphenol in accordance with literature data [9]. In the spectra of purified propofol samples, the signals of external impurities are absent.

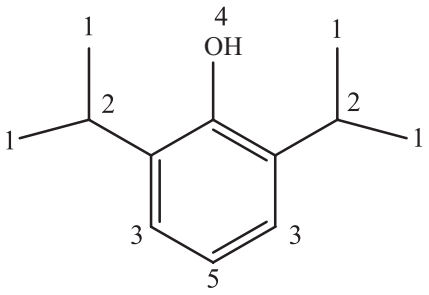

Fig. 1. Structure of the pharmaceutical substance propofol

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.01 (s, 1H, H4), 6.98–6.97 (m, 2H, H3), 6.81–6.77 (m, 1H, H5), 3.33 (hept., J = 6.9 Hz, 2H, H2) 1.16 (d, J = 6.9 Hz, 12H, H1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19–7.17 (m, 2H, H3), 7.05–7.01 (m, 1H, H5), 4.98 (br., 1H, H4), 3.28 (hept., J = 6.9 Hz, 2H, H2) 1.39 (d, J = 6.9 Hz, 12H, H1).

Preparation of the submicron emulsion consists of the preparation of aqueous and oil phases followed by their homogenization. In order to prepare the aqueous phase, we mixed exact weights of glycerol and sodium oleate with water for injection in beaker 1. Next the obtained

Table 1. Composition of the original drug Propofol-Lipuro®

Component	Quantitative content, wt %/wt
Oil phase	
Medium chain triglyceride	5
Soybean oil	5
Lecithin	1.2
Propofol	1
Water phase	
Glycerol	2.5
Sodium oleate	0.03
Water for injection (PA.2.2.0019.15)	Up to 100%

[5] Propofol-Lipuro® 10 mg/mL (1%). Bbraun.ru. B. Braun Melsungen AG; 2024. URL: https://www.bbraun.ru/ru/products/b/propofol-lipuro10mgml1.html. Accessed December 05, 2024.

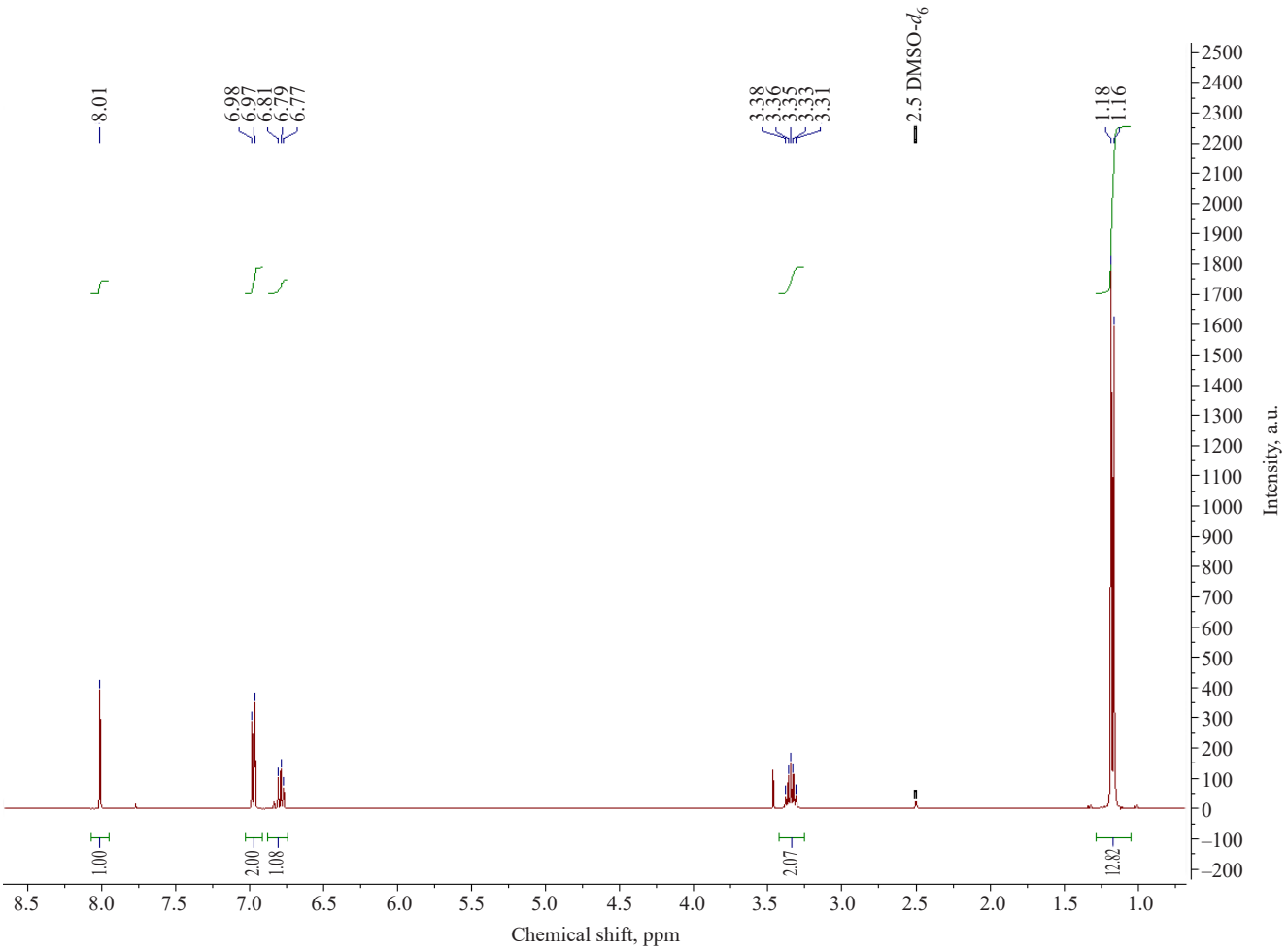

Fig. 2. ^{1}H NMR spectra of the pharmaceutical substance propofol obtained by alkylation and subsequent decarboxylation of 4-hydroxybenzoic acid

mixture was placed on a water bath at a temperature of 55–65°C and stirred using a ULABUS-2200D paddle top-driven stirrer (*ULAB*, Russia) until complete dissolution of the components.

Preparation of the oil phase was carried out as follows: accurate weights of medium-chain triglyceride and lecithin were measured into beaker 2, then the beaker was placed on a water bath at a temperature of 55–65°C and stirred with a paddle top-driven stirrer for 45 min. Exact weights of soybean oil and propofol were added to beaker 3 and stirred thoroughly for 3 min at the speed of rotation of the top-drive stirrer (500 rpm). After that, the contents of beaker 3 were added to beaker 2, and the resulting mixture was stirred for 5 min.

In this study, the submicron emulsion of propofol was obtained by high-pressure homogenization using two methods.

Method 1. Based on experimental studies [17–19], emulsion production was carried out with a preliminary stage of pre-emulsion preparation. The oil phase was added to the aqueous phase in portions with constant stirring using dispersing devices (ULABUS-2200D top-drive stirrer (*ULAB*, Russia), T25 BASIC ULTRA-TURRAX® disperser (*IKA*, Germany) and GL-P 500/30000 laboratory homogenizer (*Wiggens*, China)) for 5 min until a visually homogeneous system was obtained.

Then dispersion of pre-emulsion was carried out using a Donor-3 high-pressure homogenizer (*Donor*, Russia). Homogenization was carried out at pressures of 40, 60, 80, 100 MPa to obtain a product with the required degree of particle size.

Method 2. The aqueous phase was added into the Donor-3 high-pressure homogenizer. A syringe dispenser (*Hunan Beyond Medical Technology Co.*, China) was used to feed the oil phase into the aqueous phase at a pressure of 20 MPa. After the oil phase was completely added, the homogenization pressure was increased to 40, 60, 80, 100 MPa. Dispersion was carried out until a product with the desired particle size was obtained.

Homogenization in both cases was carried out under constant temperature control of the unit at 6°C. The temperature in the homogenization chamber was measured throughout the experiment using a GEMLUX GL-DT-11 thermometer (*GEMLUX*, China).

The pH was measured according to the pharmacopoeia article GPA 1.2.3.0004 "Ionometry" SP RF XV using pH-150MI pH meter (portable, with tripod) (*Izmeritel'naya tekhnika*, Russia) equipped with an ESC-10603/7 combined glass electrode (*Izmeritel'naya tekhnika*, Russia).

Determination of particle size and zeta potential of the submicron emulsion was carried out at the RTU MIREA Collective Use Center using a DelsaNano C laser particle analyzer (*Beckman Coulter*, USA).

The quantitative content of propofol in the final product was determined by the previously developed methodology using high-performance liquid chromatography on a Stayer system (*Aquilon*, Russia). A Luna column (*Phenomenex*, USA), 250 × 4.6 mm, filled with C18(2) sorbent with a particle size of 5 μm and a pore size of 10 nm was used. The mobile phase A was 0.276% solution of sodium phosphate monohydrate in purified water, pH of the solution was adjusted to 3.0 with 85% phosphoric acid, mobile phase B was acetonitrile.

The concentration of propofol ($C_{propofol}$) in the product (in g/L) was determined according to the following formula:

$$C_{propofol} = \frac{A_{PRL} \times W_{ST}}{A_{ST} \times 10},$$

where A_{PRL} is the area of propofol peak on the chromatogram of the test solution; A_{ST} is the area of propofol peak on the chromatogram of the standard solution; W_{ST} is the weight of propofol standard, g.

RESULTS AND DISCUSSION

The main criterion for selection of technological parameters of the submicron emulsion is compliance of the obtained product quality with the emulsion quality of the original drug Propofol-Lipuro® in terms of the following parameters: average particle size, particle size distribution by volume and number, zeta potential.

The original drug product is characterized by a narrow unimodal distribution of particle size by volume and number (Fig. 3). The average particle size in the emulsion of the original drug Propofol-Lipuro® was 186.2 ± 15.0 nm. The zeta potential value was 35 mV.

The first stage of the study consisted in studying the influence of the type of dispersing on the quality of the obtained propofol macroemulsion; the results are presented in Table 2.

As seen from the results, the propofol macroemulsion obtained when using the GL-P 500/30000 laboratory homogenizer is characterized by a smaller average particle size and the greatest stability, which is optimal for the high-pressure homogenization process further down the line.

Next, we selected the modes of high-pressure homogenization with a preliminary stage of pre-emulsion production according to Method 1. Table 3 shows the homogenization parameters, including the average particle sizes and distributions for the obtained emulsions.

According to the results of the experiments shown in Table 3, the following conclusions can be drawn. The lipid emulsions obtained in experiments 1–6, 9, 15, and 16 have a bimodal particle volume distribution, while those obtained in experiments 7, 8, 10–13, 14, 17 are characterized by a narrow unimodal distribution; however, the average particle size does not correspond to the average particle size of the original drug. The emulsions obtained

Table 2. Characteristics of propofol macroemulsion

Dispersing device type	Rotation speed of the dispersing device, rpm	Average particle size, nm	Description of macroemulsion
Overhead stirrer	2200	5350 ± 800	After 5 min of completion of the dispersion process, the formation of oil droplets on the surface of the macroemulsion was observed
Dispersant	25000	5520 ± 500	After 5 min of completion of the dispersion process, the formation of oil droplets on the surface of the macroemulsion was observed
Laboratory homogenizer	30000	2140 ± 500	No oil droplets were observed on the surface of the macroemulsion. The resulting macroemulsion was stable for 1 h

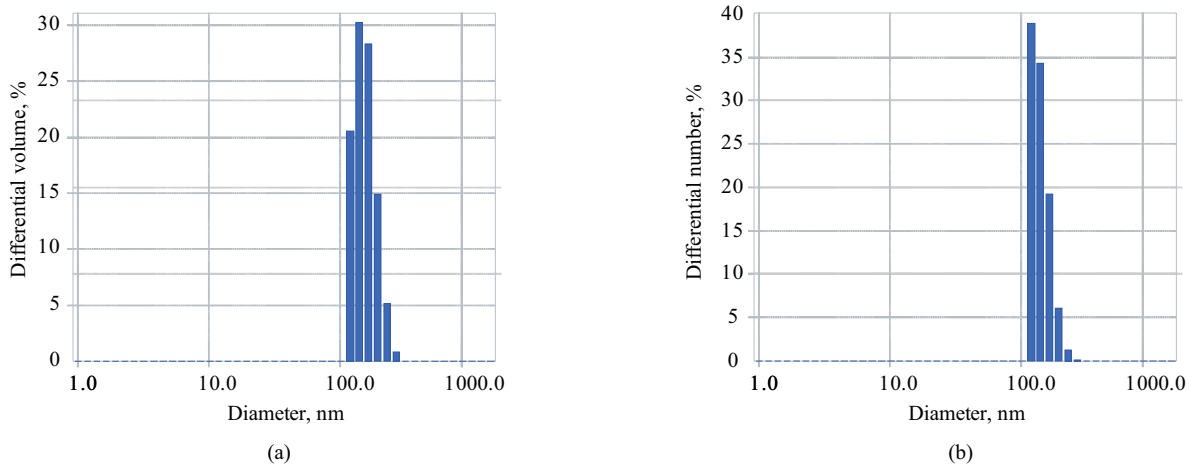

Fig. 3. Differential distribution of volume (a) and numerical (b) fraction of particles by size for a submicron emulsion of the original drug Propofol-Lipuro®

Table 3. Homogenization parameters and characteristics of the resulting emulsion according to method 1

No.	Temperature inside the unit, °C	Number of cycles at 40 MPa, pcs.	Number of cycles at 60 MPa, pcs.	Number of cycles at 80 MPa, pcs.	Number of cycles at 100 MPa, pcs.	Average particle size, nm	Particle distribution
1	24	2	–	–	–	655.8 ± 29.9	Bimodal
2	24	4	–	–	–	423.3 ± 23.0	Bimodal
3	23	6	–	–	–	334.9 ± 25.1	Bimodal
4	24	8	–	–	–	320.7 ± 17.9	Bimodal
5	23	10	–	–	–	276.4 ± 12.4	Bimodal
6	24	–	2	–	–	578.7 ± 15.8	Bimodal
7	24	–	4	–	–	439.3 ± 14.5	Unimodal
8	25	–	6	–	–	370.6 ± 21.6	Unimodal
9	25	–	8	–	–	307.5 ± 29.4	Bimodal
10	25	–	10	–	–	271.1 ± 11.2	Unimodal
11	25	–	–	2	–	264.7 ± 18.9	Unimodal
12	27	–	–	4	–	223.1 ± 23.1	Unimodal
13	27	–	–	6	–	215.1 ± 21.7	Unimodal
14	35	–	–	8	–	203.8 ± 15.4	Unimodal
15	34	–	–	10	–	198.8 ± 24.5	Bimodal
16	29	–	–	–	2	243.4 ± 12.3	Bimodal

Table 3. Continued

No.	Temperature inside the unit, °C	Number of cycles at 40 MPa, pcs.	Number of cycles at 60 MPa, pcs.	Number of cycles at 80 MPa, pcs.	Number of cycles at 100 MPa, pcs.	Average particle size, nm	Particle distribution
17	37	–	–	–	4	203.3 ± 16.8	Unimodal
18	42	–	–	–	6	191.9 ± 9.4	Unimodal
19	41	–	–	–	8	180.1 ± 11.2	Unimodal
20	42	–	–	–	10	174.0 ± 12.5	Unimodal

in experiments 18–20 have a unimodal particle distribution with the desired average particle size corresponding to the target range of values. At the same time, it was found that increasing the pressure and the number of homogenization cycles directly decreases the particle size of the final emulsion.

At the next stage of the study, we selected the modes of high-pressure homogenization in accordance with Method 2. The oil phase injection in all experiments was carried out at a pressure of 40 MPa. Table 4 shows the homogenization parameters, distribution and average particle sizes for the obtained emulsions.

According to the results of the experiments shown in Table 4, the following conclusions can be drawn. The lipid emulsions obtained in experiments 21–23, 26, 30, 33 have a bimodal distribution of particles by volume, while those obtained in experiments 24, 25, 27, 31, 34–40 are characterized by a narrow unimodal distribution; here, the average particle size does not correspond to the average particle size of the original drug. The emulsions obtained in experiments 28, 29, 32 show a unimodal distribution of particles with the desired average particle size, which corresponds to the target range of values of the original drug Propofol-Lipuro®.

Thus, both developed methods can be used to obtain a product having characteristics similar to those of the original Propofol-Lipuro® product. Nevertheless, Method 2 is preferred due to the reduced time of obtaining the final product. Moreover, the lower homogenization pressure used to achieve the required parameters (average particle size and particle size distribution by volume and number) results in a longer service life of the working parts of the device. It should be noted that heating of the internal chamber of the unit and the product at homogenization pressures over 80 MPa can lead to oxidation of components included in the emulsion.

Table 4. Homogenization parameters and characteristics of the resulting emulsion according to method 2

No.	Temperature inside the unit, °C	Number of cycles at 40 MPa, pcs.	Number of cycles at 60 MPa, pcs.	Number of cycles at 80 MPa, pcs.	Number of cycles at 100 MPa, pcs.	Average particle size, nm	Particle distribution
21	24	2	–	–	–	464.6 ± 25.2	Bimodal
22	24	4	–	–	–	371.7 ± 22.4	Bimodal
23	24	6	–	–	–	278.0 ± 23.4	Bimodal
24	24	8	–	–	–	267.1 ± 17.5	Unimodal
25	23	10	–	–	–	244.9 ± 18.1	Unimodal
26	25	–	2	–	–	249.2 ± 26.9	Bimodal

Table 4. Continued

No.	Temperature inside the unit, °C	Number of cycles at 40 MPa, pcs.	Number of cycles at 60 MPa, pcs.	Number of cycles at 80 MPa, pcs.	Number of cycles at 100 MPa, pcs.	Average particle size, nm	Particle distribution
27	24	–	4	–	–	225.3 ± 17.1	Unimodal
28	25	–	6	–	–	202.8 ± 15.8	Unimodal
29	26	–	8	–	–	185.9 ± 12.1	Unimodal
30	25	–	10	–	–	179.2 ± 24.5	Bimodal
31	25	–	–	2	–	210.6 ± 16.4	Unimodal
32	28	–	–	4	–	195.8 ± 11.9	Unimodal
33	29	–	–	6	–	181.3 ± 21.8	Bimodal
34	33	–	–	8	–	175.1 ± 11.4	Unimodal
35	33	–	–	10	–	172.0 ± 15.6	Unimodal
36	30	–	–	–	2	180.9 ± 14.4	Unimodal
37	37	–	–	–	4	160.8 ± 13.1	Unimodal
38	42	–	–	–	6	141.4 ± 10.6	Unimodal
39	44	–	–	–	8	144.5 ± 10.1	Unimodal
40	43	–	–	–	10	139.1 ± 11.8	Unimodal

The result obtained in experiment No. 29 was chosen as the most optimal. The obtained product is characterized by a narrow unimodal distribution of particle size by volume and number (Fig. 4); the average particle size in the submicron emulsion is 185.9 ± 12.1 nm.

Five series of propofol emulsion were then prepared in accordance with the conditions of experiment No. 29, for which the following parameters were determined: pH, quantitative propofol content, and zeta potential. The obtained results are presented in Table 5.

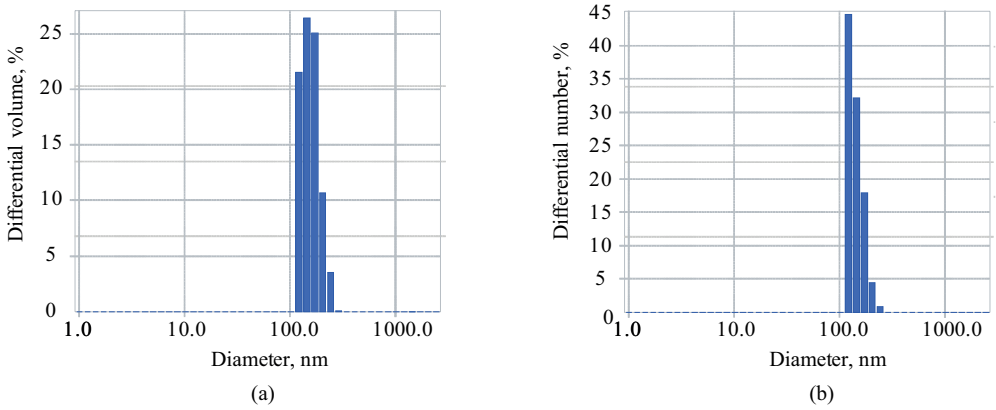

Fig. 4. Differential distribution of volume (a) and numerical (b) fraction of particles by size for a submicron emulsion obtained in experiment No. 29

Table 5. Results of determination of pH, quantitative content of propofol, and zeta potential in the obtained submicron emulsions

Series No. (number/date of manufacture)	Quantitative content, g/L	pH	Zeta potential, mV	Average particle size, nm	Particle distribution
01/15.05.2023	9.97	7.6	35.0	185.5 ± 1.31	Unimodal
02/16.05.2023	9.75	7.4	35.3	186.1 ± 1.42	Unimodal
03/17.05.2023	9.78	7.7	34.5	185.9 ± 1.26	Unimodal
04/20.05.2023	9.99	7.6	34.6	186.2 ± 1.50	Unimodal
05/21.05.2023	9.85	7.6	35.1	184.7 ± 1.38	Unimodal
Average	9.87 ± 0.13	7.60 ± 0.09	34.90 ± 0.42	185.68 ± 0.76	–

Analysis of the results confirms the possibility of obtain reproducible results by high-pressure homogenization.

The quality parameters (pH, quantitative propofol content and particle size) for 5 series of propofol emulsions correspond to the values required for this dosage form. The zeta potential value is 34.9 mV.

CONCLUSIONS

As a result of the conducted studies, a technology for obtaining a submicron emulsion of propofol for parenteral use using a high-pressure homogenizer was developed. The homogenization process carried out at a pressure of 60 MPa for 8 cycles is optimal for obtaining an emulsion with the required characteristics. A distinctive feature of this technology is the addition of the oil phase directly into the high-pressure homogenizer directly during the dispersion process.

The physicochemical characteristics of the obtained submicron propofol emulsion correspond to the original Propofol-Lipuro® product. The average value of propofol quantitative content in the 5 obtained series was 9.87 ± 0.13 g/L at a pH of 7.60 ± 0.09. The zeta potential is 34.90 ± 0.42 mV and the average particle size is 185.68 ± 0.76 nm. Particle distribution is unimodal for all obtained emulsions.

Authors' contribution

All the authors actively participated in the discussion, analysis, and design of the experiment, processing the obtained results, writing the text of the article and discussing it.

The authors declare no conflict of interest.

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