RESEARCH ARTICLE

The Physical Stability of Ciprofloxacin and Levofloxacin Parenteral Dosage Forms in the Polypropylene Plastic Container

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ABSTRACT

Polypropylene (PP) plastic container is often used as alternatives to glass containers in the primary packaging of parenteral dosage forms, but the usage poses a risk of interaction with the preparations during moist heat sterilization. Therefore, this study aimed to evaluate the physical stability of ciprofloxacin and levofloxacin parenteral dosage forms packaged in PP container after moist heat sterilization. Parenteral preparations were produced by dissolving the active ingredient ciprofloxacin lactate or levofloxacin hemihydrate in water for injection solvent. The solution obtained was then packaged in a 100 mL PP container and subjected to moist heat sterilization at 115°C for 30 minutes. The physical stability of the samples was then tested, including the weight, pH, clarity, number of particles, and sterility. The physical quality parameters before and after sterilization were compared. Data were analyzed using the paired t-test with significance at α 0.05. The results showed that parenteral preparations were sterile and maintained consistent physical stability after being sterilized, except for the number of particles. Furthermore, the number of particles in the sample met the standard requirements. Based on the results, ciprofloxacin or levofloxacin parenteral preparations in PP containers fulfilled the physical stability requirements after moist heat sterilization.

Keywords: Physical stability, Parenteral dosage forms, Polypropylene plastic container, Ciprofloxacin, Levofloxacin.

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INTRODUCTION

Ciprofloxacin and levofloxacin (Figure 1) are broad-spectrum fluoroquinolone antibiotics used to treat various infections.[1,2] In emergency conditions, such as severe infections and unconscious or uncooperative patients, parenteral dosage forms of these drugs offer a therapeutic option.[3-5] Furthermore, parenteral preparations are often given by injection and must be sterile and free from foreign particles. Several studies showed that intravenous administration ensured 100% bioavailability, allowing for a rapid physiological response.[6] Ciprofloxacin and levofloxacin are commercially available in parenteral dosage forms, typically packaged in glass containers.

Packaging serves the essential role of protecting parenteral preparations from environmental influences, microorganisms, and certain materials that can damage the quality. The packaging of pharmaceutical samples comprised the use of a container and closure. The container serves as a storage place for supplies, directly or indirectly related to the material at all times. Several studies showed that container and closure used in parenteral preparations must avoid physical or chemical interactions affecting the strength, quality, or purity of parenteral preparations. Furthermore, the storage space must not produce particles, be resistant to changes in pressure and temperature due to the sterilization process, have integrity during transportation and handling, protect against harmful radiation, be transparent for the process of observing particles or decomposition results, cost-effective, impermeable to the external environment, and possess a convenient shape for storage and transport.[7,8]

Glass container is commonly favored for parenteral preparations due to their inert nature, strength, transparency, and ease of sterilization.[7] However, these materials are susceptible to breakage and heavy mass, potentially increasing the distribution load.[9] To overcome these challenges, the use of

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plastic containers has been reported to serve as a viable option. The plastic container offers a lighter mass, flexibility, cost-effectiveness, water resistance, and mechanical strength and requires less storage space, facilitating easier distribution.[10] Plastic, a material widely used to make packaging, is composed of mixed materials containing polymers along with plasticizers, fillers, stabilizers, and other additives. These materials can be derived from thermoplastic or thermoset polymers, with thermoplastic softening when heated and hardening when cooled.[11]

Polypropylene (PP) is a thermoplastic polymer-derived container produced catalytically from propylene, with each carbon chain on the ring binding a methyl group. The molecular structure of PP presented in Figure 2 shows a crystal structure with a high level of stiffness, glass transition temperature (140–150°C), and melting point (160–166°C). PP can be molded into various shapes compared to other commercial thermoplastics.[12-14] This material also has the lowest density among plastic commodities and excellent chemical resistance, as well as can be processed through several methods, such as injection molding and extrusion. Furthermore, it is resistant to high temperatures and has good mechanical strength. PP has various advantages, including excellent resistance to dilute and concentrated acids, bases, alcohols, aldehydes, esters, aliphatic hydrocarbons, aromatic hydrocarbons, halogenation, and oxidants, with excellent heat stability. Several studies also reported that it had good transparency and could protect preparations against moisture and odors from the environment.[13,15] According to previous studies, PP also shows good moisture permease, compatibility with medicinal products, resistance to heat sterilization, and low gas absorption and permease capabilities, thereby minimizing interactions between the active ingredient and container.[7,16,17]

Moist heat sterilization, particularly through autoclaving, has been identified as the most effective method against various organisms.[18] This method helps to ensure high sterility levels with a sterility assurance level (SAL) of 10^{-6}, which is in the standard range.[7] In moist heat sterilization, there is often an increase in pressure, causing an increase in the autoclave temperature. Increased temperature can produce water vapor, which plays an essential role in the process of destroying microorganisms. However, increased temperature and pressure during the sterilization process pose several risks, including interaction between the preparation and the packaging, impact on the integrity and permeability of the packaging, and degradation of materials. The presence of these risks can affect the stability of the inventor, which is also influenced by the physicochemical characteristics of the active ingredients, excipients, packaging materials, sterilization methods, and environmental factors, such as temperature, humidity, air, and light. Several studies reported that packaging was one of the factors influencing the stability of preparations. Therefore, this study aims to evaluate the physical stability (organoleptic, weight, pH, clarity, and number of particles) of parenteral preparations of ciprofloxacin and levofloxacin packaged in PP plastic container after moist heat sterilization with an autoclave at 115°C for 30 minutes.

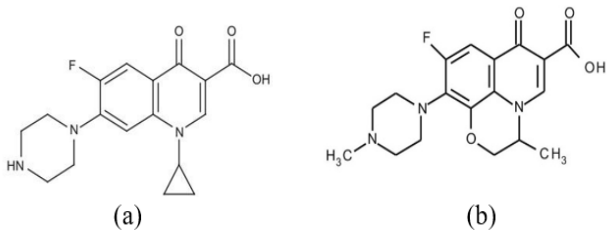

Figure 1: Molecule structure of ciprofloxacin (a) and levofloxacin (b)

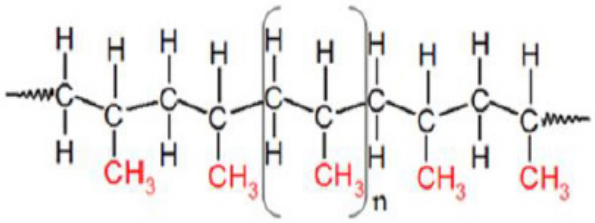

Figure 2: Molecule structure of polypropylene[7]

MATERIALS AND METHODS

Materials

The materials used in this study comprised ciprofloxacin lactate and levofloxacin hemihydrate injection grade from Shangyu Jingxin Pharmaceutical Co., Ltd.; HCl 37% (Merck Germany); NaCl pro analysis (Merck Denmark), water for injection (WFI) from PT. Satoria Aneka Industri, and a 100 mL PP plastic container from PT Satoria Aneka Industri. Furthermore, the sterility test media used were liquid thioglycolate media (merck), soybean-casein digest media (Merck), and *Staphylococcus aureus* bacteria.

Methods

Parenteral preparations of ciprofloxacin and levofloxacin

Parenteral preparations of ciprofloxacin and levofloxacin were made according to the formulas in Tables 1 and 2.

The active ingredient ciprofloxacin lactate or levofloxacin hemihydrate was dissolved in several WFI solvents, followed by the dissolution of isotonic agent NaCl. Furthermore, WFI was added to 90% of the final volume, and pH of the preparation was tested. The pH was then adjusted with 0.1 N HCl solution until a value of 4.0 ± 0.5 was obtained. WFI was added until the final volume was 100%, followed by filtration of the solution with a 0.45 µm membrane filter. The solution was filled into 100 mL PP plastic container, which was sterilized using the moist heat method with an autoclave (gravity displacement autoclave) at 115°C for 30 minutes.

Preparation Evaluation

Organoleptic

An organoleptic examination of the preparation was carried out visually regarding shape, odor, and color. Furthermore,

Table 1: Formula of ciprofloxacin parenteral

Substance	*Function*	*Level*
Ciprofloxacin lactate	Active ingredient	0.20%
NaCl	Isotonic agent	0.85%
HCl	pH *adjuster*	qs.
Water for injection (WFI)	Solvent	Ad 100 mL
pH 4.0 ± 0.5		

Table 2: Formula of levofloxacin parenteral

Substance	*Function*	*Level*
Levofloxacin hemyhidrate	Active ingredient	0.51%
NaCl	Isotonic agent	0.80%
HCl	pH adjuster	qs.
Water for injection (WFI)	Solvent	Ad 100 mL
pH 4.0 ± 0.5		

observations were made on the preparations before and after sterilization with three replications.

Clarity

Tests were carried out on preparations by shining light on the preparation container using a light intensity ranging from 100 and 350-foot candles. Furthermore, the PP plastic container was turned over slowly, and the visible particles were observed in a circular motion. Observations were made for 5 seconds from the source on a black and white background, namely 5 seconds each on the black and white part. The presence of particles in a container showed that the preparation was not clear. When no particles were visible, the particles were gently inverted and observed for heavy particles that were likely not to be suspended by agitation. Clarity tests were carried out on preparations before and after sterilization with three replications.[8]

Determination of preparation weight

The test was carried out by weighing the preparation on the Ohaus PA213 analytical balance before and after sterilization. This assessment test was carried out under the same temperature conditions with three replicates.[19]

pH test

The pH tests were carried out on preparations before and after sterilization using a pH meter GmbH Lab 850 and replicated three times.[8]

Number of particles

Testing the number of particles using a liquid particle counter (YIMA GWF-8JD) was carried out by preparing a sample in a container, followed by its transfer into a beaker glass. Subsequently, the dosage unit was mixed by inverting the unit 20 times, with sonication for approximately 30 seconds. The contents of the container were stirred slowly, and samples of 5 mL were taken in no less than three aliquots. The needle was used to pull the sample to ensure its flow into the syringe and passage through a sensor that detected the number of particles in the sample. The instrument was set to measure particles with sizes of $\geq$ 10 and $\geq$ 25 µm.[8]

Sterility test

A sterility test was carried out through direct inoculation by inserting the test sample into liquid thioglycolate media and soybean casein digest media. Furthermore, the samples in thioglycolate media were incubated at 30 to 35°C, and those in soybean casein digest media were incubated at 20 to 22°C. Due to the antibiotic activity of both preparations, dilution was carried out before the sterility test until a minimum concentration was obtained, which did not inhibit the growth of *S. aureus*. The dilution with the greatest concentration that could eliminate antibiotic activity was embedded in the sterility test medium. Sterility test results were then compared with control media for fertility and media sterility tests.[8]

Evaluation data on parenteral preparations of ciprofloxacin and levofloxacin, including weight, pH, and number of particles before and after moist heat sterilization, were analyzed using a paired t-test with α 0.05.

RESULT AND DISCUSSION

Organoleptic and Clarity

Parenteral preparations of ciprofloxacin and levofloxacin, packaged in a 100 mL PP plastic container and subjected to sterilization through the moist heat method in an autoclave at 115°C for 30 minutes, demonstrated an absence of leakage. This was consistent with Amarji *et al*., (2018) and Adejare (2021),[10,20] that PP plastic had good resistance to moist heat sterilization. Furthermore, the shape became more flexible and less rigid before being subjected to sterilization treatment. This was due to an increase in temperature and pressure in the container, causing plastic deformation during sterilization. PP plastic also had poor collapsibility properties[7], causing PP plastic to experience changes in shape after the use of autoclaving. According to Rynio *et al*. (2022),[21] moist heat sterilization at 121°C for 15 minutes on an aortic mold made of PP caused significant deformation. However, sterilization at 105°C for 3 hours did not cause changes in the shape of the aortic mold.[21] After moist heat sterilization, there was a deformation or change in the shape of the PP container, as shown in Figure 3.

The organoleptic examination results of the parenteral preparation before and after moist heat sterilization are presented in Table 3. Parenteral preparations of ciprofloxacin or levofloxacin showed that there were no changes in shape, odor, or color after the process, comparable to ciprofloxacin or levofloxacin preparation before sterilization.

Apart from organoleptic examination, clarity assessment was also carried out to observe the presence or absence of particulate matter, which could be seen visually after the sterilization process. Particulate matter could be formed due to the release of plastic container constituents into the preparation

or reactions between components in the preparation. However, both preparations remained clear after the process. This showed that moist heat sterilization with an autoclave at 115°C for 30 minutes did not affect the organoleptic and clarity of the preparation.

Figure 3: Ciprofloxacin (a) Levofloxacin (b) Parenteral preparations in PP containers before and after the sterilization process with moist heat 115°C for 30 minutes

Table 3: Organoleptic of parenteral preparations of ciprofloxacin and levofloxacin before and after moist heat sterilization by autoclaving at 115°C for 30 minutes

Organ oleptic	*Ciprofloxacin*		*Levofloxacin*	
	Before	*After*	*Before*	*After*
Form	liquid	liquid	liquid	liquid
Color	colorless	colorless	yellowish white	Yellowish white
Odor	odorless	odorless	odorless	odorless
Clarity	clear	clear	clear	clear

Physical Stability and Sterility of the Parenteral Preparation

The evaluation results of the physical stability and sterility of the parenteral preparation after moist heat sterilization are presented in Table 4. Furthermore, the preparation weight was tested to ensure that there was no reduction or increase in the preparation volume due to container leaks or the presence of water vapor. Moist heat sterilization produced water vapor as a sterilant to inactivate microorganisms. The weight examination of both ciprofloxacin and levofloxacin parenteral preparations showed no significant change, as determined by paired t-test analysis at a significance level (α) of 0.05. Based on the results, the process did not change the weight of both preparations. This showed that there was no leak in the container, leading to a decrease or increase in the volume of the preparations due to the entry of water vapor.

pH examination results showed that after the sterilization process, there was no significant change based on statistical analysis of the paired t-test at α 0.05. pH of the solution was adjusted since it can be affected by solubility and stability. Change in pH could occur during the sterilization process using heat.[22] The interaction between the components in the solution, the dissolving of gas, or the interaction between the solution and container could cause a significant change. Furthermore, changes in the preparation could have an impact on the solubility of the active ingredient and the chemical stability. Based on pH examination, moist heat sterilization did not affect the pH of the two preparations in the PP plastic container. The results were in line with Xuan *et al*., (2006)[19],

Table 4: Physical stability and sterility of ciprofloxacin and levofloxacin parenteral dosage forms before and after moist heat sterilization by autoclaving at a temperature 115°C for 30 minutes

Evaluation	*Replication*	*Ciprofloxacin*			*Levofloxacin*		
		Before	*After*	*Sig*	*Before*	*After*	*Sig*
Weight (g)	1	116.68	116.53	0.158	116.57	116.50	0.298
	2	116.91	116.62		117.23	116.29	
	3	117.08	117.04		116.05	115.89	
pH	1	4.02	4.02	0.423	4.01	4.01	0.423
	2	4.01	4.01		4.02	4.02	
	3	4.01	4.02		4.01	4.03	
Particle size ≥ 10 µm	1	466	494	0.001*	398	416	0.001*
	2	462	492		386	406	
	3	460	490		384	402	
Particle size ≥ 25 µm	1	74	98	0.034*	32	46	0.034*
	2	76	96		34	50	
	3	80	92		34	42	
Sterility	1	-	Sterile		-	Sterile	
	2	-	Sterile		-	Sterile	
	3	-	Sterile		-	Sterile	

*significant difference ($p < 0.05$)

which examined an infusion preparation of morphine sulfate in 0.9% NaCl packaged in PP plastic container. The results showed that there were no variations in organoleptic, clarity, weight, and pH after the sample was sterilized.[19]

Instead of clarity, parenteral preparations number and size of particles must meet the requirement. The foreign particle source can be from active pharmaceutical ingredients, additives, WFI solvents, or loose components of the container in the sample. The results (Table 4) showed that before the sterilization process, the number of particles with a size of ≥10 µm in the ciprofloxacin and levofloxacin preparation was approximately 460 to 466 particles/container and 384 to 398 particles/container, respectively. Meanwhile, those with a size of ≥25 µm in ciprofloxacin and levofloxacin samples were approximately 74 to 80 particles/container and 32 to 34 particles/container, respectively. After the sterilization process, both preparations showed a significant increase based on paired t-test analysis at α 0.05. However, this increase in number was within the requirement. The limit for the particle number in small volume parenteral (SVP) preparations with a size of ≥10 µm was stated to be a maximum of 6000 particles/container, while for a size of ≥25 µm, a maximum of 600 particles/container was recommended.[8]

The increase in the particle number after the moist heat sterilization process was possibly caused by the release of particles from PP plastic container and rubber cap into the preparation. This could occur due to the crystallization and physical changes in PP, causing PP container can become more brittle.[23] According to Liang *et al.* (2022), sterilization by autoclaving at 121℃ for 30 minutes on disposable surgical masks causes the release of microplastics (< 5 mm) and nanoplastics (1–1000 nm) in water.[24] The disposable surgical mask used was made from a mixture of materials containing PP plastic. The results showed that masks sterilized by autoclaving led to the release of 400 ± 8 to 978 ± 46 microplastic and 1.2 ± 0.27 × 10^9 to 1.86 ± 0.26 × 10^9 nanoplastic.[24] Furthermore, Hernandez *et al*., (2019) and Ranjan *et al*. (2020) showed that autoclaving and high temperatures increased the release of microplastics from plastic materials.[25,26]

The sterility test of both parenteral preparations after moist heat sterilization was carried out to ensure the samples were sterile. The sterility test was carried out by direct inoculation methods after dilution of ciprofloxacin and levofloxacin preparation to inactivate the antibacterial activity of both antibiotics. Minimum inhibitory concentration (MIC) test for ciprofloxacin and levofloxacin was obtained at levels of 2 x 10^{-3} and 5 x 10^{-3} mg/mL, respectively. Dilution at levels of 2 x 10^{-4} and levels of 5 x 10^{-4} for ciprofloxacin and levofloxacin successively were able to eliminate the antibiotic activity, as shown by the absence of clear zones on the nutrient agar media. Sterility test results of the samples in thioglycolate and soybean casein digest media tests showed that both parenteral preparations of ciprofloxacin and levofloxacin were sterile after moist heat sterilization by autoclaving at 115℃ for 30 minutes.

CONCLUSION

In conclusion, the use of PP plastic primary packaging in parenteral preparations of ciprofloxacin and levofloxacin could maintain the physical stability, including organoleptic, clarity, weight, and pH of the dosage solution, but the number of particles increased in the required limits. Furthermore, ciprofloxacin and levofloxacin parenteral preparations in PP container met the physical stability requirements after moist heat sterilization at 115°C for 30 minutes.

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