

Physicochemical stability of nefopam and nefopam/droperidol solutions in polypropylene syringes for intensive care units

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ABSTRACT

Introduction Nefopam has been reported to be effective in postoperative pain control with an opioid-sparing effect, but the use of nefopam can lead to nausea and vomiting. To prevent these side effects, droperidol can be mixed with nefopam. In intensive care units, high concentrations of nefopam and droperidol in syringes can be used with a continuous flow.

Objectives The first objective of this work was to study the physicochemical stability of a nefopam solution 2.5 mg/mL diluted in NaCl 0.9% in polypropylene syringes immediately after preparation and after 6, 24 and 48 hours at room temperature. The second objective was to study the physicochemical stability of mixtures of nefopam 2.5 mg/mL and droperidol 52 µg/mL diluted in NaCl 0.9% in polypropylene syringes at room temperature over 48 hours.

Materials and methods Three syringes for each condition were prepared. For each time of analysis, three samples for each syringe were prepared and analysed by high performance liquid chromatography coupled to photodiode array detection. The method was validated according to the International Conference on Harmonisation Q2(R1). Physical stability was evaluated by visual and subvisual inspection (turbidimetry by UV spectrophotometry). pH values were measured at each time of analysis.

Results Solutions of nefopam at 2.5 mg/mL and the mixture of nefopam 2.5 mg/mL with droperidol 52 µg/mL, diluted in NaCl 0.9%, without protection from light, retained more than 90% of the initial concentration after 48 hours storage at 20–25°C. No modification in visual or subvisual evaluation and pH values were observed.

Conclusion Nefopam solutions at 2.5 mg/mL and the mixture of nefopam 2.5 mg/mL with droperidol 52 µg/mL diluted in NaCl 0.9% were stable over a period of 48 hours at room temperature. These stability data provide additional knowledge to assist intensive care services in daily practice.

INTRODUCTION

Nefopam is a centrally acting non-opioid analgesic drug.¹ It has been reported to be effective in postoperative pain control with an opioid-sparing effect. The use of opioids is often associated with a high incidence of postoperative nausea and vomiting.² However, nefopam itself can induce postoperative nausea and vomiting.³ In our hospital, to prevent these side effects, droperidol is mixed with nefopam solutions in a polypropylene syringe. Droperidol is a dopamine D₂ receptor antagonist in the chemotrigger zone, in the area postrema, which gives it

a potent antiemetic effect. This drug is indicated to prevent and treat postoperative nausea and vomiting. The usual dose of droperidol per dose is 1.25 mg and repeated doses may be given every 6 hours as required⁴; the maximum daily dose of nefopam should not exceed 120 mg.⁵

In clinical practice in intensive care units, nurses use a final volume of 48 mL in syringes to achieve an accurate flow rate of 2 mL/hour over 24 hours. They often use high concentrations of drug solutions with a minimum volume to avoid fluid overload. In our hospital, the maximum daily dose of nefopam (120 mg) is usually mixed with droperidol in a syringe with a final volume of 48 mL, resulting in concentrations of nefopam of 2.5 mg/mL and of droperidol of 52 µg/mL.

In the literature, to the best of our knowledge, no stability or compatibility study of a mixture of nefopam and droperidol or a nefopam solution in polypropylene syringes has been published. McClusey *et al* studied the stability of a droperidol solution at 0.625 mg/mL in 0.9% sodium chloride (NaCl 0.9%) in polypropylene syringes and determined 180-day stability at 23–27°C when protected from light.⁶

The spontaneous degradation of nefopam leads to a diol which is the major degradation compound of this analgesic.⁷

The first objective of this work was to study the physicochemical stability of a nefopam solution at 2.5 mg/mL diluted in NaCl 0.9% in polypropylene syringes immediately after preparation and after 6, 24 and 48 hours at room temperature. The second objective was to study the physicochemical stability of a mixture of nefopam at 2.5 mg/mL and droperidol at 52 µg/mL diluted in NaCl 0.9% in polypropylene syringes at room temperature over 48 hours.

MATERIALS AND METHODS

Chemicals and reagents

Monopotassium phosphate KH₂PO₄ (Merck, batch: AM09735277618), orthophosphoric acid 85% (VWR Chemicals, batch: 15D200503), heptane sulfonic acid sodium salt (VWR Chemicals, batch: 18E184103), trimethylamine (VWR Chemicals, batch: 14J280506) and acetonitrile (VWR Chemicals, batch: D7G058267G, D5N045046A) were used for the mobile phase. Hydrochloric acid 1.0M (VWR Chemicals, batch: 17110005), hydrochloric acid 0.1 M (VWR Chemicals, batch: 17110001), sodium hydroxide 1.0M (VWR Chemicals, batch: 17110003), sodium hydroxide 0.1 M (VWR Chemicals, batch: 17110001) and hydrogen peroxide



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30% (Merck; batch: K48743810713) were used. Water for chromatography was obtained from a reverse osmosis system (Millipore Iberica, Madrid, Spain). Nefopam 20 mg/2 mL solution for infusion concentration (Medisol, batch H1030), droperidol 1.25 mg/1 mL (Aguettant, batch 4303323) and 0.9% NaCl 500 mL in glass vials (Lavoisier, batch: 8F390) were used for the validation of the analytical method and for the stability study.

Preparation of test solutions

For the preparation of a nefopam solution at 2.5 mg/mL, six ampoules of nefopam at 20 mg/2 mL were used and completed with 0.9% NaCl in polypropylene syringes to obtain a final volume of 48 mL. For the preparation of a mixture of nefopam at 2.5 mg/mL and droperidol at 52 µg/mL in polypropylene syringes, six ampoules of nefopam at 10 mg/mL and two ampoules of droperidol at 1.25 mg/mL were used and then diluted with 0.9% NaCl to obtain a final volume of 48 mL. These solutions were stored in polypropylene syringes (BD Plastipak, 50 mL Luer-lok batch: 1808208). Three syringes were prepared for the two conditions. The syringes were stored at room temperature (20–25°C), not protected from light.

HPLC assay

Nefopam solutions and the nefopam/droperidol mixture were analysed by a stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) method with photodiode array (PDA) detection.

The HPLC system consisted of an ELITE LaChrom VWR/Hitachi plus autosampler, a VWR PDA detector L-2455 and a VWR L-2130 HPLC pump. Data were acquired and integrated using EZChrom Elite (VWR, Agilent). The column used was LiChrospher 100 RP-18, LiChroCART 125–4, 12.5 cm length, 5 µm particle size (Analytical Chromatography, Merck).⁸ The mobile phase consisted of 25% acetonitrile and 75% phase A, which is composed of 25% KH₂PO₄ buffer at 0.2 M with 0.01 M heptane sulfonic acid sodium salt and 1 mL/L trimethylamine, adjusted to pH 3.0 with orthophosphoric acid 85%.

The flow rate was set at 2 mL/min with an injection volume of 10 µL. The detection wavelength was set at 225 nm for nefopam and 246 nm for droperidol. The temperature of the injector was set at 15°C and the temperature of the column oven at 30°C. The calibration curve was constructed from plots of peak area versus concentration. The linearity of the method was evaluated at five concentrations (nefopam: 0.75, 1.0, 1.25, 1.5 et 1.75 mg/mL; droperidol: 15, 20, 25, 30 and 35 µg/mL).

A mixture of nefopam 2.5 mg/mL and droperidol 50 µg/mL was prepared and diluted in ultrapure water. This mixture was used to realise standard curves by dilution with ultrapure water. The intra-day reproducibility was evaluated as recommended by the International Conference on Harmonisation (ICH) Q2 (R1)⁹ using three determinations for each concentration at (nefopam/droperidol) 0.75 mg/mL/15 µg/mL, 1.25 mg/mL/25 µg/mL and 1.75 mg/mL/35 µg/mL. For inter-day precision, three

determinations for each concentration at (nefopam/droperidol) 0.75 mg/mL/15 µg/mL, 1.25 mg/mL/25 µg/mL and 1.75 mg/mL/35 µg/mL were prepared and assayed daily on three different days.

Evaluation of the stability in the autosampler was performed. Solutions of nefopam and droperidol diluted in ultrapure water were stored in the autosampler at 15°C. Chemical stability was evaluated at different times up to hours.

The diode array detector allows the evaluation of the UV spectrum of the chromatographic column effluent every 0.4 s, thus allowing evaluation of the UV purity of an eluting peak. Variations in the UV spectrum over the elution profile of the peak of interest would indicate that the peak is contaminated, that the analytical method does not separate nefopam and droperidol from their degradation products, and that the method is therefore unsuitable.¹⁰

The stability-indicating capability was evaluated by analysing forced degraded nefopam solutions and droperidol solutions.

Acidic conditions

For nefopam, 1 mL of a 5.0 mg/mL nefopam solution prepared in ultrapure water was diluted with 1.0 mL HCl 0.2 M, stored for 24 hours at 80°C, neutralised by 1.0 mL NaOH 0.2 M and diluted with 1 mL ultrapure water to obtain a theoretical concentration of 1.25 mg/mL.

For droperidol, 1 mL of a 125 µg/mL droperidol solution prepared in ultrapure water was diluted with 1.0 mL HCl 0.1 M or HCl 0.2 M, stored for 24 hours at 80°C, neutralised by 1.0 mL NaOH 0.1 M or NaOH 0.2 M, respectively, and diluted with 1.0 mL ultrapure water to obtain a theoretical concentration of 31.25 µg/mL. Another batch was prepared by adding 1.0 mL HCl 1 M at 1 mL of a 125 µg/mL droperidol solution for 1, 2 and 4 hours and diluted with 1.0 mL NaOH 1 M and 1.0 mL ultrapure water.

Alkaline degradation

For nefopam, 1 mL of a 5.0 mg/mL nefopam solution prepared in ultrapure water was diluted with 1.0 mL NaOH 0.01 M for 5 min, neutralised by 1.0 mL HCl 0.01 M and diluted with 1.0 mL ultrapure water to obtain a theoretical concentration of 1.25 mg/mL.

For droperidol, 1 mL of a 125 µg/mL droperidol solution prepared in ultrapure water was diluted with 1.0 mL NaOH 0.1 M, stored for 24 hours at 80°C, neutralised by 1.0 mL HCl 0.1 M and diluted with 1.0 mL ultrapure water to obtain a theoretical concentration of 31.25 µg/mL.

Oxidative degradation

One mL of a 5.0 mg/mL nefopam solution and 1 mL of a 125 µg/mL droperidol solution were diluted with 1.0 mL H₂O₂ 3.0%, respectively, stored at 20–25°C for 1 hour and diluted with 2.0

Table 1 Results of the validation of the analytical method of nefopam and droperidol

	Equation of calibration curve	Determination coefficient (R ²)	Intra-day (RSD)	Intermediate precision (RSD)
Nefopam	y=36 111.36 x – 770 270.3	0.9998	(0.07–0.91%)	0.75 mg/mL: 0.60% 1.25 mg/mL: 0.69% 1.75 mg/mL: 0.54%
Droperidol	y=47 941.85 x – 63 531.5	0.9998	(0.17–2.68%)	15 µg/mL: 1.44% 25 µg/mL: 1.52% 35 µg/mL: 0.73%

mL ultrapure water to obtain a theoretical concentration of 1.25 mg/mL and 31.25 µg/mL, respectively.

Heat degradation

A solution of 1.25g/mL nefopam and a solution 31.25 µg/mL droperidol were exposed to a temperature of 80°C for 24 hours.

Light degradation

A solution of 1.25 mg/mL nefopam and a solution of 31.25 µg/mL droperidol were stored under a sun-like spectrum lamp at 254 nm (Vilbert Lourmat) for 75 min and 10 min, respectively.

Sample dilution for analysis by RP-HPLC

At each time of analysis, 5.0 mL were removed from each syringe. The solutions were diluted before analysis with ultrapure water to obtain a concentration of 1.25 mg/mL for nefopam and 25 µg/mL for droperidol.

Samples were prepared in triplicate for each syringe. After dilution, each sample was analysed by RP-HPLC. This process was repeated after 6, 24 and 48 hours. Total run time was set at 17 min. We adapted the analysis time after forced degradation. The analysis time was 30 min but no peak of degradation was observed after 14 min during the forced degradation.

Chemical stability was defined as not less than 90% of the initial nefopam and droperidol concentration and in relation with the evolution of potential degradation products.^{9 11}

pH measurement

pH measurement was performed using a Bioblock Scientific pH meter. Analysis was carried out for each concentration and each solvent after preparation and after 6, 24 and 48 hours. pH values were considered to be acceptable if they did not vary by more than 1.0 pH unit from the initial measurement.¹⁰ We measured pH for each syringe, for each condition.

Determination of physical stability

Physical stability was defined as the absence of particulate formation, haze, colour change and gas evolution.¹² The samples were visually inspected against a white/black background with unaided eye at each analysis time. The subvisual aspect was assessed using a Safas Monaco UV mc² spectrophotometer. The absorbance was measured at 350, 410 and 550 nm.¹²

RESULTS

RR-HPLC

Calibration curves for both drugs were linear. The results of the validation of the analytical method are presented in table 1.

For the evaluation of the stability in the autosampler, solutions were stable with a degradation rate less than 0.5% for each molecule during 24 hours.

The UV spectral purity of the nefopam peak in chromatograms of the degraded samples was compared with the spectrum of the undegraded sample of nefopam. The same process was performed for droperidol. These procedures were in accordance with the acceptance standard.

Stability-indicating capacity was proved by using various stressed conditions for two independent solutions of nefopam and droperidol. The retention time was 4.5 min for nefopam and 6.0 min for droperidol. The resolution between the two peaks was greater than 1.5, which demonstrated an acceptable separation. The chromatogram of the mixture without stressed degradation is presented in figure 1. Figures 2 and 3 show nefopam

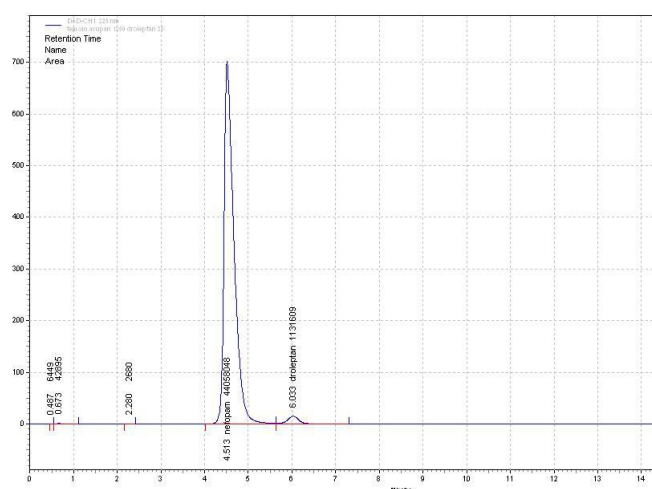


Figure 1 Chromatogram of a mixture of nefopam 2.5 mg/mL and droperidol 52 µg/mL in 0.9% NaCl with detection at 225 nm.

solution after acidic stressed conditions and droperidol solution after photolysis, respectively.

After acidic and UV stressed degradations, 20% and 15% of nefopam were degraded respectively. In alkaline conditions, the nefopam solution was precipitated and, in oxidative conditions, the nefopam solution was not degraded. After alkaline and UV stressed degradations, 30% and 21% of droperidol were degraded, respectively. In acidic and oxidative conditions, the droperidol solution was not degraded. In heat conditions, neither of the two molecules was degraded. No degradation products interfered with the molecules of interest. Mass balance of nefopam and droperidol, respectively, are shown in the online supplementary files.

Chemical stability of solutions

HPLC assay

The percentage of nefopam diluted in 0.9% NaCl at 2.5 mg/mL after storage at 20–25°C for various time points is shown in table 2. The percentage of the nefopam/droperidol mixture diluted in 0.9% is shown in table 3. After 48 hours, nefopam

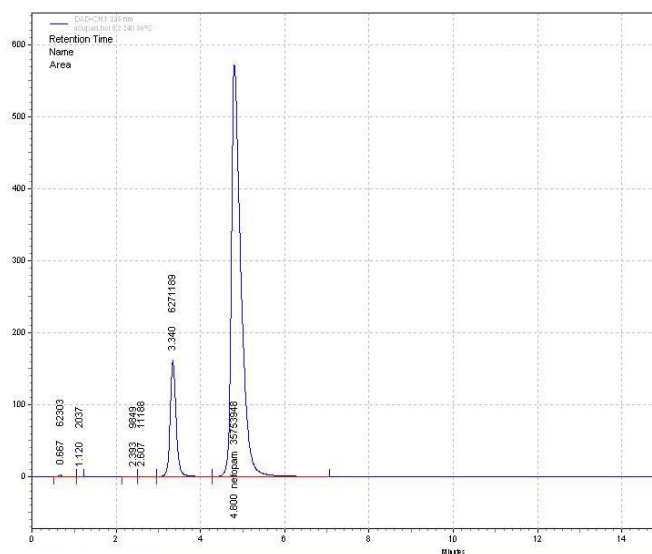


Figure 2 Chromatogram of nefopam after acidic degradation (HCl 0.2M, 24 hours, 80°C).

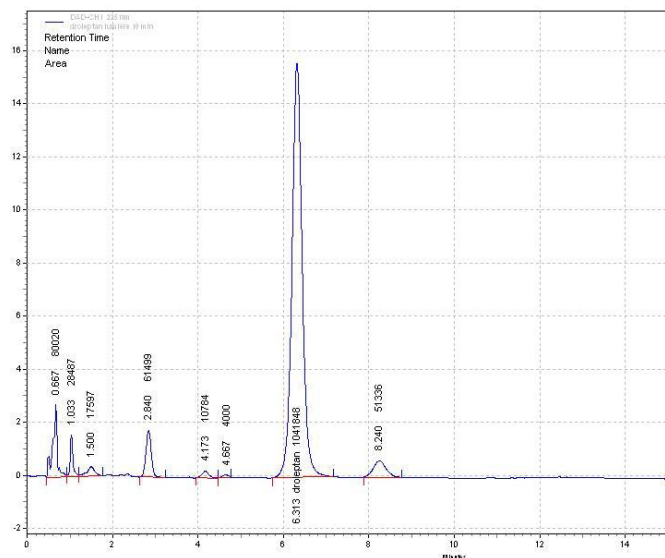


Figure 3 Chromatogram of droperidol after photolysis stressed conditions (10 min).

solutions or mixtures with droperidol in 0.9% NaCl retained between 90.0% and 110.0% of the initial concentration. No additional peak was observed during the stability study.

pH measurements

During the study, for the nefopam-droperidol mixtures and for nefopam solutions, means of pH values were 5.25 ± 0.04 and 5.34 ± 0.03 respectively.

Physical stability of solutions

Visual aspect

No visual modification was observed during the stability study for the nefopam solution and for the mixture. Solutions remained limpid, without change of colour, precipitation or gas formation.

Subvisual evaluation

Concerning turbidity assays, no change was observed during the stability study for the mixture and the solution of nefopam. Whatever the storage conditions and the concentrations, values of absorbance at 350, 410 and 550 nm remained inferior to 0.010 AU.

DISCUSSION

This study showed that solutions of nefopam at 2.5 mg/mL and a mixture of nefopam 2.5 mg/mL with droperidol 52 µg/mL, diluted in NaCl 0.9%, without protection from light, retained more than 90% of the initial concentration after 48 hours storage at 20–25°C.

During the forced degradation of droperidol, a degradation product with a retention time of 4.67 min (relative retention 0.74) was obtained. This time is close to the retention time of nefopam at 4.8 min. During the stability study of nefopam, the purity of the nefopam peak was verified.

For the nefopam/droperidol mixture in syringe S2, the percentage obtained for nefopam and for droperidol after 6, 24 and 48 hours storage is around 105% of the initial concentration. The hypothesis for this increase is related to a concentration value after the preparation that is small relative to the theoretical value. This may be due to a problem of homogenisation.

The stability of nefopam with another analgesic drug has already been investigated. Balayssac *et al* have demonstrated the stability of a mixture of nefopam and ketoprofen or paracetamol in binary or ternary for 24 hours at room temperature in glass vials.¹³ Hamdi *et al* studied the stability of a mixture of nefopam with ketoprofen, ketamine or acetaminophen, but the analytical method used for the determination of the chemical stability was not demonstrated to be stability-indicating at this time.¹⁴ No stability study of a nefopam mixture with a drug of the same pharmacological class has previously been performed.

The stability of droperidol with another analgesic drug has been evaluated. Chen *et al* demonstrated a 15-day stability for a mixture 0.08 mg/mL butorphanol tartrate and 0.05 mg/mL droperidol in PVC bags at 25°C or between 2°C and 8°C.¹⁵ Lebitasy *et al* determined the 32-day stability of a mixture of droperidol 0.025 mg/mL with tramadol hydrochloride 1 mg/mL between 2°C and 8°C.¹⁶

Our study confirms the good stability of droperidol and adds new knowledge on the stability of nefopam.

CONCLUSION

Nefopam solutions at 2.5 mg/mL or a mixture of nefopam 2.5 mg/mL with droperidol 52 µg/mL diluted in NaCl 0.9% were physically and chemically stable over a period of 48 hours at room temperature. No modifications in visual or subvisual evaluation and pH values were observed during the stability study. These stability data of a highly concentrated solution provide additional knowledge to assist intensive care services in daily practice.

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Contributors EDH carried out the experiment and analysed the data. EDH wrote the manuscript with support from JV, IC and BD. JV supervised the project. All authors provided critical feedback.

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Competing interests None declared.

Patient consent for publication Not required.

Table 2 Stability of nefopam 2.5 mg/mL diluted with 0.9% sodium chloride (NaCl 0.9%)

Syringe	Initial nefopam concentration (mg/mL)	Percentage of initial concentration±SD (%)			
		0 hour	6 hours	24 hours	48 hours
S1	2.60	100.00±0.26	100.28±0.18	100.53±0.02	100.39±0.02
S2	2.58	100.00±0.22	101.14±0.25	100.86±0.12	101.28±0.12
S3	2.61	100.00±0.15	99.78±0.27	100.28±0.27	99.64±0.20

Note: Drug concentrations in samples taken at time zero were designated as 100%. Samples were prepared in triplicate for each syringe.

Table 3 Stability of a mixture of 2.5 mg/mL nefopam and 52 µg/mL droperidol diluted in 0.9% sodium chloride

Drug	Initial concentration	Syringe	Percentage of initial concentration±SD (%)			
			0 hour	6 hours	24 hours	48 hours
Nefopam (mg/mL)	2.48	S1	100.00±0.21	102.04±0.22	99.16±1.08	100.59±0.54
	2.45	S2	100.00±0.55	104.40±0.25	103.54±0.34	105.27±0.53
	2.58	S3	100.00±0.48	99.89±0.38	99.25±0.07	100.65±0.02
Droperidol (µg/mL)	56.08	S1	100.00±0.21	101.91±0.18	98.52±0.83	99.81±0.67
	54.44	S2	100.00±0.69	105.91±0.38	104.03±0.78	106.26±0.80
	57.01	S3	100.00±0.49	99.82±0.28	99.25±0.38	100.57±0.51

Note: Drug concentrations in samples taken at time zero were designated as 100%. Samples were prepared in triplicate for each syringe.

What this paper adds

What is already known on this subject

- ▶ To prevent the side effects of nefopam, droperidol can be used.
- ▶ In the literature, to the best of our knowledge, no stability study of a nefopam/droperidol mixture in the same container or a nefopam solution highly concentrated has been published.

What this study adds

- ▶ Nefopam solutions at 2.5 mg/mL and a nefopam 2.5 mg/mL-droperidol 52 µg/mL mixture diluted in NaCl 0.9% were stable over a period of 48 hours at room temperature.
- ▶ These stability data provide additional knowledge to assist intensive care services in daily practice.

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