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Physicochemical stability of Norepinephrine bitartrate in Polypropylene Syringes at High Concentrations for Intensive Care Units.

Étude de stabilité physico-chimique de noradrénaline bitartrate dans des seringues en polypropylène à des concentrations élevées pour les services de soins intensifs.

AUTHORS

D'HUART Elise, Pharm Resident¹, VIGNERON Jean, PharmD¹, CLAROT Igor, Ph.D², DEMORE Béatrice, Ph.D^{1,3}.

¹ Pharmacy Department, University Hospital of Nancy, Allée du Morvan, 54511 Vandoeuvre-lès-Nancy, France.

² Université de Lorraine, CITHEFOR, Nancy, France.

³ Université de Lorraine, EA 4360 APEMAC, Nancy, France.

Address

Contact for correspondence: Elise d'Huart

Pharmacy Department

Centre Hospitalier Universitaire

Hôpital Brabois Adultes

Allée du Morvan

F-54511 Vandoeuvre-lès-Nancy, France

Tel: +33 3 83 15 44 10

Fax: +333 83 15 35 27

dhuartelise@gmail.com

Keywords: norepinephrine; intensive care unit; HPLC; stability.

HIGHLIGHTS

- In the literature, to the best of our knowledge, there is no stability data available on norepinephrine at high concentrations up to 1.16 mg/mL.
- This drug is usually used in intensive care units for the restoration of blood pressure.
- These stability data of highly-concentrated solutions provide additional knowledge to assist intensive care services in daily practice.

ABSTRACT

Objectives

Norepinephrine is usually used in emergency situations such as in intensive care units (ICUs) for the restoration of blood pressure. The objective was to study the stability of highly-concentrated solutions of norepinephrine at 0.50 mg/mL and 1.16 mg/mL, diluted in glucose 5% (G5%) in polypropylene syringes, protected or not from light, up to 48 hours.

Materials and method

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

Results

Solutions of norepinephrine at 0.50 and 1.16 mg/mL, diluted in G5%, with or without protection from light, retained more than 95.0% of the initial concentration after a 48-hour storage at 20-25°C. No visual and subvisual modification occur during the stability study. No degradation product appearing during the stressed degradation was observed during the study but an additional peak with a relative retention at 0.66 was observed and constant. This peak was identified as 5-hydroxymethylfurfural, a degradation product of glucose.

Conclusion

Norepinephrine diluted in G5% at 0.50 mg/mL and 1.16 mg/mL was physically and chemically stable over a period of 48 hours at room temperature. These stability data of highly-concentrated solutions provide additional knowledge to assist intensive care services in daily practice.

Keywords: norepinephrine; intensive care unit; HPLC; stability.

RESUME

Objectifs

La noradrénaline est généralement utilisée dans des situations d'urgence, telles que dans les unités de soins intensifs, pour rétablir la tension artérielle. L'objectif était d'étudier la stabilité de solutions hautement concentrées de noradrénaline à 0,50 mg/mL et 1,16 mg/mL, diluées dans du glucose à 5% (G5%) dans des seringues en polypropylène, protégées ou non de la lumière, jusqu'à 48 heures de conservation.

Matériels et méthodes

La stabilité chimique a été analysée par chromatographie liquide à haute performance couplée à un détecteur à barrette de diode, à chaque moment de l'analyse. La méthode a été validée conformément à l'International Conference on Harmonisation Q2(R1). La stabilité physique a été évaluée par un examen visuel et subvisuel. Trois seringues pour chaque condition ont été préparées. A chaque moment de l'analyse, trois échantillons ont été analysés pour chaque seringue. Les valeurs de pH ont été évaluées à chaque moment de l'analyse.

Résultats

Les solutions de noradrénaline à 0,50 et 1,16 mg/mL, diluées dans du G5%, avec ou sans protection contre la lumière, ont conservé plus de 95% de leur concentration initiale après une conservation de 48 heures à 20-25 °C. Les solutions sont restées claires, sans changement de couleur ni précipitation pendant la durée de l'étude. Concernant l'examen subvisuel, les valeurs d'absorbance étaient inférieures à 0,010 UA. Aucun produit de dégradation mis en évidence lors de la dégradation forcée n'a été observé au cours de l'étude. Un pic supplémentaire avec une rétention relative à 0,66 a été observé et était constant durant l'étude. Ce pic a été identifié comme étant du 5-hydroxyméthylfurfural, un produit de dégradation du glucose.

Conclusion

La noradrénaline diluée dans du G5% à 0,50 mg/mL et à 1,16 mg/mL a été démontrée physiquement et chimiquement stable sur une période de 48 heures à température ambiante. Ces données de stabilité de solutions hautement concentrées fournissent des connaissances supplémentaires pour aider les services de soins intensifs dans leur pratique quotidienne.

Mots clés : noradrénaline, soins intensifs, CLHP, stabilité

INTRODUCTION

Norepinephrine bitartrate is a drug of the catecholamine family. This drug is usually used in emergency situations such as in intensive care units (ICUs) for the restoration of blood pressure in case of acute hypotension. The recommended initial dose for continuous infusion is a flow rate of 0.1 to 0.3 $\mu\text{g}/\text{kg}/\text{min}$ of norepinephrine. High doses from 3 to 5 $\mu\text{g}/\text{kg}/\text{min}$ can be used in the treatment of septic shock or hemorrhagic shock [1].

To avoid fluid overload, ICUs often use a minimum volume of infusion by using more concentrated drug solutions. High doses of norepinephrine can be administered over 24 hours with an electrical syringe pump. In clinical practice in ICUs, nurses use a final volume of 48 mL in syringes to have an accurate flow rate of 2 mL/h over 24 hours.

In the literature, to the best of our knowledge, no stability studies show the stability of highly-concentrated norepinephrine syringes at room temperature, only stability studies on highly-diluted solutions of norepinephrine are available. Peddicord *et al.* [2] determined a 24-hour stability for norepinephrine solutions at 0.064 mg/mL diluted in 0.9% sodium chloride (0.9% NaCl) or 5% glucose (G5%) in PVC bags, stored at 23°C, protected from light. Baumgartner *et al.* [3] determined a 24-hour stability for norepinephrine solutions at 0.004 and 0.008 mg/mL diluted in 0.9% NaCl or G5% in PVC bags, stored at 25°C, without protection from light. Walker *et al.* studied the stability of norepinephrine at 0.064 $\mu\text{g}/\text{mL}$ in 0.9% NaCl and in G5% at 4°C for up to 61 days [4].

Brustugun *et al.* observed that light is a factor of instability for norepinephrine solutions [5]. Alwood *et al.* demonstrated the influence of a pH superior to 6.0 on the stability of norepinephrine. They determined a higher stability with G5% as solvent in comparison with 0.9% NaCl [6].

The objective was to study the stability of norepinephrine solutions at 0.50 mg/mL and 1.16 mg/mL, diluted in G5% in polypropylene syringes, protected or not from light, after the preparation and after a 6-hour, 24-hour and 48-hour storage at room temperature. The concentration at 0.50 mg/mL corresponds to a one-day syringe for a dose at 0.24 $\mu\text{g}/\text{kg}/\text{min}$ for a patient with an average weight of 70 kg. The concentration at 1.16 mg/mL corresponds to a dose at 0.56 $\mu\text{g}/\text{kg}/\text{min}$.

MATERIALS AND METHOD

Stability study of norepinephrine

Chemicals and reagents

For the mobile phase, heptane sulfonic acid sodium salt (VWR Chemicals, batch: 18B134102), orthophosphoric acid 85% (VWR Chemicals, batch: 15D200503) and acetonitrile (Carlo Erba Reagents, batch: D8E017238E) were used. Hydrochloric acid 1M (VWR Chemicals, batch: 17110005) and 0.1M (VWR Chemicals, batch: 17110001), sodium hydroxide 1M (VWR Chemicals, batch: 17110003) and 0.1 M (VWR Chemicals, batch: 17070001), hydrogen peroxide 30 % (Merck, batch: K48743810713) and 5-hydroxymethyl-2-furaldehyde (5-HMF) 99% (Aldrich Chemistry, batch: MKAA1503) were used for the forced degradation and the validation of the analytical method. Water for chromatography was obtained from a reverse osmosis system (Millipore Iberica, Madrid, Spain). Norepinephrine 8 mg/mL sulphite-free, solution for infusion (Mylan, batch: H2051), G5% Lavoisier 500 mL in a glass vial (Chaix et du Marais, Lavoisier, batch : 8F006) were used for test solutions.

Preparation of test solutions

Stability study in polypropylene syringes: for the preparation of the concentration at 0.50 mg/mL, three ampoules of norepinephrine 8 mg/4 mL were used. For the preparation of the concentration at 1.16 mg/mL, seven ampoules of norepinephrine 8 mg/4 mL were used. These solutions were stored in polypropylene syringes (BD Plastipak™, 50 mL BD Luer-lok™ syringe, Ref: 300865, batch: 1808208) or in amber polypropylene syringes (BD Plastipak™, 50 mL BD Luer-lok™ syringe, Ref: 300869, batch: 1807228). The final volume of the syringe was completed with G5% to obtain 48 mL. The syringes were stored at room temperature (20-25°C), protected or not from light. Three syringes were prepared for each condition.

HPLC Assay

Norepinephrine solutions were analysed by a stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) method with photodiode array detection [4].

The HPLC system consisted of an ELITE LaChrom VWR/Hitachi plus autosampler, a VWR photodiode array (PDA) detector L-2455 and a VWR L-2130 HPLC-pump. Data was acquired and integrated by using EZChrom Elite (VWR, Agilent). The column used was LiChrospher® 100 RP-18, LiChroCART® 125-4, 12.5 cm in length, 5 µm particle size (Analytical Chromatography, Merck). The mobile phase was constituted of a mixture of acetonitrile (acetonitrile HPLC gradient grade, VWR, France) and 0.05M phosphoric acid containing 1 mg/mL of heptane sulfonic acid sodium salt.

The flow rate was set at 1.0 mL/minute, with an injection volume of 10 µL. The detection wavelength was set at 280 nm. The temperature of the injector was set at 20°C and the temperature of the column oven at 25°C. The calibration curve was constructed from plots of peak area versus concentration. The linearity of the method was evaluated with five concentrations (80, 100, 120, 140 and 160 µg/mL).

A solution of norepinephrine at 400 µg/mL was prepared with ampoules of norepinephrine at 8 mg/4 mL. This solution at 400 mg/mL 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) [7], using three determinations for each concentration at 80, 120 and 160 µg/mL. For interday precision, three determinations for each concentration at 80, 120 and 160 µg/mL of norepinephrine solutions were assayed daily on three different days. To demonstrate the specificity of the method and the absence of interaction between norepinephrine and the solvent, a solution of G5% was analysed by HPLC.

The evaluation of the stability in the autosampler was performed. Solutions of norepinephrine diluted in ultrapure water were stored in the autosampler at 25°C. Chemical stability was evaluated at different times up to 24 hours.

The Diode Array Detector allows the evaluation of the UV spectrum of the chromatographic column effluent every 0.4 second, 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 norepinephrine from its degradation products, and that the method is therefore unsuitable [8].

The stability-indicating capability was evaluated by analysing forced degraded norepinephrine solutions.

Acidic conditions: one mL of a 480 µg/mL norepinephrine solution was diluted with 1.0 mL HCl 0.5 M, stored at 20-25°C for 6 hours, neutralised by 1.0 mL of NaOH 0.5 M and diluted with 1.0 mL of ultrapure water to obtain a theoretical concentration of 120 µg/mL.

Alkaline degradation: one mL of a 480 µg/mL norepinephrine solution was diluted with 1.0 mL NaOH 0.01 M, stored at 20-25°C for 5 minutes, neutralised by 1.0 mL of HCl 0.01 M and diluted with 1.0 mL of ultrapure water to obtain a theoretical concentration of 120 µg/mL.

Oxidative degradation: one mL of a 480 µg/mL norepinephrine solution was diluted with 1.0 mL H₂O₂ 30% stored at 20-25°C and diluted with 2.0 mL of ultrapure water to obtain a theoretical concentration of 120 µg/mL.

Heat degradation: a solution of 120 µg/mL norepinephrine was exposed to a temperature of 100°C for 6 hours.

UV degradation: a solution of 120 µg/mL norepinephrine was exposed for 4, 6, 25 and 30 hours under a sun-like spectrum lamp at 254 nm (Vilbert Lourmat®).

Sample dilution for analysis by RP-HPLC

At each time of the analysis, 5 mL were removed from each syringe. The solutions were diluted before analysis with ultrapure water to obtain a concentration at 120 µg/mL (central point of the standard curve) for syringes at 0.50 mg/mL and a concentration at 116 µg/mL for syringes at 1.16 mg/mL.

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 20 minutes.

Chemical stability was defined as not less than 90% of the initial norepinephrine concentration and in relation with the evolution of potential degradation products [7,9].

pH measurement

pH measurement was performed using a Bioblock Scientific pH meter. Analysis was carried out for each concentration 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 [9]. We measured pH for each syringe, for each condition.

Determination of physical stability

Physical stability was defined as the absence of particle formation, haze, colour change and gas evolution [10]. The samples were visually inspected against a white/black background with the unaided eye by two different technicians at each analysis time. The subvisual aspect was assessed by using a Safas Monaco UV mc² spectrophotometer. The absorbance light was scanned at 350, 410 and 550 nm [10].

RESULTS

Stability study of norepinephrine

Reversed Phase HPLC

The calibration curve was linear, the determination coefficient was 0.9997. The equation of the calibration curve was $y = 18940.8x - 61132.9$. The intra-day precision expressed as relative standard deviation (RSD) was between 0.07% and 2.65%. The intermediate precision expressed as relative standard deviation (RSD) was 1.43% at 80 µg/mL, 0.32% at 120 µg/mL and 0.66% at 140 µg/mL.

For the evaluation of the stability in the autosample, solutions were stable with a degradation rate less than 0.3%.

The UV spectral purity of the norepinephrine peak in chromatograms of the degraded samples was compared with the spectrum of the undegraded sample of norepinephrine obtained at time 0. These procedures were in accordance with the acceptance standard.

Stability-indicating capacity was proved by using various stressed conditions. The retention time of norepinephrine was around 5.8 minutes. The chromatogram of norepinephrine without stressed degradation is presented in figure 1 and after alkaline stressed condition is presented in figure 2 for example.

After acidic, alkaline and heat stressed degradations, 9.2 %, 24.7 % and 10.9 % of norepinephrine were degraded respectively. In oxidative and UV conditions, norepinephrine was not degraded after adding H₂O₂ 30% or after exposition under a sun-like spectrum lamp. The mass balance and the relative retentions calculated versus the norepinephrine peak are presented in table 1.

Chemical stability of solutions

HPLC Assay

For specificity evaluation, the chromatogram of a solution of G5% is presented in figure 3. A peak with a retention time of 3.8 minutes and a relative retention at 0.66 is observed.

The percentages of norepinephrine diluted in G5% at 0.50 mg/mL and 1.16 mg/mL after storage at 20-25°C for various time points are shown in table 2. The chromatogram of norepinephrine at 0.50 mg/mL after preparation is presented in figure 4. An additional peak was observed for each sample with a retention time of 3.8 minutes (relative retention at 0.66). No degradation product that appeared during stressed degradation was observed during the stability study.

pH measurements

During the stability study, no modification of pH measurements was observed. Table 3 summarizes the pH values obtained for the 3 syringes, at each condition, after preparation and after 48 hours.

Physical stability of solutions

Visual aspect

No visual modification was observed during all the stability study. Solutions remained limpid, without change of colour, precipitation or gas formation.

Subvisual evaluation

Concerning turbidity assays, no change was observed. 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 demonstrated that solutions of norepinephrine at 0.50 and 1.16 mg/mL, diluted in G5%, with or without protection from light, retained more than 95.0 % of the initial concentration after a 48-hour storage at 20-25°C. This result is in accordance with a poster realised by Velghe *et al.* [11]. They determined a 28-day stability for norepinephrine at 0.2 and 0.5 mg/mL in 0.9% NaCl and G5%.

Walker *et al.* observed a better stability with solutions of norepinephrine protected from light in comparison with solutions not protected [4]. In our stability study, we have not observed differences between results obtained for solutions protected or not from light. Light seems to have an impact less important for high concentrations of norepinephrine solutions than for diluted solutions.

During the evaluation of the specificity, a G5% solution was analysed by HPLC and a peak was observed on the chromatogram with a retention time of 3.8 minutes. This peak was absent during the evaluation of the linearity, repeatability and the intermediate precision of the analytical method because all samples of norepinephrine were diluted in ultrapure water. During the stability study, norepinephrine was diluted in G5% and an additional peak with a retention time of 3.8 minutes was equally observed on chromatograms.

For the identification of this additional peak, a solution of 5-hydroxymethylfurfural (5-HMF) at 0.05 mg/mL in ultrapure water was prepared and analysed by HPLC. 5-HMF is a product formed during thermal processing or heat sterilization of glucose. The maximum absorption of 5-HMF was obtained at a wavelength of 284 nm, which is close to the wavelength used by our analytical method for the determination of norepinephrine (280 nm) [12]. The analysis by HPLC of this solution showed a peak of 5-HMF with a retention time of 3.8 minutes as observed in figure 5. The spectrum of 5-HMF was identical to the spectrum of the peak at 3.8 minutes observed in chromatograms of norepinephrine solutions diluted in G5% and the chromatogram of the G5% solution. The additional product with a retention time of 3.8 minutes observed on the chromatogram of norepinephrine diluted in G5% during the stability study is identified as 5-HMF.

In solutions of norepinephrine at 0.50 and 1.16 mg/mL diluted in G5%, 5-HMF was stable in time. For this stability study, a glass vial of G5% was used. We analysed by HPLC solutions of G5% contained in different containers (Ecoflac®, BBraun, batch: 18101450; Easyflex®, MacoPharma, batch: 17A11F; Viaflo®, Baxter, batch 18F13E4B). In all cases, we observed the peak of 5-HMF on chromatograms in different proportions. We prepared a solution of glucose at 5g/100 mL with 5 grams

of glucose precisely weighed (D (+)- Glucose anhydrous, VWR Chemicals®, batch : 16K104113). After analysis by HPLC of this solution, no peak with a retention time of 3.8 minutes was observed. This difference confirms that the peak of 5-HMF was in relation with the sterilization process of the G5%, used to prepare the syringes.

CONCLUSION

Norepinephrine diluted in G5% at 0.50 mg/mL and 1.16 mg/mL was physically and chemically stable over a period of 48 hours at room temperature. These stability data of highly-concentrated solutions provide additional knowledge to assist intensive care services in daily practice.

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Conflict of interest: none

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REFERENCES

- [1] Norepinephrine sulphite-free 2 mg/mL. Solution for solution for infusion. Summary of Product Characteristics. Updated June 2016. Mylan.
- [2] Peddicord TE, Olsen KM, ZumBrunnen TL, Warner DJ, Webb L. Stability of high-concentration dopamine hydrochloride, norepinephrine bitartrate, epinephrine hydrochloride, and nitroglycerin in 5% dextrose injection. Am J Health-Syst Pharm 1997;54:1417-9.
- [3] Baumgartner TG, Knudsen AK, Dunn AJ, Kilroy RA. Norepinephrine stability in saline solutions. Hosp Pharm 1988 ; 23:44,49, 59.
- [4] Walker S.E, Law S, Garland J, Fung E, Iazetta J. Stability of Norepinephrine Solutions in Normal Saline and 5% Dextrose in Water. Can J Hosp Pharm 2010; 63,2: 113-8.

- [5] Brustugun J, Kristensen S, Tonnesen HH. Photostability of sympathomimetic agents in commonly used infusion media in the absence and presence of bisulfite. *PDA J Pharm Sci Technol* 2004;58,6: 296-308.
- [6] Allwood MC. The stability of four catecholamines in 5% glucose infusions. *J Clin Pharm Ther* 1991; 16: 337-40.
- [7] International Conference on Harmonisation: Validation of Analytical Procedures: Text and Methodology Q2(R1). Guideline 2005.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1_Guideline.pdf [accessed 23 February 2018).
- [8] Metha A.C. Practice research: Strategies for stability studies on hospital pharmaceutical preparations. *Int J Pharm Pract* 1993;2:49-52.
- [9] Sautou V, Brossard D, Chedru-Legros V, Craustre-Manciet S, Fleury-Souverain S, Lagarce F et al. Methodological guidelines for stability studies of hospital pharmaceutical preparations. SFPC and GERPAC, 1st ed. 2013. 75 pages. https://www.gerpac.eu/IMG/pdf/guide_stabilite_anglais.pdf
- [10] Bardin C, Astier A, Vulto A, Sewell G, Vigneron V, Trittler R et al. Guidelines for the practical stability studies of anticancer drugs: A European consensus conference. *Ann Pharm Fr.* 2011; 69,4: 221-31.
- [11] Velghe C, Genay S, Feutry F, Barthélémy C, Décaudin B, Odou P. Stabilité de la noradrénaline conditionnée en poche et en seringue aux concentrations thérapeutiques usuelles. Poster presented at Hopipharm 2016 at Clermont-Ferrand, France. [Accessible www.stabilis.org, 02 November 2018].
- [12] Zhang H, Ping Q, Zhang J, Li N. Determination of Furfural and Hydroxymethyl furfural by UV Spectroscopy in ethanol-water hydrolysate of Reed. *Journal of Bioresources and Bioproducts* 2017;2,4:170-4.

Figure 1 : Chromatogram of norepinephrine 120 µg/mL in ultrapure water without stressed conditions.

Figure 1 : Chromatogramme d'une solution de noradrenaline à 120 µg/mL diluée dans de l'eau ultra-pure sans conditions de dégradation.

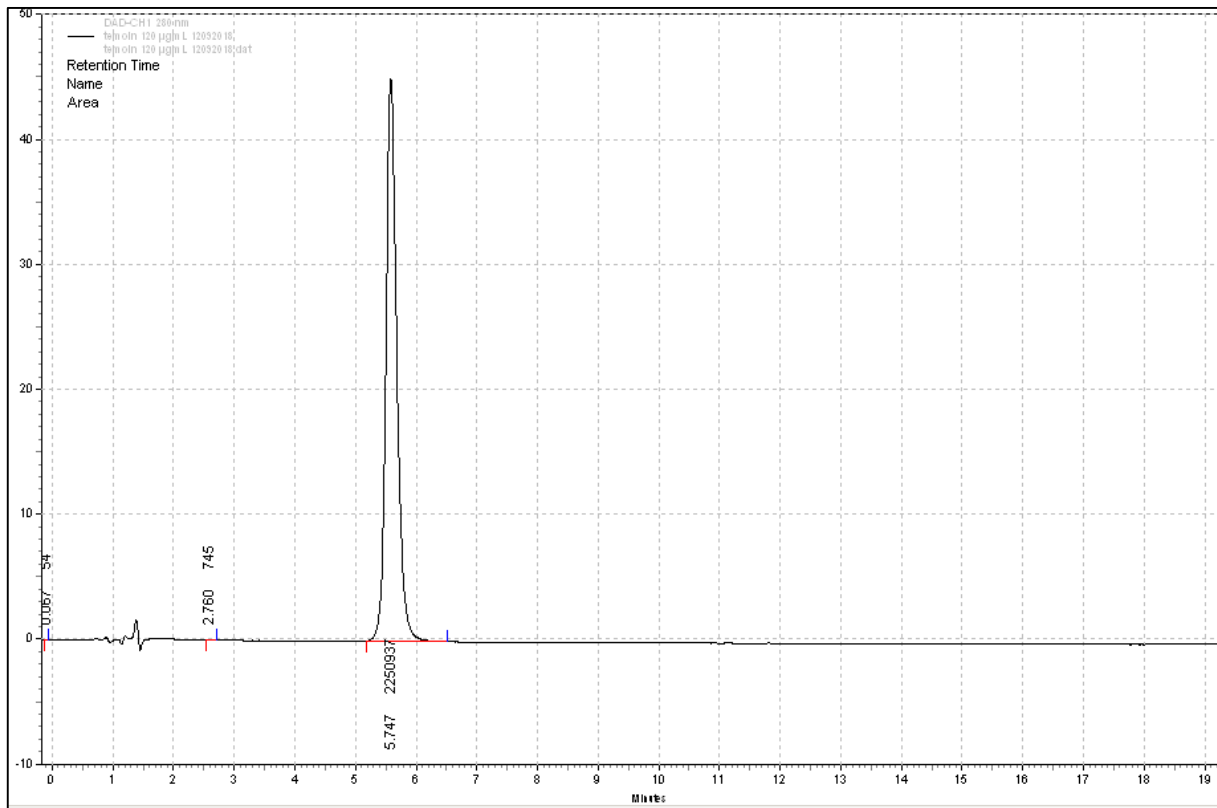


Figure 2 : Chromatogram of norepinephrine 120 $\mu\text{g/mL}$ in ultrapure water after alkaline stressed conditions (NaOH 0.01M, 5 minutes)

Figure 2 : Chromatogramme d'une solution de noradrénaline à 120 $\mu\text{g/mL}$, diluée dans de l'eau ultrapure dans des conditions de stress alcalines (NaOH 0,01 M, 5 minutes)

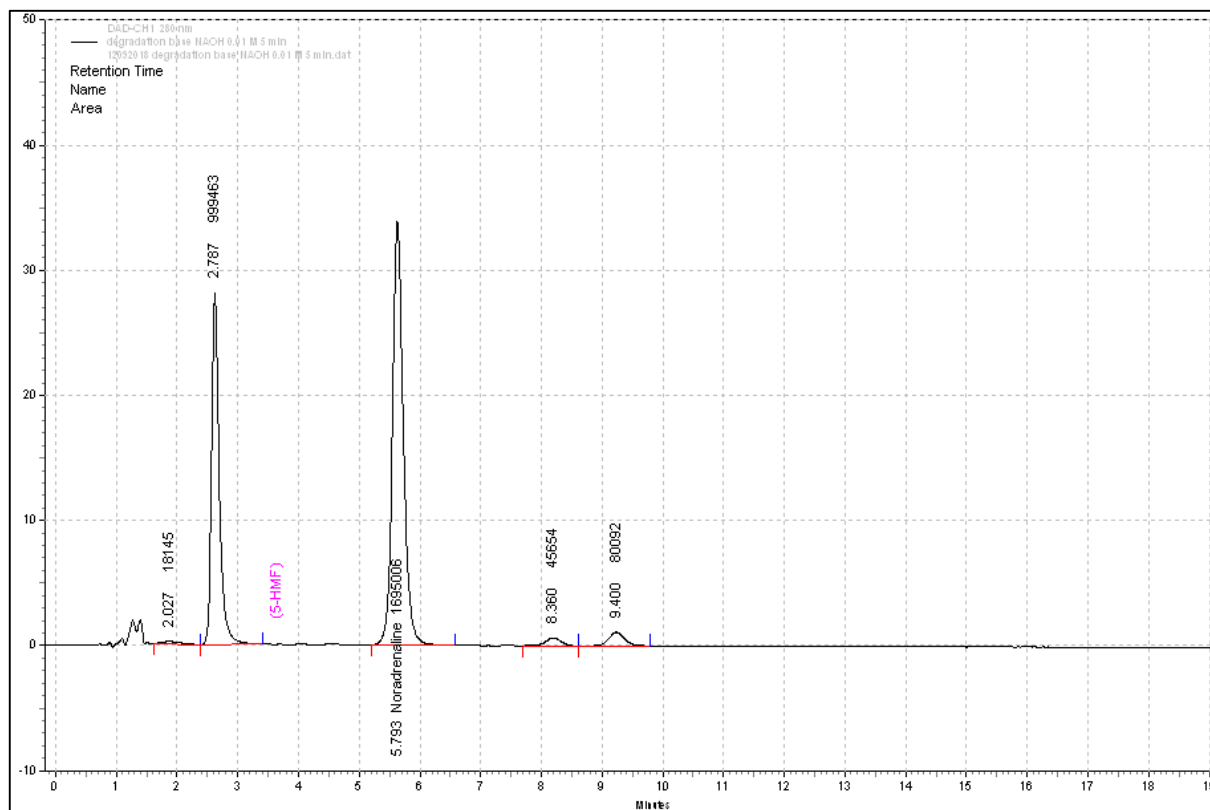


Figure 3: Chromatogram of a glucose 5% solution.

Figure 3: Chromatogramme d'une solution de glucose 5%.

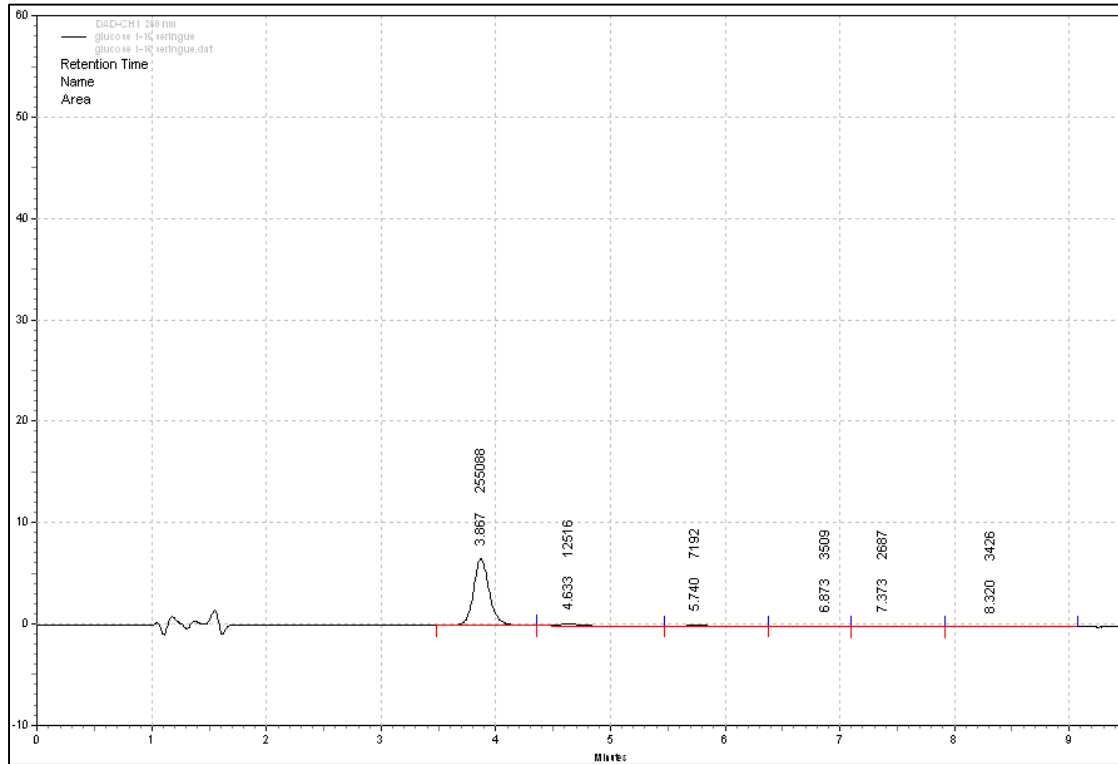


Figure 4 : Chromatogram of a norepinephrine solution at 0.5 mg/mL diluted in glucose 5% after preparation.

Figure 4 : Chromatogramme d'une solution de noradrénaline à 0,5 mg/mL diluée dans du glucose 5%, après préparation.

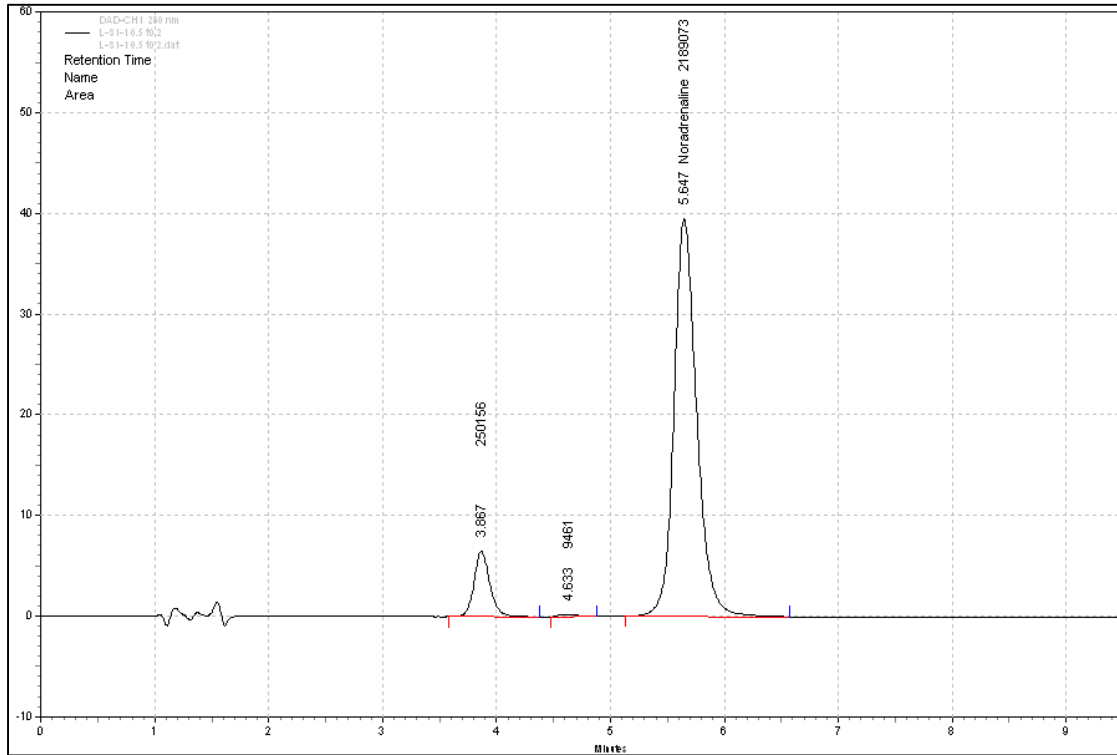


Figure 5: Chromatogram of 5-HMF at 50 mg/L in ultrapure water.

Figure 5 : Chrommatogramme d'une solution de 5-HMF à 50 mg/mL dans de l'eau ultrapure.

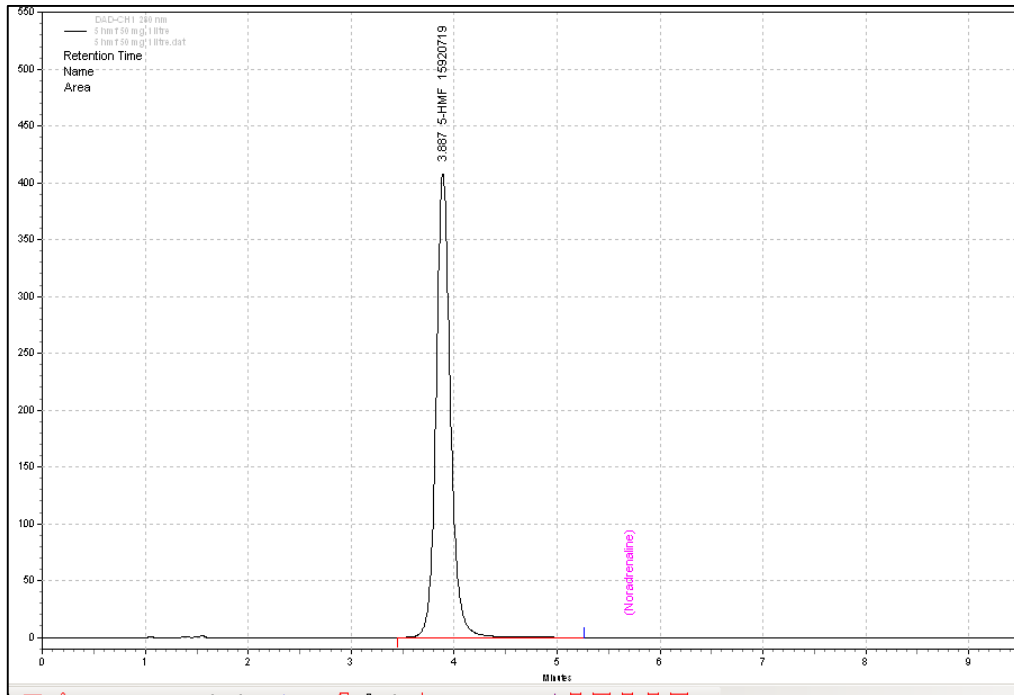


Table1: Mass balance of norepinephrine solutions after various stressed degradations.

Tableau 1 : Bilan massique de solutions de noradrenaline après des dégradations forces.

Peaks	Retention time (minutes)	Relative retention	Without stressed degradation	Area						
				Acidic degradation			Alkaline degradation		Heat degradation	
				HCl	0.5M	6h	NaOH	0.01M	5 min	100°C
Norepinephrine	5.75	1.00	2250937	2044681			1695006		2004918	
1	2.35	0.41							6108	
2	2.79	0.48		282586			999463			
3	3.09	0.54							8434	
4	3.43	0.60							2439	
5	7.63	1.33							8175	
6	8.36	1.45		52782			45654		12243	
7	9.40	1.64		69422			80092		15606	
Mass balance			2250937	2449471			2820215		2057923	
% degradation				9.2%			24.7%		10.9%	

Table 2: Stability of norepinephrine diluted in glucose 5% (G5%).

Tableau 2 : Stabilité de la noradrenaline diluée dans du glucose 5% (G5%)

Light conditions	Concentration (mg/mL)	Syringe	Mean % of initial concentration \pm SD*%			
			0 hour	6 hours	24 hours	48 hours
Not protected from light	0.5	S1	100.00 \pm 1.15	101.01 \pm 0.18	97.07 \pm 1.34	95.97 \pm 1.03
		S2	100.00 \pm 1.41	102.56 \pm 0.27	99.56 \pm 0.18	99.33 \pm 0.61
		S3	100.00 \pm 1.25	101.15 \pm 0.38	100.52 \pm 0.41	99.43 \pm 0.16
	1.16	S1	100.00 \pm 0.28	99.56 \pm 0.87	99.06 \pm 0.34	98.41 \pm 0.04
		S2	100.00 \pm 0.14	100.97 \pm 0.57	99.74 \pm 0.55	98.79 \pm 0.15
		S3	100.00 \pm 0.11	100.65 \pm 0.83	99.28 \pm 0.27	99.14 \pm 0.46
Protected from light	0.5	S1	100.00 \pm 0.41	100.36 \pm 0.62	99.97 \pm 0.99	98.77 \pm 0.58
		S2	100.00 \pm 0.06	99.14 \pm 0.36	99.05 \pm 0.99	98.75 \pm 0.25
		S3	100.00 \pm 0.24	100.30 \pm 0.27	100.28 \pm 1.82	99.71 \pm 0.15
	1.16	S1	100.00 \pm 0.95	100.43 \pm 0.91	99.11 \pm 0.39	98.05 \pm 0.60
		S2	100.00 \pm 0.55	99.38 \pm 0.16	96.81 \pm 0.23	98.20 \pm 0.37
		S3	100.00 \pm 0.26	100.50 \pm 0.22	99.46 \pm 0.92	99.41 \pm 0.74

Note: Drug concentrations in samples taken at time zero were designated as 100%. *SD=Standard Deviation. Samples were prepared in triplicate.

Table 3 : pH measurements

Tableau 3 : Mesures de pH

Light conditions	Concentration (mg/mL)	Syringe	pH values	
			0 hour	48 hours
			Mean \pm SD*	
Not protected from light	0.5	S1	3.62 \pm 0.03	3.63 \pm 0.03
		S2		
		S3		
	1.16	S1	3.5 \pm 0.01	3.50 \pm 0.01
		S2		
		S3		
Protected from light	0.5	S1	3.61 \pm 0.00	3.61 \pm 0.01
		S2		
		S3		
	1.16	S1	3.49 \pm 0.00	3.49 \pm 0.01
		S2		
		S3		

*SD: standard deviation