

# Development and stability testing of a concentrated injectable clonidine solution for intrathecal analgesia

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## ABSTRACT

**Study objectives:** To develop a concentrated injectable clonidine solution (2 mg/mL) to be used in an implantable infusion system and to test its long-term stability.

**Methods:** Formulations for injectable solutions of clonidine 2 mg/mL at pH 4.1 and pH 7.3 were developed. Samples were prepared under aseptic conditions, sterilised by moist heat and stored at 40°C ± 2°C for up to six months. Photostability was tested after one month. Clonidine concentrations were measured by high-performance liquid chromatography (HPLC). Samples were visually inspected and the pH was measured at each time point.

**Results:** Clonidine concentration remained stable either at pH 4.1 or 7.3. No colour change or precipitation occurred during the study period. The pH of the samples prepared initially at pH 7.3 remained stable, whereas the pH of the samples at pH 4.1 showed a tendency to increase and displayed a high variability. Exposure to light did not influence the stability of the preparations.

**Conclusion:** Formulation of clonidine 2 mg/mL at pH 7.3 is stable at 40°C for at least six months without protection from light and is therefore a good option for long-term use in implantable infusion systems.

## KEYWORDS

Analgesia, clonidine, long-term stability, photostability, pH

## INTRODUCTION

Clonidine, an alpha-2 adrenoreceptor agonist, shows analgesic action mediated through non-opioid mechanisms when administered intrathecally to patients with neuropathic pain. For the treatment of chronic pain, intrathecal administration of clonidine-opioid admixtures with implanted infusion pumps is used successfully. The combination with clonidine allows the use of lower opioid doses and therefore reduces side effects [1, 2]. The only commercially available injectable clonidine solution is marketed under the name of Catapresan (Boehringer Ingelheim), at a concentration of 0.15 mg/mL. The availability of a concentrated injectable clonidine solution would be useful for filling

infusion pumps with a higher dose; this would decrease the rate of infusion and the frequency of refilling the pumps. The aim of this study was to develop a concentrated clonidine solution to be used in an implantable infusion system and to test its long-term stability.

## METHODS

### Solution preparation

Clonidine solutions at a concentration of 2 mg/mL were prepared by dissolving clonidine hydrochloride (Clonidine PhEur, BUFA bv, Uitgeest, the Netherlands, batch number 03K20GR and 04L06JR) in a solution of sodium chloride 0.9% (Bioren SA, Couvet, Switzerland). The pH was adjusted by adding hydrochloric acid 0.01 mol/L or sodium hydroxide solution 0.01 mol/L (Titrisol, Merck KGaA, Darmstadt, Germany) as required, to obtain either a pH of 4.1 or a pH of 7.3. The solutions were filtered (Minisart 0.2 µm syringe filter), placed in 5 mL glass vials sealed with brombutyl teflon stoppers and sterilised in the autoclave (121°C, 25 minutes). Preparation was carried out in a clean room in a horizontal laminar-airflow hood (Formulation for injectable clonidine solution 0.6 mg/mL and 1.2 mg/mL at pH 4.1. Personal communication from Nicolas Schaad, Head of Pharmacy, Pharmacie Interhospitalière de la Côte (PIC), Morges, Switzerland).

### Stability study

Two batches of clonidine solution at each pH were prepared and their conformity to the specifications indicated

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in the “injectable drugs” monograph of the European Pharmacopeia [3] was tested. The vials were stored for six months at  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . The concentration of clonidine, measured by HPLC, was controlled at two time points (0 and 6 months). The pH and the visual aspect of the solutions were controlled at four time points (0, 1, 3 and 6 months) [4].

#### HPLC method

A Merck-Hitachi HPLC system consisting of pump, automatic sample injector, column oven, degasser and UV detector was used. A Nucleosil 100-5C18 column (125 x 4.6 mm ID, Macherey-Nagel, Dürren, Germany) was used. The mobile phase was 18% of acetonitrile and 82% of phosphate buffer at pH 7.00 with 0.01% triethylamine. All substances used were of analytical quality. The flow rate was 1.0 mL/minute and the column temperature was set at  $35^{\circ}\text{C}$ . UV detection was at 271 nm.

Samples were prepared by diluting 150  $\mu\text{L}$  of standard solution (clonidine 2 mg/mL) or 150  $\mu\text{L}$  of experimental samples with 850  $\mu\text{L}$  water, and 20  $\mu\text{L}$  aliquots were injected. Concentrations of clonidine were calculated using peak areas versus standard concentration. Results were expressed as mean  $\pm$  standard deviation (Méthode analytique pour le dosage du chlorhydrate de clonidine dans les solutions injectables de chlorhydrate de clonidine 0.6 mg/mL et 1.2 mg/mL. Personal communication from Professor Jean-Luc Veuthey, Head of Department, Université de Genève, Section des sciences pharmaceutiques, Laboratoire de chimie analytique pharmaceutique).

This method displayed good linearity (correlation coefficient of 0.997 in the range of 0.180 to 0.420 mg/mL) and precision (coefficient of variation 1.02%) with accuracy of  $100.37\% \pm 1.05\%$ .

Forced degradation experiments were conducted in order to validate that the method indicated stability. Standard solutions were exposed to an elevated temperature ( $40^{\circ}\text{C}$ ) and ultraviolet light for 500 hours. The chromatogram of the sample exposed to the elevated temperature remained unchanged whereas the sample exposed to ultraviolet light showed rapid clonidine degradation with two additional chromatographic peaks (Validation de la méthode analytique pour le dosage du chlorhydrate de clonidine dans les solutions injectables de chlorhydrate de clonidine 0.6 mg/mL et 1.2 mg/mL. Personal communication from Professor Jean-Luc Veuthey, Head of Department, Université de Genève, Section des sciences pharmaceutiques, Laboratoire de chimie analytique pharmaceutique).

#### pH determination

The pH of the solutions was measured with a pH meter with an Ag/AgCl combined pH electrode (Radiometer Analytical SAS, PHM210 pHC3001-8, Lyon, France).

#### Photostability study

Four vials of each preparation were exposed to daylight for a month. At the end of the exposure period clonidine concentration and pH were measured and the vials were examined for any changes in appearance [5, 6].

## RESULTS

#### Stability study

All samples fulfilled the specifications indicated in the “injectable drugs” monograph of the European Pharmacopeia. No colour change or precipitation was observed in the vials during storage at  $40^{\circ}\text{C}$  for six months. The concentration of clonidine showed no significant change during the whole study period (Table 1). The pH values of the solutions at pH 4.1 were influenced by the sterilisation process and showed

Table 1: Test results of the stability study

Formulation pH	Batch	Particle contamination		Physical aspect	Sterility	Bacterial endotoxins (EU/mL)	Clonidine concentration (mg/mL)	
		$\geq 10 \mu\text{m}/5 \text{ mL}$	$\geq 25 \mu\text{m}/5 \text{ mL}$				day 0	After 6 months
4.1	1	50	2	Colourless, clear	Fulfilled	<0.02	$1.990 \pm 0.025$	$2.058 \pm 0.025$
	2	40	2	Colourless, clear	Fulfilled	<0.02	$1.976 \pm 0.025$	$2.016 \pm 0.025$
7.3	1	78	2	Colourless, clear	Fulfilled	<0.02	$1.995 \pm 0.025$	$2.031 \pm 0.025$
	2	44	2	Colourless, clear	Fulfilled	<0.02	$1.985 \pm 0.025$	$2.025 \pm 0.025$

Table 2: pH values at time points 0, 1, 3 and 6 months

Formulation pH	Batch	pH value day 0		pH value 1 month	pH value 3 months	pH value 6 months
		Before sterilisation	After sterilisation			
4.1	1	4.13 ± 0.00	4.38 ± 0.11	4.73 ± 0.22	4.71 ± 0.21	5.23 ± 0.42
	2	4.12 ± 0.02	4.52 ± 0.09	4.56 ± 0.17	4.83 ± 0.24	5.04 ± 0.75
7.3	1	7.32 ± 0.00	7.29 ± 0.00	7.34 ± 0.00	7.37 ± 0.01	7.34 ± 0.03
	2	7.29 ± 0.00	7.28 ± 0.00	7.35 ± 0.00	7.37 ± 0.01	7.39 ± 0.03

a tendency to increase and a high variability whereas the pH values of the solutions at pH 7.3 were stable (Table 2).

### Photostability study

Concentrations of clonidine and pH values were stable during the exposure period. There were no changes in the visual aspect of the solutions (Table 3).

Table 3: Test results of the photostability study

Formulation pH	Time point	Clonidine concentration (mg/mL)	pH value	Visual aspect
4.1	day 0	1.990 ± 0.025	4.85	Colourless, clear
	1 month	2.018 ± 0.025	4.89	Unchanged
7.3	day 0	1.989 ± 0.025	7.24	Colourless, clear
	1 month	1.978 ± 0.025	7.42	Unchanged

### DISCUSSION

#### Solution preparation

The choice of concentration of clonidine solution was based on a published study reporting the compatibility of clonidine 2 mg/mL with the infusion pump system used [2]. In the literature, pH values of 5 to 7 are suggested for injectable clonidine solutions [6, 7]. Because the formulation of commercially available Catapresan has a pH between 4.0 and 4.5, a pH of 4.1 was chosen for the test. The pH 7.3 was chosen because it is closer to

the physiological pH of cerebrospinal fluid.

#### Stability study

Both formulations of clonidine 2 mg/mL, i.e. with pH values of 4.1 and 7.3, were stable regarding visual aspect and concentrations of

clonidine. Concerning the pH of the solutions only the formulation at pH 7.3 was stable. The increase in pH during the study period for the formulation at pH 4.1 has been observed in an earlier study and described in the literature as a pH shift toward neutrality [6], and has probably no influence on its therapeutic use.

#### Photostability study

Formulations of clonidine did not show sensitivity to light during the exposure period although degradation upon exposure to light is theoretically possible. Another study observed evidence of clonidine hydrochloride reactivity with light but concluded that it is not sufficiently reactive to require protection from light [6].

#### CONCLUSION

The clonidine formulation with a pH of 7.3 was stable for at least six months at 40°C, and without protection from light. The availability of a concentrated injectable clonidine solution, which can easily be prepared in a hospital pharmacy with facilities for sterile drug preparation, should allow us to expand the use of clonidine in intrathecal administration with implanted infusion pumps in patients with chronic pain. One advantage is that refilling the pumps could be less frequent. A second advantage is that, because the clonidine concentration is higher, more space will be available in the pump for other active agents, as long as they are compatible with the concentrated clonidine. This opens new therapeutic options for the treatment of chronic pain.

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