Microbiological stability of a 10 µg/mL clonidine solution for paediatric use

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COM25-66642

Context : Clonidine is used for the treatment of opioid withdrawal syndrome in infants. While the physicochemical stability[1] of a clonidine solution has already been demonstrated, a microbiological stability study is necessary due to differences in the materials used, in accordance with Good Preparation Practices.

Study the microbiological stability of a 10 µg/mL clonidine solution in order to determine its shelf life

Méthodes

Microbiological control of non-sterile oral products (Ph. Eur. 5. 1. 4.)

2. 6. 12. Microbial enumeration test

Determination of the dilution that neutralizes the preservative (potassium sorbate) → a difference of less than a factor of 2 in CFU between the contaminated sample and the positive control (T+)

- ✓ Testing different dilutions in phosphate buffer
- ✓ Contamination of samples and T+ by *P. aeruginosa, S. aureus, B. spizizenii, A. brasiliensis, C. albicans* (Vitroids™ discs, Millipore®)

- ✓ Seeding using membrane filtration method (EZFIT® pump, Milipore®)

2. 6. 13. Test for specified microorganisms

Determination of the smallest dilution *allowing E. coli* growth

- ✓ Testing different dilutions in tryptone salt buffer
- ✓ Contamination of samples and T + by *E. Coli*

Opening bottles	Samples from open bottles		
Day 0	+7	+14	+28
Day 1			
Day 7	+7	+14	+28
Day 14			
Day 28	+7	+14	+28
Month 3			
Month 6	+7	+14	+28

Table 1: Timeline for opening bottles

- Fertility of culture media and applicability of the method verified.
- Study conducted over 3 months with checks on open bottles on days 0, 7, and 28.
- Continuation of the stability study on opened vials with repeated openings.

Résults

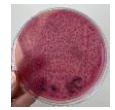
2. 6. 12. MICROBIAL ENUMERATION TEST

→ Difference of less than a factor of 2 in CFU between the diluted sample and the control preparation
→ Dilutions in phosphate buffer at 10 and 20 tested
→ 10-fold dilution selected

0.45µm MF-Milipore® cellulose ester membrane

2. 6. 13. TEST FOR SPECIFIED MICROORGANISMS : *E. Coli*

→ Dilutions in phosphate buffer at 10 and 20 tested
→ Insufficient inhibition of the preservative for 10-fold dilution
→ 20-fold dilution selected



MacConkey agar positive for E. coli for a clonidine solution 20-fold dilution

5. 1. 4. MICROBIOLOGICAL CONTROL OF NON-STERILE ORAL PRODUCTS

→ Meets the criteria set by the Ph. Eur.

	Limits Ph. Eur. 5. 1. 4	Max CFU found for the clonidine solution for 1 month of study	Max CFU found for the clonidine solution for 3 month of study
Aerobic germs	< 100 CFU/mL	30 CFU/mL	0 CFU/mL
Molds / Yeasts	< 10 CFU/mL	0	0
Specified microorganisms	Absence of *E. Coli*	Absence of *E. Coli*	Absence of *E. Coli*

Table 2: Results of microbiological testing for the 10 µg/mL clonidine solution

The neutralization of the preservative (potassium sorbate) is effective. The microbiological quality of the 10 µg/mL clonidine solution meets the criteria of the Ph. Eur.

Conclusion : The microbiological quality of the 10 µg/mL clonidine solution meets the criteria of the Ph. Eur. These results validate a shelf life of 3 months at 4 ± 2°C; the stability period after opening is 1 month. The study is continuing with checks at M6.

(1) : Formulation et étude de stabilité physico-chimique d'une suspension de spironolactone 5 mg/mL. Intérêt de l'électrophorèse capillaire vs CLHP, M. Sow, GERPAC 2024 ; (2) : Physicocheminal and Microbiological Stability of a New Oral Clonidine Solution for Paediatric Use, C. Verlhac, Pharm Technol Hosp Pharm 2018 ;3(2):79-90