A stability study of 25 mg/mL phenylephrine hydrochloride and 5 mg/mL tropicamide eye drops

Florence Stordeur, Cédric Chanat, Marie-Laure Brandely, François Chast
Pharmacy unit, GHU Paris Centre, site Hôtel-Dieu, 1 place du Parvis de Notre Dame, Paris, France

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Backgrounds and Aims

• Prematurity's retinopathy is detected by a frequent fundus performed during the first weeks of life, using a mydriatic solution. However, most of commercially available pharmaceutical specialities are not recommended or contraindicated for this type of patients.
• Thus, GHUPC Pharmacy developed for the neonatal resuscitation an eye drops formulation, including 25 mg/mL (2.5%) phenylephrine hydrochloride (alpha sympathomimetic) and 5 mg/mL (0.5%) tropicamide (anticholinergic). Both active susbtances are combined on the same vial in order to make the administration easier. Pupillary dilation is adequate and quickly obtained.
• The aim of the study was to demonstrate the physical, chemical and microbiological stability of this eye drops.

Methods

Eye drops preparation/storage

- Phenylephrine hydrochloride powder (INRESA®) dissolving into the tropicamide solution (Mydriaticum® single-dose 0.5%, THEA)
- Sterilizing filtration and aseptic filling process of 1 mL in high density polyethylene sterile vial
- Overpressure isolator placed in a grade D environment
- 3 batches of 40 units each produced by 3 different operators
- Storage : away from the light and at room temperature

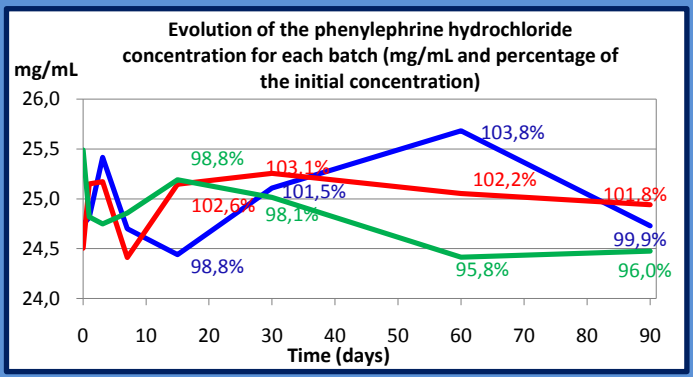
Stability study parameters

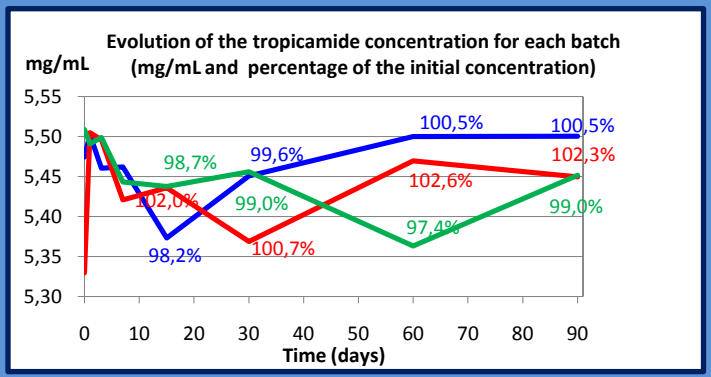
Frequency of analyses : H0, H1, H75, D7, D15, D30, M2, M3

- Active compounds content : HPLC-UV (average of 3 units/batch)
• Conditions :
- Stationary phase : Hypersil® BDS column C 18 5 µm, 250 * 4,6 mm
- Mobile phase : orthophosphoric acid buffer pH=3/acetonitrile (70/30/3.4)
- Flow: 1,2 mL/mn - Temperature : 25°C - Pression <250 bar
• forced degradation study done which makes it Stability-indicating assay method (SIAM)
- pH and osmolality (average of each batch)
- Visual appearance (color, particle visible by the naked eye)
- Vials weighing (40 units/batch)
- Sterility test monitored using BacT/Alert® (BIOMERIEUX) application, approved by European pharmacopeia 7,7

	phenylephrine	tropicamide
Linearity	[10-40 µg/mL] r>0.999	[2-8 µg/mL] r>0.998
Accuracy : Average covery	100.00 % (IC 95 = [98.23-101.77 %]	100.10 % (IC 95% = [97.21-102.98 %]
Repeatibility : coefficient of variation	< 0.5 %	< 0.8 %
Intermediate precision : coefficient of variation	< 1,46 %	< 2.52 %
Detection limit	0.62 µg/mL	0.21 µg/mL
Quantification limit	1.87 µg/mL	0.63 µg/mL
Sensitivity limit	0.053 µg/mL	0.041 µg/mL

Results and Discusion





	Batch 1	Batch 2	Batch 3
Phenylephrine hydrochloride concentration (mg/mL)	24,95 ± 0,42	24,72 ± 0,31	24,81 ± 0,41
Tropicamide concentration (mg/mL)	5,46 ± 0,04	5,39 ± 0,08	5,48 ± 0,04
pH	4,98 ± 0,02	4,99 ± 0,03	4,99 ± 0,01
Osmolality (mOsm/kg)	514 ± 10	517 ± 9	508 ± 7
Color	colourless	colourless	colourless
Particle visible by the naked eye	nil	nil	nil
Bottles mass loss	0,37%	0,26%	0,27%
Sterility within 3 months	kept	kept	kept

• Phenylephrine hydrochloride and tropicamide contents remained in ± 5% of the target value in the three batches.
• We did not note any variation of the solution aspect.
• pH as well as osmolality were kept constant.
• This shows that no degradation of the solution occured.
• Evaporation process inside eye drops is negligible.
• Sterility was maintained after 3 months.

Conclusion

• This study allowed to validate the physical, chemical and microbiological stability of phenylephrine hydrochloride and tropicamide eye drops conserved inside LDPE conditioning, away from light and at room temperature for three months.
• These results join stability data concerning especially phenylephrine hydrochloride.
• This contributes to adopt new management to produce this eye drops, and to reduce costs.

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