Physicochemical stability of voriconazole at 1 mg/mL in polypropylene syringes for intravitreal injection

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Background and importance

Voriconazole

- **Used off-label in ophthalmology** for the treatment of **fungal endophthalmitis**
- **Administered by intravitreal (IVT) injection**, commonly at a dose of 100 µg in 0.1 mL (1 mg/mL) [1-5]
- **No licensed, ready-to-use voriconazole formulation available on the market** for intravitreal administration

→ **In practice :** preparation of **hospital-compounded syringes, commonly made of polypropylene**

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No stability data available in the literature in polypropylene syringes at 1 mg/mL

Necessity of stability data

Aim and objectives

To evaluate the physicochemical stability of voriconazole

- Container: **polypropylene syringes**
- Concentration: **1 mg/mL**
- Solvent: **0.9% sodium chloride** (0.9% NaCl)
- Storage: **2–8 °C, protected from light**
- Analysis: **on days 0, 1, 3, 7, 14 and 28**

Materials and methods

1) **Validation of the analytical method (RP-HPLC) as recommended by International Conference on Harmonization (ICH) Q2(R1)**

- **Method:** HPLC-DAD detector at 256 nm
- **Column:** LiChrospher® 100 RP-18 (Merck) 12.5 cm, Ø=4mm, particle size = 5 µm
- **Mobile phase:** 60% ultra-pure water and 40% acetonitrile
- **Flow rate:** 1 mL/min
- **Injection volume:** 50 µL
- **Analysis time:** 10 min
- **Forced degradation:** HCl 5M (6h) ; NaOH 0.1M (10 min); heat (5h at 80°C), UV (5h under a lamp at 254 nm); H_2O_2 30%

2) **28-day stability study**

Three 60 mL polypropylene syringes containing voriconazole at 1 mg/mL in 0.9% NaCl were prepared.

	Chemical stability		Physical stability	
	pH	**HPLC**	**Visual inspection**	**Subvisual inspection**
Stability criteria	pH variation less than 1 unit	90% IC < C° < 110% IC + monitoring of degradation products	Absence of precipitation, aggregation, color change or gas formation	Containers < 100 mL: < 6000 particles of 10 µm and < 600 particles of 25 µm
References standards	European consensus conference (Bardin *et al.*, Ann Pharm Fr, 2011)	Food and Drug Administration, 2008	European Pharmacopoeia, monograph 2.9.20	European Pharmacopoeia, monograph 2.9.19
Instrumentation	CRISON PH 25 pH-meter	HPLC LaChromElite VWR	Naked eye	PAMAS SVSS (Germany) particle counter

IC = Initial concentration C° = Concentration at each analysis time point

Results

1) **HPLC method**

- **Linearity:** R^2 > 0.999 (standard curve 5 points: 600-1400 µg/mL)
- **Stability indicating capacity:** degradation products observed (with 2–16% degradation)
- **Repeatability:** [0.12 % – 1.51 %]
- **Intermediate precision:** [0.54 % – 2.52 %]

2) **Physical stability**

Visual inspection No precipitation, aggregation, or color change

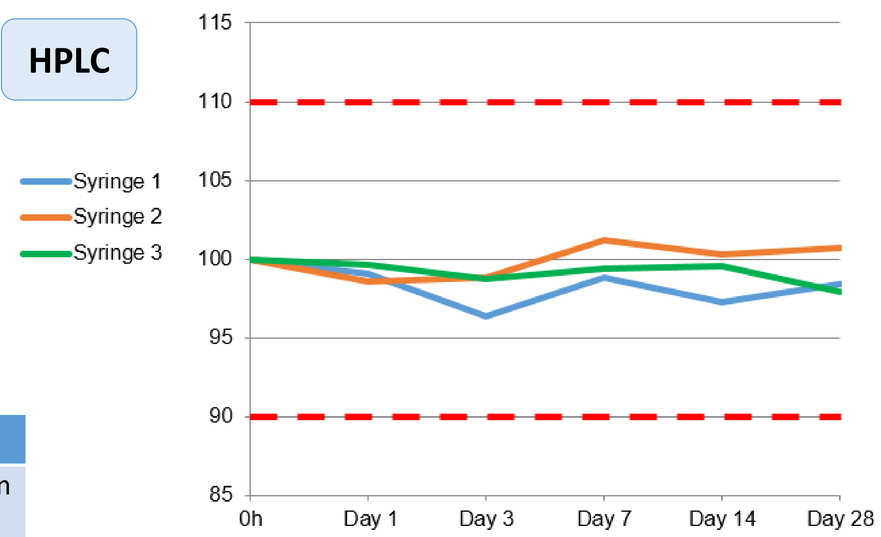
Subvisual inspection Particle counter (PAMAS) ✓ = Compliant

	0h		Day 1		Day 3		Day 7		Day 14		Day 28	
Particle size	10 µm	25 µm	10 µm	25 µm	10 µm	25 µm	10 µm	25 µm	10 µm	25 µm	10 µm	25 µm
Syringe 1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Syringe 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Syringe 3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

3) **Chemical stability**

pH Variation (compared with baseline) : **[–0.21 ; +0.58]**

HPLC



Mean voriconazole concentrations (%) over time

Each data point = mean concentration from three measurements (triplicate).
Exception: T0h – syringes 2 and 3: two measurements (duplicate) due to analytical error.

Degradation products (DP): No significant DP detected

Conclusion and relevance

Voriconazole 1 mg/mL in polypropylene syringes diluted in 0.9% NaCl is physicochemically stable for 28 days when stored at 2–8 °C, protected from light

→ **supports the hospital preparation** of voriconazole in polypropylene syringes and **enables advance preparation over a 28-day period**

Implications for practice

- ✓ **Rapid availability for patients in clinical emergencies** through advance preparation of ready-to-use prefilled syringes.
- ✓ **Optimization of hospital pharmacy workload** through batch preparation, enabling compounding during lower-activity periods.
- ✓ **Reduction of drug wastage and cost savings** through more efficient use of drug vials: a single vial can be used to compound multiple prefilled syringes for future use without generating waste.

REFERENCES

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