

LOEUILLE Guillaume¹, VIGNERON Jean^{1,4}, D'HUART Elise^{1,4}, CHARMILLON Alexandre², DEMORE Béatrice^{1,3,4}

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1 Pharmacy, CHRU de Nancy, Allée du Morvan, 54511 Vandoeuvre-lès-Nancy, France

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

2 Infectious diseases department, CHRU de Nancy, Allée du Morvan, 54511 Vandoeuvre-lès-Nancy, France 4 Infostab, French non-profit association, 54180 Heillecourt France

INTRODUCTION

- **Ceftolozane (cef)/tazobactam (taz)** 1/0,5 g (ZERBAXA®): combination of a new 3th generation cephalosporin and a β-lactamase inhibitor.
- **Ceftolozane/tazobactam** is used to treat **severe infection** (multi-resistant germs as *Pseudomonas aeruginosa*)
- The usual dose is **3/1.5 g** per day and **6/3 g** per day for serious infection (divided in 3 injections per day).
- β-lactam antibiotics have a **time-dependent** activity, the **continuous administration** of which improves therapeutic effectiveness.
- Should be validate **long terms stability**.

PURPOSE

Studied the physicochemical stability of **ceftolozane/tazobactam**

	Normal saline (0.9 % NaCl) and Dextrose 5% in Water (D5W)	62.5/31.3 mg/mL	20-25 °C	T0h, 8h, 24h, 48h
		25/12.5 mg/mL	37 °C	

MATERIALS AND METHOD

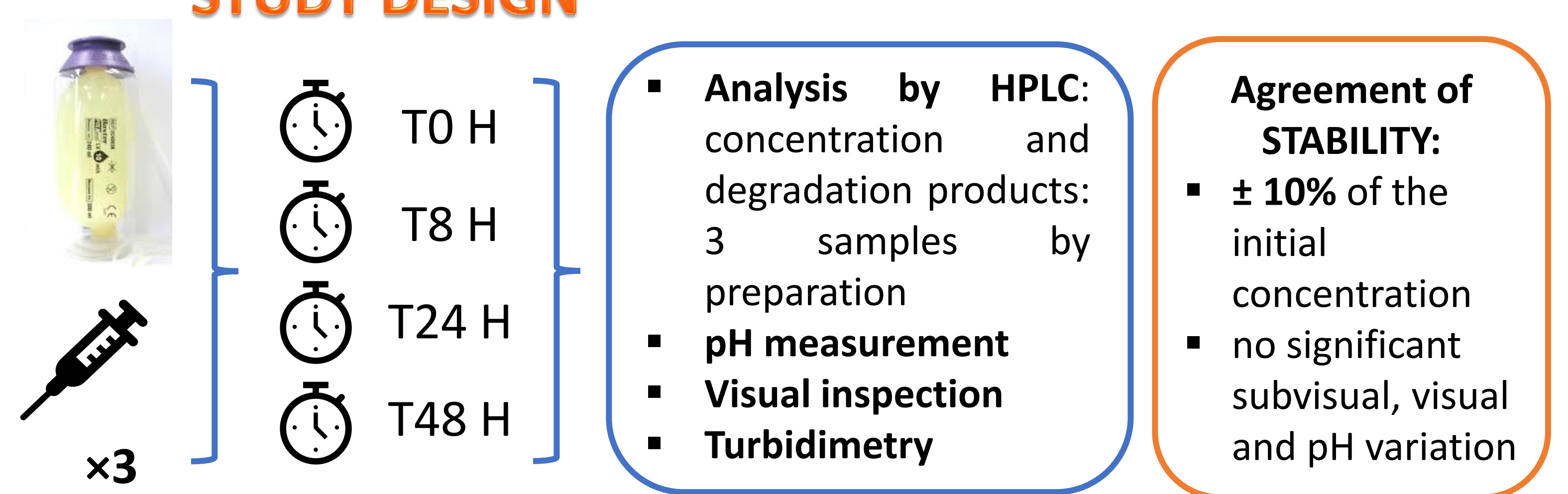
CHEMICAL STABILITY

- Method:** RP-HPLC with DAD detector at 220 nm
- C18 LiCrospher® 12.5 cm, particle size = 5 μm
 - **Mobile phase:** isocratic: potassium phosphate buffer (50 mM) / acetonitrile 1000/26 (v/v), pH = 3.4 adjusted with HCl 1 M
 - **Flow rate:** 1mL /min
 - **Injection volume:** 20 μL
- **VALIDATION ACCORDING TO THE ICH Q2(R1)**
- **Forced degradation** → : HCl 1M (3h30); NaOH 0.01 M (15 min); UV (45 min at 254 nm); heat (3h at 70°C)
 - **Linearity:** standard curve with 5 points: 50 - 150 μg/mL (cef)
 - **Repeatability and intermediate precision:** 50-100-150 μg/mL (cef)
 - **pH measurement** (Bioblock Scientific pH meter)

PHYSICAL STABILITY

- **Visual inspection:** search for colour change, precipitation and gaz formation
- **Subvisual inspection:** turbidimetry by spectrophotometry at 350, 410 and 550 nm (Safas Monaco UV m²)

STUDY DESIGN

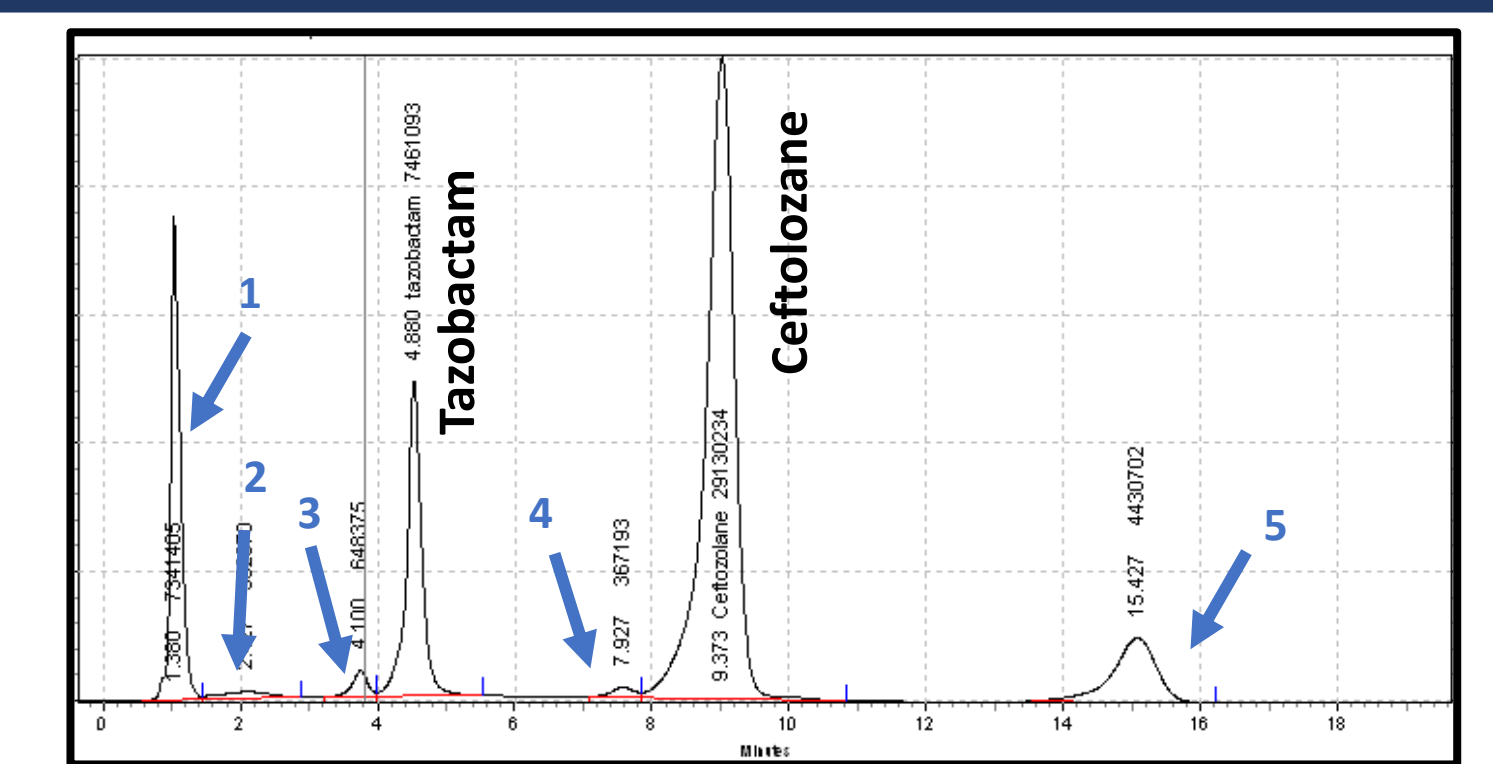
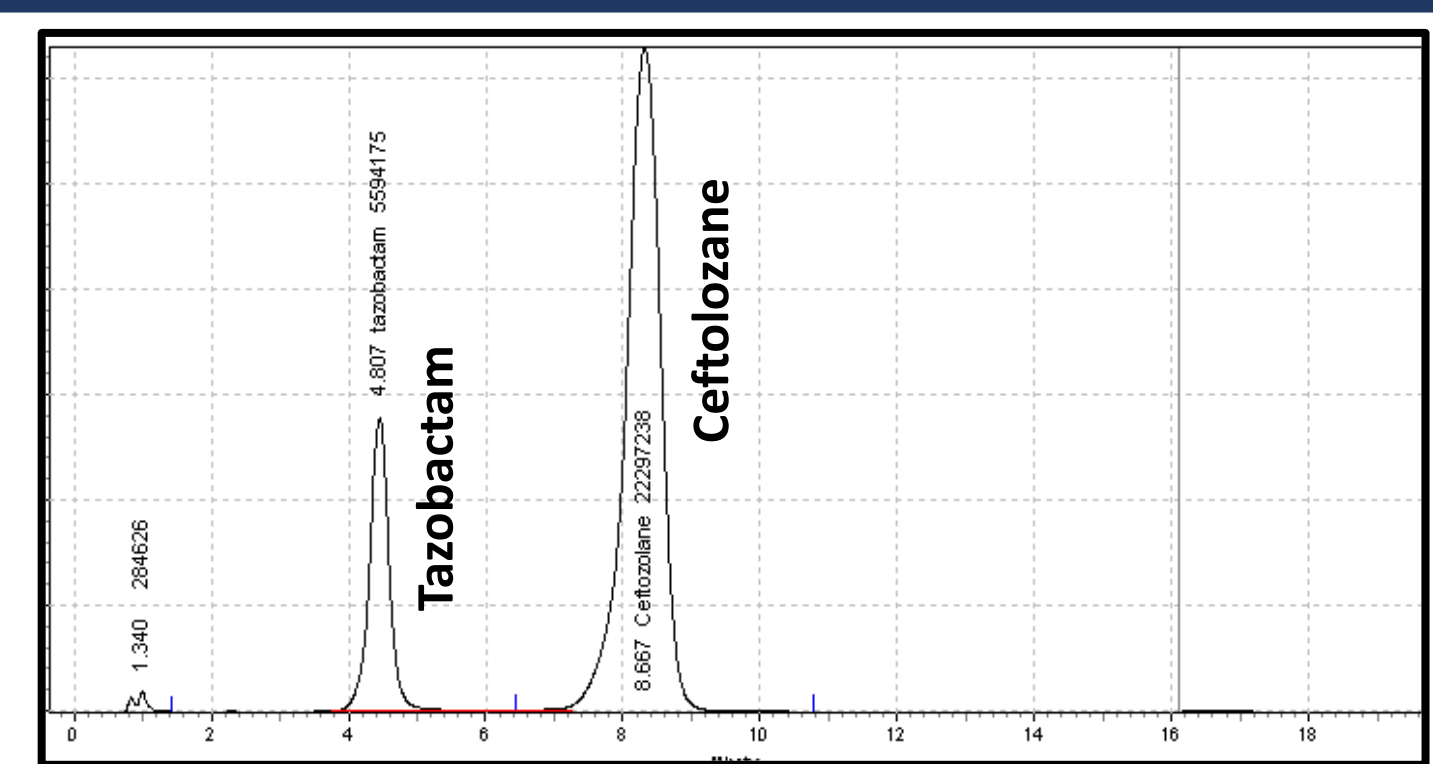


ICH: International conference on harmonisation.

RESULTS

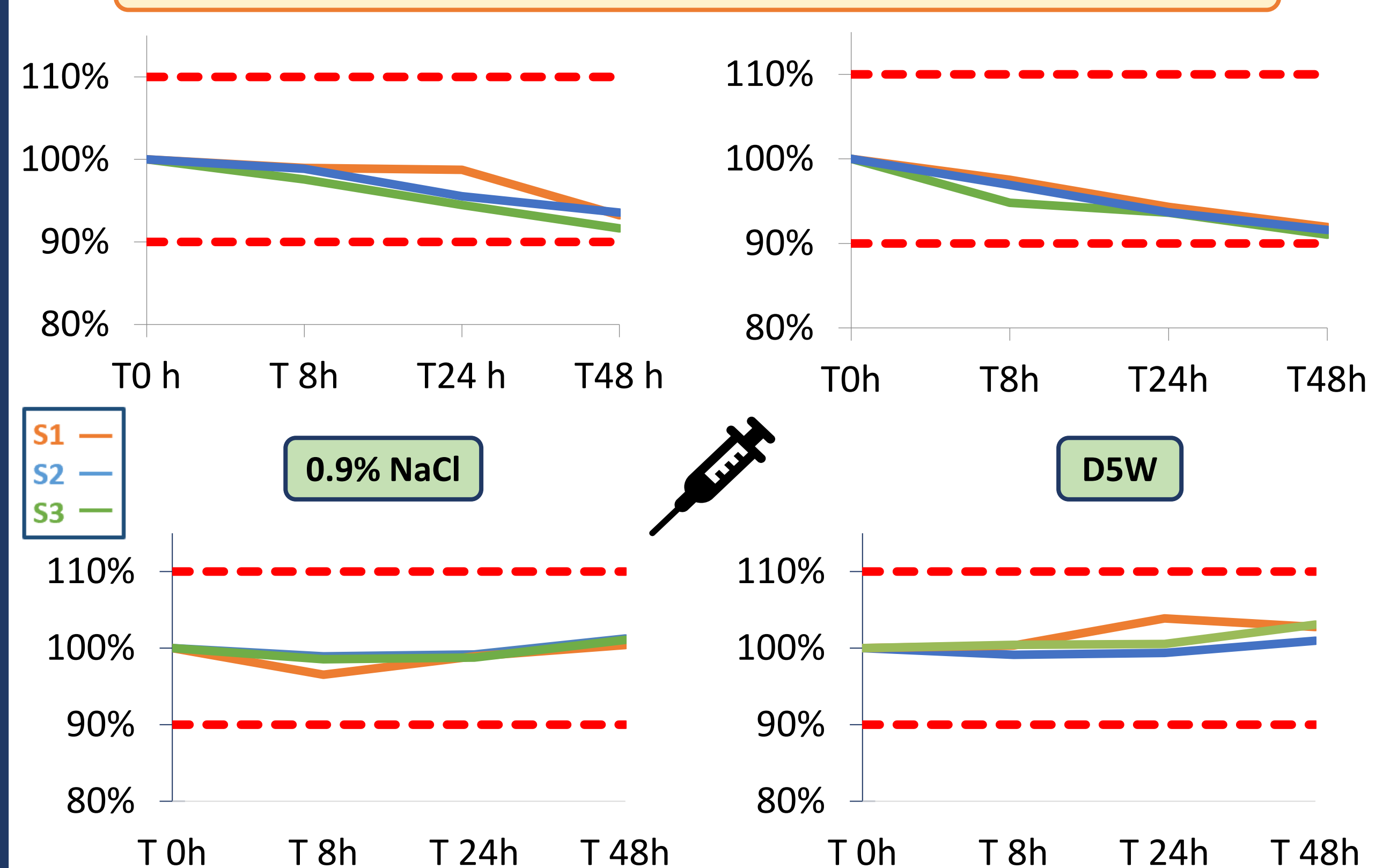
METHOD VALIDATION

- **Linearity :** R² > 0.9999 (cef) and (taz)
- **Repeatability and intermediate precision :** CV < 2%
- **Retention time:** 4.8 min (taz) and 8.7 min (cef)
- **Stability indicating capacity :** detection of 13 degradation products (in all stressed conditions)

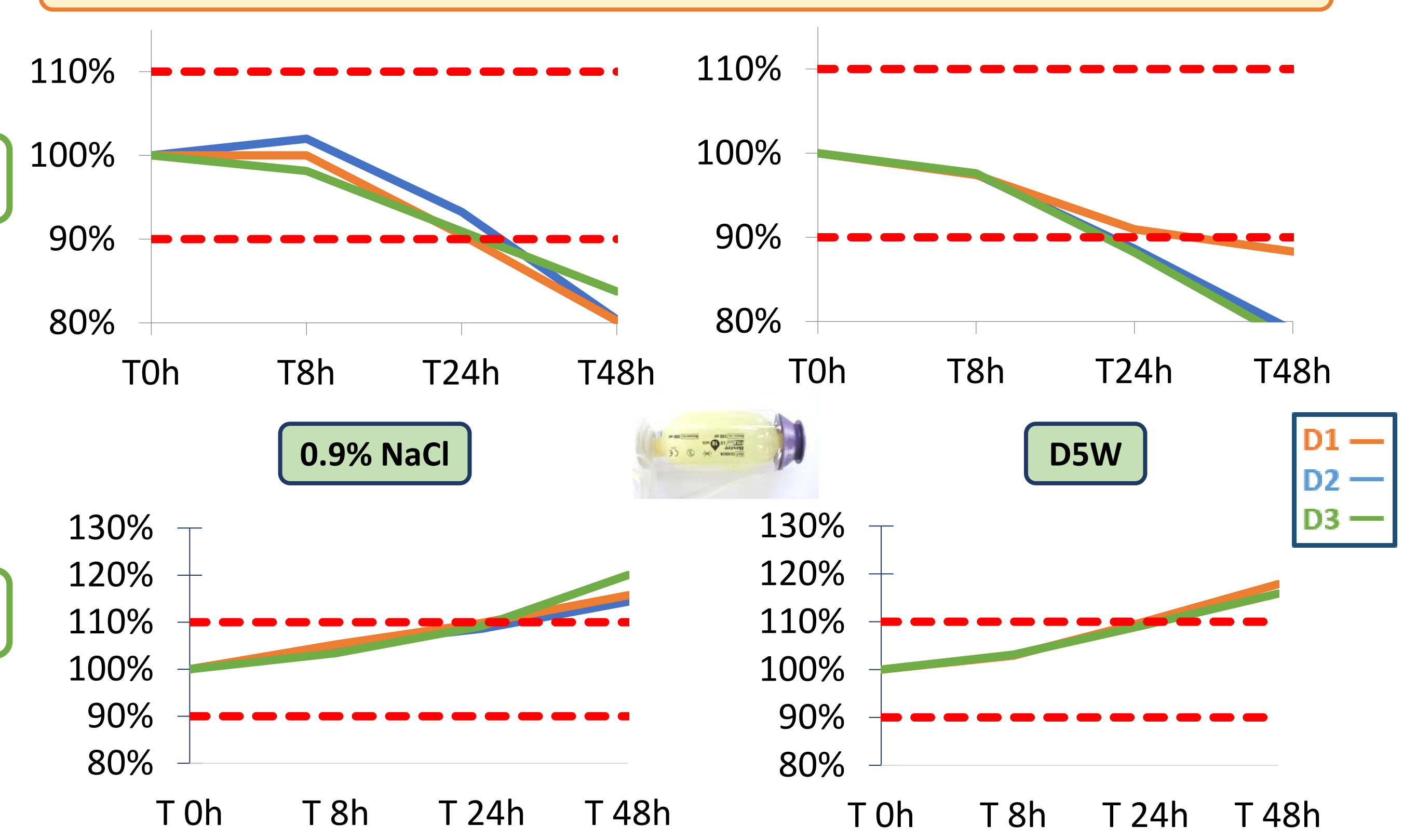


CHEMICAL STABILITY

Storage : 20-25°C, light, concentration: 62.5/31.3 mg/mL



Storage : 37 °C, protect from light, concentration: 25/12.5 mg/mL

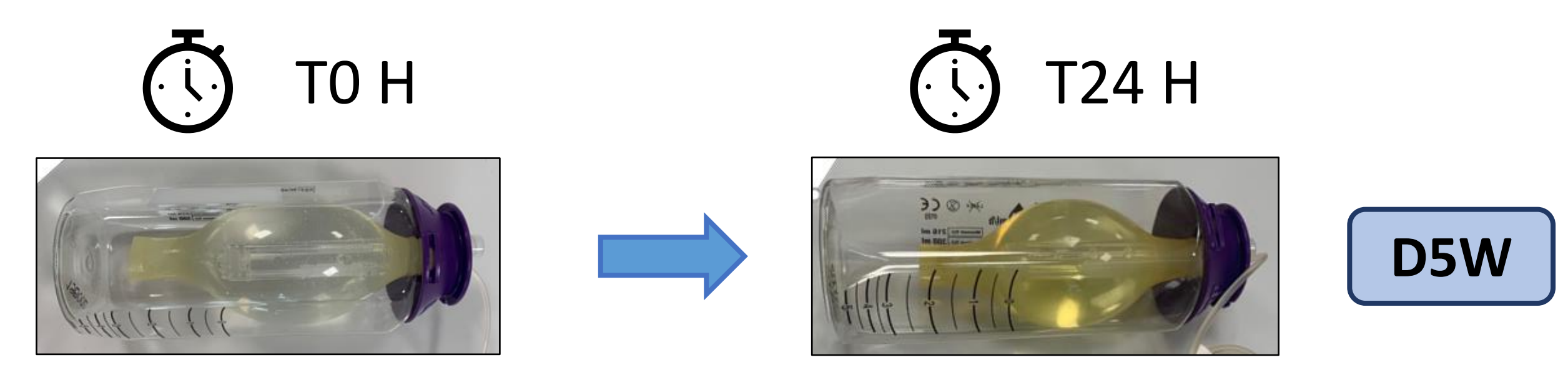


- **Degradation product:** peak n°1 with a retention time at 1.34 min also observed after the forced degradation gradually increased in all condition.

- **pH measurements :** decreased slightly with maximum variation : **0.7 unit pH** (5.95 → 5.26), T0h → T48h for elastomeric devices. (D5W)

PHYSICAL STABILITY

- **Visual aspect:** **yellowing** at 24 hours in elastomeric devices (0.9% NaCl an D5W)
- **Subvisual aspect:** ↗ significant of the absorbance values at **350 and 410 nm** wavelength after 24 hours in **elastomeric devices** (0.9% NaCl an D5W).



CONCLUSION

- Physicochemical stability of **ceftolozane/tazobactam** at **62.5/31.5 mg/mL** in 0,9% NaCl and **D5W** was proved for **48h** in **syringes**
- Administration by **continuous infusion** in a minimal volume of solution.

- In **elastomeric devices**, **ceftolozane/tazobactam** at **25/12.5 mg/mL** was **stable at 37°C** in the **D5W** and **0.9% NaCl** for **8 hours**
- Possible stability of 12 hours, further study to be carried out.