Assessment of the relevance of measuring osmolality as a criterion for the stability of drug solutions

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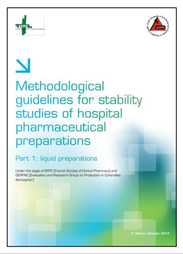
INTRODUCTION

- **Stability studies of drugs** are important for the **realization of preparations in advance** or **standardized doses**. In addition to HPLC analytical methods, **osmolality measurement** is used by some authors **as a criterion to evaluate the stability** of a drug in solution. To the best of our knowledge, no scientific publication correlates osmolality with the stability of a solution.
- **Osmolality measurement is recommended by :**



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OBJECTIVES

- To study the **relevance** of **osmolality measurement** by measuring the variation of this parameter on injectable solutions whose **instability** has been **chemically demonstrated** by high performance liquid chromatography (HPLC) in the literature.

MATERIAL AND METHOD

Bibliography research

Selection of **5 anticancer drugs and 6 antibiotics** whose **chemical instability** had been demonstrated in the literature over a **short period**, ranging from **2 to 48 hours**.

Realization of the preparation according to the publications

3 identical samples per selected preparations.

Measurements of the osmolality of each sample

3 measurements of each sample on **freshly prepared preparations** and at different times **until a chemical degradation** demonstrated by HPLC of **at least 10% and up to 50%.**

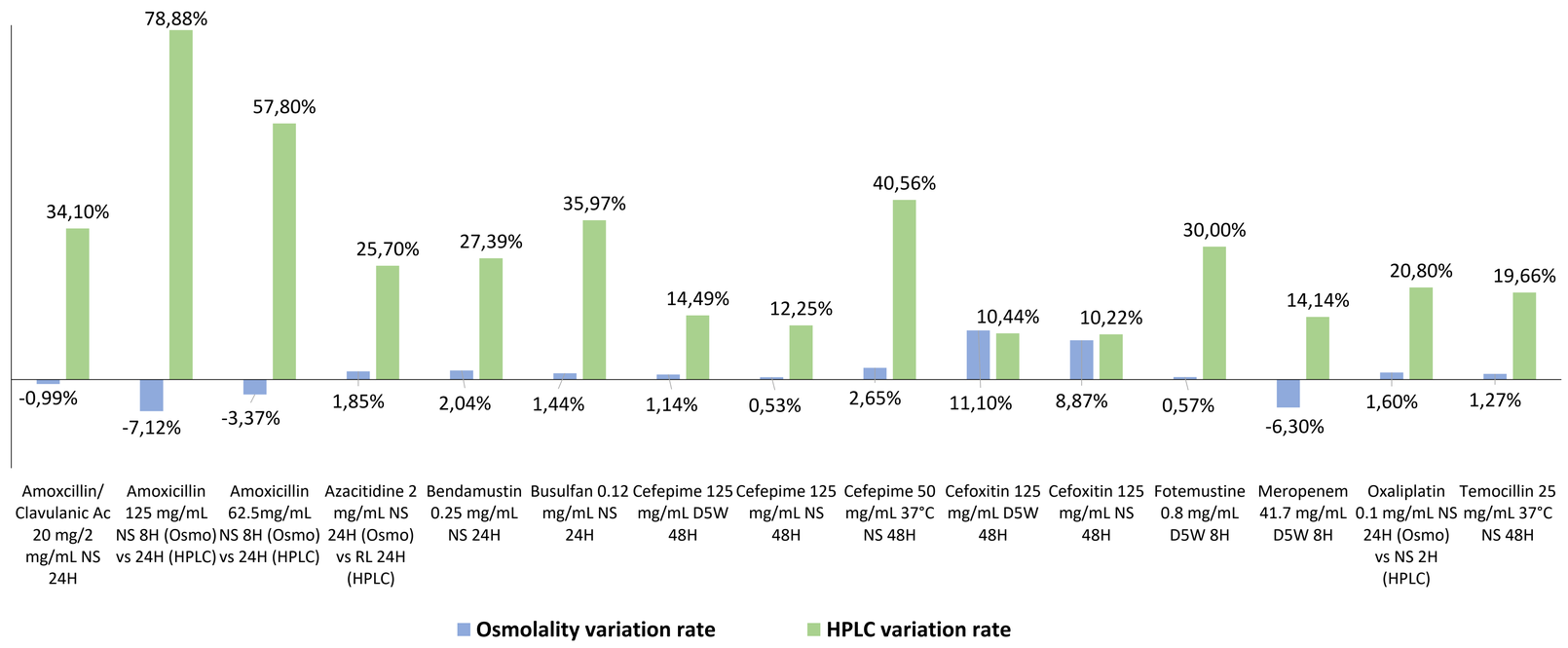
RESULTS AND DISCUSSION

ANTICANCERS DRUGS		
Azacitidine	2 mg/mL qs RL (HPLC) – NS (Osmolality)	
Bendamustin	0.25 mg/ mL qs NS	
Busulfan	0.12 mg/ mL qs NS	
Fotemustine	0.8 mg/mL qs D5W	
Oxaliplatin	0.1 mg/ mL qs NS	
ANTIBIOTICS		
Amoxicillin	62.5 mg/mL (3 g/48 mL) qs NS	125 mg/mL (6 g/48 mL) qs NS
Amoxicillin/ Clavulanic Ac	20 mg/2 mg/mL (2 g/200 mg/100 mL) qs NS	
Cefepime	125 mg/mL (6 g/48 mL) qs NS or D5W	50 mg/mL (3 g/60 mL) qs NS 37°C
Cefoxitin	125 mg/mL (6 g/48 mL) qs NS or D5W	
Meropenem	41.7 mg/mL (2 g/48 mL) qs D5W	
Temocilin	25 mg/mL (3 g/120 mL) qs NS 37°C	

RL = Ringer's Lactate ; NS = Normal Saline ; D5W = Dextrose 5% in water

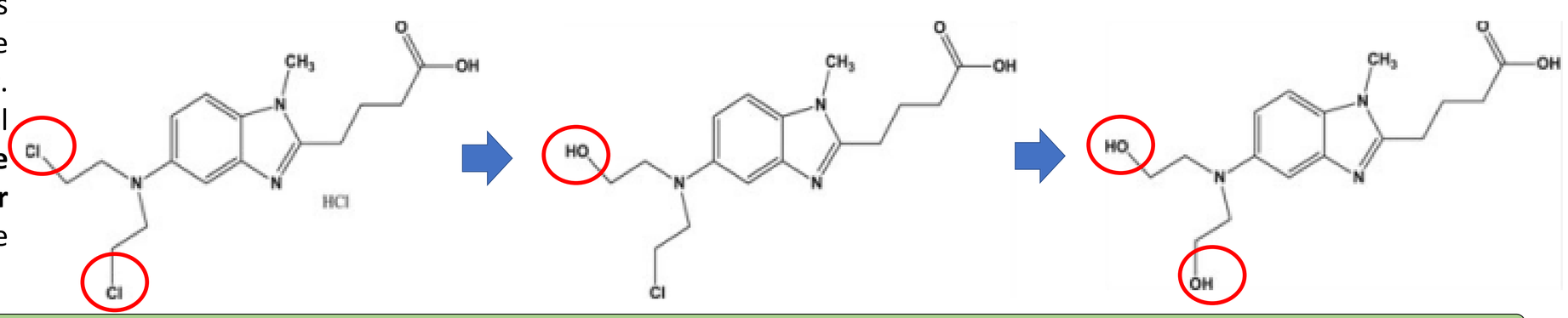
Variation rate of osmolality is inconsistent with chemical degradation measured by HPLC, exept for the cefoxitin 125 mg/mL

Comparison between **variation rate of osmolality** and **chemical degradation rate demonstrated by HPLC** between freshly prepared solutions and the time until the chemical degradation of the molecule

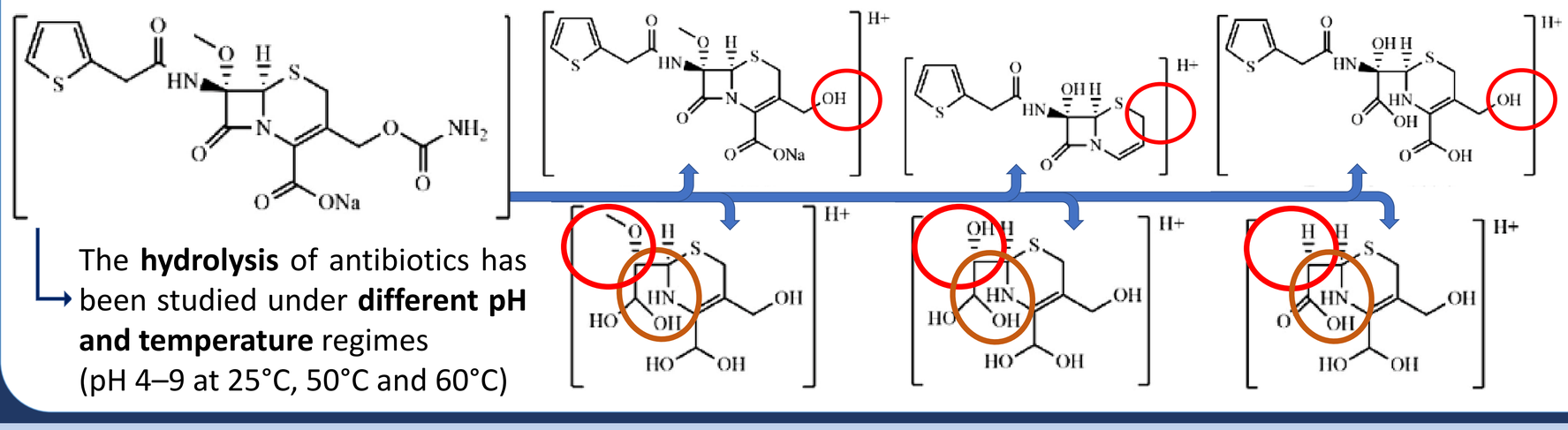


Example of chemical degradation of **BENDAMUSTINE**

The **chlorides** of the nitrogenous mustard of the bendamustine are **substituted by hydroxyle groups**. The substitution of one chemical entity by another does **not increase the number of chemical entities per kilogram of solvent** and therefore **no increase of the osmolality.**



Study of chemical degradation of **CEFOXITIN**



The **hydrolysis** of antibiotics has been studied under **different pH and temperature** regimes (pH 4–9 at 25°C, 50°C and 60°C)

Hydrolysis of the molecule causes **side chain eliminations** or **ring opening**. Thus, a molecule of cefoxitin hydrolyzes into **several degradation products**, thus increasing the number of chemical entities per kilogram of solvent and therefore **increase of the osmolality.**

CONCLUSION

One molecule out of the 11 selected has an osmolality that varies in accordance with the chemical degradation demonstrated by HPLC :

- Osmolality variation dependent on the degradation mechanism of the molecule,
- **Osmolality does not seem to be a conclusive stability criterion.**

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