INTEREST OF EXTENDING THE PHYSICOCHEMICAL STABILITY OF TEMOZOLOMIDE SOLUTIONS IN ROUTINE

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Alkylating agent

Temozolomide (TMZ)

First-line treatment for glioblastoma (association with radiotherapy, STUPP protocol)

Intraveinous (IV) form = alternative of oral form for patients suffering from swallowing problems

Low stability period of TMZ IV

14h at 24°C and **24h** at 4°C for lyophilized powder in water according to the Summary of Product Characteristics (SPC)

➔ **Organisational and high risk of financial loss (750 € per preparation)**

➔ **Impact on patients care during the week-ends**

<u>Objective</u>: To evaluate the stability of reconstituted TMZ in different solvents with different temperature conditions

MATERIAL AND METHOD

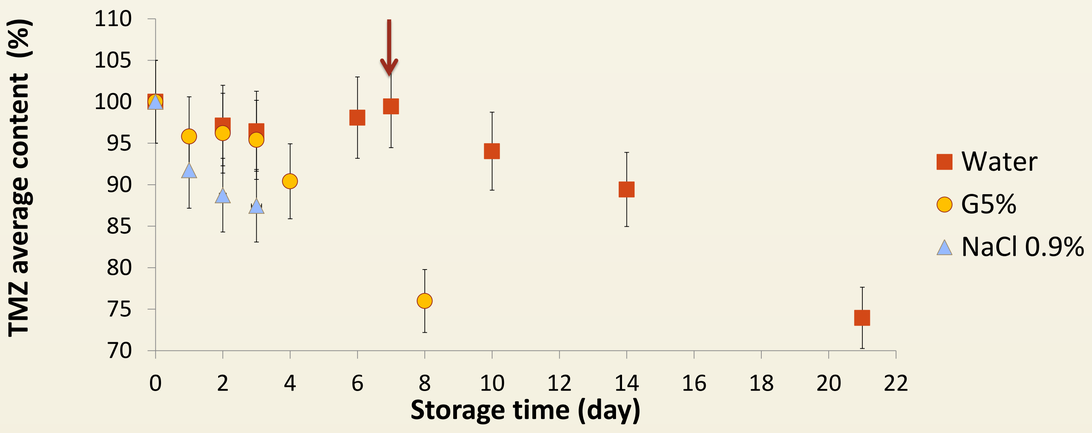
- Stability indicating high performance liquid chromatography method was developed and validated (ICH guidelines)
- Samples were stored at different temperature conditions, then extemporaneously analyzed by HPLC
- Limpidity of the solutions was assessed visually under white background

Drug product	Packaging	Solvent	Storage conditions	Bags	Concentration	Assays
IV TMZ 2.5 mg/mL Lyophilized powder reconstituted in water	Empty propylene infusion bags without light protection (SLB®) of 250 mL	Pure in water	4°C ± 1°C	8	2.5 mg/mL	*Day 0, D1, D2, D3, D6, D7, D10, D14, D15, D21*
			24°C ± 1°C	8		
			50°C	8		
		Sodium chloride 0.9%	4°C ± 1°C	8	0.5 mg/mL	*D0, D1, D2, D3, D4, D7*
			24°C ± 1°C	8		
		Glucose 5% w/v	4°C ± 1°C	8	0.5 mg/mL	
			24°C ± 1°C	8		

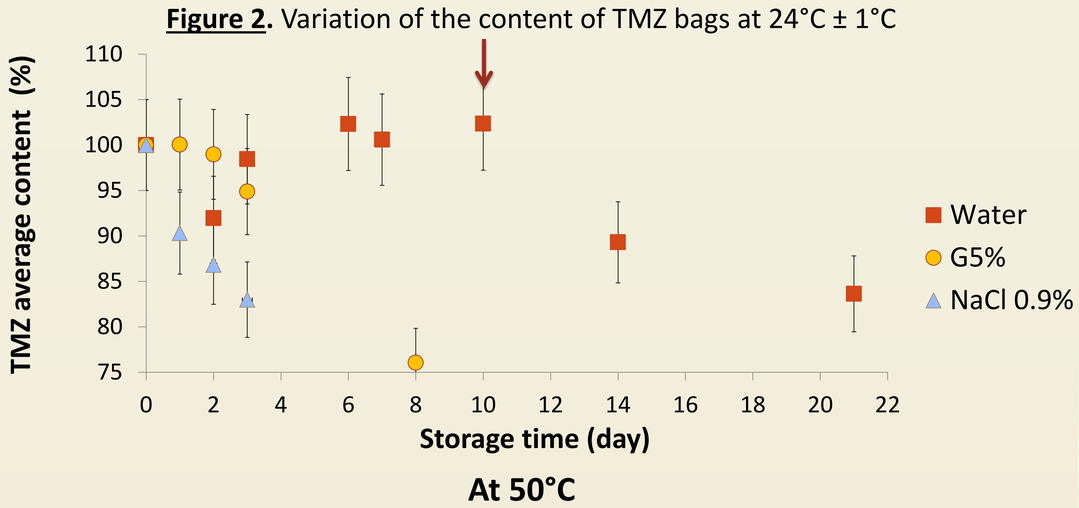
RESULTS AND DISCUSSION

Quantitative approach

<u>Figure 1</u>. Variation of the content of TMZ bags at 4°C ± 1°C



<u>Figure 2</u>. Variation of the content of TMZ bags at 24°C ± 1°C



At 50°C

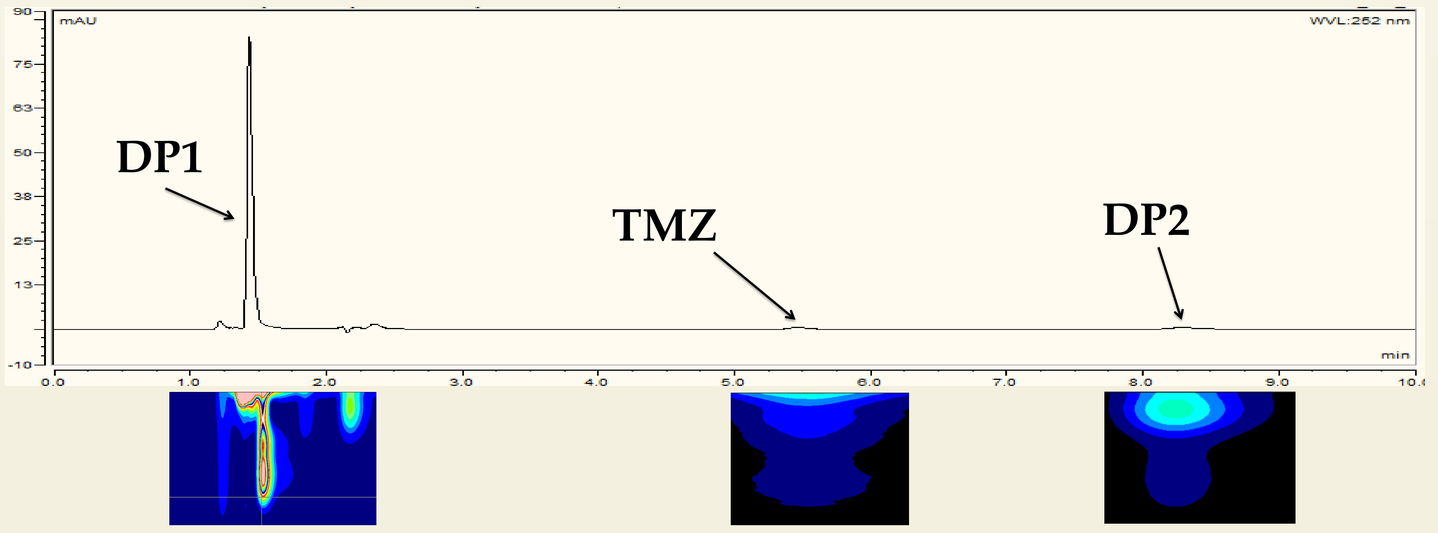
➔ Stability < 24h

➔ Redness of the solution

Qualitative approach

- With all solvents : formation of **2 degradation products** (**<u>DP1</u>** and **<u>DP2</u>**)

(Relative Retention Time = 0.4 and 1.5 min respectively)



<u>Figure 3</u>. Chromatogram and UV absorption of TMZ and its **degradation** products

- TMZ undergoes spontaneous hydrolysis under physiological pH to MTIC* (active molecule) rapidly degraded to AIC [1].
- Reversible precipitation in one bag stored at 4°C was observed.

➔ Important to check the limpidity prior to each administration

- **Precipitation was not accompanied by the lost of content**
- No physicochemical incompatibility with the bag component observed
- Long term stability of the reconstituted TMZ in the bottle was not assessed

CONCLUSION

To conclude, given the positive results obtained at 4°C and 24°C in water respectively of 7 and 10 days, a change in practices may improve the production unit organization and prevent financial loss. It's worth to verify the limpidity prior to each administration, or even consider using of inline filter as precipitation was not accompanied by the lost of content. Extensive testing is in progress to understand the intrinsic stability of the API in the drug product.

[1] Theriaque

* MTIC: 3-methyl-triazenyl-imidazole-4-carboxamide, AIC: 4-amino-5-imidazole-carboxamide