DEVELOPMENT OF A STABLE PARENTERAL SOLUTION OF TOPIRAMATE FOR EMERGENCY TREATMENT OF STATUS EPILEPTICUS

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Background and objectives

Topiramat for treatment of Status epilepticus (SE)

- Status epilepticus is a neurological emergency **(“Time is brain”)**
- Increased pharmacoresistance, morbidity and mortality when not treated immediately[1]
- Control of SE with topiramate in 70% of patients who did not respond to first line treatment[2]
- Status Quo: **no i.v. formulation available**
- Application of **tablets via enteral feeding tube**
- Problem: **unpredictable pharmacokinetics**, as rapid therapeutic drug levels are needed

➢ **Development of a stable and practical i.v. formulation with a stability of ≥ 3 months**

Materials and methods

Development of different i.v. formulations:

- 200 mg topiramate per dose
- Evaluation of adding a solubilizer (Meglumin)
- Evaluation of stability with different pH values (precipitation)
- Isotonic solution: 270-330 mOsmol/kg

Formulations for stability testing:

- **Ready to use:**
  4 mg/ml 50 ml, 0.025 M phosphate buffer (pH: 8)
  8 mg/ml 25 ml, 0.025 M phosphate buffer (pH: 8)
- **Infusion concentrate:**
  20 mg/ml 10 ml, solubilizer: Meglumin 2% (pH: 9.6)

Stability indicating measurements (days 90 / 180):

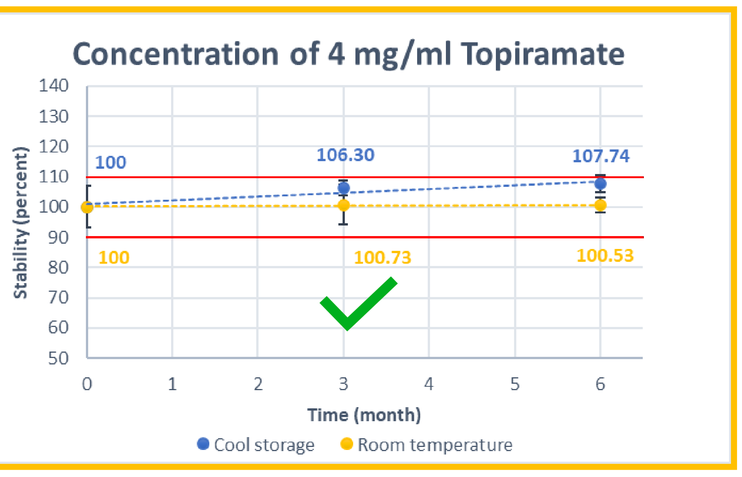
- 3 batches
- 2 storage conditions: 2-8°C, room temperature
- Brown glass vials (light protection suggested by USP[3])

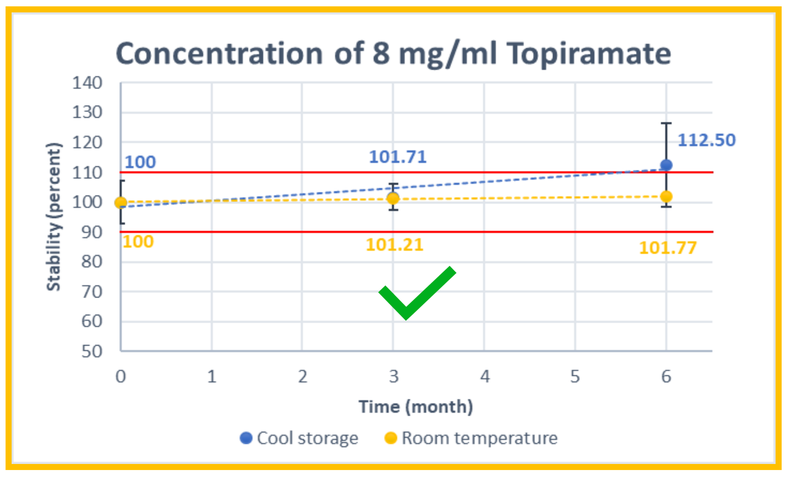
Concentration of topiramate (LC-MS/MS, method analogous to TDM of topiramate)

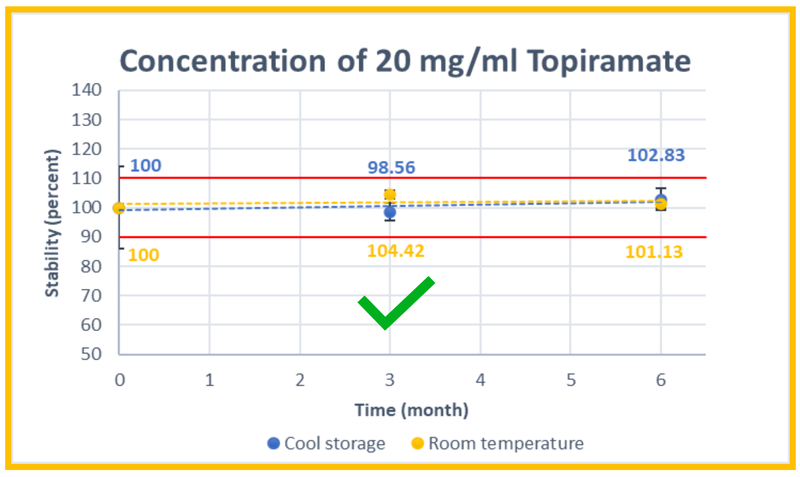
Potentiometric determination of pH (Ph. Eur.) 2.2.3

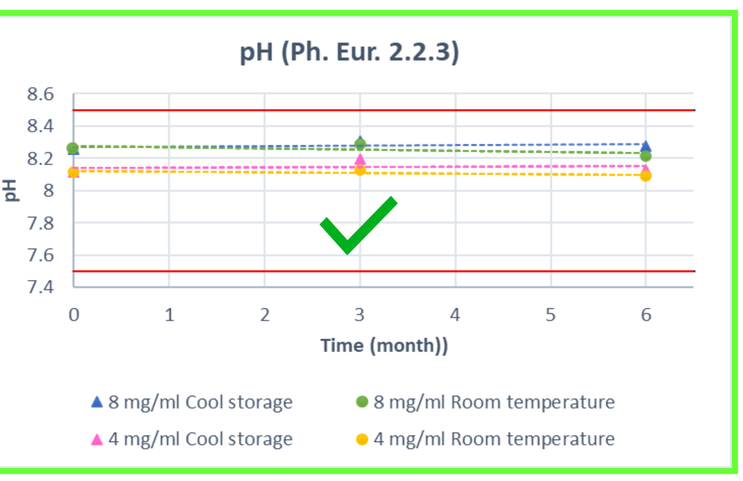
Clarity and degree of coloration (Ph. Eur.) 2.2.1, 2.2.2.

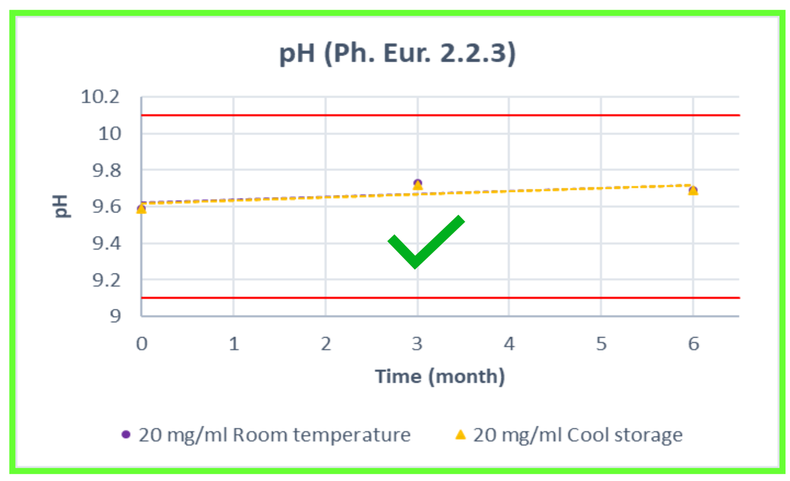
Results











Clarity and degree of coloration (Ph. Eur 2.2.1, 2.2.2)

✓ **Topiramate formulations 4 mg/ml, 8 mg/ml and 20 mg/ml showed no change in coloration and clarity at day 180 at 2-8°C and room temperature**

Conclusions

✓ **4 mg/ml, 8 mg/ml and 20 mg/ml were stable at room temperature**

✓ **4 mg/ml, 8 mg/ml and 20 mg/ml passed the pH requirements at cool storage and room temperature for the period of 180 days**

✓ **4 mg/ml, 8 mg/ml and 20 mg/ml remained clear and colorless for the period of 180 days for both storage conditions.**

➢ **Addition of a solubilizer (e.g. meglumin or cyclodextrin as used in literature[4]) has no additional benefit on 180 day stability**

➢ **Lower phosphate buffer concentrations (0.025 M in our formulation vs. 0.1 M as in literature[4]) show sufficient stability and should be preferred**

➢ **Physiological pH value is favored (pH 8 as in 4 mg/ml and 8 mg/ml vs. pH 9.6 as in 20 mg/ml)**

➢ **Storage at room temperature and «ready to use» infusion is preferred for the ICU**

Topiramate 4 mg/ml 50 ml was selected as final product.
Next to its 6-month stability, it is the most practical formulation for the ICU as its ready to use.

Literature:

[1] Chen, J. WY., Wasterlain, C. G. Status epilepticus: pathophysiology and management in adults. The Lancet Neurology. März (2006), S. 5(3):246-56.

[2] Hottinger, A., Sutter, R., Marsch, S., Rüegg, S. Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. CNS Drugs. 26(9), 1. September (2012), S. 761-72.

[3] The United Status Pharmacopeial Convention, Interim Revision Announcement. May (2017).

[4] Cloyd, J. C. US 2009/0239942 A1 United States, (2009).

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