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Compounding and quality control of two pediatric topiramate pharmaceutical preparations

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In pediatric wards, topiramate is prescribed as an antiepileptic at non-licensed dosages. Compounding is the best way to obtain topiramate drug adapted to pediatric patients, but this practice requires to control the quality of batches and to manage a stability study to establish a beyond-use-date. With this objective, 6 mg.mL^{1} topiramate oral suspension and 9 mg capsules were realized, and our laboratory was mandated for their quality control. Previously described dosing methods did not allow us to determine topiramate content in prescribed preparations. An original HPLC-UV derivatization dosing method of topiramate was validated and was proved to be stability indicating. This derivatization methodology, but also total aerobic microbial count (TAMC) and total combined yeasts and mold count (TYMC) allowed the quality control of topiramate capsules and topiramate suspension. Beyond-use-dates can be attributed with regards to United States Pharmacopoeia recommendations, and a stability study was performed on 6 mg.mL^{-1} topiramate suspension to confirm empirical data. Topiramate pediatric suspension was found to be stable for two months at +2/+8 °C, one month after opening and one day at ambient temperature.

1. Introduction

Topiramate is a sulfamate substituted monosaccharide with antiepileptic properties. In pediatric patients, topiramate was shown to be effective when used adjunctively for refractory partial-onset seizures and generalized tonic-clonic seizures (Ormrod and McClellan 2001; Riesgo et al. 2012). A few studies have evaluated the safety and efficacy of topiramate in neonates, especially in case of hypoxic ischemic encephalopathy (Filippi et al. 2010; Marques et al. 2019). Topiramate can cause metabolic acidosis, especially in neonates and infants having lower serum bicarbonate levels than adults (Baum and Quigley 1995). On a cohort of ten premature infants treated by oral topiramate for seizures, four developed necrotizing enterocolitis although a causal relationship has not been established by the authors (Courchia et al. 2018). Nevertheless, in treatment of neonatal seizures, topiramate is considered as efficacious as older medications but with higher tolerability (Ahrens et al. 2019). Topiramate dosage is patient-dependent and can be modified according to efficacy and occurrence of side effects. Topiramate prescriptions in pediatric wards involve a wide variety of dosages that cannot be covered by marketed oral drugs. Therefore, compounding remains the only alternative for each pediatric patient to have a suitable treatment. When topiramate should be prescribed to neonates, some prescribers prefer capsules to dissolve them in a low amount of liquid (to minimize the liquid absorption by the neonate), but with older pediatric patients, the suspension appears to be more practical. Topiramate, a class III compound in the Biopharmaceutic Classification System (Ramirez et al. 2010), is highly soluble, and the bioequivalence of a liquid oral form and sprinkled capsules was already studied on healthy adults (Johnson and Johnson 2011). Then, even if liquid formulation and capsules are not designed to be administered to the same patients, literature study suggests their bioequivalence.

In our hospital, pediatric topiramate is prescribed and extemporaneously compounded as a 6 mg.mL^{-1} liquid formulation or as capsules with a broad range of dosages. To improve the quality of topiramate pharmaceutical preparations and to decrease the time spent in compounding, pharmacy department decided to implement topiramate preparations. Oral suspension (6 mg.mL^{-1}) and 9 mg capsules were chosen to cover the main part of usual prescriptions (Tullock et al. 2012). Compounding of these preparations in advance as large batches for multiple patients could be performed, with subsequent quality control and stability studies.

Our quality control laboratory managed the validation of topiramate dosing method. In the United States Pharmacopoeia (USP), topiramate dosing method involves HPLC analysis (USP 2019) with a refractometer (topiramate active pharmaceutical ingredient, capsules and tablets) or with derivatization with 9-fluorenylmethyl chloroformate (oral suspension).

Since our laboratory did not possess a refractometer, we tried first the USP method with 9-fluorenylmethyl chloroformate (FMOC-Cl). This method is described for a 20 mg.mL^{-1} oral suspension in a 1:1 mixture of Ora-Sweet® and Ora-Plus® (Perrigo). In our hospital, for pediatric compounding, pharmacists and prescribers prefer InOrpha® (Inresa) or Syrspend® (Fagron) vehicles, as they did not contain parabens (Binson et al. 2019), and have lower osmolalities (Bourbon et al. 2019; Helin-Tanninen et al. 2012). For 6 mg.mL^{-1} topiramate liquid formulation, Syrspend® (dry) was chosen.

Unfortunately, our trials to develop topiramate dosing method with FMOC-Cl were unsuccessful, as the derivatization product was well-observed by HPLC-UV but the intermediate precision (% RSD between-day) was not sufficient to validate the method. We hypothesized that the excipients of Syrspend® interfered with the derivatization reaction. Therefore, we developed a novel method

that can be used for routine quality control of topiramate samples: a derivatization reaction of topiramate with phenylisocyanate. We also performed microbiological analyses and a stability study on 6 mg.mL^{-1} suspension. Herein, we present the results of our investigations.

2. Investigations and results

2.1. Topiramate compounding

Compounding area is an ISO 8 (class D) cleanroom with air flow treatment. Compounding of three experimental batches of 50 capsules containing 9 mg topiramate was performed by qualified personnel fully equipped (gloves, mask, gown, disposable gown, disposable head, and shoe covers) as follows. Pharmaceutical grade topiramate (450 mg, compliant with the monograph of the European Pharmacopoeia) was weighed on a precision balance. To minimize sub-dosing, in a 25 mL measuring cylinder 2 mL of microcrystalline cellulose were added, then 450 mg of topiramate, and finally microcrystalline cellulose qs 10 mL. A spatula tip of red carmine was added, and the mixture was transferred to a mortar to be gently mixed. Fifty hard gelatin capsules (size 4, ivory) were placed on a manual capsule-filling machine. The caps were separated from the empty bodies and the entire mixture was inserted into the capsule bodies. The caps were then replaced, and the capsules were sealed.

Compounding of one experimental batch of 6 mg·mL^{-1} topiramate oral suspension was also performed by mixing in a mortar of 31.5 g of Syrspend powder SF PH4 and 3.0 g of topiramate API. Then, 485 mL of sterile water were added in a planetary mixer and slowly mixed as the powder mixture was gradually incorporated. When the powder was totally added, the mixture was stirred for 10 min, and the stirring was stopped for 10 min. Finally, the mixture was gently stirred again for 10 min and equally divided into 25 mL fractions in 30 mL brown glass bottles.

2.2. Topiramate dosing method validation

First, a 240 µg·mL^{-1} stock solution of topiramate was prepared: 24 mg of topiramate Active Pharmaceutical Ingredient (API) were weighed, solubilized in 6 mL of acetonitrile and vortexed for 1 min. Ultrapure water (6 mL) was added, and the mixture was vortexed for 1 min. 3 mL were aliquoted in a 25 mL volumetric flask. A borate buffer (boric acid 6.25 g·L^{-1}, potassium chloride 7.50 g·L^{-1}, pH adjusted at 7.8 with NaOH 1M) was added qs 25 mL to obtain a 240 µg·mL^{-1} stock solution of topiramate.

The derivatization procedure was performed on this stock solution: 1000 µL of topiramate stock solution, 500 µL of triethylamine solution (100 µL of triethylamine and 14.6 mL of acetonitrile, stability 6 months at +4/+8°C) and 500 µL of phenylisocyanate solution (50 µL of phenylisocyanate qs 10 mL acetonitrile, not stable and made extemporaneously) were mixed and vortexed 5 min. The mixture was put in an oven at 50 °C for 5 min and filtered through a 0.45µm cellulose filter. This derivatized solution (theoretical topiramate concentration of 120 µg·mL^{-1}) can then be diluted with borate buffer to achieve desired concentrations.

A chromatogram of a 60 µg.mL^{-1} derivatized topiramate solution in represented in Fig. 1.

A topiramate blank containing only reactants allowed us to identify topiramate derivatized product as the first peak (retention time = 3.1–3.2 min). The two other peaks (retention time = 3.8 and 7.7 min) were attributed to the reactants in excess or their degradation products.

Linearity of HPLC-UV standard curve for derivatized topiramate was determined with five concentrations ranging from 15 to 120 µg·mL^{-1} (theoretical concentrations of topiramate) prepared in sextuplicate. As this method was designed only for the quality control of topiramate preparations, LOD and LOQ were not determined, and were defined to be equal to the lowest level of linearity (15 µg·mL^{-1}). Repeatability, intermediate precision, accuracy and uncertainty were determined at three levels of concentration. As we decided to make dilutions of both topiramate preparations at

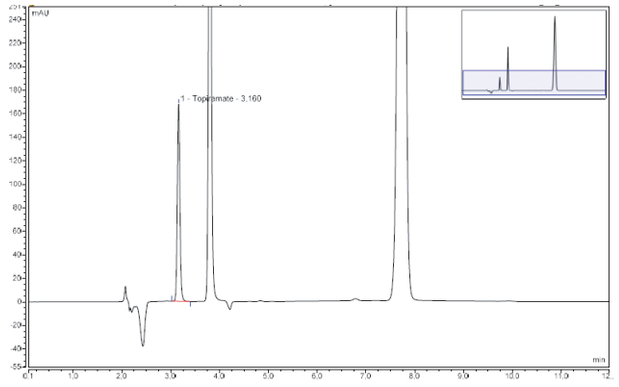

Fig. 1: Representative derivatized topiramate chromatogram

60 µg·mL^{-1} and normal values are +/- 10% of theoretical concentration, these three levels were 54 µg·mL^{-1}, 60 µg·mL^{-1} and 66 µg·mL^{-1}. Results are reported in Table 1.

Table 1: Repeatability, intermediate precision and accuracy

Samples	Repeatability (% RSD within-day)	Intermediate precision (% RSD between-day)	Accuracy (Bias in %)
Topiramate 54 µg.mL^{-1}	0.688%	2.327%	-0.400%
Topiramate 60 µg.mL^{-1}	0.631%	1.560%	0.517%
Topiramate 66 µg.mL^{-1}	0.966%	2.013%	0.642%

In the literature, phenylisocyanate derivatization of aminosides was reported to be a very robust reaction (Kim et al. 2001, 2003; Patel et al. 2015). To investigate this parameter, we made experiments with slight variations in the protocol. First, the influence of the temperature was studied at 40°C, 50°C and 60°C. Then, the time in the oven was also studied with samples put during 3 min, 5 min, 7 min and 15 min in the oven at 50°C. Samples analyzed in triplicate with these various experimental conditions gave us similar results, with recovery rates (RR) near 100%. The lowest value was found for the sample put during 15 min at 50°C, with RR = 96.7%.

To determine topiramate content in 6 mg.mL^{-1} oral suspension, 2 mL were solubilized in 5 mL of acetonitrile and vortexed 1 min. 5 mL of ultrapure water were added, and the mixture was vortexed 1 min again. Then, 2.4 mL were aliquoted and borate buffer was added qs 20 mL to obtain a topiramate solution with theoretical concentration of 120 µg·mL^{-1}. This solution was vortexed 1 min, and 2 mL were filtered through a Millipore 0.45 µm cellulose filter. 500 µL were aliquoted and mixed with 250 µL of triethylamine solution and 250 µL of phenylisocyanate solution. The resulting mixture was vortexed 5 min and put in an oven at 50°C for 5 min to be finally filtered on 0.45 µm cellulose filter.

The matrix effect of Syrspend® was evaluated by the calculation of the recovery rates (RR) of doped samples. A sample of 6 mg.mL^{-1} was analyzed (two aliquots, each analyzed twice). Then, 20 mg of topiramate was added to 10 mL of the suspension to obtain an 8 mg·mL^{-1} suspension which was analyzed (five aliquots, each analyzed twice). Finally, 40 mg of topiramate was added to 10 mL of the 6 mg·mL^{-1} suspension to obtain a 10 mg·mL^{-1} suspension (five aliquots, each analyzed twice). The RR were calculated by comparing the observed concentrations with the theoretical concentrations, and were all found to be near 100%, excluding a matrix effect of Syrspend® (6 mg.mL^{-1} RR = 99.1%; 8 mg.mL^{-1} RR = 100.2%: 10 mg.mL^{-1} RR = 98.4%).

To determine topiramate content in 9 mg capsules, a capsule was opened, solubilized in 4.5 mL of acetonitrile and vortexed 1 min. 4.5 mL of ultrapure water were added, the mixture was vortexed again 1 min and the afterward procedure was similar to the one previously described for oral suspension.

Chromatograms of derivatized topiramate oral suspension and topiramate capsule showed no interferences due to excipients after the derivatization procedure.

2.3. Forced degradation studies

Forced degradation studies intend to demonstrate the stability indicating character of the chromatographic method. A 60 µg·mL^{-1} stock solution of topiramate was exposed to several stressed conditions including intensive heating, oxidation, light and extreme pH values. Before derivatization, eventual chemical compounds were deactivated: HCl was neutralized by a saturated carbonates solution, NaOH by glacial acetic acid and hydrogen peroxide by heating at 60°C during 5 min. The resulting mixture was afterward derivatized by the previously described procedure.

Topiramate under light irradiation with a sunlamp for 11 days was not degraded. Under acidic conditions (HCl 1M, 30 min), a 9.8% decrease of topiramate derivatized product was observed, without formation of any additional peak. Under basic conditions (NaOH 4M, 30 min), a 41.4% decrease of derivatized compound content and one additional peak (RT = 2.9 min) were observed. Topiramate was found to be very sensitive to oxidation conditions (H_2O_2 0.03%, 10 min), with a 38.1% decrease of topiramate derivatized compound and the detection of eight additional peaks (RT= 2.7 min, 3.0 min, 4,5 min, 4,8 min, 5,3 min, 8.0 min, 9.4 min and 9.9 min). Topiramate was also very sensitive to heat conditions (80°C, 1 h), with a 97.4% decrease of topiramate derivatized compound and the detection of one additional peak (RT = 2.9 min). Resolution coefficients of degradation products peaks were calculated taking topiramate peak as reference and were found higher than 1 (smallest coefficient was found with oxidative conditions equal to 1.49). Representative chromatograms can be found in supplementary material.

2.4. Microbiological analyses

Microbiological analyses of topiramate 9 mg capsules and topiramate 6 mg.mL^{-1} suspension were done under a microbiological safety cabinet by surface-spread method. Suitability of the method was proved according to European Pharmacopeia: five reference strains (*Staphylococcus aureus* NCTC10788, *Bacillus subtilis* NCTC10400, *Pseudomonas aeruginosa* NCTC12924, *Candida albicans* NCPF3179 and *Aspergillus braziliensis* NCPF2275) were suspended in pH 7.2 sterile phosphate buffer to obtain 100-1000 CFU.mL^{-1}. Then, 100 µL (10 – 100 CFU) of each strain suspension were aliquoted in five tubes containing 5 mL of pharmacopeia diluent (reference strains alone), in five tubes containing 4 mL of pharmacopeia diluent and 1 mL of topiramate oral suspension, and in five tubes containing 5 mL of pharmacopeia diluent and one topiramate capsule. Two tubes were prepared as negative controls with 4 mL of pharmacopeia diluent/1 mL of topiramate suspension and 5 mL of pharmacopeia diluent / one topiramate capsule. Each tube was vortexed during 2 min.

Four time, 500 µL were aliquoted from each tube to inoculate two tryptic soy agars and two Sabouraud agars. Tryptic soy agars were incubated for 3 days in an incubator at 30-35°C and Sabouraud agars for 5 days at 20-25°C. At the end of the incubation, for each reference strains, mean number of CFU of "topiramate suspension + reference strain" samples and mean number of CFU of "topiramate capsule + reference strain" did not vary more than twice the from mean number of CFU of "reference strain alone" samples. These results prove that this surface-spread method allows the quantification of micro-organisms without any inhibitory effect of the tested preparations.

Following the microbiological method validation, experimental batches were analyzed. For topiramate oral suspension, total aerobic microbial count (TAMC) was lower than 200 CFU/mL and total combined yeasts and mold count (TYMC) was lower than 20 CFU/mL. For topiramate capsules, TAMC was lower than 2000 CFU/g and TYMC was lower than 200 CFU/g.

2.5. Stability study

Significant changes as a 5% variation from baseline was suggested in the literature for cytotoxic (Bardin et al. 2011) or narrow therapeutic index drugs (Sautou et Lagarce 2019) such as first-generation antiepileptic drugs. Topiramate is a second-generation antiepileptic drug, not known to have a narrow therapeutic index (Brittain and Wheless 2015; Arnone 2005). As reported in several other stability studies on pharmaceutical preparations (Roche et al. 2020; Berton et al. 2020; Friciu et al. 2017; Curti et al. 2019), we defined therefore significant changes as a 10% variation from baseline.

Stability of topiramate suspension was evaluated for 3 months under refrigerated conditions (2°C/8°C), with analyses at time 0 and weeks 1, 2, 3, 4, 6, 8 and 12. Stability was also assessed for one month (analyses at time 0 and weeks 1, 2, 3 and 4) after opening (simulated use, bottles opened daily – except the weekend – with dipping of the graduated cylinder for administration) under refrigerated conditions (2°C/8°C) and for one week (analyses at time 0, day 1 and week 1) under ambient conditions (25°C/60% HR). We studied four parameters on three independent batches: topiramate concentration (triplicate), pH and viscosity (one batch analyzed) and microbiological contamination (triplicate for initial and final points and one batch analyzed for other points).

Under refrigerated conditions pH and viscosity remained stable: pH between 4.15 and 4.39 (3.75-4.59 = 10% variation from baseline) and viscosity between 105 and 125 Cp (94-128 Cp = 10% variation from baseline + measurement uncertainty). After one week of storage at ambient temperature, viscosity became higher than 128 Cp. During our study, microbiological contamination was found to be lower than the method detection limit (TAMC and TYMC lower than 10 CFU/mL), with a noticeable exception at the third month under refrigerated conditions. One sample was found to be highly contaminated on Sabouraud agars. This contamination was also visually detected by a cloudy brownish suspension.

Topiramate concentration was found to be stable for two months under refrigerated temperature (2°C/8°C), for one month after opening under refrigerated conditions and for one week at ambient temperature (25°C) without appearance of noticeable degradation product. However, at three months, under refrigerated conditions, topiramate concentration dramatically decreased for the three tested samples, with a variation higher than 10% from baseline. For topiramate content after opening, the same tendency of decrease was observed from T0 to week 3, and week 4 higher mean value (5.92 mg/mL) was correlated with an important standard deviation, but the minimal value was still higher than 10% variation from baseline. Results are summarized in Tables 2-4 and Fig. 2-3 (the thick line represents topiramate content and the thin lines represent standard deviation calculated from Excel® software).

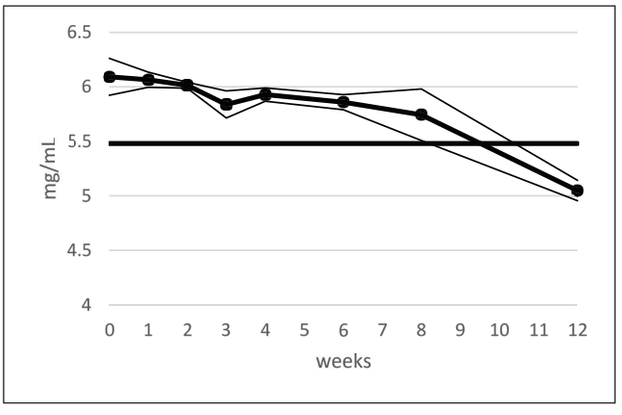

Fig. 2: Topiramate suspension stability under refrigerated conditions

Table 2: Topiramate suspension stability, 2°C/8°C

	T0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12
Concentration (mg/mL)[a]	6.09 +/- 0.17	6.07 +/- 0.07	6.01 +/- 0.03	5.84 +/- 0.12	5.93 +/- 0.06	5.86 +/- 0.07	5.74 +/- 0.24	5.05 +/- 0.09
pH	4.17	4.25	4.18	4.15	4.23	4.25	4.39	4.36
Microbiological contamination	< LOD[b]		< LOD		< LOD		< LOD	Non-compliant[c]
Viscosity (Cp)	111	126	105		120		125	115

[a] Mean value of triplicate analysis [b] LOD = Limit Of Detection, 10 CFU/mL [c] total combined yeasts and mold count > 20 CFU/mL

Table 3: Topiramate suspension stability, 2°C/8°C, simulated use

	T0	Week 1	Week 2	Week 3	Week 4
Concentration (mg/mL)[a]	6.09 +/- 0.17	5.98 +/- 0.13	5.92 +/- 0.16	5.69 +/- 0.13	5.92 +/- 0.34
pH	4.17	4.23	4.21	4.33	4.23
Microbiological contamination	< LOD[b]	< LOD	< LOD	< LOD	< LOD
Viscosity (Cp)	111	114	118		113

[a] Mean value of triplicate analysis [b] LOD = Limit Of Detection, 10 CFU/mL

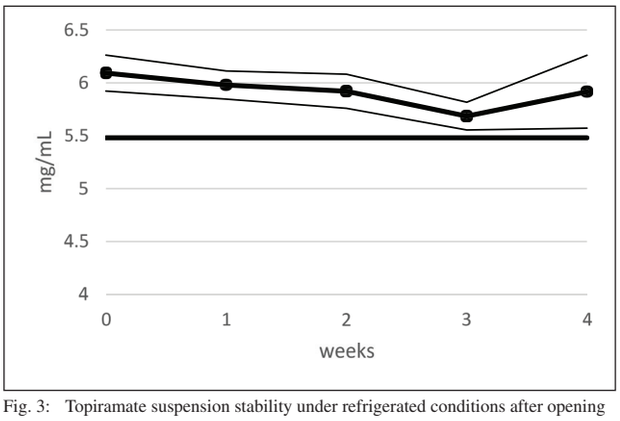

Fig. 3: Topiramate suspension stability under refrigerated conditions after opening

Table 4: Topiramate suspension stability, ambient temperature

	T0	Day 1	Week 1
Concentration (mg/mL)[a]	6.09 +/- 0.17	5.91 +/- 0.12	6.22 +/- 0.20
pH	4.17	4.25	4.27
Microbiological contamination	< LOD[b]	< LOD	< LOD
Viscosity (Cp)	111	116	130

[a] Mean value of triplicate analysis [b] LOD = Limit of detection, 10 CFU/mL

3. Discussion

Phenylisocyanate derivatization was described for HPLC-UV aminosides analysis (Kim et al. 2001, 2003; Patel et al. 2015). Our laboratory uses this reactant routinely for quality control of amikacine and gentamicine preparations (Curti et al. 2017), and we noticed a good reproducibility of the reaction. The advantages of phenylisocyanate for primary or secondary amines derivatization reactions are the almost quantitative reaction yields, the stability of derivatization products and the absence of influence of water on reaction yields. As phenylisocyanate reacts with primary amines to form a urea moiety, topiramate can be derivatized.

Sample treatment is quite simple, with two dilutions steps followed by derivatization, and without extraction step. The finding of an internal standard with a similar behavior than derivatized topiramate appeared complex. Therefore, we made the choice of external standardization, which was confirmed by method validation.

Retention time for topiramate derivatized product was 3.1–3.2 min. No interference between derivatized topiramate peak and topiramate degradation products or excipients in the topiramate capsule or Syrspend® oral suspension preparations was observed. Thus, the HPLC dosing method used to determine topiramate content in oral suspension or in capsules was confirmed to be stability-indicating. Additional experiments were also conducted with Inorpha® and Ora-Blend® oral suspensions and no interference between derivatized topiramate and excipients was observed. Therefore, this dosing method can be applied to a wide variety of pharmaceutical preparations of topiramate.

Microbiological analyses suitability for topiramate pharmaceutical preparations was also validated. Results obtained during our stability study need to be correlated to the environment were the preparations are realized. Nevertheless, we proved that microbiological analyses of topiramate suspension in Syrspend® and topiramate capsules can be realized by surface-spread method without any inhibitory effect of the tested preparations. Sample filtration was not required for these preparations. Routinely, batches of topiramate suspension and capsules are analyzed by surface-spread method for the quantification of micro-organisms. Specified micro-organisms (*Escherichia coli*) is also researched for suspension, with a validated method described in supplementary materials.

Stability study was realized on topiramate suspension compounded with Syrspend®. Beyond-Use-Date (BUD) of topiramate suspension was found to be equal at two months (+2/+8°C). Our results are slightly lower than those reported in the United State Pharmacopoeia with 90 days of stability for 20 $mg.mL^{-1}$ topiramate suspension in 1:1 Ora sweet: Ora plus, but are consistent with the maximum of 35 days of stability for preserved aqueous nonsterile preparation in USP <795> (USP 2019). Moreover, parabens (components of Ora) can be avoided with a Syrspend® (dry) formulation. Another study (Polonini et al. 2017) reported a higher 90 days stability of topiramate suspension in Syrspend® (liquid) with HPLC-UV analysis, but these differences can be explained by the difference of preservatives content between the two formulations, as we have observed a microbiological contamination at the 90th day of our study. As Syrspend® (liquid) contains sodium benzoate, Syrspend® (dry), free from preservatives, should be preferred for neonates with immature metabolism. Taking into consideration the higher stability of dry forms compared to liquid forms, beyond-use-date of topiramate capsules was also defined at two months (ambient storage) while waiting from a new stability study (consistent with the maximum of 180 days of stability for solid dosage forms in USP <795> (USP 2019)).

HPLC-UV topiramate dosing method with phenylisocyanate derivatization we developed herein is a valuable alternative for topiramate USP methods. The formulation process of 9 mg topiramate capsules and 6 $mg.mL^{-1}$ topiramate oral suspension production was validated, and their release was secured. Large batches production is nowadays possible. Topiramate pediatric suspension without potentially harmful excipients was found to be stable for two months at (+2/+8°C), one month after opening and one day at ambient temperature. These data allowed the harmonization and the securing of compounding processes and emphasize the fundamental role of quality control laboratories in large hospital structures.

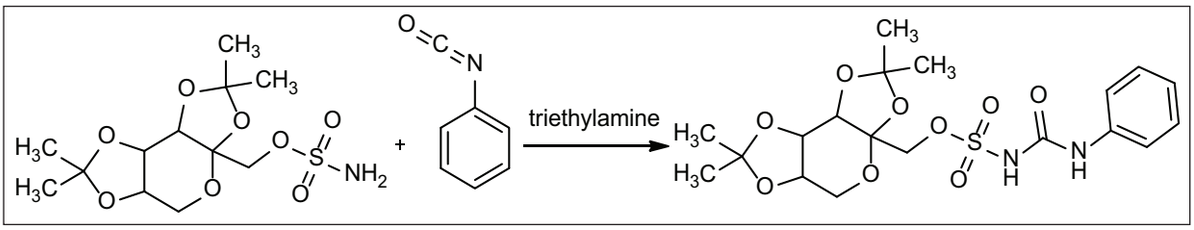

Fig. 4: Topiramate derivatization with phenylisocyanate.

4. Experimental

4.1. Instrumentation and reactants

Topiramate of pharmaceutical grade (Fagron SAS 94320 Thiais, France) was used for method validation, forced degradation study and compounding. The HPLC mobile phases were prepared using ultrapure water (HiPerSolv Chromanorm®, VWR International) and acetonitrile (HiPerSolv Chromanorm®, VWR International) of HPLC grade. Other chemical products used were: sodium dihydrogen phosphate (Merck), triethylamine (VWR Life Science), phenylisocyanate (Sigma-Aldrich), boric acid (VWR Chemicals), potassium chloride (Merck) and sodium hydroxide (Rectapur Prolabo).

Volumes were aliquoted with a precision pipette (Thermo Scientific Finnpipette® F2 500 µL) and pH were measured with a Thermo Scientific Orion 4 Star® pH-meter, calibrated with Radiometer Analytical standard etalons® (pH 4.005, pH 7.000 and pH 10.012). Viscosity was determined with a viscometer (Brookfield® LVDV-1M), equipped with a thermostatically-controlled low volume adaptor and its mobile (SC4-31). Measures were done at 100 rpm, 25°C.

Microbiological analyses were validated with five European Pharmacopeia reference strains (Biomérieux Bioball®). Microbiological analyses were done on Tryptic Soy Agar (TSA) (Biomérieux) and Sabouraud chloramphenicol gentamicine agar (Biomérieux) under a Microbiological Safety Cabinet (MSC) (Herasafe® KS, Thermo Scientific). 9 mL tubes of pharmacopeia diluent (Dominique Dutcher) and incubators (Heratherm® and Heraeus® Thermo Scientific) were also used.

Stability studies were realized in a climatic chamber with controlled parameters 25°C / 60% HR (Memmert) and in a fridge (Facis) with daily controlled temperatures.

4.2. Chromatographic conditions

The mobile phase consisted in a mixture of acetonitrile (48%, v/v) and an aqueous solution (52%, v/v) containing 6.00 g/L of sodium dihydrogen phosphate and triethylamine (3%, v/v). Its pH was equal to 9.0 +/-0.1. The mobile phase was filtered through a Millipore 0.45 µm cellulose filter and used in isocratic mode with a flow of 1 mL/min for 12 min. Wavelength for derivatized topiramate detection was 274 nm, injection volumes were 50 µL and column temperature was 52°C. The chromatographic method was carried out on an automatic high-performance liquid chromatography Dionex Ultimate 3000® with a UV diode array detector. The apparatus was connected to an HP 1702 computer equipped with chromatographic data processing software (Chromeleon® Chromatography Management System, Version 6.80 SRH Biold 3161, 1994-2011 Dionex Corporation). A C18 column (XTerra®, 4.6 X 250 mm, 5µm) was used to achieve topiramate separation.

4.3. Chemical equation

Phenylisocyanate reacts with primary amines to form a urea moiety, as reported in Fig. 4.

Conflicts of interest: All Authors declare that they have no conflicts of interest.

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