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# Stability of regularly prescribed oral liquids formulated with SyrSpend® SF

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The purpose of this research was to evaluate the stability of 12 oral liquid formulations frequently compounded in hospital and community settings formulated in a specific vehicle: SyrSpend® SF. The stability of melatonin, glycopyrrolate, ciclosporin, chloral hydrate, flecainide acetate, tiagabine HCl, labetalol HCl, ciprofloxacin HCl, spironolactone/hydrochlorothiazide, hydrocortisone, itraconazole and celecoxib in SyrSpend SF PH4 (liquid) was investigated at 0, 30, 60 and 90 days and stored at both controlled room temperature and refrigerated. Itraconazole samples were also investigated at 15 and 45 days. No change in odor, color or appearance was observed in the formulations during the test period. Based on the results, a beyond-use date of 30 days can be assigned to tiagabine HCl 1.0 mg/ml in SyrSpend SF when stored at controlled room temperature, and 90 days under refrigeration, improving stability data previously published using other vehicles. A beyond-use date of 60 days can be assigned to chloral hydrate 100.0 mg/ml. In this case, stability is not enhanced by refrigeration. With the rest of the formulations, less than 10% API loss occurred over 90 days at either controlled room temperature or under refrigeration. Including for example itraconazole 20.0 mg/ml, thus providing extended stability compared to simple syrup and other oral liquid vehicles. The findings of this study show that SyrSpend SF is an appropriate suspending vehicle to be used for personalized formulations of the APIs studied here.

## 1. Introduction

Oral medications are usually dispensed as capsules or tablets, neither of which allows for easy dose individualization (Allen 2012). Oral liquids are prescribed for children to permit easy customization of the dose and for children and adults to address difficulties in swallowing tablets or capsules (Allen 2012; Aliot et al. 2011; Nahata et al. 2003; Nahata 1991; Zerbit et al. 2014). Therefore, personalized formulations of oral suspensions are often required in today's therapeutics, emphasizing the need for appropriate compounding formulas and stability data.

SyrSpend SF is a ready-for-use suspending vehicle designed for the compounding of oral liquid personalized formulations. Based on modified food starch, SyrSpend SF has shown beneficial suspending properties and good compatibility with a broad range of active pharmaceutical ingredients (APIs) (Vu et al. 2008; Geiger et al. 2012a; Sorenson and Whaley 2013; Geiger et al. 2013a; Whaley et al. 2012a; Voudrie and Allen 2010; Whaley et al. 2012b; Voudrie et al. 2011; Geiger et al. 2012b, 2015; Ferreira et al. 2016; Polonini et al. 2016a, b).

In this study, we have focused on oral liquid formulations which are regularly prescribed in hospital and community practice and that have not been studied to date in SyrSpend SF. Table 1 summarizes the 12 formulations selected for this study, their therapeutic indication and the main reasons that justify the preparation of personalized oral liquids for each of these APIs.

The objective here was to evaluate the stability of these formulations in SyrSpend SF and, more specifically, to assess their stability over a period of 90 days, under two different storage conditions: controlled room temperature (25±2 ºC) and controlled refrigerated temperature (5±3 ºC).

**Table 1: Description of the 12 formulations selected for this study, their indication in therapeutics and the main reasons that justify the preparation of a personalized oral liquids in each case**

| Oral liquid formulation | Indication | Justification for personalization |
|---|---|---|
| Melatonin 3.0 mg/ml | Treatment for initial insomnia in children with ADHD taking stimulant medication (15) | Young children may need suspension, not commercially available (1, 2, 4) |
| Glycopyrrolate 0.5 mg/ml | A synthetic anticholinergic that acts at peripheral muscarinic receptors, has been used off-label for excessive drooling in children with neurodevelopmental disabilities for years (17) | Due to the need for accurate dose adjustments in pediatric populations, a liquid dosage form (not commercially available) may be required (17) |
| Ciclosporin 100.0 mg/ml | Inmunosupressor, in transplantations and some autoimmune diseases (2) | Young children may need a liquid dosage form, not commercially available (2) |
| Chloral hydrate 100.0 mg/ml | Nonbarbiturate sedative and hypnotic in paediatric population (2) | Young children may need a liquid dosage form, not commercially available (2) |
| Flecainide acetate 20.0 mg/ml | Pediatric arrhytmias (3) | Dose adjustment required according to age, body weight, symptoms and other factors (3) |
| Tiagabine HCl 1.0 mg/ml | Tiagabine is used for adjunctive therapy for the treatment of refractory partial seizures (4) | Young children may need a liquid dosage form, not commercially available (1-3) |

| Oral liquid formulation | Indication | Justification for personalization |
|---|---|---|
| Ciprofloxacin HCl 50.0 mg/ml | Adults: infections of the respiratory, genital, urinary and gastro-intestinal tracts, skin and soft tissues and some bone and joint infections. Paediatrics: cystic fibrosis, complicated urinary tract infections and other severe infections (20) | Dose adjustment required according to age, body weight, the severity of the infection and the patient's creatinine clearance (20) |
| Hydrocortisone 1.0 mg/ml | Cortisol is an essential stress hormone and replacement with oral hydrocortisone is lifesaving in patients with adrenal insufficiency. Loss of cortisol rhythmicity is associated with fatigue, depression and insulin resistance (19) | Tailoring hydrocortisone dose to circadian rhythm, weight-related and clinical pharmacokinetics monitoring (19) |
| Itraconazole 20.0 mg/ml | Systemic fungal infections (18) | Flexibility to tailored itraconazole treatment for use in all patients, including children and those requiring intensive care (18) |
| Celecoxib 10.0 mg/ml | Celecoxib is a selective cyclo-oxygenase 2 inhibitor that relieves pain without affecting platelet function (19) | Young children and some adults with swallowing difficulties may need a liquid dosage form, not commercially available (19) |
| Spironolactone 5.0 mg/ml + Hydrochlorothiazide 5.0 mg/ml | Diuretics used in treatment of edematous states associated with cardiac, renal, and hepatic failure and the treatment of hypertension (21) | Two drug association non commercially available (21). Commonly used in the pediatric and adult populations which may have difficulties swallowing the solid form (22) |

## 2. Investigations and results

High-performance liquid chromatography was used for both the stability study and a forced degradation study that was also performed with the aim of identifying all degradation products that may be produced during storage of the samples.

The stability of melatonin, glycopyrrolate, ciclosporin, chloral hydrate, flecainide acetate, tiagabine HCl, labetalol HCl, ciprofloxacin HCl, spironolactone/hydrochlorothiazide, hydrocortisone, itraconazole and celecoxib in SyrSpend SF PH4 (liquid) was investigated at 0, 30, 60 and 90 days and stored at both controlled room temperature and refrigerated. Itraconazole samples were also investigated at 15 and 45 days.

With respect to methods validation, the analytical characteristics are summarized in Table 2, including linearity, limit of detection (LOD), limit of quantification (LOQ), and accuracy. All analytical methods met their respective acceptance criteria (Table 2).

API degradation was studied after having subjected the formulations to stress conditions (forced degradation studies). The API degradation results are shown in Table 3, with a description of the conditions applied. This information, together with spectral analysis, was used to optimize the resolution and specificity of the analytical methods used in the stability assay, and to gain insight on the degradation processes taking place in the formulations.

**Table 2: Summary of analytical characteristics of the methods developed**

| Compd. | Linear range (µg/ml) | y - intercept | Slope | R2 | LODa (µg/ml) | LOQb(µg/ml) | Accuracy (Recovery, %) |
|---|---|---|---|---|---|---|---|
| Melatonin | 4.64 - 18.37 | 33.66 | 161.54 | 0.9999 | 0.01 | 0.02 | 100.2 |
| Glycopyrrolate | 4.90 - 19.10 | 46.97 | 198.50 | 0.9998 | 0.02 | 0.06 | 101.3 |
| Ciclosporin | 9.79 - 83.69 | -16.70 | 26.50 | 0.9995 | 1.03 | 3.45 | 100.4 |
| Chloral hydrate | 6.79 – 25.67 | -3345 | 1305 | 0.9947 | 0.64 | 2.12 | 103.6 |
| Flecainide acetate | 5.57 - 20.94 | 0.36 | 5.13 | 1.000 | 0.01 | 0.04 | 100.2 |
| Tiagabine HCl | 4.29 - 23.63 | 5.01 | 47.02 | 0.9998 | 0.03 | 0.11 | 98.6 |
| Labetalol HCl | 4.62 - 20.17 | 14.56 | 96.01 | 0.9975 | 0.03 | 0.09 | 104.9 |
| Ciprofloxacin HCl | 3.89 - 20.50 | -20.79 | 88.45 | 0.9990 | 0.03 | 0.09 | 98.3 |
| Hydrocortisone | 5.76 - 21.05 | 5.76 | 18.88 | 1.000 | 0.01 | 0.04 | 99.5 |
| Itraconazole | 4.71 - 19.93 | -35.71 | 47.59 | 1.000 | 0.08 | 0.27 | 99.7 |
| Celecoxib | 4.11 - 21.59 | -18.40 | 89.51 | 0.9998 | 0.01 | 0.03 | 99.7 |
| Spironolactone | 4.73 - 19.42 | -1.33 | 26.48 | 0.9999 | 0.02 | 0.05 | 100.8 |
| Hydrochlorothiazide | 4.53 - 19.36 | 1.04 | 52.78 | 0.9998 | 0.01 | 0.04 | 100.3 |

a) LOD: limit of detection.
b) LOQ: limit of quantification (20 µl injections).
All analytical ranges (µg/ml) were adequate to quantify the compounds in the concentrations used in the formulations (mg/ml). Acceptance criteria were: R2 > 0.99, accuracy = 100% ± 5%

**Table 3: Conditions of the forced degradation studies**

| Compd. | Forced degradation conditions | Effectiveness of drug degradation |
|---|---|---|
| Melatonin | UV light (365 nm) for 7 days | 22% (±2.4 RSD[a]; n=2) |
| Glycopyrrolate | UV light (365 nm) and pH 12 for 7 days | Fully degraded |
| Ciclosporin | UV light (365 nm) for 7 days | 44% (±37 RSD; n=2) |
| Chloral hydrate | pH 12 + UV light(365 nm) during 1 hour | 33% (±48 RSD; n=3) |
| Flecainide acetate | UV light (365 nm) and heat (70 ºC) for 7 days | 13% (±7 RSD; n=2) |
| Tiagabine HCl | UV light (365 nm) and heat (70 ºC) for 7 days | 81% (±13 RSD; n=2) |

| Compd. | Forced degradation conditions | Effectiveness of drug degradation |
|---|---|---|
| Labetalol HCl | pH 9 (with phosphate buffer) + UV light (365 nm) for 3 days | 67% (±7 RSD; n=2) |
| Ciprofloxacin HCl | pH 9 (with phosphate buffer) + UV light at 365 nm for 4 days | 65% (±2.4 RSD; n=2) |
| Hydrocortisone | pH 12 for 1 day | 50% (±4.2 RSD; n=2) |
| Itraconazole | UV light (365 nm) and heat (50 ºC) for 7 days | 47% (±14.6 RSD; n=2) |
| Celecoxib | UV light (365 nm) and heat (70 ºC) for 7 days | 39% (±1.5 RSD; n=2) |
| Spironolactone | UV light (365 nm) and heat (40 ºC) for 7 days | 68% (±12 RSD; n=2) |
| Hydrochlorothiazide | UV light (365 nm) and heat (70 ºC) for 4 days | 85% (±4.7 RSD; n=2) |

a) RSD: Relative Standard Deviation
The objective was to chromatographically identify all degradation products that may be produced during storage of the samples.

Finally, the results of the stability assays are shown in Table 4. It was observed that the oral suspensions exhibited no change in odor, color or appearance during the test period. The stability results are expressed as relative percent of recovery (time 0 = 100%).

**Table 4: Stability assay of the SyrSpend SF formulations, stored at both controlled room temperature and refrigerated. Acceptance criteria were: 90-110% of initial concentration at time 0**

| | | Room temperature | | Refrigerated | |
|---|---|---|---|---|---|
| Formulation | Time (days) | Drug recovery (%) | SD | Drug recovery (%) | SD |
| **Melatonin** | 0 | 100.0 | 1.6 | 100.0 | 0.7 |
| **3.0 mg/ml** | 30 | 96.9 | 8.7 | 98.3 | 2.6 |
| | 60 | 93.5 | 5.4 | 95.8 | 3.4 |
| | 90 | 97.6 | 2.1 | 102.1 | 6.7 |
| **Glycopyrrolate** | 0 | 100.0 | 6.4 | 100.0 | 0.2 |
| **0.5 mg/ml** | 30 | 95.1 | 1.3 | 95.1 | 1.1 |
| | 60 | 98.5 | 1.3 | 97.9 | 0.2 |
| | 90 | 92.1 | 1.4 | 90.9 | 0.9 |
| **Ciclosporin** | 0 | 100.0 | 5.0 | 100.0 | 1.4 |
| **100.0 mg/ml** | 30 | 98.2 | 4.8 | 97.6 | 5.9 |
| | 60 | 102.5 | 3.1 | 96.9 | 2.7 |
| | 90 | 103.1 | 2.3 | 97.4 | 1.9 |
| **Chloral hydrate** | 0 | 100.0 | 3.2 | 100.0 | 10.9 |
| **100.0 mg/ml** | 30 | 97.5 | 1.7 | 94.3 | 6.4 |
| | 60 | 91.8 | 14.6 | 92.1 | 12.6 |
| | 90 | 88.1 | 12.4 | 88.4 | 9.1 |
| **Flecainide acetate** | 0 | 100.0 | 3.2 | 100.0 | 1.8 |
| **20.0 mg/ml** | 30 | 94.3 | 0.8 | 92.1 | 1.1 |
| | 60 | 98.3 | 0.9 | 98.9 | 1.4 |
| | 90 | 97.0 | 2.4 | 100.4 | 2.6 |
| **Tiagabine HCl** | 0 | 100.0 | 1.5 | 100.0 | 1.0 |
| **1.0 mg/ml** | 30 | 93.0 | 1.7 | 98.7 | 1.2 |
| | 60 | 87.9 | 0.7 | 96.6 | 1.2 |
| | 90 | 83.3 | 0.7 | 94.8 | 1.9 |
| **Labetalol HCl** | 0 | 100.0 | 2.7 | 100.0 | 2.2 |
| **40.0 mg/ml** | 30 | 96.5 | 1.3 | 97.5 | 2.8 |
| | 60 | 97.9 | 2.4 | 97.5 | 0.6 |
| | 90 | 98.0 | 1.6 | 96.0 | 2.0 |
| **Ciprofloxacin HCl** | 0 | 100.0 | 1.8 | 100.0 | 1.4 |
| **50.0 mg/ml** | 30 | 99.9 | 2.0 | 95.8 | 1.9 |
| | 60 | 104.7 | 0.7 | 99.7 | 0.3 |
| | 90 | 110.4 | 3.9 | 97.9 | 1.3 |
| **Hydrocortisone** | 0 | 100.0 | 0.6 | 100.0 | 3.6 |
| **1.0 mg/ml** | 30 | 99.6 | 2.7 | 96.6 | 1.1 |
| | 60 | 96.1 | 1.9 | 96.9 | 2.2 |
| | 90 | 97.9 | 1.6 | 96.3 | 1.6 |
| **Itraconazole** | 0 | 100.0 | 8.4 | 100.0 | 13.7 |
| **20.0 mg/ml** | 15 | 96.3 | 3.4 | 97.5 | 7.8 |
| | 30 | 105.1 | 2.4 | 99.1 | 2.8 |
| | 45 | 92.1 | 14.8 | 103.5 | 1.5 |
| | 60 | 95.2 | 2.4 | 104.0 | 8.9 |
| | 90 | 91.2 | 8.3 | 91.7 | 5.8 |
| **Celecoxib** | 0 | 100.0 | 1.3 | 100.0 | 0.8 |
| **10.0 mg/ml** | 30 | 101.5 | 3.0 | 102.9 | 1.1 |
| | 60 | 100.5 | 2.7 | 102.1 | 2.4 |
| | 90 | 101.3 | 4.9 | 104.8 | 1.1 |
| **Spironolactonea** | 0 | 100.0 | 8.0 | 100.0 | 1.6 |
| **5.0 mg/ml** | 30 | 98.8 | 3.4 | 95.7 | 9.5 |
| | 60 | 89.9 | 7.2 | 84.4 | 1.4 |
| | 90 | 102.8 | 6.5 | 100.7 | 7.6 |
| **Hydrochloro-** | 0 | 100.0 | 2.2 | 100.0 | 18.2 |
| **thiazidea** | | | | | |
| **5.0 mg/ml** | 30 | 103.6 | 12.0 | 131.0 | 6.7 |
| | 60 | 114.3 | 22.8 | 114.3 | 12.6 |
| | 90 | 102.6 | 10.0 | 112.7 | 11.9 |

a) Spironolactone and hydrochlorothiazide were combined in the same formulation

## 3. Discussion

The acceptance criteria for the oral liquid formulations to be considered stable were that the relative percentage of recovery should lie within 90-110% (Trissel 2012).

With this criteria in mind, data in Table show that tiagabine HCl 1.0 mg/ml when stored at controlled room temperature fell out of specifications at 60 days and above, and thus, according to these results, a beyond-use date of 30 days is recommended. However, when stored under refrigeration, tiagabine HCl 1.0 mg/ml was stable throughout the whole time of the study (90 days). When compared with previously published data in other vehicles, these findings suggest that the stability of tiagabine is improved when formulated in SyrSpend SF (Nahata and Morosco 2003). Also, in the case of chloral hydrate 100.0 mg/ml, stability-indicating HPLC analysis of API concentration found a chloral hydrate loss >10% at 90 days at either controlled room temperature and under refrigeration. Therefore a beyond-use date of 60 days is recom-

mended. In the case of itraconazole, the concentration average at 90 days at either controlled room temperature and under refrigeration was >90% but when considering its standard deviations, the % recovered drops below the cutoff value of 90.0%. Therefore a beyond-use date of 60 days is recommended for both temperatures. In contrast to these three cases (tiagabine HCl, itraconazole and chloral hydrate), with the rest of the formulations it was observed that less than 10% API loss occurred over 90 days at either controlled room temperature or under refrigeration.

In the case of hydrochlorothiazide and spironolactone (formulated together in the same formulation) the heterogeneity of the results obtained needs further discussion. Although the formulation of hydrochlorothiazide/spironolactone in SyrSpend SF was stable throughout the whole time of the study (90 days), it was observed that some crystals formed after some time on the 1:500 sample dilutions, a required step when preparing the samples for HPLC injection. These dilutions were made with water. The dilutions were prepared shortly before HPLC injection and then were kept for a few days before discarding. Some crystalization was observed and noted down at the moment of discarding the spironolactone/hydrochlorothiazide dilutions of the SyrSpend SF suspensions. Our hypothesis is that this crystal formation process observed on the diluted spironolactone/hydrochlorothiazide samples may have had an impact on the API concentration actually in suspension. This fact would explain the heterogeneity in API concentration among the samples, with data above 100% of recovery and greater SD than in any other case. However, as stated above, no crystallization was observed on the non-diluted SyrSpend SF formulations of spironolactone/hydrochlorothiazide.

In summary, the stability obtained in SyrSpend SF was comparable (Johnson et al. 2011; Gupta 2001; Gupta 2003) or superior (Nahata and Morosco 2003; Allen and Erickson 1996a, b; Jacobson et al. 1995; Johnson et al. 2011) to what has previously been reported with the same APIs formulated in other oral liquids. These findings support, for example, that compounding itraconazole 20.0 mg/ml oral suspensions in SyrSpend SF may provide extended stability compared to simple syrup (Jacobson et al. 1995) and other oral liquid vehicles (Johnson et al. 2011).

The findings of this study show that SyrSpend SF is an appropriate suspending vehicle to be used for personalized formulations of the APIs studied here. Since SyrSpend SF contains an effective preservative system, microbiological instability is not expected to become an issue. Therefore, a beyond-use date of 90 days can be assigned to tiagabine HCl 1.0 mg/ml in SyrSpend SF when stored under refrigeration and 30 days at controlled room temperature based on our physical-chemical study results. A beyond-use date of 60 days can be assigned to chloral hydrate 100.0 mg/ml and itraconazole

20.0 mg/ml. In this case, stability is not enhanced by refrigeration. Finally, the results suggest that a beyond-use date of at least 90 days could be assigned to any of the other SyrSpend SF formulations studied in this work, even when stored at controlled room temperature. In summary, the stabilities obtained with SyrSpend SF were comparable or superior to what has been previously reported in the literature for the same compounds in other pharmaceutical vehicles.

## 4. Experimental

### *4.1. Chemical reagents*

APIs and analytical standards used in this study are listed in Table. SyrSpend SF PH4 (Liquid. composition: purified water, modified food starch, sodium citrate, citric acid, sucralose, sodium benzoate (<0.1 %, preservative), malic acid and simethicone) (batch 14E02E) was provided by Fagron. High-performance liquid chromatographic (HPLC)-grade water (resistivity 18.2 MW, obtained with ARIUM 611UV equipment), acetonitrile (Sigma Aldrich, batch SZBC150SV), and phosphoric acid (PanReac, batch 96684HFR) were used in this study.

### *4.2. Equipment and chromatographic conditions*

High-performance liquid chromatography with diode array detection (HPLC-DAD) HP Agilent Series 1100 was used for both the stability study and a forced degradation study that was also performed with the aim of identifying all degradation products that may be produced during storage of the samples. A 10 µg/g solution of the corresponding analytical standard for each API was used for optimization of the analytical methods.

Specific chromatographic conditions are listed in Table 6. The analytical characteristics of the methods developed for each compound are summarized in Table2. All preparations were filtered with 0.45 mm Sartorius nylon syringe filters prior to injection.

### *4.3. Forced degradation studies*

Forced degradation studies were performed prior to the stability assay. The objective was to identify each API together with all degradation products that may be produced during storage of the samples. This information was used for proper characterization of the degradation phenomena occurring during the stability phase of the study, thus allowing for optimization of the analytical methods, checking for significant overlapping.

The forced degradation conditions applied to each compound were determined from the literature (Trissel 2012). These conditions are summarized in Table 3. The purity of the peaks was confirmed by spectral analysis, using the corresponding API unstressed analytical standard as reference.

### *4.4. Stability assay*

The appropriate amount of API was levigated with SyrSpend SF using geometric dilution to form a smooth suspension. The dispersion was then transferred to a 100 ml volumetric flask and brought to volume with SyrSpend SF to achieve the desired final concentration for each oral liquid formulation. The 100 ml of sample was then distributed into 4 low actinic glass bottles (20 ml each). These bottles were labeled for each of the time points considered in the assay (0, 30, 60 and 90 days), and assayed for API concentration after the corresponding elapsed time, then discarded.

In the case of itraconazole, the 100 ml sample was distributed into 6 low actinic glass bottles (15 ml each). These bottles were labeled for each of the time points considered in the itraconazole assay (0, 15, 30, 45, 60 and 90 days). The rationale for these specific time points (intermediate points at 15 and 45 days) was the faster degradation rates expected for itraconazole based on available literature (Jacobson et al. 1995; Johnson et al. 2011).

**Table 5: Source of drug substances and analytical standards used in this study**

| Drug | Drug Source | Analytical Standard |
|---|---|---|
| Melatonin | Melatonin raw powder (Fagron, batch 13H29-B03-293065) | Sigma Aldrich, SLBK0706V |
| Glycopyrrolate | Glycopyrrolate raw powder (Fagron, batch 14A14-B06-292838) | Eurofins, batch JOJ363 |
| Ciclosporin | Ciclosporin raw powder (Fagron, batch 13B19NO2) | Eurofins, batch I11Z033 |
| Chloral hydrate | Chloral hydrate raw powder (Fagron, batch 20130903) | Eurofins, batch SZBE0150V |
| Flecainide acetate | Apocard 100 mg tablets (MedaPharma S.A.U., batch GPG073A) | Eurofins, batch G0K124 |
| Tiagabine HCl | Gabitril 15 mg oral tablets (TevaPharma B.V., batch W020406) | Eurofins, batch F0E178 |
| Labetalol HCl | Trandate 200 mg tablets (Kern Pharma, S.L., batch H002 CAD 06/2017) | Fluka, batch LRAA1069 |
| Ciprofloxacin HCl | Ciprofloxacin HCl raw powder (Fagron, batch 14B25-B02-292846) | Eurofins, batch P500167 |
| Hydrocortisone | Hydrocortisone raw powder (Fagron, batch 13L31-B06-294874) | Eurofins, batch 8.1 |
| Itraconazole | Itraconazole raw powder (Fagron, batch L14070008OF194389) | Eurofins, batch G0K425 |
| Celecoxib | Celebrex 200 mg capsules (Pfizer, S.L., batch E10351530) | Sigma Aldrich, batch 2558935 |
| Spironolactone | Spironolactone raw powder (Fagron, batch 12E07-U06-005744) | Eurofins, batch LOL557 |
| Hydrochlorothiazide | Hydrochlorothiazide raw powder (Fagron, batch 10G21-B02) | Eurofins, batch 7 |

**Table 6: Summary of chromatographic conditions of the methods developed.**

| Drug | Mobile phase | Flow (ml/min) | Wavelength (nm) | Ref. |
|---|---|---|---|---|
| Melatonin | 75/25 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 225 | (26) |
| Glycopyrrolate | 65/35 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 192 | (27) |
| Ciclosporin | 15/65/20 (0.12 M $H_3PO_4$pH 2 /Acetonitrile /Methanol) | 1.5 | 205 | (28-30) |
| Chloral hydrate (derivatized)[a] | 60/40 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 1 | 220 | (42,43) |
| Flecainide acetate | 60/40 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 298 | (31) |
| Tiagabine HCl | 50/50 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 260 | (32) |
| Labetalol HCl | 70/30 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 233 | (33) |
| Ciprofloxacin HCl | 75/25 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 280 | (34) |
| Hydrocortisone | 40/60 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 254 | (37-38) |
| Itraconazole | 40/60 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 262 | (39) |
| Celecoxib | 20/80 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 254 | (40) |
| Spironolactone | 40/60 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 238 | (35-36) |
| Hydrochlorothiazide | 85/15 (0.12 M $H_3PO_4$ pH 2/Acetonitrile) | 0.5 | 225 | (52) |

a) Chloral hydrate had to be derivatized prior to injection. See text for details (section 2.5).
The columns were thermostathised at 30 °C in all cases, except in ciclosporin analysis (70 °C). Volume of injection was 20 µL. An Ultrabase C18 silica 100 x 4.6 mm, 5 µm particle size column was used in all cases except for ciclosporin and chloral hydrate, where a 250 mm length column of the same kind was used.

The whole process, including the elaboration of the samples as described above, was replicated 3 times per time point and storage condition: controlled room temperature (25±2 ºC) and controlled refrigerated (5±3 ºC).
The chemical stability of the oral suspension was assessed by comparing API concentration over time with respect to specifications (90-110% of initial concentration at time 0) at the end of shelf-life.

### *4.5. Chloral hydrate*

Chloral hydrate was derivatized with 1,2-benzenedithiol prior to injection, yielding a new compound that absorbs at the ultraviolet region (220 nm). 30 µL of 1,2-benzenedithiol reactive (1000 ppm) was sufficient for the complete derivatization of chloral hydrate in the diluted samples. The reaction took place at 70 °C (for 1 h). Then, it was allowed to cool down before injected into the HPLC (Bruzzoniti et al. 2001; Kraemer et al. 1997).

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Conflicts of interest: see above, others not declared.

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