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STABILITY OF CILAZAPRIL IN PEDIATRIC ORAL SUSPENSIONS PREPARED FROM COMMERCIALLY AVAILABLE TABLET DOSAGE FORMS

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Abstract: Cilazapril is a drug commonly used in management of heart failure in pediatric population. On pharmaceutical market it is available only in inconvenient for pediatric use tablet dosage forms. Until now, no oral liquid formulation containing cilazapril has been evaluated. Therefore, the aim of this study was to prepare easy to made and palatable 1 mg/mL oral liquid formulation with cilazapril (with consideration of original and generic cilazapril tablet and different packages) and subsequent investigation of physicochemical stability of these suspensions. Formulations were compounded using cilazapril obtained from original or generic cilazapril marketed tablet formulations and Ora-Blend® suspending agent. Stability of prepared suspensions stored in closed amber glass or amber plastic PET bottles in the temperature of 298 K was estimated throughout 28 day shelf-life period. Chemical stability was assessed by HPLC cilazapril stability indicating method. Physical stability was evaluated by appearance, taste, smell, pH and rheological assessments. Cilazapril oral suspensions at concentration of 1 mg/mL demonstrated satisfactory stability over 28 day long storage at room temperature. Cilazapril concentrations remained within acceptable limit (± 10%) stored in closed amber bottles made of glass or PET material. Moreover, suspensions physical properties remained unaffected. Cilazapril – Ora-Blend® pediatric oral liquid is easy to made, palatable and stable when stored at room temperature for 28 days. Stability of cilazapril oral liquid remains unchanged while using cilazapril tablets produced by different manufacturers and bottles made of amber glass or PET material.

Keywords: angiotensin-converting enzyme inhibitor, cilazapril, pediatric oral suspension, stability

Cilazapril is a specific, selective and long-acting angiotensin converting enzyme inhibitor, which is widely used in therapy of hypertension and heart failure in adults (1–3). It is one of the angiotensin enzyme inhibitors that is also important and widely used in treatment of congestive heart failure in children population (4, 5). Reported pediatric experience with cilazapril is limited, but owing to those clinical studies we possess the knowledge that cilazapril given once a day at dose 0.04 mg of cilazapril/kg of body weight is effective in treating children. Cilazapril doses should be given orally starting from the small doses increasing to reach the final dosage over 1–2 weeks. Effects of such therapy are satisfactory. Cilazapril in children improves cardiac function, reduces left ventricular overload, left ventricular hypertrophy and improves left ventricular function by decreasing mass and wall thickness of left ventricle. Moreover, these beneficial effects persist long-term without tolerance development and are characterized by low adverse effect profile (6, 7).

In case of cilazapril therapy essential disadvantage is the lack of proper dosage formulation for children, which are unable to swallow a tablet. Cilazapril is marketed in form of tablets (0.5, 1.0, 2.5 and 5.0 mg cilazapril content) by original and number of generic manufacturers. Good alternative dosing option would be an oral liquid formulation. Preparing stable medications proper to children is challenging. To develop a pharmaceutical formulation many features must be considered such as: excipients, storage conditions, packing, chemical stability of drug substance and final appearance. All mentioned above features that prepared formulation should possess, contribute to better compliance and palatability (8). Presented study is aimed at preparation of an oral liquid with cilazapril and its stability evaluation, because until now neither pediatric oral compounding formulas nor stability data are avail-

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able in the worldwide scientific literature. Needed drug product should be compatible, stable, efficacious, palatable, easy to administer and well tolerated by fastidious pediatric patient.

Cilazapril solubility in water is low (9). Therefore, it is not possible to achieve cilazapril aqueous solution and the only reasonable liquid dosage form for studied drug seems to be an oral suspension (10). Moreover, according to data obtained in the course of previous authors' study (11), it was stated that cilazapril decomposition proceeds by hydrolysis reaction forming biologically active, nevertheless impossible to absorb cilazaprilat molecule. Though, reasonable would be water avoidance or assurance of such environment that prevents hydrolysis occurrence. Ora-Blend® suspending agent was chosen, because it possesses acidic pH (3.5–5.0), ensured by buffering agents, that is considered to be optimal for stability of most hydrolyzable drugs. Moreover, Ora-Blend® vehicle ensures easy manufacturing procedure. Amber bottles (glass and plastic PET) were chosen, while in pharmacopeia it is suggested to protect cilazapril substance from light (9).

Summing up, the aim of this study was to produce easy to prepare, stable cilazapril oral suspension. Stability in prepared oral liquids was tested in oral suspension prepared utilizing original and generic cilazapril 5 mg tablets after storage in amber PET bottles and amber glass bottles at room temperature (298 K).

EXPERIMENTAL

Preparation of cilazapril 1 mg/mL suspensions

Original (lot: E0128B01U1, expiry date: 09. 2013) and generic (lot: 010612, expiry date: 12. 2013) cilazapril 5 mg tablets were utilized to prepare oral suspensions. In each case 20 tablets were ground in a mortar to a fine powder. Subsequently, obtained powder was levigated with a small amount of Ora-Blend® (lot: 1125072, expiry date: 03. 2013) vehicle to make a paste. Following portions of vehicle were added to obtain liquid, which was subsequently transferred into graduated cylinder. Finally, after rinsing a mortar with vehicle, prepared oral liquid was filled up to 100 mL with Ora-Blend®. Ora-Blend® is ready-made vehicle, which acts as a suspending and flavoring agent, making oral suspension palatable to children. So prepared suspensions were put in amber glass or plastic PET bottles and stored at 298 K over four weeks time.

Stability study

Prepared oral liquids (original drug – formulation A – Ora-Blend® suspension in glass bottle, original drug – Ora-Blend® suspension in plastic PET bottle, generic drug – formulation B – Ora-Blend®

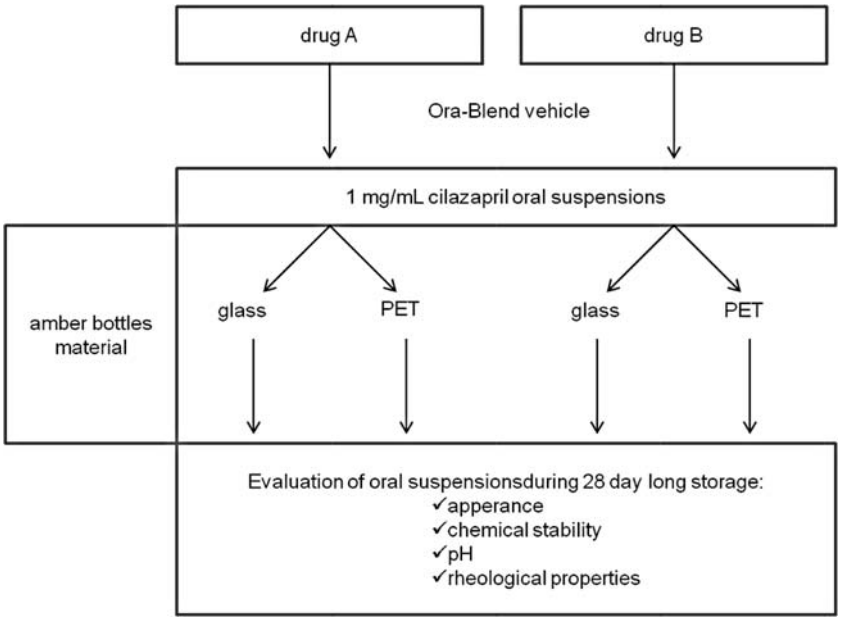

Figure 1. Stability evaluation scheme of cilazapril oral suspensions

suspension in glass bottle, generic drug – Ora-Blend® suspension in plastic PET bottle) were placed in thermostatic chamber ST1+ (Pol-Eko, Poland) with accuracy control 0.1 K set at 298.0 K. Bottles were screwed-capped. Samples were collected on the 0 day, when the suspensions were prepared and on days 7, 14, 21 and 28, during the storage. Before sample collection, each bottle with oral suspension was shaken for 1 min by hand. The samples were assayed by HPLC method with UV detection on the day of sample collection. Specific stability protocol was established for different bottle packs. Bottles used were sterile, in order to avoid microbiological changes in oral liquids and amber, while in pharmacopoeia it is advised to protect cilazapril substance from light (Fig. 1).

Physical stability study

Prepared oral liquids with cilazapril were studied at every sampling for changes in odor by smelling, in favor by spill and spit method and for a change in appearance by vision.

The pH values at every sampling were evaluated by means of calibrated pHmeter MP225 Mettler-Toledo.

Rheological properties of prepared oral suspensions were evaluated on 0 and 28 day of the study. Rheological parameters were determined using rheometer HAAKE RheoStress (Thermo Electro Corporation) equipped with plate-plate measuring system (PP35Ti rheometer RS1 rotor). The system temperature was set at 298 K (thermostat HAAKE DC 30, Thermo Electro Corporation), the same temperature in which oral suspensions were stored for 28 days.

HPLC assay method

The quantitative analysis of cilazapril content in oral suspensions was conducted by means of validated, cilazapril stability indicating HPLC method (12). The Shimadzu HPLC system consisted of: Shimadzu LC-6A liquid chromatograph pump with 7725 Rheodyne value injector (20 µL fixed loop), Shimadzu SPD-6AV UV-VIS spectrophotometric detector and Shimadzu C-R6A Chromatopac integrator. Chromatographic separation was achieved on the column: LiChroCART® 250-4 HPLC-Cartridge, LiChrospher® 100 RP-18 (5 µm) (Merck, Germany). The mobile phase was composed of acetonitrile–methanol–phosphate buffer (pH 2.0) (60 : 10 : 30, v/v/v). The flow rate of mobile phase was set at 1.0 mL/min, column worked at ambient temperature and the injection volume was 20 µL. The detector wavelength was set at 212 nm. As an internal standard 0.02 mg/mL oxymetazoline hydrochloride methanolic solution was used.

Samples for HPLC analysis were prepared according to presented below procedure. Volume 2.5 mL of shaken for 1.0 min oral suspension was weighed and transferred quantitatively into 25.0 mL volumetric flask, filled up to the volume with methanol and shaken for 15 min. Subsequently, this suspension was centrifuged at 5800 rpm (MPW-54, MPW) for 10 min. Supernatant was filtered through 0.45 µL membrane syringe filter. Afterwards, 1.0 mL of obtained solution was mixed with 0.5 mL of 0.02% methanolic solution of oxymetazoline hydrochloride (internal standard). Such solution was subjected to HPLC analysis for cilazapril content.

RESULTS AND DISCUSSION

HPLC method selectivity

The HPLC method with UV detection previously developed and validated for purpose of stability study of cilazapril in solid state (12) turned out to be suitable for evaluation of cilazapril stability in oral suspension made of cilazapril commercial

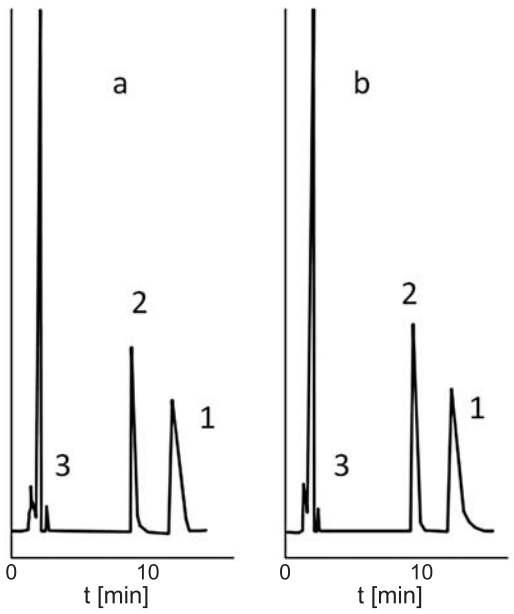

Figure 2. Stability indicating HPLC method, proper for the stability evaluation of cilazapril in Ora-Blend® vehicle. Method is selective towards cilazapril in the presence of excipients of tablet pharmaceutical formulation and contained in Ora-Blend® vehicle. Chromatograms are obtained from analysis of: a) cilazapril oral liquid obtained with original cilazapril tablets (formulation A) and b) cilazapril oral liquid obtained with generic cilazapril tablets (formulation B). Peak (1) match the internal standard and (2) – cilazapril and (3) Ora-Blend® and tablet excipients

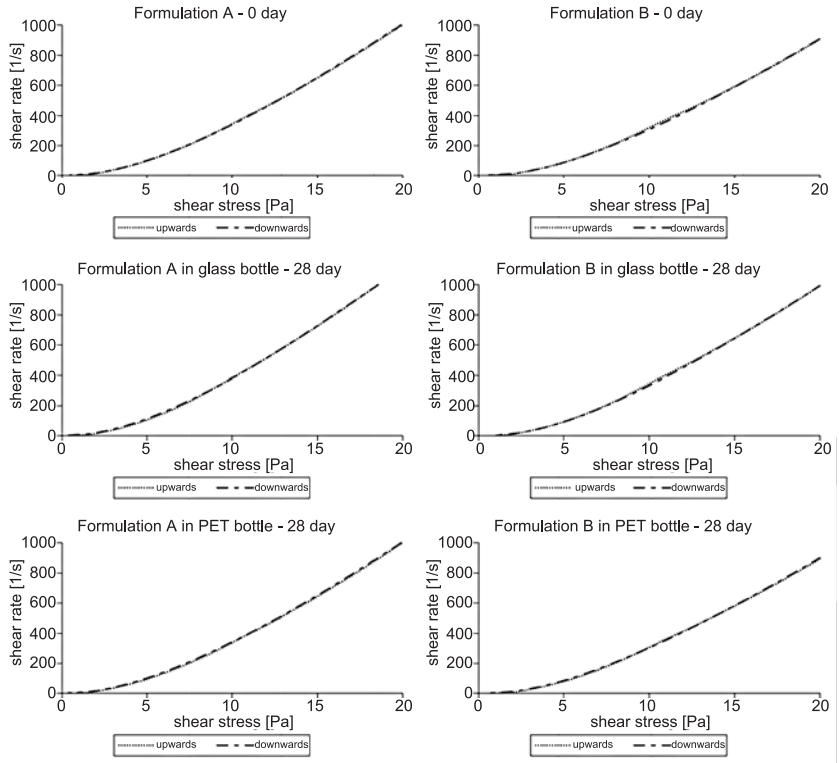

Figure 3. Thixotropic curves of 1 mg/mL cilazapril oral liquids – formulation A and B at 0 day and after 28 day storage at 298 K in amber glass or amber PET bottles

Table 1. Organoleptic properties of 1 mg/mL cilazapril oral suspensions.

Organoleptic properties*	1 mg/mL cilazapril oral suspension	
	formulation A	formulation B
appearance	reddish granular suspension	white granular suspension
taste	berry-citrus and sweet, very slightly bitter	
smell	sweet and fruity	

*No changes in organoleptic properties was observed after 28 day storage at 298 K

tablets (original – formulation A or generic – formulation B). The selectivity of this method was confirmed in the presence of cilazapril tablets and Ora-Blend® excipients. The symmetrical peak of cilazapril, observed at retention time of 8.9 min, was clearly separated from the peaks of excipients and internal standard used (Fig. 2). Throughout the study, degradation of cilazapril occurred, but only in range of ± 5% of initial cilazapril concentration (100%), which is acceptable for drug stability in oral suspension. Very low, near the chromatogram base line peak of degradation product appeared during the 28 day long study. It is characterized by retention time 3.1 min. This retention time is equal with the retention time of cilazaprilat according to authors earlier studies concerning cilazapril stability (11).

Physical stability

Crushed and pulverized tablets of cilazapril (original drug A and generic drug B) were checked for taste by spill and spit method. In both cases taste was unpalatable, bitter and characterized by very unpleasant taste. Ora-Blend® flavors masked unpleasant taste successfully, appearance, and taste of liquid was enhanced.

Table 2. The pH of 1 mg/mL cilazapril oral liquid prepared from original drug tablet (formulation A) and generic drug tablet (formulation B) in Ora-Blend® vehicle stored at 298 K.

Formulation/ Bottle	pH (mean* ± SD)				
	0 day	7 days	14 days	21 days	28 days
A					
glass	4.747 ± 0.005	4.828 ± 0.008	4.727 ± 0.005	4.522 ± 0.004	4.607 ± 0.009
PET	4.747 ± 0.005	4.708 ± 0.086	4.787 ± 0.025	4.537 ± 0.011	4.602 ± 0.017
B					
glass	4.745 ± 0.006	4.838 ± 0.004	4.852 ± 0.024	4.552 ± 0.020	4.647 ± 0.005
PET	4.745 ± 0.006	4.835 ± 0.009	4.540 ± 0.012	4.545 ± 0.013	4.66 ± 0.000

*mean from six independent measurements

Table 3. Rheological properties of 1 mg/mL cilazapril oral liquid prepared from original drug tablet (formulation A) and generic drug tablet (formulation B) in Ora-Blend® vehicle stored at 298 K.

Formulation/ Bottle	*K*		*n*	
	0 day	28 days	0 day	28 days
A				
glass	0.39	0.26	0.55	0.62
PET	0.39	0.26	0.55	0.62
B				
glass	0.44	0.26	0.55	0.63
PET	0.44	0.35	0.55	0.59

Table 4. Stability of 1 mg/mL cilazapril oral liquid prepared from original drug tablet (formulation A) and generic drug tablet (formulation B) in Ora-Blend® vehicle stored at 298 K.

Formulation/ Bottle	Percent of initial concentration (mean* ± SD) [%]				
	Initial concentration [mg/mL]	7 days	14 days	21 days	28 days
A					
glass	1.04 ± 0.02	103.24 ± 0.15	101.18 ± 1.54	102.43 ± 1.99	103.13 ± 1.30
PET	1.02 ± 0.01	101.13 ± 0.47	98.43 ± 1.81	100.92 ± 1.10	98.85 ± 0.76
B					
glass	1.01 ± 0.05	98.91 ± 1.98	102.20 ± 3.53	97.14 ± 0.76	99.11 ± 3.74
PET	1.02 ± 0.02	97.81 ± 1.42	99.68 ± 3.52	98.88 ± 3.90	102.43 ± 0.42

*mean from two independent measurements

Prepared oral liquids were acceptable in terms of appearance, smell and taste (Table 1). It is essential, because it contributes to better compliance.

Differences in appearance are caused by different original and generic tablet film coating. Original drug coating is *inter alia* made of red iron dioxide contributing to reddish oral liquid color.

Evaluation of physical properties during stability study of cilazapril oral suspension did not indicate any changes. The flavor, odor or appearance did not seem to change during 28 days of the study.

The pH of suspensions remained stable when stored for given conditions, regardless of tablets used (original and generic) and bottle material. No statistically significant differences at $\alpha = 0.05$ were observed for pH values evaluated during the study (Table 2).

Moreover, pH levels maintained in Ora-Blend® buffering pH range (sodium phosphate monobasic

and citric acid), which is 3.5–5.0. Thus, it can be concluded that buffering system of vehicle ensured stable pH in oral liquid throughout the storage time. Rheological analyses were carried out at the day of oral liquids preparation and after 28 days long storage in amber glass and PET bottles at 298 K temperature. Such parameters as: flow curves, thixotropic curves were evaluated. In all rheological tests oral liquids were subjected to increasing shear rate and, as a consequence, liquid structure was destroyed and liquid started to flow. Nevertheless, when rate shear values decreased, suspension structure was rebuilt, what can be clearly seen on thixotropy curves (Fig. 3). Moreover, from the shape of upwards part of thixotropic curve (the flow curve) in can be concluded that the prepared suspensions are pseudoplastic, shear thinning fluids. Such rheological properties of prepared oral liquids are owing to Ora-Blend® suspending agent. Ora-Blend® is compounded of synergistic blend of suspending agents, which form gel-like matrix counteracting settling down of suspended drug particles.

For mathematical description of studied liquids behavior viscosity Ostwald model was used:

$$\tau = K \cdot \gamma^n \quad (1)$$

where τ [N/m] is shear stress; γ [1/s] is shear rate; n signifies flow behavior index and K fluid consistency coefficient (13). As it results from data presented in Table 3, flow behavior index value < 1 gives evidence that fluid is shear thinning. Changes between K and n parameters observed throughout storage in amber glass or plastic PET bottles through 28 days time in 298 K temperature were minimal and indicated the evidence that 28 day storage did not affect rheological properties of prepared liquids.

Chemical stability

Cilazapril in oral suspensions retained its potency during the storage, while concentration remained within the limits specified in pharmacopoeia (±10%) (Table 4).

CONCLUSIONS

Presented study provides evidence on 28 day stability of cilazapril suspension oral liquid. Stable, that means that throughout 28 day storage in capped bottles of amber material glass or plastic PET retains within specified limits the same properties as at the time of its manufacture.

Cilazapril oral suspensions in concentration of 1 mg/mL are stable for 28 days in room temperature (298 K), regardless of tablets used (original or generic) and bottle material used.

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