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BRIEF REPORT

Analysing the stability of two oral carbamazepine suspensions

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KEYWORDS
Carbamazepine;
Stability;
Oral suspension;
Compounded medication

Abstract
Objective: To assess the physical, chemical and microbiological stability of two oral suspensions of carbamazepine at concentrations of 2.5% and 5%.
Methods: Both oral suspensions were compounded from powdered carbamazepine and Ora-Sweet SF® and Ora-Plus® commercial compounding excipients. At the 2, 4 and a 6-month marks, different quality assays were performed, comprising physical (pH, state of the suspension, organoleptic properties), chemical (HPLC) and microbiological assays.
Results: The final concentration at 6 months for both the 2.5% and 5% carbamazapine suspensions was 22.9 and 45.9 mg/ml respectively, with calculated richness values between 90 and 110% fulfilling USP23 NF18 requirements. No changes in physical properties and no culture growth were observed during the study period.
Conclusion: Both oral suspensions are physically, chemically and microbiologically stable for at least 6 months when preserved at room temperature in amber glass flasks.

PALABRAS CLAVE
Carbamazepina;
Estabilidad;

Análisis de la estabilidad de dos suspensiones orales de carbamazepina

Resumen
Objetivo: Analizar la estabilidad fisicoquímica y microbiológica de dos suspensiones orales de carbamazepina al 2,5 y al 5%.

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Suspensión oral;
Formulación magistral

Método: Las suspensiones orales se elaboraron a partir de carbamazepina en polvo y los vehículos comerciales Ora-sweet SF® y Ora-plus®. Se realizaron controles de calidad físicos (pH, estado de la suspensión y características organolépticas), químicos (cromatografía líquida de alta resolución [HPLC]) y microbiológicos a los 2, 4 y 6 meses de la preparación.
Resultados: La concentración a los 6 meses de las suspensiones de carbamazepina al 2,5% y al 5% resultó de 22,9 mg/ml y de 45,9 mg/ml, respectivamente, con valores de riqueza obtenidos mediante la cromatografía líquida de alta resolución se encontraron entre el 90 y el 110%, tal y como exige la Farmacopea Americana 23 NF18. Durante el período del estudio no se observó modificación de los parámetros físicos ni crecimiento en los cultivos microbiológicos realizados.
Conclusiones: Ambas suspensiones orales son estables física, química y microbiológicamente durante al menos 6 meses a temperatura ambiente y en frasco de vidrio topacio.

Introduction

Carbamazepine is the antiepileptic drug of choice for partial epileptic seizures and generalised tonic-clonic seizures. It is also indicated for trigeminal and glossopharyngeal neuralgia, bipolar disease and severe behavioural disorders. It is especially recommended for children, given that it has a slight depressant effect on the central nervous system, and a better adverse effect profile than phenytoin and phenobarbital. It has good bioavailability when administered orally, which is improved when taken with food and which is greater for liquid forms.[1] Drug metabolism is mainly hepatic (98%); its main metabolite being carbamazepine 10,11-epoxide, which is pharmacologically active. It causes a dose-dependent enzyme self-induction, which varies greatly among individuals. As such, treatment safety and efficacy can be optimised when dosage is personalised by means of monitoring carbamazepine plasma concentration.

In Spain, carbamazepine is only marketed in solid oral dosage forms (Tegretol®, Novartis Farmacéutica, Barcelona, Spain, in 200 mg and 400 mg tablets), which is not the case in other European countries where carbamazepine can be found as a liquid oral suspension (2%). Carbamazepine in liquid dosage form is extremely useful as a more precise dose can be administered when personalising treatment in accordance with plasma levels. It is also beneficial for dysphagic people or children. As such, the pharmaceutical industry has left a gap, which calls for pharmacists to compound a liquid oral dosage which can be administered to these groups. In most cases, these liquid dosage forms are compounded using carbamazepine preparations on the market (i.e. Tegretol® tablets). However, this method poses problems associated with current drug compounding regulations,[2] and because unwanted excipients may be incorporated into the final product. Given this situation, this study is to assess the physical, chemical and microbiological stability of two carbamazepine oral suspensions at 2.5% and 5% concentrations, based on the pure active ingredient.

Methods

We prepared 2 carbamazepine oral suspensions at concentrations of 2.5% (25 mg/ml) and 5% (50 mg/ml). We compounded the suspensions in accordance with Spanish compounding regulations.[2] We used carbamazepine powder as a raw material (Carbamazepina Ph Eur®, Laboratorio Fagrón Ibérica, Barcelona, Spain) and a 50/50 ratio of Ora-sweet SF® and Ora-plus® (Paddock Laboratories, Minnesota, USA). Ora-sweet SF® is a sugar- and alcohol-free syrup vehicle which contains sorbitol, glycerine and sodium saccharin. Ora-plus® is an oral suspending vehicle which contains different suspending agents such as carboxymethylcellulose sodium, microcrystalline cellulose, xanthan gum and carrageenan, amongst others. Suspensions were compounded in the following way: we weighed the necessary amount of carbamazepine powder and we crushed it in a mortar for three minutes until we obtained a fine powder. Then, we added the powder to a mixture of Ora-sweet and Ora-plus (50/50 ratio). We put the suspension in an amber glass flask and labelled it appropriately. We kept the carbamazepine suspension at room temperature (24-27 ºC) throughout the study period and conducted quality control tests 24 hr after compounding, and at the 2, 4, 6 month-marks for:

1) Physical assays: pH testing (pH meter 2000™ (Crison, Barcelona, Spain), calibration 4 and 7.01), state of suspension, gases released and sensory characteristics (smell, colour, etc.).
2) Chemical assays: calculating the amount of the substance in the sample (richness) using high performance liquid chromatography (HPLC). We used the HPLC Hitachi D-7000™ system for analysis (Hitachi High-Tech, Tokyo, Japan), and we employed the following chromatographic conditions:
   - Mobile phase composition: phosphate buffer (pH 5.3): acetonitrile: methanol (55:17:28).
   - Column: LICHROCART®; LiChrospher® 100 RP-18 (5 ìm), (Merck KGaA, Darmstadt, Germany).