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BRIEF REPORT

Analysing the stability of two oral carbamazepine suspensions

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KEYWORDS
Carbamazepine;
Stability;
Oral suspension;
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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).

Figure HPLC chromatogram for carbamazepine. Retention times (RT) of the mobile phase (RT=0.39; RT=0.55 and RT=0.75) and the carbamazepine standard (100 ppm [RT=2.43]).

- UV detection at 210 nm.
- Injection volume: 20 ìl.
- Flow rate: 20 ml/min.

We created calibration curves for each of the measurements taken during the study period. To be able to obtain calibration curves we prepared liquid standards at 10, 20, 50, 100 and 200 ppm in HPLC-quality methanol (LabScan, Gliwice, Poland), using the same batch of carbamazepine that was used in the compound medications (Figure).

Lastly, we calculated the samples' concentrations by extrapolating the calibration curve peaks obtained using the standards' chromatograms.

c) Microbiological assays: We studied the aerobic and anaerobic bacteria growth. We used the direct plate culture method in a blood agar, polivitex agar and SCs culture media with an aliquot of 1 ml of the compounded suspensions. We performed each assay twice, and incubated them at 37 ºC for 48 hours before checking for bacterial growth on the media.

Results

Carbamazepine suspensions at 2.5% and 5% had an initial carbamazepine concentration of 22.9 mg/ml and 49.5 mg/ml, respectively, which is different from the theoretical initial concentration of 0.08% and 0.01%, respectively. Both suspensions were light pink and slightly viscous, with a faint fruity smell. They were both easily dispersible, were bubble-free and had a pH of 4.5 (±0.2). The excipients had these same characteristics so that carbamazepine did not modify the sensory properties of the compound for the concentrations tested. Ora-plus® was practically odourless and milky white in colour, whereas Ora-sweet® had a slight pinkish tinge, and provided the preparation with a characteristic smell and sweet flavour. Both excipients had a pH level of almost 4.5, compared with carbamazepine's basic pH level (7.0). The physical parameters did not change in any of the tests throughout the study period.

There was no bacteria growth in any of the microbiological cultures throughout the study, even though the suspensions were always conserved at room temperature. The excipients used contained preservatives and complied with the United States Pharmacopoeia with regards microbiological contamination. As such, no problems were expected for this matter.

Table shows the chemical HPLC assay results, which determined the carbamazepine concentrations for both suspensions. Carbamazepine richness was calculated based on the concentrations measured for each of the tests performed. Suspension at 2.5% results were: initial 92.4%; at 2 months 94%; at 4 months 102.4%; and at 6 months 91.6% Suspension at 5% results were: initial 99%; at 2 months 101.6%; at 4 months 103.6%; and at 6 months 92.7% Richness values obtained in all assays were between 90% and 110% for both suspensions, as required in the American pharmacopoeia NF18.[3] We can therefore guarantee chemical stability until the 6-month mark, although it is clear that from that point concentrations seem to reduce, and there is a certain tendency for the HPLC peaks to split.

Discussion

Making carbamazepine available as a liquid oral dosage form is of great interest, given that there are no drugs with these characteristics currently on the market. Carbamazepine has low-water-solubility, which means that it can be used to make suspensions for administering the drug via liquid oral dosage forms. Thus, different guides for administering drugs via a nasogastric tube recommend compounding an extemporaneous carbamazepine suspension at 4%[4] and diluting it in a similar water volume to minimise carbamazepine adhering to the nasogastric tubes.[5] This extemporaneous formula is often compounded from tablets using a simple syrup as an excipient, meaning that the preparation should be kept in a refrigerator and used within 3-month period.[6] There are very few studies on compounding and stability of a liquid oral dosage form of carbamazepine and those that were found were very outdated. One of the main studies was Burckart et al (1981), which examined the stability of an oral suspension of carbamazepine at 4% in sorbitol 70%,[7] obtaining an easily redispersed suspension with a 90-day expiry period. The problem of this preparation is that it has high concentration of sorbitol, which may cause intestinal discomfort and diarrhoea. Although our compound does contain sorbitol due to Ora-sweet®, its concentration is less than 10% meaning that it is less likely to cause diarrhoea. The results obtained in our study allow carbamazepine suspension's expiry period to be extended and provide a clear methodology for compounding the oral suspension. Given that we have used a sugar-free excipient, it can be indicated in diabetic patients and since there are preservatives in the excipient, there is less risk of the preparation gaining bacteria contamination, allowing a longer expiry period. Suitability of this compound should be confirmed by means of bio-availability and/or clinical effectiveness tests.

To conclude, both of the carbamazepine suspensions that we have compounded are physically, chemically and microbiologically stable for at least 6 months at room temperature when kept in an amber glass flask. This allows us to guarantee a 6-month expiry period for this compound

Table 1 Carbamazepine concentrations (mg/ml) throughout the study period

	24 hr	2 months	4 months	6 months	Average (SD)
Concentration for 25 mg/ml sample	23.1	23.5	25.6	22.9	23.7 (1.2)
Concentración medida para la muestra de 50 mg/ml	49.5	50.3	51.3	45.9	49.2 (2.3)
Detection limit (mg/ml)	5.6	16.2	8.1	4.3	–
Linear regression (r)	0.982	0.955	0.979	0.986	–

r indicates correlation coefficient; SD, standard deviation.

medication. We have therefore been able to provide a liquid oral dosage form of carbamazepine at standardised concentrations, covering the needs of patients that are not able to take solid oral dosage forms or for dosages that can not be adapted to marketed preparations.

Conflict of interest

The authors affirm that they have no conflict of interest.

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