

Assessment of stability in extemporaneously prepared venlafaxine solutions

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ABSTRACT

Study objectives: To investigate the stability of venlafaxine oral liquids at two temperatures.

Methods: Solutions of venlafaxine 5 mg/mL were prepared from commercially available tablets in a mixture of OraSweet and OraPlus solutions. They were stored in amber-coloured glass bottles at 4°C and 25°C. The concentrations of venlafaxine were determined in solutions stored at both the temperatures by a stability-indicating high-performance liquid chromatography (HPLC) method. The initial and final pH of the solutions were compared. A loss exceeding 10% of the initial concentration of venlafaxine was considered excessive degradation.

Results: The recovery of venlafaxine from tablets was 100% ± 2.1%. No significant difference was found between initial and final pH values for the two formulations. The solution stored at 4°C was stable for 15 days and the solution stored at 25°C was stable for 10 days.

Conclusion: Venlafaxine 5 mg/mL oral solution stored at 4°C could be used to facilitate drug administration for paediatric or adult patients by nurses.

KEYWORDS

Oral liquids, stability, venlafaxine

INTRODUCTION

Venlafaxine, which is both a serotonin and noradrenaline re-uptake inhibitor, is known to be effective in treating major depression and generalised anxiety disorder in adult patients [1-4]. The EMEA and the FDA approved venlafaxine for these indications. Venlafaxine is usually administered at a dose of 75 mg per day in two or three divided doses. Clinical studies have been conducted in children in various doses to treat depression, hyperactivity disorder or social phobia [5-7]. Venlafaxine is only available as capsules or tablets, which are difficult for young children or older adults to swallow. The available strengths also make it difficult to give a dose based on body weight. One alternative is for the pharmacist to prepare a solution extemporaneously by dissolving or suspending tablets or capsules to create palatable syrups. The purpose of the present study was to develop a formulation for venlafaxine that is palatable, possesses acceptable appearance

and is stable for at least 90 days. Venlafaxine seems to be stable under basic and oxidative conditions but less stable under acidic conditions. No stability data are available.

MATERIALS AND METHODS

Preparation of venlafaxine suspension

Twenty 50-mg venlafaxine tablets (Effexor, Wyeth Pharmaceuticals, Lot 21438) were crushed with a pestle and mortar to obtain a fine powder. The powder was placed in a 250-mL volumetric flask and equal amounts of OraSweet (Paddock Laboratories, Lot 182963) and OraPlus (Paddock Laboratories, Lot 132736) were then added to the flask to obtain a volume of 200 mL of solution. The flask was shaken to ensure thorough mixing and aliquoted into five 50-mL amber-coloured glass bottles. Five such bottles were prepared for each study condition. Each tablet contains 50 mg venlafaxine base, 100 mg cellulose, 36.6 mg lactose, 0.6 mg magnesium stearate, 6 mg sodium starch

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glycolate and iron oxides. OraSweet contains sucrose, glycerine, sorbitol, citrus-berry flavour, sodium phosphate and citric acid with a pH of approximately 4.2. It is preserved with methylparaben and potassium sorbate. OraPlus consists of microcrystalline cellulose, sodium carboxymethylcellulose, xanthan gum, carrageenan, sodium phosphate and citric acid, with a pH of approximately 4.2. It is also preserved with methylparaben and potassium sorbate.

Storage of solutions

Bottles were placed either in a 4°C stability chamber (n = 5) or in a controlled environment room at 25°C ± 3°C (n = 5) with no exposure to direct light. Two bottles were placed at 40°C for forced degradation studies.

Sample preparation for analysis

At the predetermined time interval, the solution in each bottle was observed for appearance and the pH determined. A 20 µL sample of each bottle was taken and diluted to 800 µL with sterile water. 200 µL of quinine 1 mg/mL made by dilution of quinine hydrochloride 10 mg/mL (Agence Générale des Equipements et Produits de Santé) with sterile water was added as the internal standard. The samples were centrifuged at 3,000 rpm for five minutes. One hundred microlitres of supernatant was injected into the HPLC system.

Instrumentation

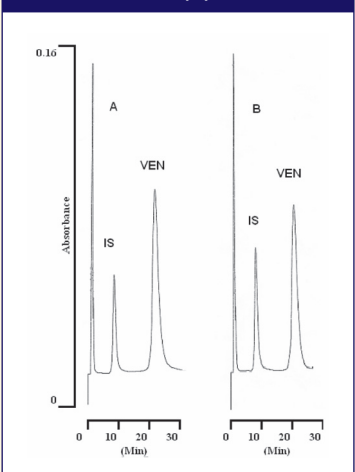
All HPLC analyses were conducted on Shimadzu instruments (Shimadzu Corporation) equipped with a variable wavelength detector (model LC-6A, Shimadzu France), an isocratic pump (model SPD-6A, Shimadzu France), and a recording integrator (model C-R6A, Shimadzu France). The HPLC method employed a C18 column (Symmetry RP-C18 column, 5 µm, 4.6 × 25 mm, Waters). A digital pH meter (model pH302, Hanna Instruments) was used for pH determination.

HPLC analysis

For the estimation of venlafaxine in solutions made with OraSweet and OraPlus, the stability-indicating HPLC method of Makhija SN and Vavia PR [8] was adapted for this study. The mobile phase containing acetonitrile (Lichrosolv, Merck) and sterile water for irrigation (Versol, Aguettant) (75:25, v/v) was pumped at a flow rate of 1.5 mL/minute. An injection volume of 20 µL was used and the system was monitored at 224 nm. Venlafaxine and quinine were eluted in about 22 and nine minutes, respectively (see Figure 1). Calibration curves were prepared using venlafaxine 3 mg/mL and quinine 1 mg/mL solutions. Standards were diluted in sterile water to give venlafaxine concentrations of 15, 30, 60, 90, 120, 180 and 240 µg/mL. The standard curve was constructed by plotting the peak to area ratio of venlafaxine to quinine versus the

venlafaxine concentration and was used to calculate the drug concentration in the samples. The data were subjected to linear least-square regression analysis and the plot was found to be linear over the range tested with a regression coefficient of 0.994 (n = 5). The equation was a slope of 0.025 ± 0.0004 and an intercept of -0.079 ± 0.05 . Both intraday and interday coefficients of variation were <3% for the concentrations tested (30, 90 and 180 µg/mL, n = 5). The detection limit was 1.4 µg/mL (signal noise 3:1).

Figure 1: Chromatogram of venlafaxine (VEN) and internal standard (IS) in solutions stored at 4°C (A) and 25°C (B)



Stability-indicating ability of LC assay

A study was performed to determine whether venlafaxine could be recovered from any degradation products, and confirm that the assay was stability-indicating (see Figure 2). Samples of venlafaxine 5 mg/mL were placed in glass tubes and mixed with acid (hydrochloric acid 1 N, Normex, Carlo Erba) or base (sodium hydroxide 32%, Anlypur, Labosi). Other samples were mixed with hydrogen peroxide (hydrogen peroxide 3% w/w, Cooper). Table 1 reveals the effect of different factors on forced degradation of venlafaxine. The reduction in the peak area did not take into account possible products of degradation that could co-elute with venlafaxine. Two bottles were stored at 70°C for a forced degradation study. At day 30, the degradation of venlafaxine was complete and no peak of degradation product was detected during the study period.

Data analysis

Mean concentration of each sample time was determined and converted to percentages of initial concentration. The initial concentration (day 0) of venlafaxine in each solution was designated as 100%, and subsequent sample concentrations were

Figure 2: Chromatogram of forced degraded venlafaxine (VEN) with hydrogen peroxide (C), acid (D) and base (E)

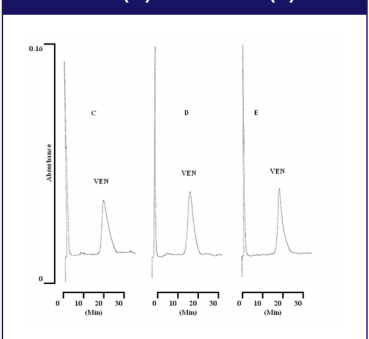


Table 1: Effect of alkaline hydrolysis, acid hydrolysis, oxidative degradation and elevated temperature (40°C) on venlafaxine LC assay

Method used	Quantity (µg/mL)	Peak purity (%)	pH of solution
Control	121.56 ± 6.08	101.30 ± 5.06	3.96 ± 0.02
Alkaline hydrolysis	98.60 ± 2.95	82.17 ± 2.46	1.57 ± 0.01
Acid hydrolysis	84.22 ± 3.36	70.19 ± 3.29	10.61 ± 0.03
Oxidative degradation	85.30 ± 3.84	71.08 ± 3.70	3.84 ± 0.02
Exposed to 40°C	96.94 ± 0.96	79.75 ± 0.79	3.80 ± 0.04

expressed as percentages of the initial concentration. The time at which <90% of the initial concentration remained was considered to indicate a significant loss in terms of stability and a significant reduction in the patient's dose.

RESULTS AND DISCUSSION

A stability-indicating method was adapted from Makhija SN and Vavia PR [8] and validated to test venlafaxine in a mixture of OraSweet and OraPlus solutions. No peak of product degradation was observed for all forced degradation conditions. On exposure to oxidative degradation, alkaline or acid hydrolysis and elevated temperature, venlafaxine was not rapidly degraded and had a peak purity of at least 70% (see Table 1). The recovery of venlafaxine from tablets was 100% ± 2.1%. The complete recovery of venlafaxine hydrochloride was related to its high water solubility, which has been reported to be 572 mg/mL. The chemical stability data for 5 mg/mL venlafaxine solutions, stored at 4°C and 25°C for varying periods of time, are shown in Table 2. No degradation product was observed during the stability study period. The percentages of initial concentration of venlafaxine showed that the compound is more stable

Table 2: Chemical stability of 5 mg/mL venlafaxine solutions stored at 4°C and 25°C

Day	Initial concentration remaining ^a (%)	
	4°C ^b	25°C ^c
1	100.01 ± 6.78	99.46 ± 5.83
2	100.15 ± 4.58	97.00 ± 3.48
3	98.44 ± 3.45	96.42 ± 3.28
6	97.45 ± 3.88	95.37 ± 3.16
8	96.85 ± 3.45	95.02 ± 5.95
9	96.35 ± 4.56	94.10 ± 4.28
10	95.76 ± 4.36	92.16 ± 5.30
13	96.15 ± 4.24	91.22 ± 4.33
22	83.26 ± 2.46	83.29 ± 4.81
23	82.74 ± 1.40	82.03 ± 3.68
28	80.52 ± 2.75	79.28 ± 3.45
29	80.75 ± 2.45	77.71 ± 2.89
43	70.35 ± 3.24	65.64 ± 3.29
91	36.89 ± 3.75	34.20 ± 4.21
93	34.61 ± 2.75	30.67 ± 4.36

^a: Mean ± standard deviation of duplicate determinations for each bottle (n = 5); ^b: the actual initial concentration (mg/mL) was 5.29 ± 0.53, pH = 3.95 ± 0.02; ^c: the actual initial concentration (mg/mL) was 4.81 ± 0.35, pH = 3.97 ± 0.01.

if refrigerated. The mean concentrations of venlafaxine in solutions stored at 4°C and 25°C were >90% after 15 and 10 days, respectively. No significant difference of initial and final pH of solutions was observed after the 90-day study period.

CONCLUSION

An oral liquid form of venlafaxine 5mg/mL in OraSweet and OraPlus mixture, prepared from commercially available tablets, was shown to be chemically stable for 15 days under refrigeration. This oral solution can be safely used as an alternative to the administration of dry venlafaxine forms for paediatric or adult patients.

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