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Influence of temperature on the degradation of climbazol in aqueous diluted solutions

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Abstract

The objective of this research is to evaluate the stability of climbazol. Thermodegradation of solutions of climbazol at various temperatures (50, 70 and 90°C) was studied. This degradation appeared to follow first-order kinetics whatever the temperature. The experiments revealed an activation energy E_a of 5.4 kcal mol^{-1} and a time necessary to obtain a decrease of 10% of the initial concentration, $t_{90\%}$, of 81.9 days for climbazol in aqueous diluted solution at 20°C.

Keywords: Climbazol; Thermodegradation; Aqueous diluted solutions

1. Introduction

A lot of shampoos exist on the market. The anti-dandruff shampoos have a major importance on the market because 70% of the population suffer from a pityriasic state which is aesthetically unpleasant [1–4].

Climbazol, an antifungal from the imidazole class of substances, is an anti-dandruff active ingredient with excellent efficacy. It can be used in shampoos, conditioners and hair tonics [4].

Climbazol has a good efficiency against moulds, yeasts and dermatophytes. Its particularly good efficacy (minimal inhibition concentration 0.1–0.25 μg/ml) against *Pityrosporum ovale* justifies its use as an anti-dandruff agent. Some studies have demonstrated the efficacy of shampoos containing 0.5, 0.75 or 2% of climbazol. Besides, climbazol and ketoconazol showed similar in vitro activity against *Malassezia furfur*, an anthropophilic fungus causative agent of several skin disorders [5–7].

Climbazol (commercial name Baypival^R) is a safe substance; the oral LD_{50} determined on rats is 400 mg/kg and the dermal LD_{50} on rats is superior to 5000 mg/kg. Dermal tolerability tests of Baypival^R in humans have been carried out. Shampoos (based on alkylether sulphate) containing concentrations of Baypival^R between 0.5 and 2% and hair tonics (based on alcohol/water) containing 0.5% Baypival^R produced no irritation or other adverse effects.

In this study, we tested the influence of temperature on the stability of climbazol in aqueous diluted solution at a concentration of 5.40×10^{-5} M.

Another anti-dandruff agent, piroctone olamine, is used to formulate shampoos and it has a very low acute oral toxicity (LD_{50} for rats is 8.1 g/kg and for mice 5 g/kg) even for humans [8–10]. It can be interesting to compare the thermostability of these two molecules.

2. Experimental

2.1. Chemistry

Climbazol was purchased from Bayer (batch No. 203610905). Climbazol, or [1-imidazolyl-1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one] (Fig. 1), is a white to slightly yellowish crystalline powder. There is a weak characteristic odour (phenolic odour). Climbazol is scarcely sol-

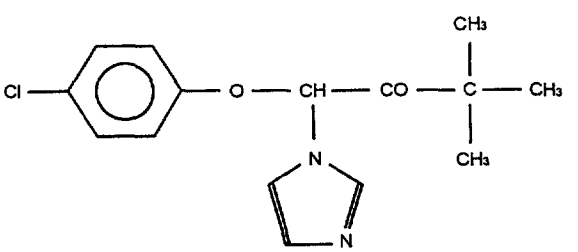

Fig. 1. Structural formula of climbazol.

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uble in water at 20°C. All chemicals were of analytical quality. Distilled water was obtained from an Autostill 4000X (Jencons) apparatus. Demineralized, deionized water was obtained from a MilliQ system (Millipore). Liquid chromatography (LC) quality acetonitrile was purchased from Merck. All solvents and solutions for LC analysis were filtered through a 0.45 μm Millipore filter and vacuum degassed by sonication before use.

2.2. Thermodegradation study

Aqueous diluted solutions (5.40×10^{-5} M) of climbazol were prepared with distilled water. These solutions were enclosed in small glass bottles (Duran, Schott, 100 ml) hermetically sealed by a polypropylene cork. The solutions were stored in thermostatically controlled ovens (Memmert, type UE-200), at 50, 70 and 90°C. Samples were withdrawn at specific time intervals over 230 days and cooled to room temperature. The concentration of climbazol was then determined. In parallel, solutions of climbazol (5.40×10^{-5} M) were stocked at 20°C in a thermostated cabinet (Aqualytic-Bioblock) for 20 months. The analysis was performed on three samples at a time and the difference between the groups of three was less than 1%.

2.3. Preliminary study

The value of the absorption peak of climbazol was determined by a spectrophotometric method (Hitachi UV/visible double-beam spectrophotometer, model U 2000). The slit width was fixed at 2 nm. Solutions were recorded in 1 cm quartz cells over the 200–400 nm range ($\Delta\lambda=2.3$ nm). The scan speed was 400 nm min^{-1}.

2.4. Assay

The climbazol concentrations initially and at time t were determined using high-performance liquid chromatography (HPLC). It was carried out with a system consisting of a Waters model 6000 A pump, a Waters Lambda Max model 481 LC variable-wavelength detector and a Merck D-2500 model integrator (Hitachi). Each solution was analysed under the following conditions: column LiChrosorb RP-18, 10 μm (250 mm×4.6 mm i.d.) (Merck); mobile phase acetonitrile/0.05 M sodium perchlorate (pH 3.0, adjusted with perchloric acid) (40:60, vol./vol.); volume injected 10 ml; temperature 20°C; flow rate 2 ml/min.

2.5. Data analysis

The order of the thermodegradation reaction was determined by the least-squares method of linear adjustment and by calculating the correlation coefficients, in order to choose between the zero-order kinetics and the first-order kinetics. The degradation rate constants k are determined from the slope of the line of peak area versus time. The degradation rate constants and the half-lives at 50, 70 and 90°C were calculated in accordance with the determined order of the reaction. These thermal treatments or accelerated stability studies are based on the Arrhenius relationship, where the degradation rate constant of the substance is a function of the temperature, according to the equation

$$\log k=\log A-(E_a/2.303RT) \quad (1)$$

where k is the degradation rate constant (d^{-1}), A is a constant for a given reaction, E_a represents the heat of activation (cal mol^{-1}), R is the universal gas constant and T is the absolute temperature (K) [11–18]. The statistical analysis of the results was conducted using the Student t test ($p<0.05$).

3. Results and discussion

The optimum sensitivity of climbazol was obtained at 220 nm (Fig. 2). Thus the detector was set to this wavelength.

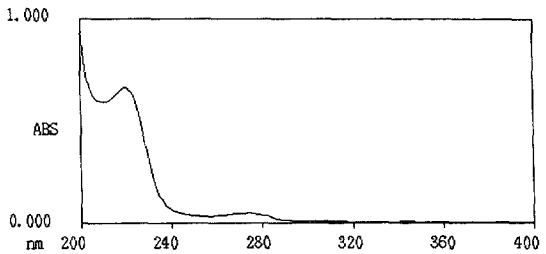

Fig. 2. Spectra obtained with the 5.40×10^{-5} M climbazol in aqueous diluted solution between 200 and 400 nm.

Table 1
C/C_0 ratio for various temperatures at various time intervals for climbazol in aqueous diluted solution (5.40×10^{-5} M)

Time (days)	90°C	70°C	50°C
0	1.000	1.000	1.000
1	0.994	0.996	0.997
10	0.928	0.953	0.970
20	0.860	0.907	0.941
30	0.796	0.863	0.913
40	0.738	0.821	0.886
50	0.684	0.872	0.859
60	0.634	0.744	0.834
70	0.587	0.708	0.809
80	0.544	0.674	0.785
90	0.504	0.642	0.761
100	0.467	0.611	0.739
110		0.581	0.716
120		0.553	0.695
130		0.527	0.674
140		0.501	0.654
150		0.477	0.635
160			0.616
170			0.597
180			0.580
190			0.562
200			0.545
210			0.529
220			0.513
230			0.498

Table 2
Degradation rate constants ($p<0.05$) for climbazol (pH 6.50) and half-times at various temperatures

Temp. (°C)	Degradation rate constants (10^{-3})	Half-time (days)
50	3.03±0.14	228.7
70	4.94±0.16	140.6
90	7.62±0.24	91.1

Under the experimental conditions, a linear response was obtained over climbazol concentrations ranging from 5 to 25 mg l^{-1}. The regression equation is

$$y=11.60x+0.000834 \quad (r=0.998) \qquad (2)$$

where x is the concentration (mol l^{-1}) and y is the area of the peak. r is the correlation coefficient.

The thermodegradation of climbazol in aqueous diluted solution was expressed as the rate of change of peak area. The HPLC analysis demonstrates the gradual decrease of the drug concentration during the thermal treatment. The percentage of substance remaining at various temperatures was calculated (Table 1). The degradation rate constants and the half-times concerning climbazol in aqueous diluted solution (5.40×10^{-5} M) can be found in Table 2.

The thermodegradation of climbazol in aqueous diluted solution followed apparent first-order kinetics and is described by the following equation:

$$C/C_0=e^{-kt} \qquad (3)$$

where C and C_0 are the climbazol concentrations at time t and initially and k is the apparent first-order degradation rate constant (Fig. 3).

Therefore, the Arrhenius relationship Eq. (1) (Fig. 4) gives us the activation energy E_a which is equal to 5.4 kcal mol^{-1} (a result inferior to the value obtained with piroctone olamine which is 19.0 kcal mol^{-1}) [15]. By extrapolation at 20°C, it can be deduced that $t_{90\%}$ (the time necessary to obtain a decrease of 10% of the initial concentration) for climbazol is 81.9 days and $t_{50\%}$ (the time necessary to obtain a decrease of 50% of the initial concentration) is 538.8 days. So, we can class anti-dandruff agents according to their ther-

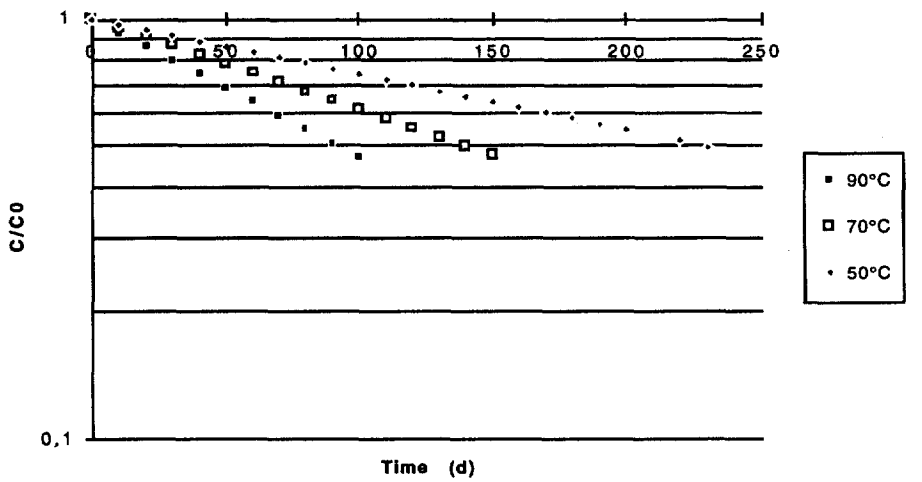

Fig. 3. Thermodegradation of climbazol in aqueous diluted solution (5.40×10^{-5} M) at 50, 70 and 90°C.

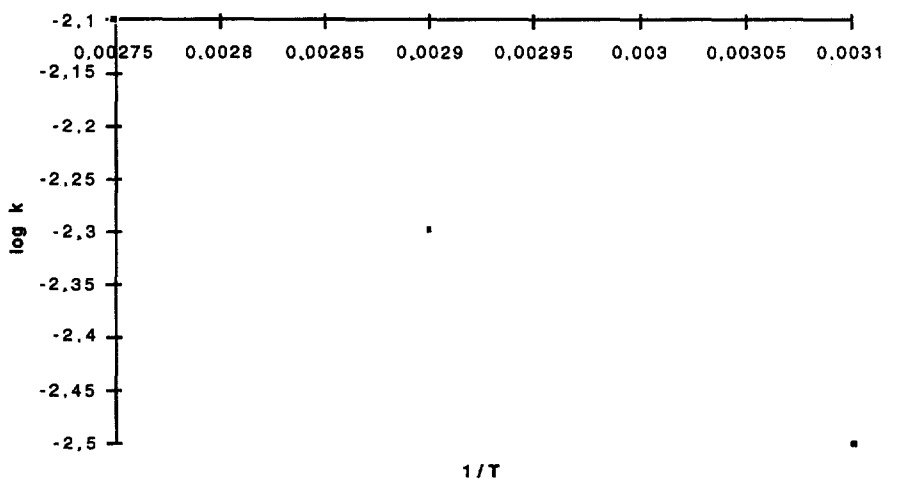

Fig. 4. Arrhenius relationship $\log k=f(1/T)$ for climbazol in aqueous diluted solution (5.40×10^{-5} M).

Table 3
Comparison between results obtained in real time at 20°C and by the accelerated stability test

Time (days)	Concentration		Standard deviation
	Determined (10^{-5} M)	Extrapolated (10^{-5} M)	
60	5.17	5.16	0.0019
120	4.76	4.78	0.0042
180	4.43	4.42	0.0023
240	4.08	4.09	0.0025
300	3.78	3.79	0.0026
360	3.52	3.51	0.0028
420	3.23	3.25	0.0062
480	3.00	3.01	0.0033
540	2.80	2.78	0.0071
600	2.76	2.58	0.0019

mal stability. Climbazol is more stable than sulfoprolamine and less stable than piroctone olamine [15]. Table 3 shows that the accelerated storage test is an excellent model to study the thermostability of this molecule.

Now, it should be interesting to study the influence of the presence of surfactants or pH on climbazol stability.

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