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Nonisothermal stability tests of famotidine and nizatidine

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Abstract

Nonisothermal stability tests have been proposed as an attractive and alternative method to the conventional isothermal stability tests. The stability and the degradation properties of famotidine and nizatidine were investigated using both isothermal and nonisothermal stability test techniques. Linear and logarithmic temperature programs were used and the degradation rate constant and activation energies were calculated using a computer program, which was written in BASIC. Also the advantages and disadvantages of these temperature programs are compared. The method to estimate parameters is based on nonlinear curve fitting the nonisothermal concentration–time–temperature curve equation. The nonisothermal stability test results were compared with the results of isothermal stability tests and similar results were obtained.

Keywords: Famotidine; Nonisothermal stability; Isothermal stability; Linear and logarithmic temperature programs; Stability

1. Introduction

The field of nonisothermal kinetics and stability tests has grown considerably in popularity since the classic treatment by Rogers [1] in 1963. Since then a number of studies have been published in the literature, utilizing this technique [2,3].

Normally, the isothermal stability tests need longer periods to carry out and considerably expensive equipment, like a temperature controlled cabinet, etc. are required. The nonisothermal method has been reported as an alternative to isothermal and accelerated tests, and, therefore, is a useful method for the quick assessment of stability characteristics of pharmaceutical prototype formulations during the development stage [4].

Different temperature programs such as flexible, cyclic, linear, logarithmic, hyperbolic, stepped, etc. have been used [4–14] in the literature with the nonisothermal method. The temperature is continuously varied throughout the experiment and the temperature can be controlled by a computer during the experiment [9–13].

Both isothermal and nonisothermal kinetic methods are based on the Arrhenius relationship. The nonisothermal kinetics method (also called 'nonisothermal accelerated kinetics method'), which is mathematically simple, normally requires only simple tools, that are immediately available in laboratories and other facilities. It is realistic to fit into the time frame of the pharmaceutical industry (i.e. 8 working h per day) [4,15].

Although the nonisothermal method has some advantages, some of the authors indicated that it cannot be suitable for all kind of dosage forms [16]. However, some of the nonisothermal stability tests have been published for solid dosage forms of drugs in the literature, but it has been concluded that, these kinds of tests are more suitable for solutions and suspensions, rather than solid dosage forms [12]. Occasionally this kind of test gives good results for solid dosage forms. The design of nonisothermal stability test has also been reported as nonvalid for substances, which degrade fast, such as aspirin [12]. However, the results of the nonisothermal and isothermal methods have been compared with solutions and no significant differences were obtained [13,17].

Famotidine and nizatidine, both histamine H_2-receptor antagonists, are structurally related to cimetidine

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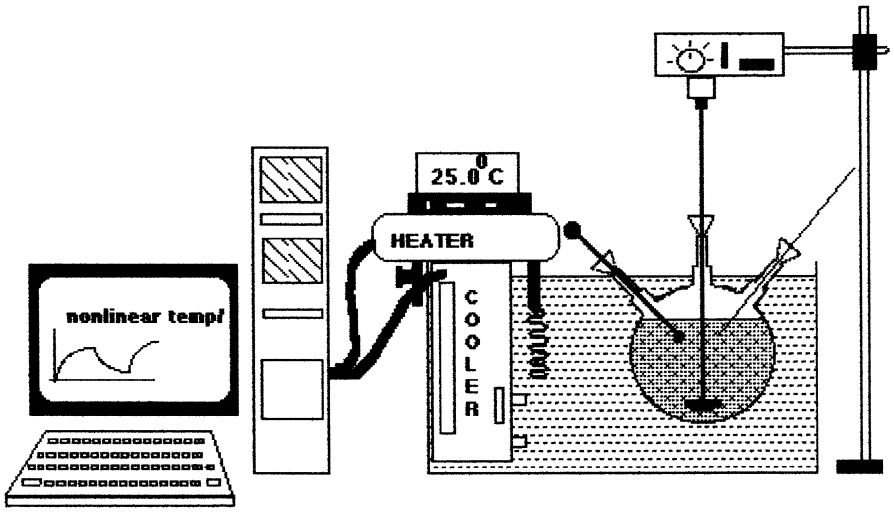

Fig. 1. Layout of the apparatus used in nonisothermal kinetic experiments.

and ranitidine. In common with these drugs, famotidine and nizatidine are potent inhibitors of basal and stimulated gastric acid secretion in animals and man [18].

The objective of this study was to compare the use of isothermal and nonisothermal techniques. A comparison of isothermal and nonisothermal (linear increasing, logarithmic increasing and logarithmic decreasing) temperature programs were performed. The advantages and disadvantages of these temperature programs are compared with fast (famotidine) and slow reacting systems (nizatidine). The stability and degradation properties of famotidine and nizatidine in solution were investigated and the results of the nonisothermal were compared with those of the isothermal method.

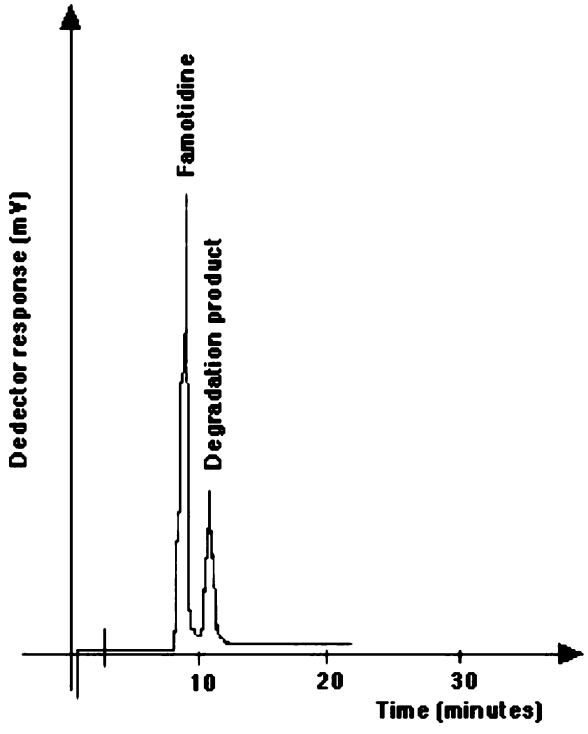

Fig. 2. HPLC chromatograms of the degradation products and famotidine.

2. Materials and methods

2.1. Materials

Famotidine was kindly provided from İltaş Lab. (Istanbul, Turkey) and nizatidine by Eli Lilly (Indianapolis, USA). Other chemicals were of reagent grade.

Thermostated water bath: has a temperature programmer, which is controlled by a computer. High performance liquid chromatography: The HPLC work was performed with Hewlett–Packard pump model 1050; a valve injector, Rheodyne fitted with a 20 μl loop; a Lichrosorb RP 18 column, 10 μm, 250 mm × 4.1 mm and a Hewlett–Packard series 1050 UV-detector with variable wavelength.

2.2. Methods

2.2.1. Isothermal study

Type 1 glass ampoules were filled with the famotidine and nizatidine solutions (0.02 mg ml^{-1}) and stored at 25, 30, 40, 60 °C. Samples were collected and assayed using HPLC for famotidine and samples of nizatidine were analyzed by using derivative a UV spectrophotometer.

2.2.2. Nonisothermal study

The reaction vessel was immersed in a controlled temperature water bath and the initial concentration and the temperature was determined first and the temperature of the bath was then progressively raised

to increase the reaction rate. The temperature changes were controlled by a computer according to the method. Linear and logarithmic temperature programs were used. The apparatus is shown in Fig. 1.

For famotidine, the temperature programmer was set to 25 °C (starting temperature) and was increased linearly to 80 °C during 3 h (linear program). In the logarithmic program, the temperature was increased logarithmically from 25 to 85 °C during 45 min. The test solution was stirred vigorously during the experiment. The samples were collected directly from the solution by a syringe. They were kept in the sample vial without any loss. All samples were analyzed using HPLC.

For nizatidine, the temperature was changed from 70 to 90 °C logarithmically over 4 h with a logarithmic increasing temperature program. Logarithmic decreasing temperature program was carried out from 80 to 50 °C over a period of 5 h. The temperature programmer was controlled by a computer. The test solutions were stirred vigorously throughout the entire experiment. Samples were taken by a syringe directly into a sample vials, without any moisture loss. After removal, each vial was immediately refrigerated for later analysis. All samples were assayed for drug by derivative UV spectrophotometer.

2.2.3. HPLC assay for famotidine

Samples were analyzed with HPLC, using a C18 reverse phase column. The mobile phase consisted of 15% methanol, 16% phosphate buffer and 69% water. The flow rate was 2.0 ml min^{-1}. Famotidine was detected at 267 nm. All the experiments were done in triplicate.

2.2.4. Assay for famotidine

Samples were analyzed by using derivative UV spectrophotometer.

3. Result and discussion

The samples of famotidine were analyzed using HPLC and the chromatograms are shown in Fig. 2.

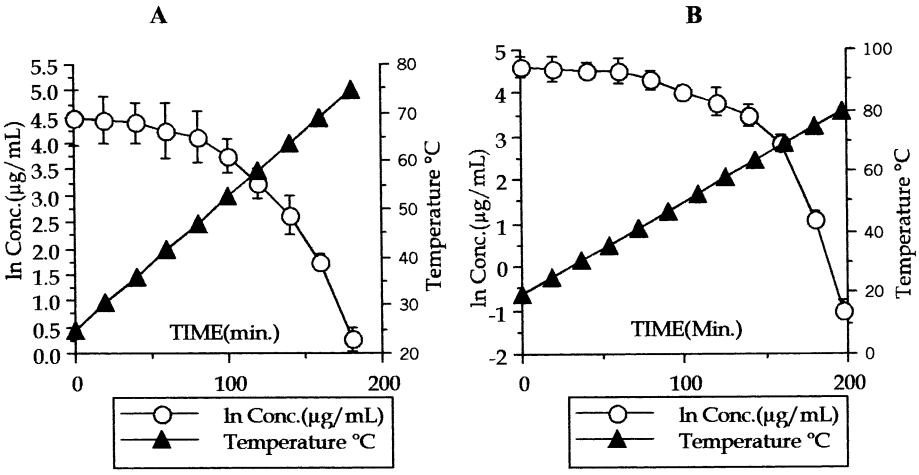

Fig. 3. The time–temperature–concentration plot of famotidine at a linear temperature program ($\mu = 0.26$; A, $\mu = 0.5$; B).

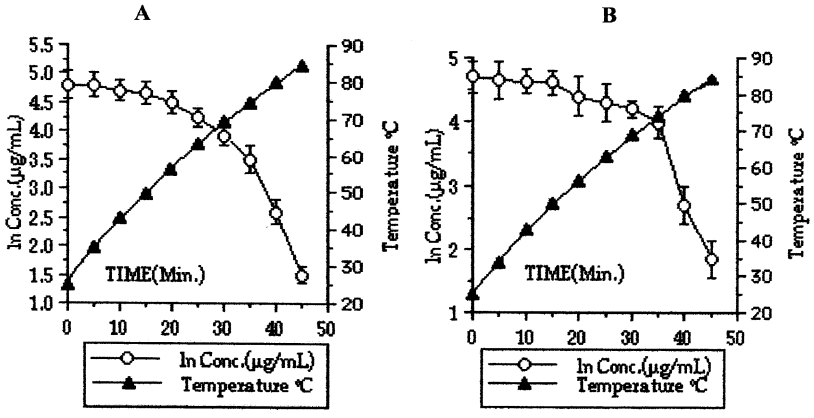

Fig. 4. The time–temperature–concentration plot of famotidine at logarithmic increasing temperature program ($\mu = 0.26$; A, $\mu = 0.5$; B).

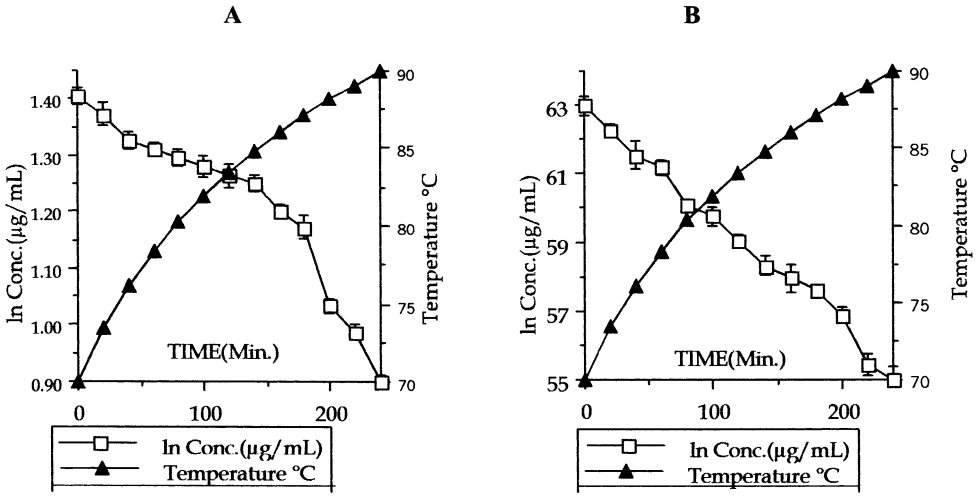

Fig. 5. The time–temperature–concentration plot of nizatidine at logarithmic increasing temperature program ($\mu = 0.26$; A, $\mu = 0.5$; B).

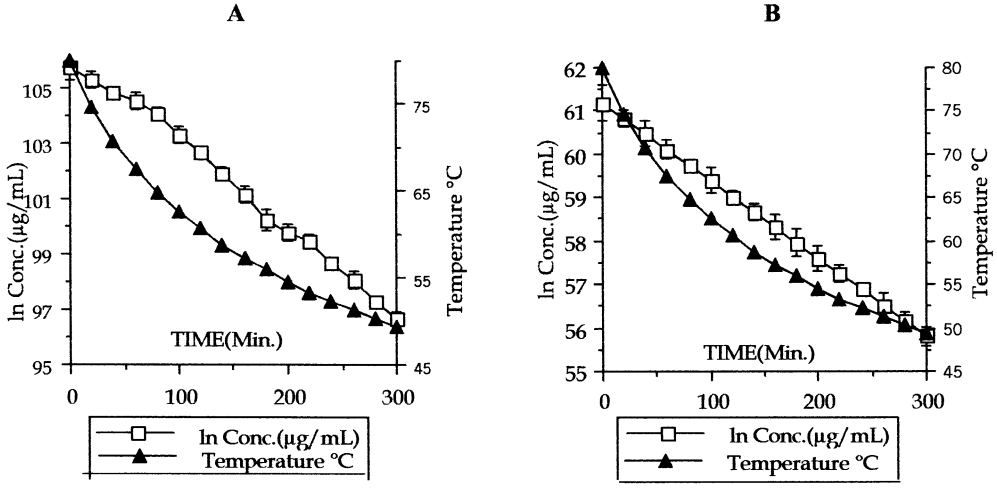

Fig. 6. The time–temperature–concentration plot of nizatidine at logarithmic decreasing temperature program ($\mu = 0.26$; A, $\mu = 0.5$; B).

In Figs. 3 and 4, the time–temperature–concentration plots of famotidine were illustrated for the linear and the logarithmic increasing temperature program.

In Figs. 5 and 6, the time–temperature–concentration plots of nizatidine were illustrated for the logarithmic increasing and decreasing temperature program. The degradation rate constant can be calculated from the slope of the tangent of the curve at any time. A computer program (NONISO) was used for the kinetic calculations [19,20].

During the changes, the tangent of any point on the ln C_t time curve, gives the decomposition rate constant (k_T) of the drug at that particular temperature. The differential form of the equation is as follows:

$$k_T = \frac{-\mathrm{d}(\ln C_t)}{\mathrm{d}t} \quad (1)$$

where C_t is the concentration and k_T is the rate constant at time t.

The ln C_t data can be fitted to a polynomial function versus time, which can then be differentiated at the sampling points to yield the corresponding rate constant.

This expression can be represented by equation (2).

$$k_T = \frac{-\mathrm{d}(\ln C_t)}{\mathrm{d}t} = -k_T$$
$$= a_1 + 2a_2 t + 3a_3 t^2 + \ldots + n a_n t^{n-1} \quad (2)$$

This polynomial curve fitting was used. k_T values were calculated by polynomial fitting and all data were transformed as a function of time.

Differentiation of the polynomial expression and solution at the experimental time points provides isothermal rate constants at the experimental temperatures. For instance, using the 36 min (30.5 °C) time point and the coefficients (a_1–a_6) results for famotidine:

Table 1
The degradation rate constants and the activation energies of famotidine

Programs	k_{25} ($\mu = 0.26$) (h^{-1})	E_a ($\mu = 0.26$) (J mol^{-1})	C.I. (95%)	SEM	k_{25} ($\mu = 0.5$) (h^{-1})	E_a ($\mu = 0.5$) (J mol^{-1})	C.I. (95%)	SEM
Isothermal	4.53×10^{-3}	51 900	50 000–54 200	900	1.07×10^{-2}	36 400	35 600–37 200	400
Linear nonisothermal	4.89×10^{-3}	51 000	30 900–71 100	9100	1.06×10^{-2}	36 800	13 100–60 500	10 800
Log-up nonisothermal	4.93×10^{-3}	51 100	43 100–59 100	3600	1.19×10^{-2}	37 300	9300–65 300	12 400

k_T is the rate constant at 298. K, E_a is the activation energy, C.I. is the confidence interval and SEM is the standard error of mean.

Table 2
The degradation rate constants and the activation energies of nizatidine

Programs	k_{25} ($\mu = 0.26$) (h^{-1})	E_a ($\mu = 0.26$) (J mol^{-1})	C.I. (95%)	SEM	k_{25} ($\mu = 0.5$) (h^{-1})	E_a ($\mu = 0.5$) (J mol^{-1})	C.I. (95%)	SEM
Isothermal	2.26×10^{-3}	57 800	57 600–58 000	100	1.14×10^{-2}	21 300	11 400–31 2200	3300
Linear nonisothermal	3.50×10^{-3}	18 8000	10 500–27 100	3800	6.21×10^{-5}	34 100	0–90 200	25 500
Log-up nonisothermal	2.19×10^{-3}	11 800	0–42 800	14 600	3.96×10^{-2}	5230	3900–6560	630

k_T is the rate constant at 298. K, E_a is the activation energy, C.I. is the confidence interval and SEM is the standard error of mean.

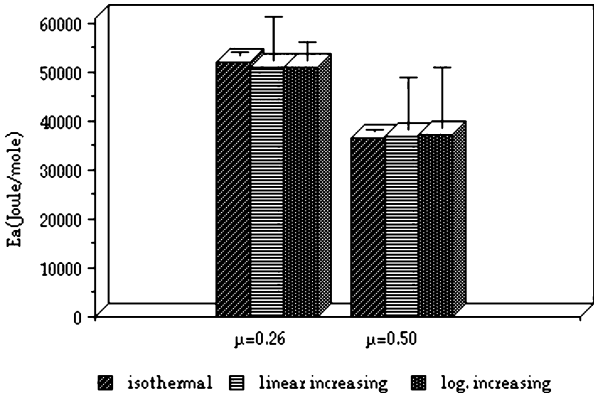

Fig. 7. The values of E_a for famotidine at pH 1.2, $\mu = 0.26$ and 0.50.

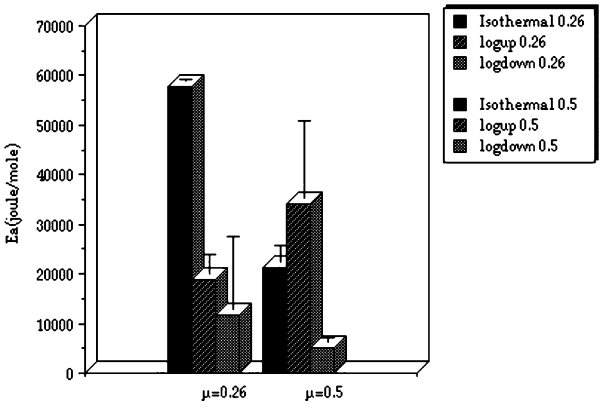

Fig. 8. The values of E_a for nizatidine at pH 1.2, $\mu = 0.26$ and 0.50.

$$-k_T = -3.62 \times 10^{-3} + 2 \times 1.29 \times 10^{-4}(36) - 3 \times 3.65 \times 10^{-6}(36)^2 + 4 \times 3.59 \times 10^{-8}(36)^3 - 5 \times 1.85 \times 10^{-10}(36)^4 + 6 \times 3.18 \times 10^{-13}(36)^5$$

$$k_T = 3.21 \times 10^{-3} \ \text{min}^{-1}$$

Tables 1 and 2 show the calculated kinetic parameters of famotidine and nizatidine for the nonisothermal and isothermal stability tests.

The logarithmic increasing temperature program spends the majority of the experiment at an elevated temperature, which is ideal for slow reacting systems. For a fast reacting system, the linear increasing temperature program allows for easy initial sampling [21].

Fig. 7 shows the E_a values of famotidine at pH 1.2 ($\mu = 0.26$ and 0.50). The results agreed very well with the results of isothermal tests [22]. Nonisothermal and isothermal test results were compared and the degradation rate constants and E_a values were found to be quite close to each other.

Fig. 8 shows the E_a values of nizatidine at pH 1.2 ($\mu = 0.26$ and 0.50).

In our study, two different ionic strengths were used to determine the degradation rate of famotidine and nizatidine in aqueous solutions. Increased degradation rates were observed, when ionic strength was increased. The highest degradation rate constants were obtained at $\mu = 0.5$.

Table 3
The E_a values for famotidine and nizatidine

	Mean (E_a)	C.I. (95%)	SEM	Mean	C.I. (95%)	SEM
Famotidine		$\mu = 0.26$			$\mu = 0.5$	
Isothermal	51 900	50 000–54 200	900	36 400	35 600–37 200	400
Linear nonisothermal	51 000	30 900–71 100	9100	36 800	13 100–60 500	10 800
Log-up nonisothermal	51 100	43 100–59 100	3600	37 300	9300–65 300	12 400
Nizatidine		$\mu = 0.26$			$\mu = 0.5$	
Isothermal	57 800	57 600–58 000	100	21 300	11 400–31 200	3300
Log-up nonisothermal	18 800	10 500–27 100	3800	34 100	0–90 200	25 500
Log-down nonisothermal	11 800	0–42 800	14 600	5230	3900–6560	630

The linear increasing temperature program was believed to be an adequate temperature program. Linear increasing experiments have been run to a greater extent than other nonisothermal programs, possibly due to equipment availability. In linear increasing temperature program, the temperature rises at a slower rate than a logarithmic program, allowing easier sampling. But if the experiment is going to be done using high temperatures, the logarithmic increasing program can be also used. In both temperature programs, famotidine can give enough degradation products to be detected. On the other hand, logarithmic increasing temperature programs were thought to be the best for famotidine, considering suitable time intervals for sampling. As noted by Rosenberg et al., logarithmic increasing programs have the advantage of starting at a convenient temperature (low enough for minimal initial degradation) and then rising rapidly to an elevated temperature. Therefore, the temperature program spends the majority of the experiment at an elevated temperature, which is ideal for slow reacting system like nizatidine. For a fast reacting system like famotidine, this temperature program allows for easy initial sampling, and relatively short experimental times [21].

Logarithmic decreasing temperature programs may be ideal for a slow reacting (as found to be for nizatidine) system, because of high initial temperature. However, the logarithmic decreasing temperature program requires a specialized instrument. The temperature is high enough for the start of the experiment and then ramped down accurately, according to the time–temperature program. Accomplishing this temperature program requires both heating and cooling accessories.

The results in Table 3 show large confidence intervals for some of the cases. This is characteristic of logarithmic transformations. The confidence intervals are calculated first and then back transformed which result in wide margins. We do not believe this fail subtracts from the value of the method. SEMS, on the other hand, are relatively smaller.

The isothermal accelerated stability test takes at least 1 month, but the nonisothermal stability programs takes one; at most 2 days. In the industry and after economical considerations, the nonisothermal stability test appears to be quite an acceptable method. Moreover, this kind of test has advantages for the new drugs to get quick information.

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