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Synthesis of diketopiperazine: A kinetic study by means of thermoanalytical methods

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ABSTRACT

The enalapril maleate (EM) decomposition to diketopiperazine was monitored in helium flow by thermogravimetry at different heating rates between 0.2 and 5 °C min^{-1}. The activation energy value was obtained (198 kJ mol^{-1}) from the Kissinger–Akahira–Sunose isoconversional method. Isothermal experiments were simulated (125, 130, 135 and 155 °C) using the model-free method, employing only the activation energy value. The reaction model of the process was studied by means of the master-plot method. The reaction mechanism depends on the temperature; for experiments below 235 °C, the probable mechanism is nucleation. Instead, when the temperature overcomes the EM melting point, the reaction occurs in liquid state and its kinetics is better described by first order reaction. To avoid the complexity of model changes, experimental results are fitted using the model-free method.

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1. Introduction

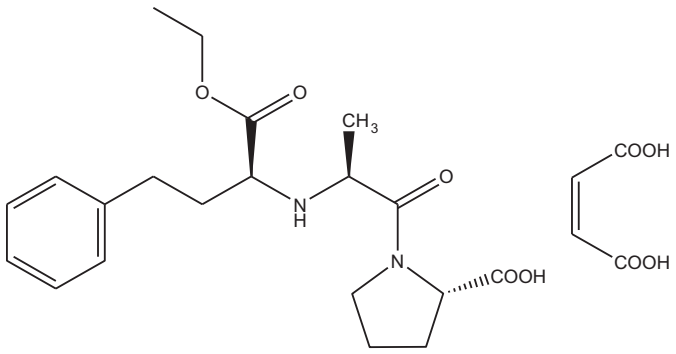
Enalapril maleate (EM) is a salt of enalapril and maleic acid. The EM is a prodrug used for the treatment of hypertension and, as such, it is not manifested by a direct biological activity. After oral administration, EM is converted into Enalaprilat, the real active compound that acts through the inhibition of the angiotensin converting enzyme [1].

On the other hand, EM degradation in solid-state occurs and the degradation rate increases with heating temperature and time. Additionally, it has been shown that the rate and pathways of EM degradation in solutions are pH-dependant [2]. At pH below 5, the major degradation product is diketopiperazine derivative (DKP), and at pH above 5, the major degradation product is enalaprilat.

In other words, Enalapril has two major degradation ways in solid state: hydrolysis of ethylic ester to enalaprilat and intermolecular cyclization to a diketopiperazine derivative [3]. The degradation pathway recognized for the formation of enalapril diketopiperazine (DKP) involves two neighboring amino acids via intramolecular cyclization [4–7].

In this investigation we are interested in the preparation of DKP, since it is used as standard for the quality controls of EM in the pharmaceutical industry. To obtain DKP, the synthetic methods reported in literature involve the EM heating under its melting point to promote the intramolecular reaction described before [8]. In our experiment, this method is not efficient, because we obtained DKP in low yields (14%) and several subproducts were produced.

To gain insight in the process involved in the preparation of DKP as a degradation product, in this investigation we studied the kinetics of EM. To this end, a set of thermo analytical experiments were performed.



Enalapril maleate (MW 492.5)

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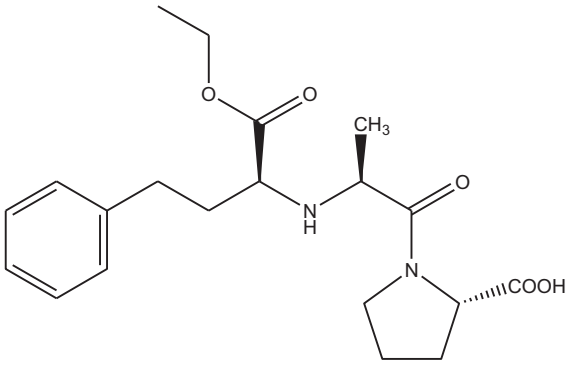
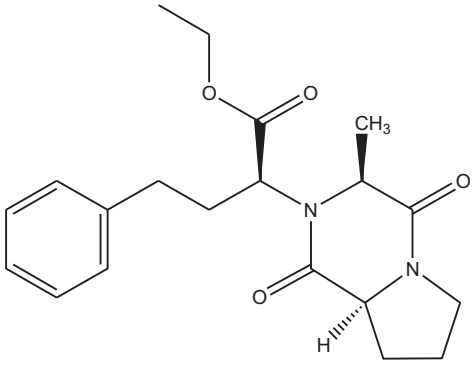
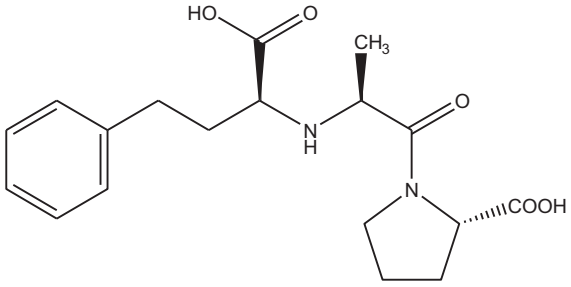
Enalapril (MW 476.4)



Enalapril (MW 476.4)



Enalapril diketopiperazine (MW 358.4)



Enalaprilat (MW 348.4)

Enalapril diketopiperazine (MW 358.4) Enalaprilat (MW 348.4)

The reaction can be kinetically evaluated by means of thermoanalytical methods mainly, thermogravimetry. A wide range of calculation techniques has been proposed for deriving the Arrhenius parameters and extrapolated to other temperatures.

In this work isoconversional, model-fitting and master-plot methods from non isothermal thermogravimetric data are used. The model-free method is used to simulate the isothermal experiments. An available enalapril maleate (provided by UPM, "Facultad de Ciencias Exactas") was used for the experiments.

As stated before, the purpose of this study is to perform an analysis of enalapril maleate degradation to obtain a representation of reaction data. The information obtained will help us to determine the optimal conditions to prepare DKP.

2. Experimental

2.1. Thermo degradation of enalapril maleate

The thermo degradation of enalapril maleate was investigated by means of dynamic thermogravimetry (TGA) using a Shimadzu TGA-50 equipment under atmospheric pressure. The method of multiple heating rate programs (multiple temperature programs) was used as recommended by the ICTAC Kinetics Committee [9]. Studies were carried out at constant heating rates between 0.2 and 5 °C min^{-1} in He stream (50 cm^3 min^{-1}) flowing onto the cylindrical sample holder. In all experiments we employed the method of multiple heating rate programs, the first stage is a heating at 20 °C min^{-1} up to 105 °C and the second stage is at the selected heating rate. Isothermal experiments were carried out at 125, 130, 135 and 155 °C. In isothermal experiments, the heating rate between room temperature and the selected T is 20 °C min^{-1} and the mass is 10 mg.

3. Kinetic analysis

Experimental data for the kinetic analysis of solid reactions can be obtained by means of dynamic thermogravimetry at constant heating rate. Under such conditions, the reaction rate is usually expressed by the general equation:

$$\frac{d\alpha}{dt} = Af(\alpha)\exp\left(-\frac{E_a}{RT}\right) \quad (1)$$

where α is the conversion, A is the pre-exponential factor, E_a is the activation energy, $f(\alpha)$ is the differential conversion function, and R is the gas constant.

If experiments are performed at constant heating rate ($dT = \beta dt$), Eq. (1) can be expressed like a derivative as a function of the temperature

$$\frac{d\alpha}{dT} = \left(\frac{A}{\beta}\right) f(\alpha)\exp\left(-\frac{E_a}{RT}\right) \quad (2)$$

Introduction of the explicit value of the heating rate reduces the applicability of Eq. (1) to processes in which the sample temperature does not deviate significantly from the reference temperature.

Integration of kinetic equation (Eq. (2)) leads to the following equation

$$g(\alpha) = \int \frac{d\alpha}{f(\alpha)} = \frac{A}{\beta}\int \exp\left(-\frac{E_a}{RT}\right) dT = \left(\frac{AE_a}{R\beta}\right)\int \exp\frac{(-x)dx}{x^2}$$
$$= \left(\frac{AE_a}{R\beta}\right) p(x) \quad (3)$$

where $g(\alpha)$ is the integral form of the reaction model, and $p(x)$ is the temperature integral, for $x = E_a/RT$.

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