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APPLICATION OF THERMOGRAVIMETRY IN THE QUALITY CONTROL OF CHLORAMPHENICOL TABLETS

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Abstract

The stability and thermal behaviour of chloramphenicol and various of its mixtures were investigated. The thermogravimetric and stability constant results showed that the chloramphenicol base is thermally more stable than the tablet in the studied formulation. The reduction in stability was attributed to the presence of starch in the formulation. The thermal decompositions of the chloramphenicol base and the tablet obey first-order kinetics.

Keywords: chloramphenicol, DSC, quality control, TG

Introduction

A number of studies have been made with DSC and TG in order to determine the physico-chemical nature and the thermal behaviour of different drugs, e.g. polymorphics, anhydrous and hydrated. Similar studies have involved the addition of new excipients [3, 4].

The application of thermal methods, and especially DTA, DSC and TG, is of great importance in the solution of pharmaceutical problems such as the determination of purity, the quantitative and qualitative analysis of drug formulations, tests of stability and the determination of kinetic parameters [1, 5, 6]. Thermogravimetric data can be used in the quality control of pharmaceuticals, as concerns possible interactions in the processing of drugs [2].

In the present work, a study was made of the thermal behaviour of chloramphenicol, with regard to chemical-kinetic parameters applicable to the quality control of the product.

Experimental

The chloramphenicol base and tablet, starch, talc, PVP, vitamin B_1, magnesium stearate, vitamin B_2, vitamin B_6 and nicotinamide were acquired in the Laboratory

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of Pharmaceutical Technology in UFPB. The composition of each chloramphenicol tablet was: chloramphenicol 500 mg, starch 75 mg, talc 20 mg, PVP 25 mg, vitamin B_1 10 mg, magnesium stearate 5 mg, vitamin B_2 4 mg, vitamin B_6 4 mg, and nicotinamide 4 mg. The chloramphenicol and other ingredients were sifted and homogenized by using a 100 mesh sieve.

Binary and ternary mixtures were prepared with the same concentrations as in the tablet, i.e. chloramphenicol:starch, chloramphenicol:talc, chloramphenicol:vitamin B_1, chloramphenicol:vitamin B_2, chloramphenicol:vitamin B_6, chloramphenicol:nicotinamide, chloramphenicol:PVP, chloramphenicol:magnesium stearate, chloramphenicol:starch:vitamin B_1, chloramphenicol:starch:nicotinamide, chloramphenicol:starch:PVP, and chloramphenicol:starch:magnesium stearate.

The thermal curves were obtained with a Shimadzu thermobalance, model TG-50, with a synthetic air flow of 50 ml min^{-1} and a heating rate of 10°C min^{-1}. The DSC curves were recorded with a Shimadzu differential scanning calorimeter, model DSC-50, in the temperature range 25–500°C, using an aluminium pan, at a heating rate of 10°C min^{-1}. A nitrogen atmosphere was used, at a flow rate of 50 ml min^{-1}. The TG and DSC curves were analyzed with the aid of the Tasys software from Shimadzu. The DSC temperature scale was calibrated with the USP phenacetin melting point reference standard.

The reaction rate constants were determined isothermally at 135, 150, 165, 180 and 200°C and at 120, 130, 140, 150, 165, 180 and 200°C, during 300 min, for the chloramphenicol base and tablet, respectively, using the Arrhenius equation.

Results and discussion

Figure 1 shows the thermoanalytical profiles of starch (curve 1), the chloramphenicol base (curve 2), the chloramphenicol tablet (curve 4) and the binary mixture of chloramphenicol and starch (curve 3). The chloramphenicol base has a stability higher than that of the chloramphenicol tablet. The chloramphenicol base undergoes thermal decomposition in three steps, in the temperature intervals 206–293, 293–506 and 506–704°C. The chloramphenicol tablet presents three stages of decomposition, in the temperature intervals 200–283, 282–518 and 518–704°C.

The thermogravimetric curves of the binary mixtures of chloramphenicol:starch, chloramphenicol:vitamin B_1, chloramphenicol:vitamin B_2, chloramphenicol:vitamin B_6, chloramphenicol:nicotinamide, chloramphenicol:PVP, chloramphenicol:talc, and chloramphenicol:magnesium stearate revealed that the mixture of chloramphenicol:starch exhibited the largest reduction in the temperature of decomposition of chloramphenicol. The mixture containing magnesium stearate underwent thermal decomposition at the same temperature. The results confirm that the constituents in smaller concentrations do not exert significant effects in reducing the thermal stability of chloramphenicol.

The thermogravimetric curves of the ternary mixtures of chloramphenicol: starch:vitamin B_1, chloramphenicol:starch:PVP, chloramphenicol:starch:nicotinamide, chloramphenicol:starch:talc, and chloramphenicol:starch:magnesium stearate displayed thermal behaviour similar to that of the binary mixture of chloramphenicol:starch. The

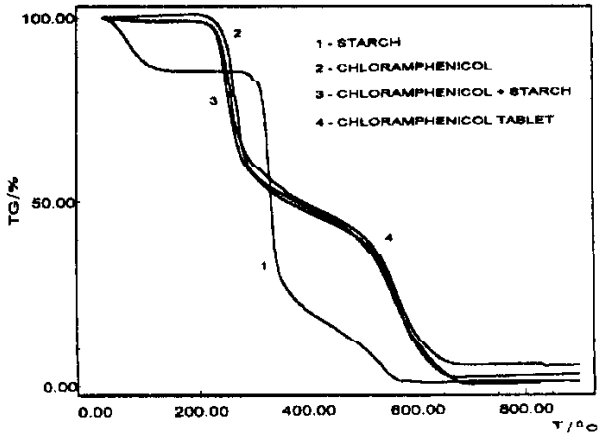

Fig. 1 TG curves of chloramphenicol salt and tablet, starch and its binary mixture with chloramphenicol. Measurements were performed with a Shimadzu thermobalance, model TG-50. Samples (10–12 mg) were heated at 10°C min^{-1} in a dynamic air atmosphere

thermogravimetric curves of the different binary and ternary mixtures provided evidence of only minor interactions between the chloramphenicol base and the ingredients of the formulation. Starch is the second component (as concerns mass) in the formulation and for this reason is mainly responsible for the reduction in the temperature of decomposition of the chloramphenicol base. The presence of water in the starch (curve 1 of Fig. 1) may be one of the causes of the decrease in stability of the tablet in relation to the base. The other components of the formulation do not significantly influence the temperature of decomposition of chloramphenicol.

Kinetic studies of the thermal decompositions of the chloramphenicol base and the chloramphenicol tablet under isothermal conditions demonstrate that the log*m* *vs.* *t* dependences are linear, a sign of a first-order reaction.

The rate constants of thermal decomposition of the chloramphenicol base and the chloramphenicol tablet were calculated from the following equation for a first-order reaction:

$$\frac{\Delta[P]}{\Delta(t)} = K_1[P]$$

Table 1 shows the reaction rate constants. It can be seen that the values for the chloramphenicol base are lower than those for the chloramphenicol tablet, indicating the higher stability of the drug substance.

The rate constant k depends on the absolute temperature according to

$$k = A\exp\left(-\frac{E}{RT}\right)$$

where the pre-exponential factor, A, is temperature-independent. A was calculated through linear regression of a plot of k *vs.* $1/T$. The activation energies for the chloramphenicol base and tablet were calculated via the equation

$$\ln k = \ln A - \frac{E}{RT}$$

where R=8.314 J K^{-1} mol^{-1}, T is the absolute temperature, E is the activation energy, A is the pre-exponential factor and k is the rate constant.

Table 1 Rate constants (k) and activation energies (E) of thermal decomposition chloramphenicol base and chloramphenicol tablet

Temperature/ °C	Chloramphenicol base		Chloramphenicol tablet	
	k/s^{-1}	E*/kJ mol^{-1}	k/s^{-1}	E**/kJ mol^{-1}
120	–	–	8.03E–07	102.1
130	–	–	1.07E–06	103.7
135	5.05E–07	128.5	–	–
140	–	–	1.46E–06	105.2
150	8.13E–07	131.6	2.35E–06	106.1
165	5.51E–06	129.3	6.46E–06	106.2
180	1.65E–05	129.6	1.90E–05	105.7
200	7.95E–05	129.1	8.41E–05	104.6

* Mean value and standard deviation were 129.6 and 1.2

** Mean value and standard deviation were 104.8 and 1.5

The A values of $1.45 \cdot 10^{10}$ and $2.96 \cdot 10^{7}$, found for the chloramphenicol base and tablet, respectively, indicated the higher stability of the base. The activation energy data (Table 1) likewise indicated that the chloramphenicol base was more stable than the tablet. The activation energy values did not vary with temperature. Transition state theory [7] demonstrates that, in principle, ΔH does depend on temperature, but only weakly so. Therefore, both A and E can be regarded as independent of temperature.

The explanation for the non-variation in activation energy as a function of temperature for the chloramphenicol base and tablet would lie in the occurrence of decomposition processes involving exothermic steps, as can be visualized in the DSC curves (Fig. 2). The endothermic phase transition corresponding to the melting point occurred at 155.2 and 152.7°C, respectively, for the chloramphenicol base and tablet (Fig. 2, curves a and b). The exothermic phase transitions characteristic of the decomposition processes were observed at 244.1 and 257.8°C for the chloramphenicol base, and at 237.1 and 260.6°C for the chloramphenicol tablet.

The data analysis indicates interactions of starch with chloramphenicol, as confirmed by reductions in the temperature of thermal decomposition, the pre-exponential factor and the activation energy, and an increased reaction rate constant for the

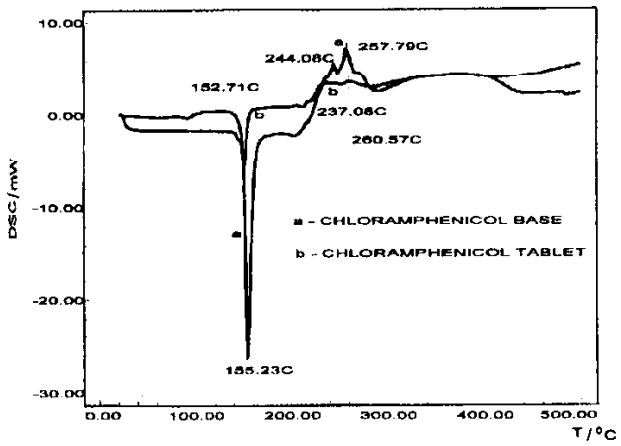

Fig. 2 DSC curves of chloramphenicol base and tablet. Measurements were performed with a Shimadzu differential scanning calorimeter, model DSC-50. Samples (3–3.5 mg) were heated at 10°C min^{-1} in a nitrogen atmosphere

chloramphenicol tablet, and demonstrates the higher stability of the chloramphenicol base.

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