Thermoanalytical Study of Cefadroxil and its Mixtures with Different Excipients

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In this study, it was studied the thermal decomposition of cefadroxil and some mixture with excipients containing the same active compound using TG/ DTG and DSC techniques. The kinetic parameters were obtained from DSC curves using the Flynn–Wall–Ozawa method, respectively a nitrogen dynamic atmosphere and different heating rates. The kinetic data showed that the cefadroxil–active substance is thermally more stable than the mixtures with any excipient. The decrease in stability was attributed to the presence of excipients in formulation and to their possible interactions with the cefadroxil. The difference in stability is bigger between the pure substance and the mixture with the magnesium stearate.

Keywords: cefadroxil; degradation behaviour; excipient; activation energy.

The application of thermal methods to organic compounds with potential pharmaceutical action can be of great use for determining their physical and chemical stability [1–3]. TG/DTG and DSC curves have related important information about the properties of materials (stability, compatibility, polymorphism, kinetic analysis, phase transitions). Kinetic parameters (activation energy, pre–exponential factor and reaction order) can be obtained by thermoanalytical methods according to progress of reactions [4–11].

The compatibility studies using thermal analysis present advantage the to readily available knowledge of any physical and chemical interactions between drugs and excipients which might cause changes of chemical nature, stability, solubility, absorption and therapeutic response of drugs.

Thermal techniques have been increasingly used for quick evaluation of possible incompatibility between formulation components through comparison of thermal curves of pure substances with curve obtained from a 1:1 mixture [12]. If mixture curve represents thermal peaks sum observed for the individual components, there is no interaction and therefore no physico–chemical incompatibility between drug and excipient [13–18].

Incompatibility can lead to the loss of biological activity of drugs through complex formation, acid–base interactions and formation of eutectic mixtures [19, 20].

The values of kinetic parameters such as the pre–exponential factor (A), the reaction order (n), and the overall activation energy (E_a) can be calculated using the different methods that are characteristic to the non–isothermal regime. These values can be of great importance in the elucidation compatibility and storing conditions, especially life–time.

In recent years, applications of these techniques in the pre-formulation stages for solid dosage form development have increased immensely. In particular, kinetic analysis in non–isothermal conditions has been proposed as a rapid method for evaluating thermal behaviour of pharmaceutical products [21,22].

In this paper, thermoanalytical techniques were used to study thermal behaviour, compatibility with excipients and kinetic analysis under non–isothermal (dynamic) conditions of cefadroxil. This substance is an antibiotic from the cephalosporin family, known as a first generation cephalosporin used to treat certain infections caused by bacteria such as pneumonia and bone, ear, skin, and urinary tract infections. Cefadroxil can kill a number of bacteria by inhibiting production of their cell walls. It is active against Streptococci and Staphylococci, including some of those resistant to penicillin.

Cefadroxil's formula is presented in figure 1.

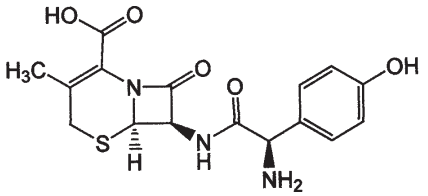

Fig.1. The chemical structure of the cefadroxil

Experimental part

The cefadroxil (*6R,7R*)–7–{[(*2R*)–2–amino–2–(4–hydroxyphenyl)acetyl]amino}–3–methyl–8–oxo–5–thia–1–azabicyclo[4.2.0]oct–2–ene–2–carboxylic acid was obtained from Romania. Excipients tested were: magnesium stearate, talc powder, microcrystalline cellulose and starch . The mixed samples consisted of equal masses of cefadroxil and each excipient was weighed individually into amber glass flasks to originate mass of 20 g of mixture. Physical mixtures were prepared in proportion (m/m) 1:1 (cefadroxil: excipient) by simple mixing.

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Differential scanning calorimetry (DSC) study was performed on Netzsch differential scanning calorimeter, model DSC–204, using aluminium crucibles under nitrogen atmosphere, with a constant flow of 50 mL·min^{-1} and a heating rate β= 5, 7, 10 and 15 K·min^{-1} up to a temperature of 500°C.

Thermogravimetrical analysis (TG and DTG) was performed on Perkin–Elmer DIAMOND equipment in temperature range 25–550°C, using an air atmosphere and under dynamic conditions in order to study the thermal stability of the active substance and of the mixtures. Samples with the mass in the range of 3 to 7 mg were put into aluminium crucibles, at a heating rate, β, of 5, 7, 10 and 15°K·min^{-1}.

Kinetic investigation of cefadroxil degradation was obtained from DSC data by application of Flynn–Wall–Ozawa isoconversional method [23].

This method is based on the measurement of the adequate temperature to certain values of the conversion α, for experiments effectuated to different rates of heating β. The corresponding equation is the following:

$$ln\beta = ln\frac{A \cdot E}{R \cdot g(\alpha)} - 5.331 - 1.052 \cdot \frac{E}{R \cdot T} \quad (1)$$

The plot lnβ *vs. (1/T)* is linear. The value of the activation energy (*E*) was obtained from the slope of the straight line *(–E/R)*.

The physical chemical properties and compatibilities of several commonly used pharmaceutical excipients (magnesium stearate, talc, microcrystalline cellulose, starch) with the cefadroxil were evaluated using thermoanalytical methods.

IR spectra of drug, excipients and drug–excipient blends were obtained at room temperature in the range 4000–400 cm^{-1} in KBr pellets using *Jasco* FTIR–670 Plus spectrophotometer.

Results and discussions

Thermal behaviour and kinetic study of cefadroxil

DSC curves of cefadroxil (fig.2.) show a sharp exothermic peak at ~210°C that corresponds to the thermal decomposition. The decomposition is defined in two exothermic stages. This is confirmed by TG/DTG curves that indicate thermal decomposition in the following temperature range: 191–320°C, 320–400°C and over 400°C a slow and continuous mass loss caused by elementary carbon formation from the previous steps, as consequence of the rupture of the azabicyclo and phenyl aromatic rings. Figure 2 illustrates DSC curves for cefadroxil, which are shifted for higher temperatures when heating rates increase.

Flynn–Wall–Ozawa's method was applied to data obtained from four DSC curves in order to determine the activation energy (E_a) at the beginning of main thermal decomposition step at around 190 to 230°C. The graphic

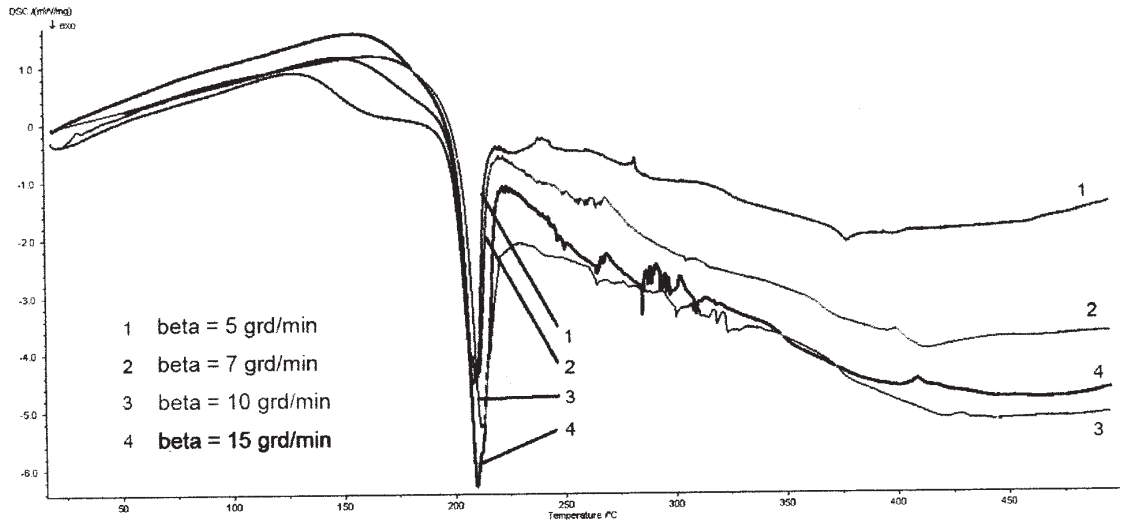

Fig.2. DSC curves of cefadroxil in dynamic nitrogen atmosphere and different heating rates

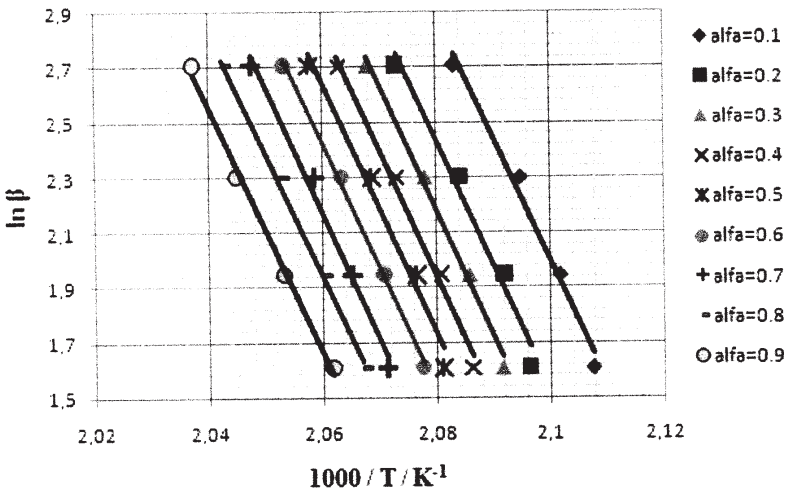

Fig.3. The Flynn–Wall–Ozawa isoconversional diagrams for cefadroxil–active substance

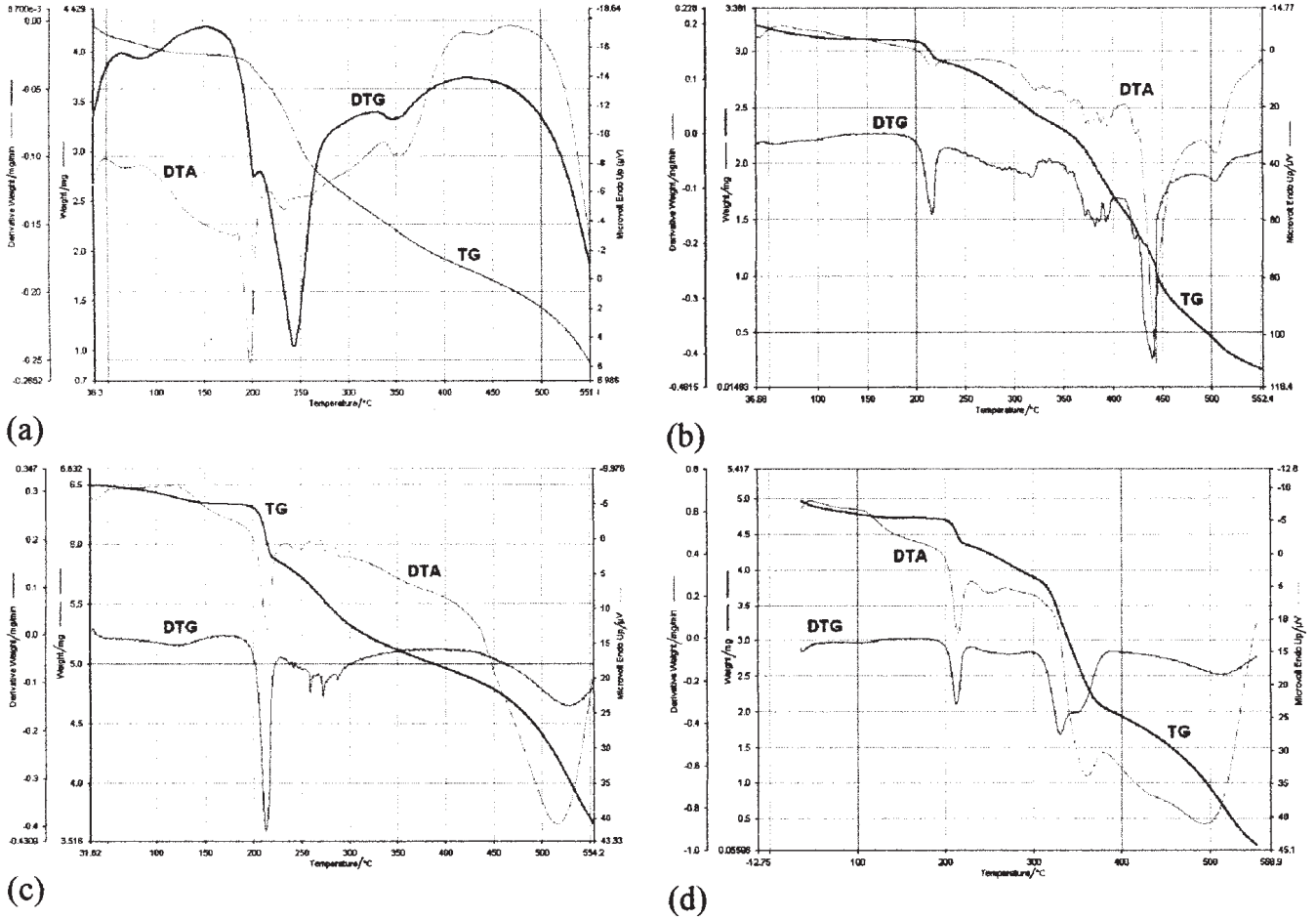

Fig.4. TG/DTG/DTA curves of cefadroxil and 1:1 physical mixtures (cefadroxil/excipient)
(a) – cefadroxil; (b) – cefadroxil + magnesium stearat; (c) – cefadroxil + talc; (d) – cefadroxil + microcrystalline cellulose

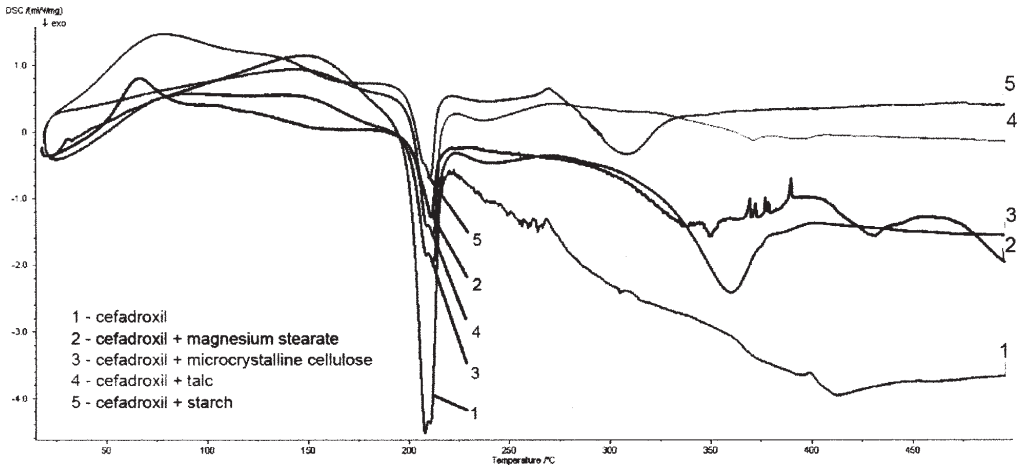

Fig.5. DSC curves of cefadroxil and cefadroxil/ excipient 1:1 physical mixtures

(fig.3) presents obtained plots, which demonstrate a fairly good correlation at four heating rates. In the first stage of cefadroxil thermal decomposition, the energy calculated was 358.53 kJ·mol^{-1} in nitrogen. The values of activation energy for the mixtures with different excipients are presented in table 1.

Compatibility study of cefadroxil with excipients

TG/DTG/DTA and DSC curves of the pure cefadroxil and the 1:1 drug:excipient physical mixtures are shown in figures 4 and 5.

Most of the thermal profiles of the mixtures can be considered as a superposition of the TG and DSC curves of the pure cefadroxil and the excipients. The DSC method is more sensitive to indicate the compatibility/incompatibility of the binary mixtures. Differences were observed in case of cefadroxil/magnesium stearate binary, which can be attributed to any incompatibility (interaction) between the two components (fig.5), sustained also by the active energy value, which is very low in comparison with the one corresponding to the active substance. According to the results obtained from TG curves, the mass losses took place through a different mechanism when the magnesium stearate was mixed with the drug, since the exothermic peak of cefadroxil shifted from 240°C (for cefadroxil) to 213°C on DTG curve of the mixture.

The melting peak of the drug (197°C) [24] could not be identified on the DSC curve, as it can be seen in figure 6. The results taken from the TG/DTG and DSC curves of the binary mixtures are collected in table 1.

IR spectra of cefadroxil and mixtures with different excipient in proportion 1:1 showed the presence of characteristic bands corresponding to drug and excipient. There was no appearance of new bands in IR spectra

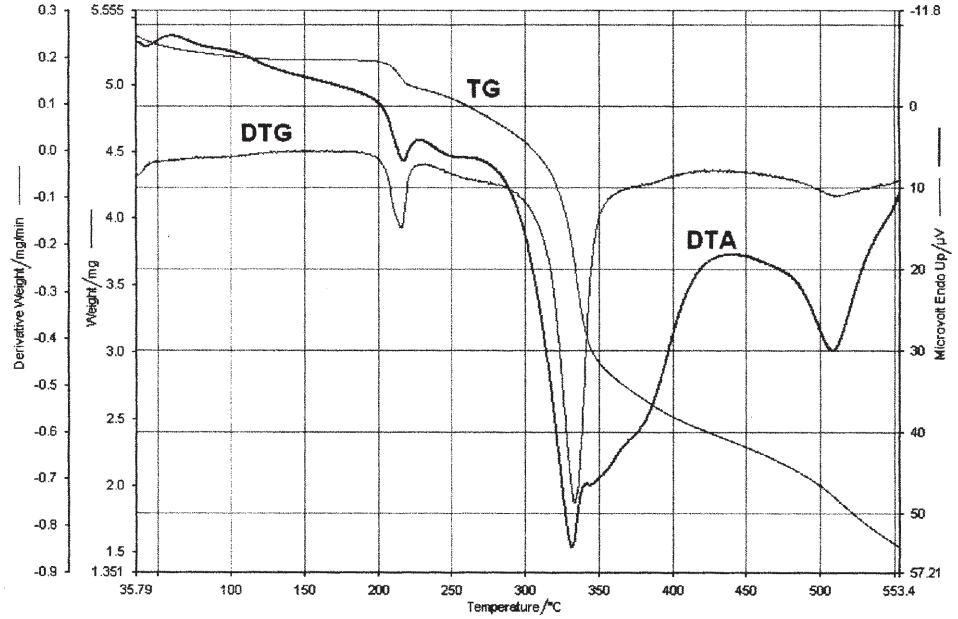

Fig.6. TG/DTG/DTA curves of the physical mixture of cefadroxil with all the four excipients

	T_{onset}DSC/°C	T_{onset}TG/°C	Δm/%	T_{peak}DTG/°C	Ea $_{FWO}$/kJ·mol^{-1}
Drug					
Cefadroxil	186	191	11.237	243.3	358.53±1.60
Drug / Excipient					
Starch	186	190	8.421	211.0	313.29±1.13
Magnesium stearate	195	190	7.315	216.6	257.99±2.62
Talc	187	188	7.692	213.0	310.25±2.55
Microcrystalline cellulose	189	192	8.200	211.3	307.58±1.19
All excipients	193	196	6.426	216.7	260.43±3.17

Table 1
THERMOANALYTICAL DATA OF CEFADROXIL AND OF DRUG:EXCIPIENT PHYSICAL MIXTURES FOR β=10°C·min^{-1}

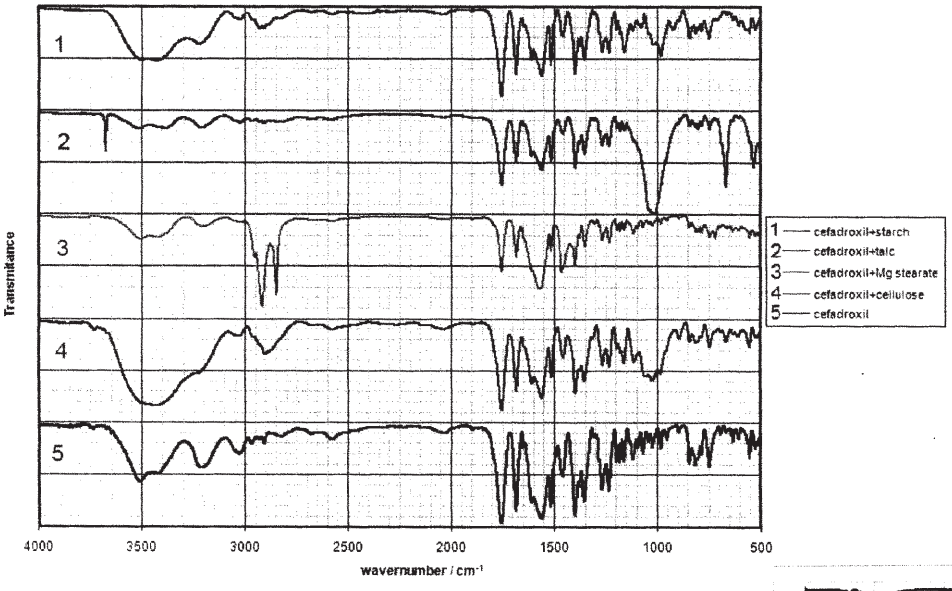

Fig.7. Infrared spectra (FTIR) of cefadroxil and cefadroxil/excipient 1:1 physical mixtures

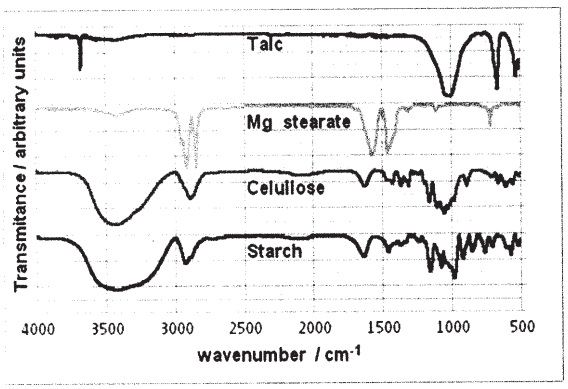

Fig.8. Infrared spectra (FTIR) of the excipients used to obtain the analyzed mixtures

confirming that change did not occur in drug structure (figs.7 and 8).

Conclusions

In non–isothermal conditions, the activation energies for the first–step of the decomposition reaction of cefadroxil were determined. The E_a calculated using dynamic method was 359.15 kJ·mol^{-1} in nitrogen. It can be used in the quality control of drug, with a view to improvement of the final product and for the determination of drug quality via the technological parameters.

The compatibilities and stabilities of some binary mixtures were studied by using TG/DTG and DSC techniques. The results showed the utility of thermal analysis as a rapid and convenient method of screening candidate excipients during preformulation studies, because it permits the ascertainment of excipients' compatibility or demonstration of drug–excipient interaction or incompatibility. During this study, it was possible to observe the interactions of the cefadroxil with talc, magnesium stearate, starch and microcrystalline cellulose.

According to the thermoanalytical studies, among all studied mixtures, only one incompatibility was found, the one between cefadroxil and magnesium stearate, result also sustained by calculated values of the kinetic parameters.

However, this excipient is used at low concentration (0.5–2.0%) in the pharmaceutical dosage forms so far, another set of stability tests should be carried out to confirm the real impact of this interaction together with other common pharmaceutical excipients.

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