J Therm Anal Calorim (2009) 97:741–745
DOI 10.1007/s10973-009-0347-2

Thermal characterization and compatibility studies of norfloxacin for development of extended release tablets

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ICTAC2008 Conference

Abstract Norfloxacin (NFX) is a synthetic antibacterial drug. The development of extended release tablets improves the patients' comfort and compliance, resulting in lower discontinuation of the therapy; with consequently decrease in bacterial resistance. In the present work, the thermal behavior of NFX was investigated using TG and DSC techniques. Isothermal and non-isothermal methods were employed to determine kinetic data of decomposition process. Compatibility studies between NFX and pharmaceutical excipients, including three hydrophilic polymers were carried out in order to develop a new formulation of NFX to obtain extended release tablets with an approved quality.

Keywords Norfloxacin · Thermal characterization · Kinetic studies · Compatibility studies

Introduction

Norfloxacin, chemically known as 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1-ethyl-fluoro-1.4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid (Fig. 1a) [1]. It is currently used as a broad spectrum antibacterial drug, being the firstly selected drug for the treatment of diseases caused by *Campylobacter*, *E. coli*, *Salmonella*, *Shigella* and *V. cholera* [2, 3]. The drug is also used for the treatment of gonorrhoea as well as infection of eyes and urinary tract [2]. Resistance in Gram-negative bacteria has become common, making the therapeutic decisions more difficult. Increasing bacterial resistance to currently available quinolones has reduced their effectiveness and may compromise future use of this class of drugs [4, 5].

The development of controlled-release formulations is a successful area in the pharmaceutical industry because expenses of new drug development are very high, and novel innovation is at an all-time low. Hydrophilic matrices are one of the most used controlled delivery systems in the world, due to the simple technology and low cost. Among the various hydrophilic polymers employed, hydroxypropyl methylcellulose (HPMC, Fig. 1b) is the most commonly used, due to its versatility, compatibility with many drugs and safety [6]. Nevertheless, high molecular mass polyethylene oxides (PEOs, Fig. 1c) have been proposed as an alternative to HPMC [7].

Thermoanalytical techniques measure changes in physical and/or chemical properties of the sample as a function of temperature. There are many possible applications in pharmaceutical industry, for example, identification, characterization of active and inactive ingredients, routine analysis, quality control and stability study [8, 9]. Kinetic parameters (activation energy, frequency factor and reaction order) can be measured by thermoanalytical methods according to progress of reactions [10–12]. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients [8, 13] and on the characterization of solid-state properties using appropriate analytical methodologies [14–16]. The compatibility studies using thermal analysis present advantageous to readily available knowledge of any physical and chemical interactions between drugs and excipients which might give rise to changes in chemical nature, stability, solubility, absorption and therapeutic response of drugs

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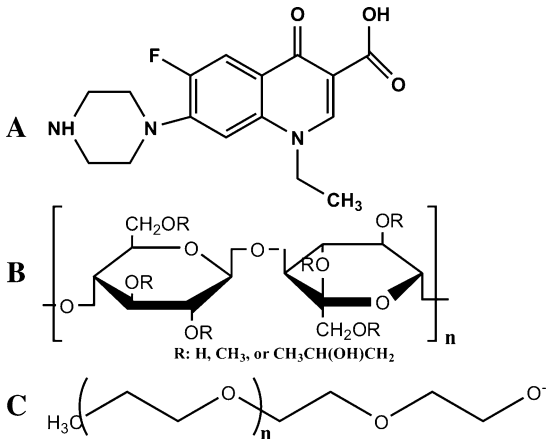

Fig. 1 Chemical structure of NFX (**a**), HPMC (**b**) and PEOs (**c**)

[12]. In particular differential scanning calorimetry (DSC) has been proposed as a rapid method for evaluating physicochemical interactions between components of the formulation through comparison of thermal curves of pure substances with curve obtained from a 1:1 mixture, and therefore selecting excipients with suitable compatibility [10, 15, 17–21].

The aim of this study was to perform the physicochemical solid-state characterization of norfloxacin and different polymers, to analyze the kinetic parameters under isothermal and non-isothermal conditions, and to carry out compatibility studies, to begin the development of a new formulation of NFX extended release tablets.

Experimental

Materials

Norfloxacin (NFX) bulk material was kindly donated by União Química Farmacêutica Nacional (Embu-Guaçu, SP, Brazil). The polymers tested were: Polyox WSR N80 NF, Polyox WSR 301 NF, and Methocel K100 Premium LV CR (all from Colorcon do Brasil, São Paulo, Brazil). The pharmaceutical excipients tested were microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, lactose monohydrated and Opadry II White.

Methods

Differential scanning calorimetry and thermogravimetric analysis

The DSC curves were obtained on Shimadzu DSC-60 cell (Kyoto, Japan) using aluminum crucibles with about 1.5 mg of samples. The temperature range was from 30 to 500 °C at a heating rate of 10 °C min^{-1} in dynamic N_2 atmosphere with the flow rate of 50 mL min^{-1}. The DSC equipment was preliminarily calibrated with standard reference of indium (m.p. 156.6 °C; $\Delta H_{fus} = -28.54$ J g^{-1}) and zinc (m.p. 419.5 °C). The compatibility studies were performed with binary mixtures of NFX and each excipient (1:1; *m/m*). Thermogravimetric (TG) experiments were measured on Shimadzu thermobalance model TGA-50 (Kyoto, Japan) in the temperature range of 30–800 °C, using platinum crucibles with approximately 4 mg of samples, under dynamic N_2 atmosphere (50 mL min^{-1}) at a heating rate of 10 °C min^{-1}. The equipment was preliminarily calibrated with standard reference of calcium oxalate. Non-isothermal kinetic investigation of NFX was performed from TG data by application of Ozawa's method [22]. The graph of mass loss versus temperature of five TG curves was obtained at different heating rates (2.5, 5.0, 10, 15, and 20 °C min^{-1}), under N_2 atmosphere. For isothermal method, the temperature was from 230 to 270 °C, with 10 °C temperature increment, in N_2 atmosphere. A graphic of ln*t* versus $1/T$ (K^{-1}) was plotted and linear regression was applied.

X-ray powder diffraction

For characterization of crystallinity, X-ray diffraction patterns were obtained on a Siemens diffractometer model D 5000, with tube of CuKα, voltage of 40 kV and current of 40 mA, in the range of 3–40 (2θ) with a pass time of 1 s.

Diffuse reflectance infrared fourier transform spectroscopy

The diffuse reflectance infrared Fourier transform spectroscopy (DRIFT) spectra were measured in a Shimadzu spectrophotometer (Prestige), in a scan range of 400–4,000 cm^{-1} with an average of over 32 scans at a spectral resolution of 4 cm^{-1} in KBr. A background spectrum was obtained for each experimental condition.

Scanning electron microscopy

The photomicrographs of NFX and the polymers were observed by using a Phillips scanning electron microscope (SEM), model XL30. Samples were mounted onto metal stubs using double-side adhesive tape, vacuum-coated with gold (350 Å) in a Polaron E 5000 and directly analyzed under SEM ($N = 50$, 200, and 1,000).

Results and discussion

DSC curve of norfloxacin (Fig. 2a) showed a sharp endothermic event (T_{peak}) at 219.4 °C ($\Delta H_{fusion} = -101.51$ J g^{-1}) corresponding to melting point followed by an exothermal

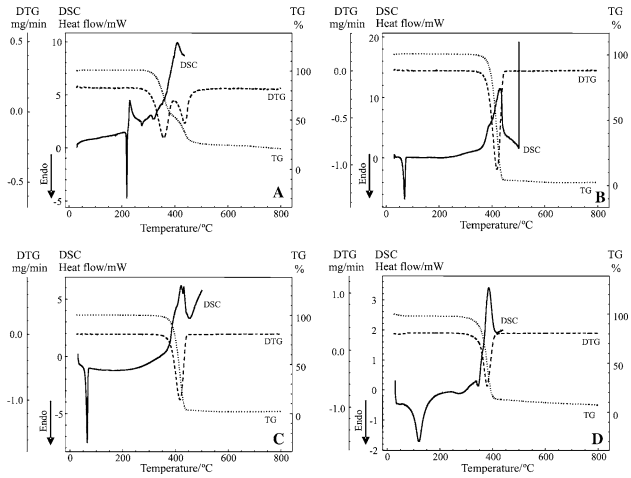

Fig. 2 DSC and TG/DTG curves of norfloxacin (**a**), Polyox WSR 301 (**b**), Polyox WSR N80 (**c**), and Methocel K100 LV CR (**d**) in dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate of 10 °C min^{-1}

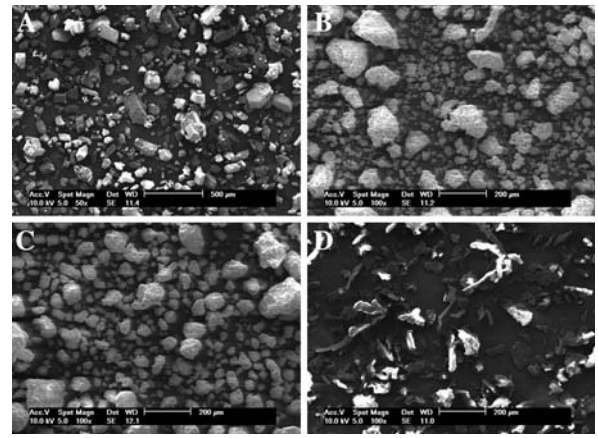

Fig. 3 SEM of NFX (**a**), Polyox WSR 301 (**b**), Polyox WSR N80 (**c**), and Methocel K100 LC CR (**d**). The photomicrograph (**a**) was taken at a magnification of 50×, and (**b**–**d**) of 100×

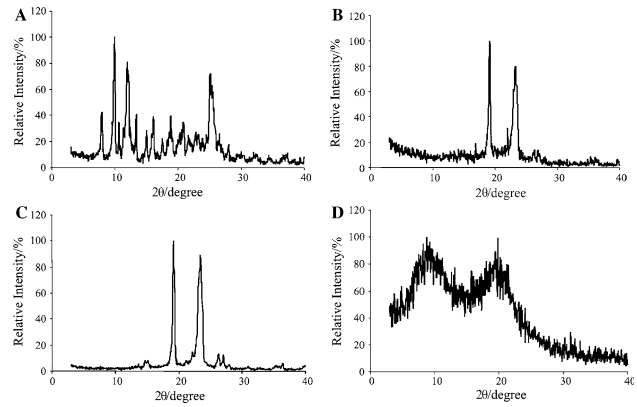

Fig. 4 X-ray diffraction spectra of NFX (**a**), Polyox WSR 301 (**b**), Polyox WSR N80 (**c**), and Methocel K100 LC CR (**d**)

event. The decomposition was defined in two major endothermic stages. This was confirmed by TG/DTG curves that indicated thermal decomposition in the following temperature range: 330–376 °C ($\Delta m = 47.4\%$) and 421–455 °C ($\Delta m = 27.8\%$). The DSC curve of Polyox WSR 301 (Fig. 2b) and Polyox WSR N80 (Fig. 2c) showed sharp endothermic peaks at 69.3 °C ($\Delta H_{fusion} = -162.70$ J g^{-1}) and 65.3 °C ($\Delta H_{fusion} = -180.36$ J g^{-1}), respectively, corresponding to melting event. The TG/DTG curves indicated one thermal decomposition step in the temperature range of 397–433 °C ($\Delta m = 95.9\%$) for Polyox WSR 301 and 394–432 °C ($\Delta m = 95.8\%$) for Polyox WSR N80. The similarity of these thermal decomposition profiles can be explained by the same polymer chemical structure; the only difference is the molecular mass, 4,000,000 Da (Polyox WSR 301) and 200,000 Da (Polyox WSR N80). Different molecular masses usually are tested in the development of extended release tablets because its increase leads to an increase in gel strength, which tends to decrease the diffusion of the drug from the matrix. DSC curve of Methocel K100 LV (Fig. 2d) showed a broad endothermic event between 93–140 °C ($\Delta H = -120.97$ J g^{-1}) and TG/DTG curves indicated thermal decomposition in the temperature range of 360–394 °C ($\Delta m = 83.6\%$).

Based on the photomicrographs obtained from scanning electron microscopy, orthorhombic crystals were observed for NFX (Fig. 3a). A particle size variation can be visualized for both Polyox samples (Fig. 3b, c). An amorphous characteristic was observed for Methocel K100 (Fig. 3d).

X-ray powder diffraction (XRPD) studies were performed in order to obtain more information about the crystalline characteristics. The 2θ values of the diffraction peaks (Fig. 4) for NFX were $2\theta = 7.87$, 9.93, 10.63, 11.98, 13.38, 14.98, 16.08, 18.88, 20.78, and 25.08. For both Polyox polymers, only two intensive peaks were observed: $2\theta = 19.13$ and 23.33. For Methocel K100, only two broad peaks, with low intensity, between $2\theta = 5.7$–13.3 and 15.53–25.5, were observed, indicating an amorphous state for this polymer.

The IR spectra of quinolones are more representative in the region 1,800–1,300 cm^{-1} [23]. The IR spectrum (Fig. 5) of NFX exhibits a stretching vibration band at about 1,716 cm^{-1} (–COOH stretching) and 1,631 cm^{-1} (pyridone keto). For Polyox WSR 301 and N80, it was observed bands in 2,915 and 1,465 cm^{-1} (stretching $–CH_2–$) and intense bands in 1,150–1,085 cm^{-1}, which is attributed to asymmetric axial deformation C–O–C, characteristic of aliphatic ethers, confirming the identification of the polymers. Methocel K100 IR spectra showed absorption bands at 3,440 cm^{-1} (O–H stretching), 2,904 cm^{-1} (C–H stretching), 1,643 cm^{-1} (C=O), and 1,066 cm^{-1} (C–O–C).

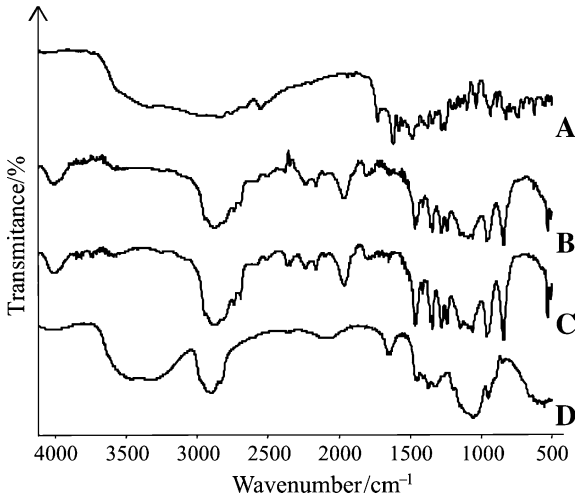

Fig. 5 DRIFT spectra of Norfloxacin (A), Polyox WSR 301 (B), Polyox WSR N80 (C), and Methocel K100 LC CR (D)

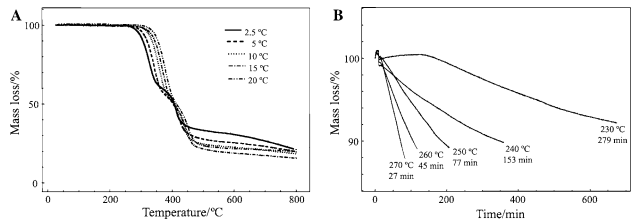

Fig. 6 **a** TG curves obtained for the non-isothermic study of NFX at 2.5, 5, 10, 15, and 20 °C min^{-1}. **b** Isothermal TG curves of NFX obtained between 230 and 270 °C, with a temperature increment of 10 °C

For non-isothermic study, the superposition of the TG curves of NFX is shown in Fig. 6a. Ozawa's method was applied in order to determine the activation energy (*E*a), Arrhenius frequency factor (A) and order of reaction at the beginning of first thermal decomposition step at around 300–350 °C. The *E*a, calculated was 126 kJ mol^{-1}, the Arrhenius frequency factor was 4.029×10^9 min^{-1} and order of reaction followed a zero order reaction ($n = 0$).

The isothermal TG curves of NFX are illustrated in Fig. 6b. These curves were used to obtain a graphic of ln*t* versus the reciprocal of temperature $1/T$ (K^{-1}). From this linear regression method, the equation obtained was $y = -16.098x + 26.382$ ($R = 0.9982$). The activation energy calculated from the product of 16.098 with the molar gas constant ($R = 8.314$) and was *E*a = 134 kJ mol^{-1}. This result is in agreement with the value obtained from the dynamic method. The selection of adequate excipients for a new formulation is based on the characteristics of the drug and its compatibility with other components. Moreover, excipients can influence the dissolution profile affecting the bioavailability of the drug. The results from the compatibility studies between NFX and excipients are shown in

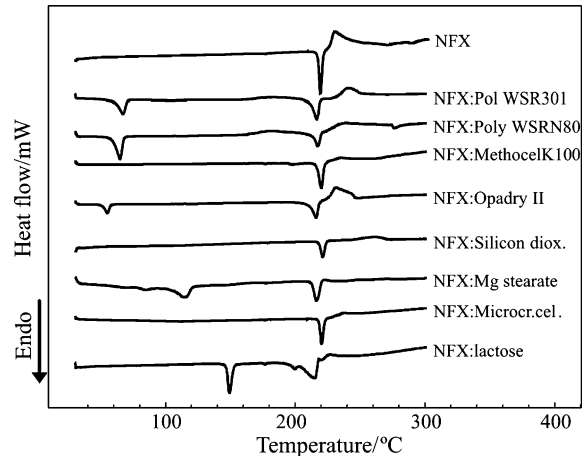

Fig. 7 DSC curves of NFX and excipients obtained in dynamic nitrogen atmosphere (50 mL min^{-1}) and heating of rate 10 °C min^{-1}

Fig. 7, where the DSC curves can be considered as superposition of the curves of pure compounds indicating that there is no interaction, and therefore no physical–chemical incompatibility.

Conclusions

The thermal behaviour and the solid-state characterization of NFX and the polymers were carried out by means of TG, DSC, DRIFT, SEM, and XRPD. The obtained isothermal and non-isothermal kinetic parameters can be used as reference values for the routine quality control of NFX. The results demonstrated the applicability of DSC as a fast screening tool for selection of adequate excipients at the early stages of pre-formulation studies. No interaction was observed for NFX and the tested excipients, making feasible the development of a high quality formulation of NFX extended release tablets.

Acknowledgements The authors wish to thank CNPq and CAPES for the support.

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