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THERMAL BEHAVIOUR AND DRUG-EXCIPIENT INTERACTION STUDIES FOR QUINIDINE

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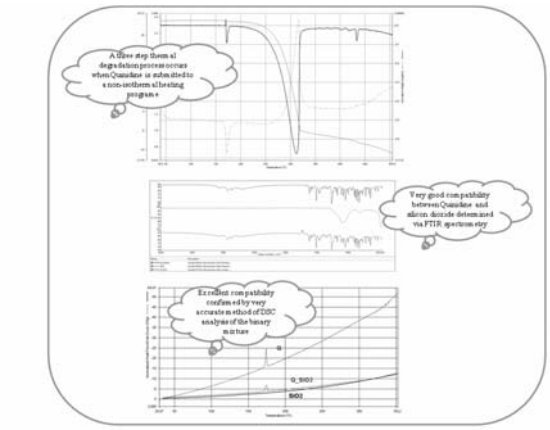
In this paper we developed a study on the thermal degradation of quinidine and on the thermally induced interactions, if any, between quinidine and several excipients. According to the European Pharmacopoeia, quinidine is an alkaloid that has two main therapeutic indications: as a class I antiarrythmic and as an antimalarial agent.
In order to perform the study, quinidine was submitted to thermogravimetric (TG), Fourier-transform infrared (FTIR) and differential scanning calorimetry (DSC) analysis. The thermogravimetric curves of quinidine were recorded in air atmosphere, while the possible interactions of quinidine with the 5 excipients used (starch, silicon dioxide, sorbitol, magnesium stearate and hydroxyehtylcellulose) were investigated by means of FTIR spectrometry and DSC analysis. The latter was performed also in air, in a programmed temperature range until 350°C. The studies showed that quinidine and the excipients used are compatible.



INTRODUCTION

Quinidine, an alkaloid[1] with the IUPAC name (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl)methanol, is a diastereomer of quinine, which is suitable as a therapeutic agent for atrial fibrillation and ventricular arrhythmias.[2] But as S. Grube *et al*. say in their paper, this alkaloid is also indicated for the treatment of malaria.[2] After oral administration, its bioavailability is about 50-80%, with a half life of 6 to 8 hours,[3] the usual dose being 200-400 mg every 4-6 hours.[2] If no side effects are observed, the dose may be carefully increased to obtain a better therapeutic effect for the patient.

Quinidine acquired its name from Pasteur in 1853 and has a long history as an antiarrhythmic, but the therapeutic benefits of quinidine do not come without hazards, the most common side effects of quinidine are gastrointestinal,[4] as F. Yang *et al.* mention in their article.

The galenic form of this product used for oral administration consists in tablets containing quinidine and excipients such as: starch, talc, lactose, magnesium stearate or gelatin. Interaction between active substance and excipients can alter stability and bioavailability of drugs, thereby, affecting their safety and/or efficacy. The successful formulation of a stable and effective

solid dosage form depends on the careful choice of the excipients.[5]

Thermal analysis was performed also for quinidine and binary mixtures of quinidine: excipient = 1 : 1 (w/w). The thermal degradation process was performed in air atmosphere at a temperature range of 40 to 500°C. The TG/DTG/DTA data was used to determine the behaviour of this alkaloid during the thermal degradation process.

FTIR measurements were performed as a simple to use, but efficient method to determine if any interactions between the atoms and functional groups in quinidine and the excipients can be determined. Samples of the binary mixtures were used to perform FTIR analysis and the spectra were used in comparison with the ones recorded for de pure compounds: the alkaloid and the excipients.

In order to complete de study we used one of the widely and suitable method that can be applied to determine interactions between the pharmaceutical agent and various excipients, i.e. differential scanning calorimetry. All the determinations were performed under the same conditions, using a controlled temperature program. As required for the previous methods, DSC curves were recorded for samples of quinidine, the excipients and binary mixtures of quinidine : excipient = 1 : 1 (w/w).

RESULTS AND DISCUSSION

TG/DTG/DTA curves recorded for quinidine show (Fig. 1) that there are three processes during the thermally induced degradation of the sample. The main one has significant mass loss and it is accompanied by an exothermic effect. This event is preceded by a small endothermic process and followed by an even smaller exothermic process nearly at the end of the temperature program. At the end of the thermal degradation process the total mass loss was of 70.31%.

The assignment of the vibration peaks for quinidine is detailed in Table 2, while the following figure (Fig. 2A-2E) shows the split spectra of: the spectra of quinidine, the spectra of one of the excipients and the spectra of the binary mixture, respectively.

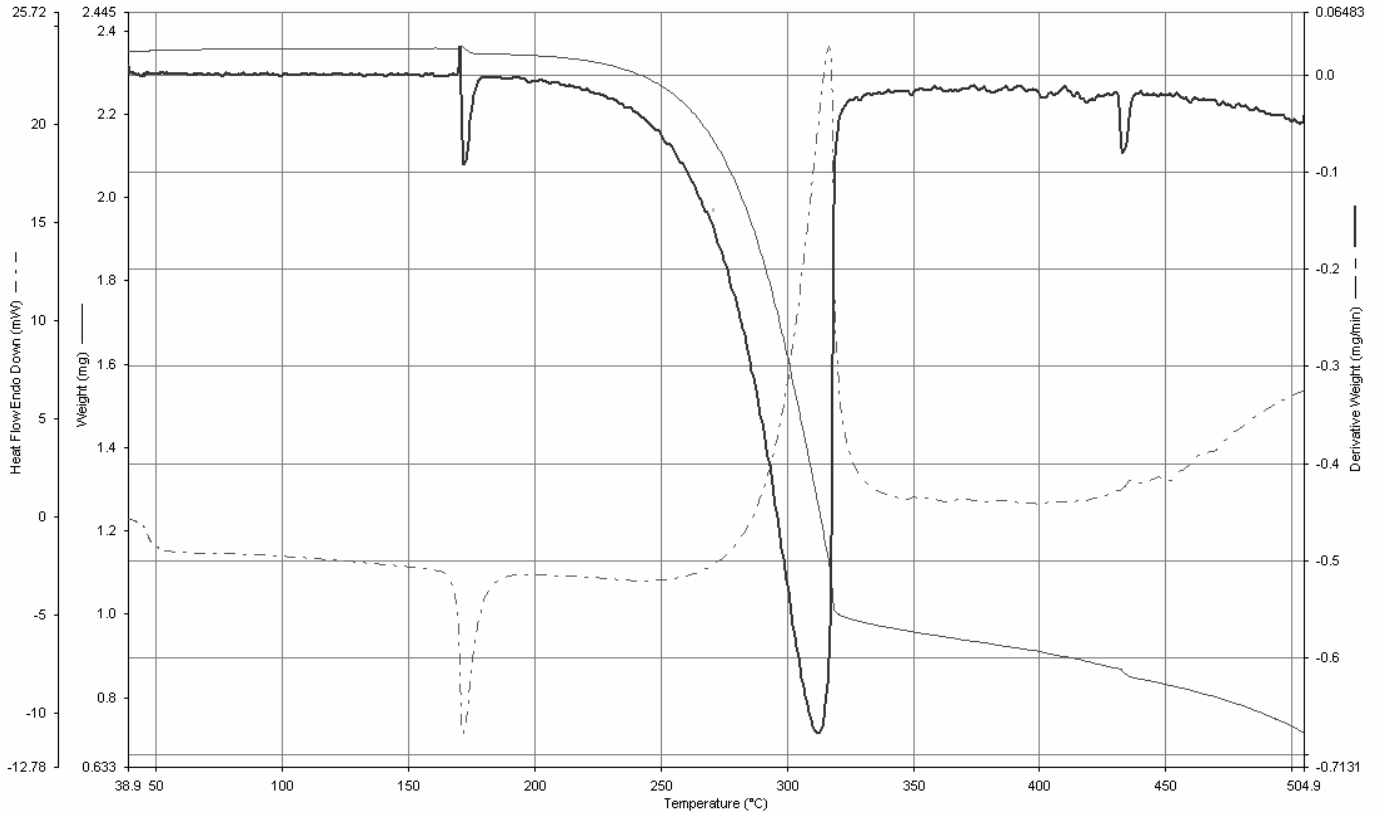


Fig. 1 − TG/DTG/DTA curves for quinidine, in air flow, from 40 to 500°C at a heating rate of 10°C·min^{-1}.

Table 1

Thermoanalytical data of quinidine

Compound	Process	T_i, °C	T_f, °C	$T_{max\ DTG}$, °C	Δm, %
Quinidine	1	166	183	173	0.55
	2	252	328	312	57.62
	3	424	440	433	0.47

Table 2

Assignment for main vibration peaks of quinidine FTIR spectrum

Frequency of vibrations, cm^{-1}	Assignment
3068	=C–H ring stretching and deformation in quinolines
2928	stretching vibrations of $–CH_2–$ group
2867	stretching vibrations of $–O–CH_3$ group
1619	–C=C non-conj. stretching vibrations
1562	–C=N stretching vibrations
1260, 1104, 1041	–C–O stretching vibrations, –O–H in plane deformations
1202, 1187, 1171	–C–N stretching vibrations in tertiary amine

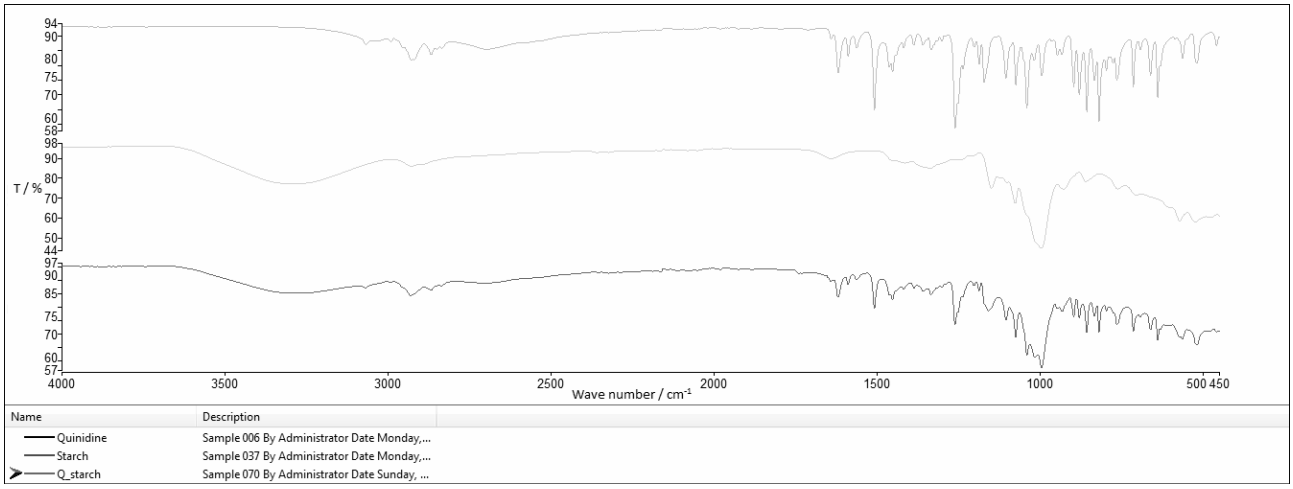


Fig. 2A − FTIR spectra of quinidine, starch and the binary mixture.

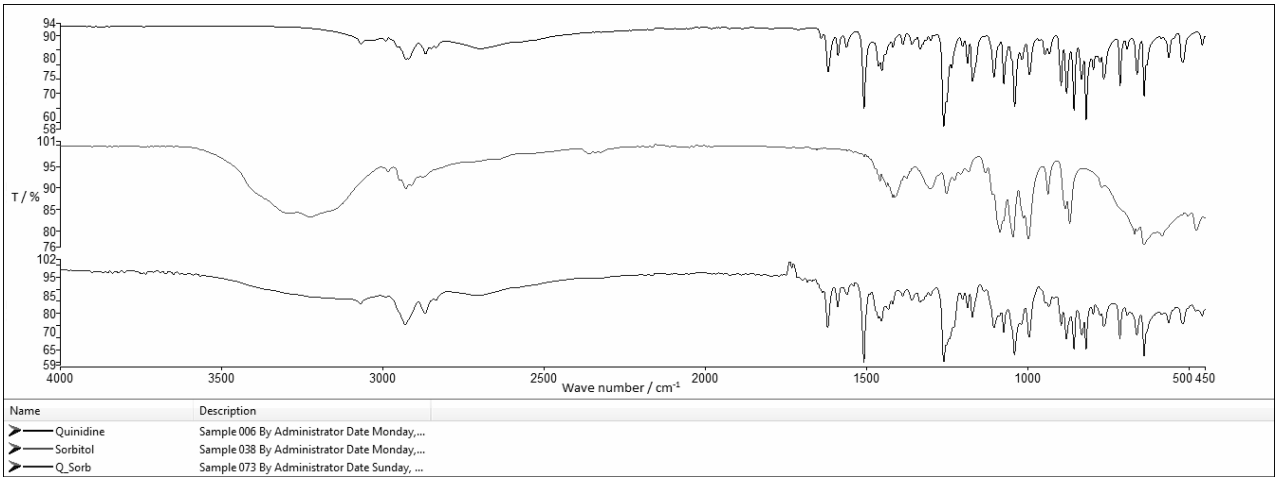


Fig. 2B − FTIR spectra of quinidine, sorbitol and the binary mixture.

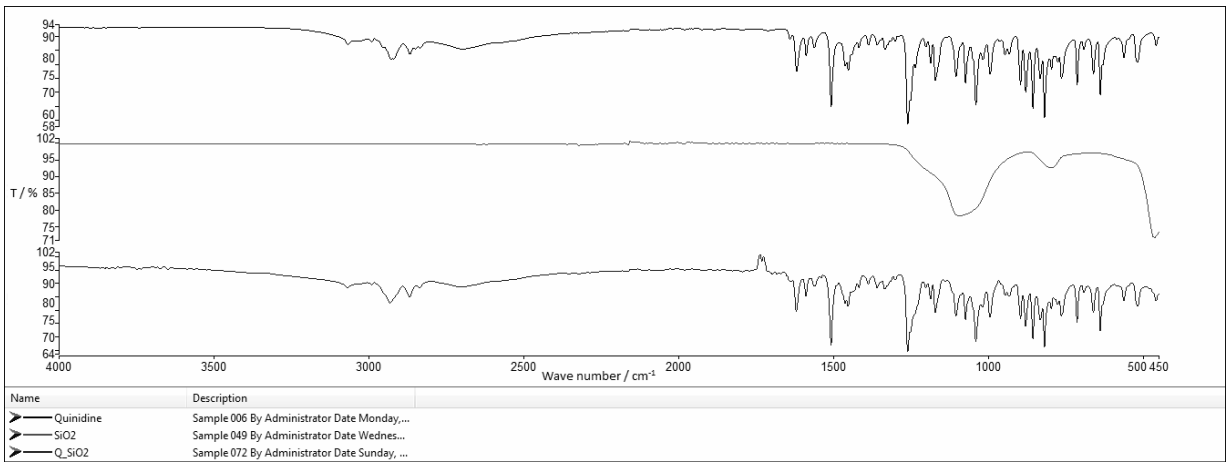


Fig. 2C − FTIR spectra of quinidine, SiO_2 and the binary mixture.

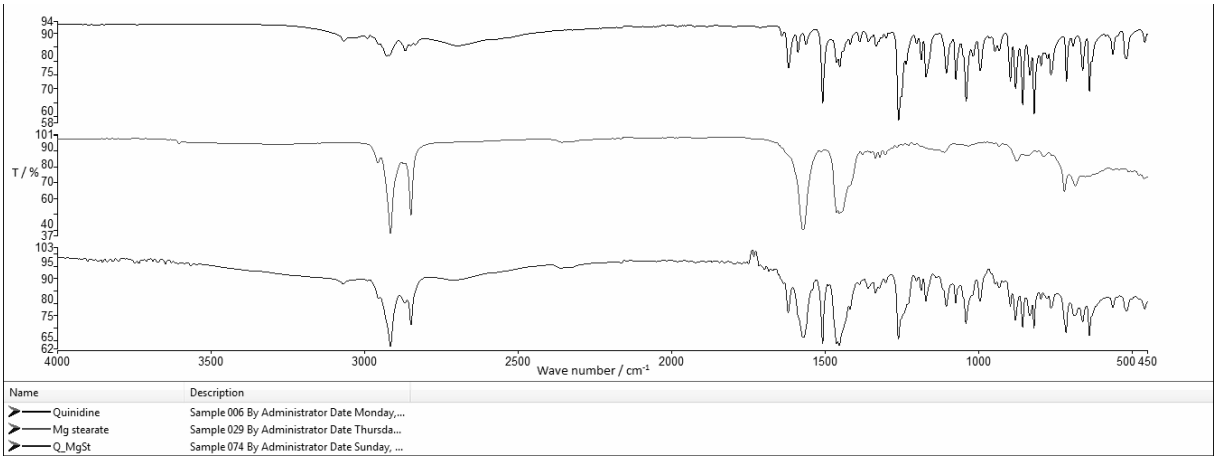


Fig. 2D − FTIR spectra of quinidine, magnesium stearate and the binary mixture.

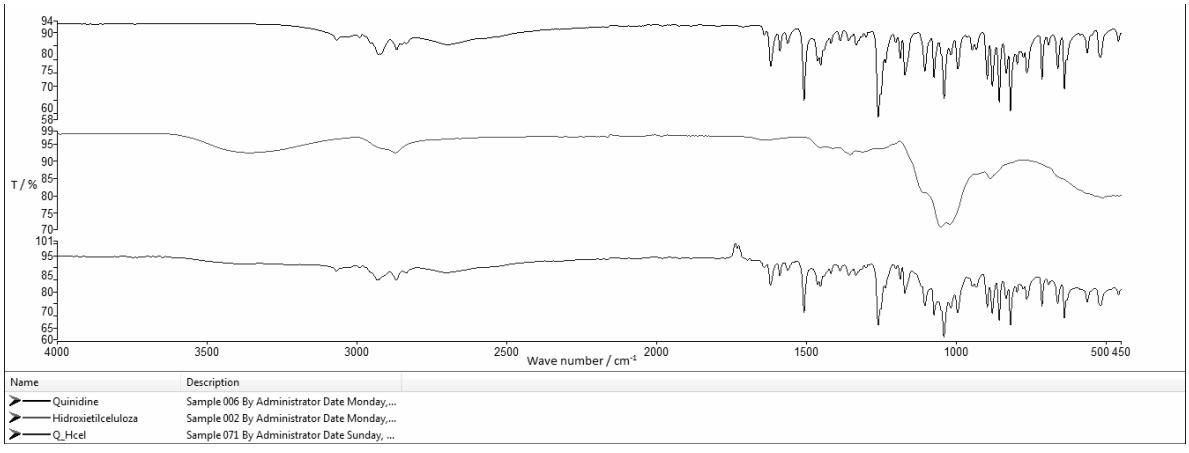


Fig. 2E − FTIR spectra of quinidine, hydroxyethylcellulose and the binary mixture.

DSC analysis was intentionally left at the end of this study because it is one of the most accurate methods that can certify if interactions do occur between quinidine and the excipients used. DSC measures the thermal effect of the analyzed sample so we made a comparison of the DSC curves for quinidine, for each of the excipient and for the binary mixtures. If the DSC curve of the mixture does not show any other thermal effects than the sum of the effects that appear on the DSC curves of the pure substances. This leads us to a conclusion, that there are no interactions in the binary mixtures. Figs. 3A to 3E show the overlapped DSC curves of quinidine, the excipient and the binary mixture.

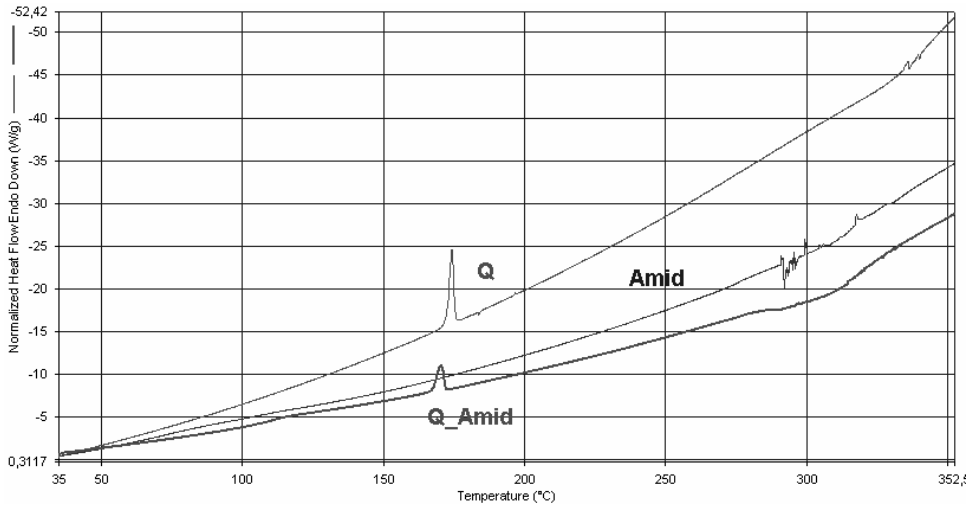


Fig. 3A − DSC curves of quinidine, starch and the binary mixture.

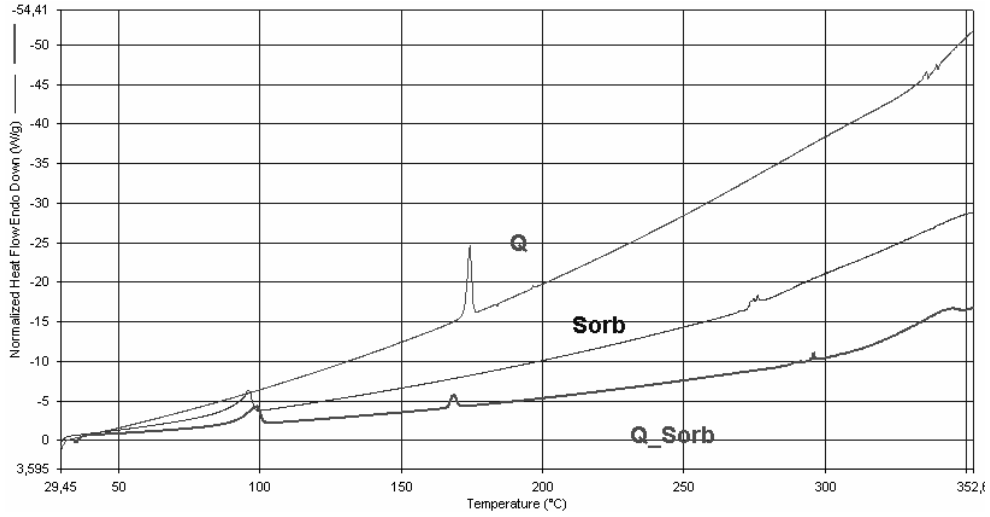


Fig. 3B − DSC curves of quinidine, sorbitol and the binary mixture.

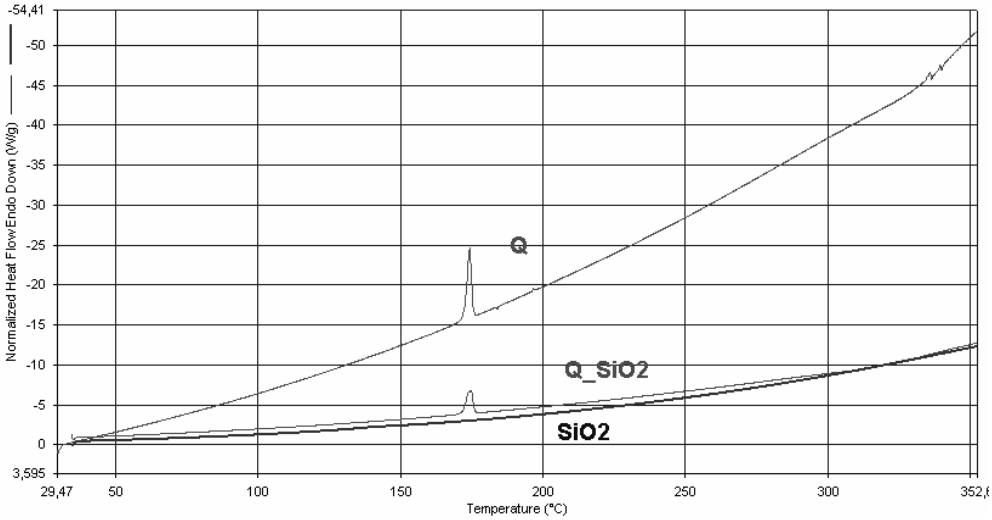


Fig. 3C − DSC curves of quinidine, SiO_2 and the binary mixture.

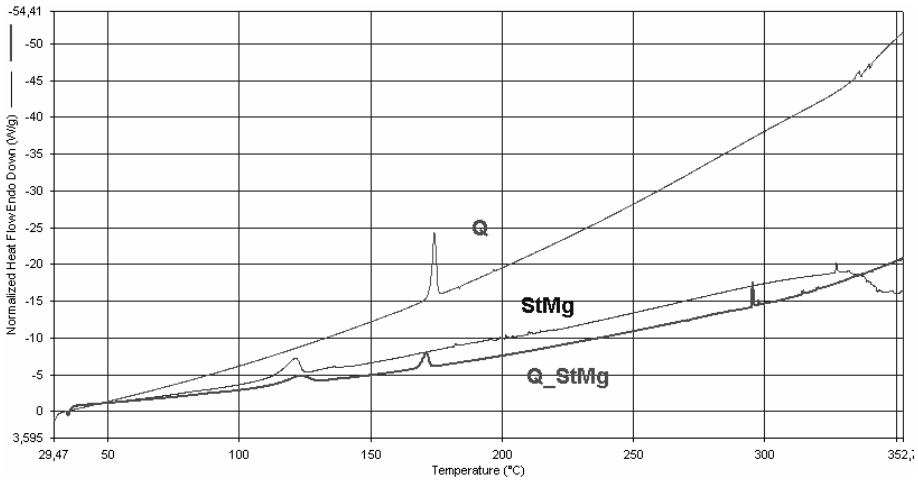


Fig. 3D − DSC curves of quinidine, magnesium stearate and the binary mixture.

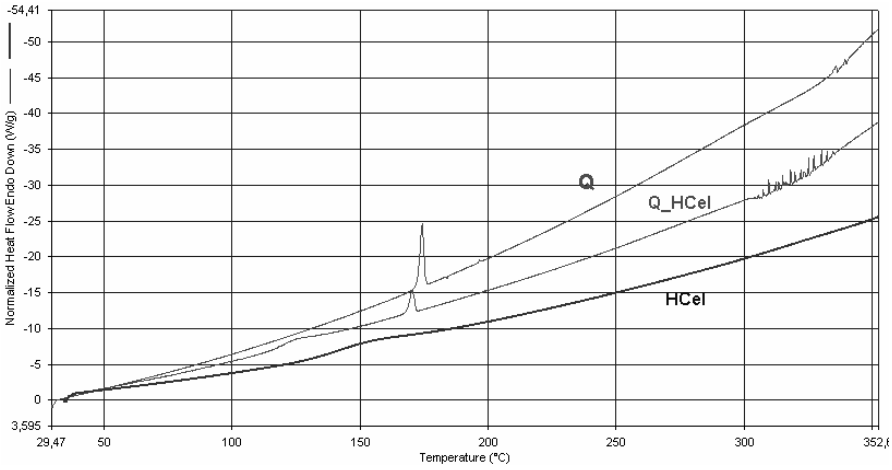


Fig. 3E − DSC curves of quinidine, hydroxyethylcellulose and the binary mixture.

EXPERIMENTAL

Quinidine was purchased from Sigma (Lot #BCBB6721V), having MW = 324 g·mol^{-1} with a mp = 168-172°C and it was used as received. The excipients were purchased as follows: magnesium stearate (UTCHIM), silicon dioxide (Aldrich), sorbitol (Fluka), hydroxyethylcellulose (Merck) and starch (Fluka).

The FTIR spectra of the compounds used in this study were recorded with a Perkin Elmer Spectrum Two spectrometer equipped with an UATR accesory for solid samples. Data recorded was further processed by using Perkin Elmer Spectrum software.

To evaluate the thermal behavior of quinidine, samples were added to aluminum crucibles and they were submitted to a controlled temperature program from 40 to 500°C in air flow of 100 mL·min^{-1}, while the samples were heated at a heating rate of 10°C·min^{-1}, as described in similar thermoanalytical studies. [6-8] This analysis was performed on a Perkin Elmer TG/DTA thermobalance. DSC data was recorded on a Perkin Elmer Pyris Diamond DSC while the samples were sealed in aluminum crucibles. The temperature programe was set from 40 to 350°C with a heating rate of 10°C·min^{-1}, while all the data was processes by Perkin Elmer Pyris software.

CONCLUSIONS

After collecting all the data from the different methods of investigation used we can conclude that quinidine is quite stable until roughly 250°C. The first thermal event is assimilated to the melting of quinidine, according to literature data. The main thermal degradation process is an exothermic one with a mass loss of 57.62%. During this process the molecular structure is broken and further studies will involve evolved gas analysis measurements to determine how the structure is degraded and what are the side products.

The main peaks of the molecular vibrations and deformations determined in the FTIR spectrum of quinidine confirm the structure of the alkaloid and they eliminate the risk that any damage was caused to the molecule during the transportation or the storage period of the active compound. The spectra recorded for all five binary mixtures of quinidine with the excipients, in comparison with the ones of

the single compounds, confirmed that no functional groups have disappeared nor new ones are formed, hence no interactions can be expected in the binary mixtures.

DSC curves come to finalize the study by confirming that the excipients used in this study are compatible with the active substance. Yet, there is one substance that is used as excipient for different active substances, hydroxyethylcellulose, which is not currently used in a galenic form with quinidine, which showed there are a few exothermic effects on the binary mixture DSC curve, that do not show neither on quinidine, nor hydroxyethylcellulose curves. This means that interactions can occur between quinidine and hydroxyethylcellulose if exposed to heat, for example when stored inappropriately for a longer period of time.

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