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Thermal behavior of verapamil in pure and in solid dosage forms

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Abstract Verapamil is a phenyl-alchil-amine type pharmaceutical largely used as a specific calcium antagonist. Knowledge of drug-excipient compatibility represents an important phase in development of different dosage forms. Hyphenated techniques are versatile for obtaining such necessary information's. The TG/DTG/DTA curves were obtained in air at different heating rates and in nitrogen. The IR spectra of pure compound and its char at 400 °C (by U-ATR technique) and the IR identification of Evolved Gasses allowed some discussions on the thermally induced events. In the solid dosage forms verapamil was mixed with talc, magnesium stearate, starch, and cellulose, and the corresponding thermoanalytical curves were compared with that one of pure I. No physical or chemical interactions were observed till 250 °C. A kinetic analysis was performed for TG step of verapamil between 250 and 350 °C. The data at four heating rates (7, 10, 12, 15 °C min^{-1}) were processed on a strategy using at last three different kinetic methods. For these, the NPK method seems to be less speculative, allowing an objective determination of the kinetic parameters.

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Introduction

Verapamil (see Scheme 1) is a phenyl-alkylamine type pharmaceutical largely used as a specific calcium antagonist [1].

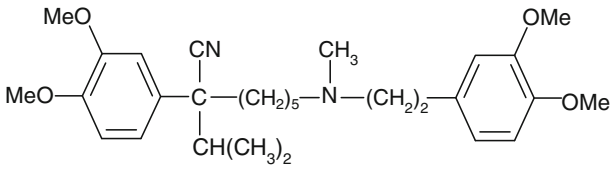
Its mechanism of action relies on the capacity of inhibiting the Ca^{2+} influx through the calcium channels [2].

Verapamil proved positive effects in patients with peripheral arterial occlusive disease [3] and a remarkable anti-inflammatory effect [4].

Verapamil is used orally as film-coated and modified release tablets; the assessments of some possible incompatibilities between the active component and different excipients are of crucial importance for the final formulation setting of a solid dosage from [5]. Excipients are considered pharmacologically inert, but physical and/or chemical interactions with the active component are possible [6].

Thermal analysis under non-isothermal conditions proved its utility for screening drug-excipient interactions. The use of hyphenated techniques allows the identification of evolved volatile compounds resulted by thermodegradation process and an accurate determination of the differences in drug's thermal behavior induced by interactions with different excipients, behavior that is described through kinetic parameters.

The topic of this study is the determination of pure verapamil (V)'s thermal behavior and the evaluation of possible interactions between this active compound and the excipients—talc (T), magnesium stearate (M), starch (S), and cellulose (C), commonly used in solid dosage forms. For this purpose a hyphenated technique for simultaneous TG/DTG/HF/EGA determinations was used. In order to assess the excipients' impact on verapamil's thermal behavior from different dosage forms, a kinetic analysis was also performed.



Scheme 1 Structure of Verapamil

Experimental part

Materials and methods

V as verapamil hydrocloride was used (molecular mass 518.5 a.m.u.).

V (Abbott India lot 5421207), T (talc powder Luzenac Pharma Italy, lot: 01067235/S450/06), M (microcrystalline cellulose ParChem Trading Israel, lot: 01061002/T320/08), S (starch Grain Processing Corporation USA, lot: 0106115072/1027–1009) and C (microcrystalline cellulose ParChem Trading Israel, lot: 01061002/T320/08). The mixed samples consisted of equal masses of verapamil hydrochloride 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 (V:excipient) by simple mixing.

All the materials were used as they were received, without further purification. The composition of the pharmaceutical dosage forms tested is shown in Table 1.

The physical binary mixtures were prepared by gently mixing at room temperature using agate mortar.

The TG/DTG/DTA measurements were carried out on a Perkin Elmer Diamond device, in dynamic air, respectively, nitrogen (100 mL min^{-1}) at heating rates of 7, 10, 12, and 15 °C min^{-1}. An open aluminum crucible was used to contain the sample and an identical empty crucible was used as reference.

For determination of the heat effects the DTA curves (in μV) were changed with the Heat flow curves (in mW), so that the peak area corresponds to an energy in J g^{-1} or kJ mol^{-1}.

For EGA the furnace was connected, by a transfer line, to the gas chamber of a Perkin Elmer SPECTRUM 100 device. The Evolved Gas spectra were drawn up at each maximum of Gramm-Schmidt profile and the volatile compounds were identified using the Sadtler Gas Vapor Library.

The FTIR spectra of the prepared samples and of the corresponding char, at 400 °C were obtained on the same spectrometer using the U-ATR technique.

Table 1 Data on prepared samples containing verapamil

Symbol	Contained excipient	Mass ratio verapamil:excipient
V	None	–
VT	Talc	1:1
VM	Magnesium stearate	1:1
VS	Starch	1:1
VC	Cellulose	1:1

Results and discussions

Thermoanalytical and FTIR data for pure verapamil

An example of TG/DTG/DTA curves in air for sample V is presented in Fig. 1.

Verapamil's melting takes place at 147.5 °C with a melting heat of 40.5 kJ min^{-1}. Between 229.5 and 350 °C a mass loss of 76.9% was observed. But this mass loss is not due to a single process. As it is shown on the DTG curve, there are two superposed processes, with DTG_{max} at 287.4 °C, respectively, 318 °C. On the DTA curve there can be also seen two different thermal effects: an endothermic effect with a maximum at 273.8 °C and a heat effect of 202.5 kJ mol^{-1}, respectively, an exothermic one with a maximum at 327.6 °C and a heat effect of −88.0 kJ mol^{-1}. Owing to these rather high-thermal effects, a significant difference between the corresponding DTG_{max} and DTA_{max} was observed.

In order to elucidate these thermally induced phenomena, the IR data is useful. The spectrum of the evolved gases, drawn up at 288 °C (first DTG_{max}) indicates water, carbon dioxide, and anisole-like derivatives as major compounds in EG (see Fig. 2).

The presence of anisole type volatile substances in EG is due to the breaking of the two 1,2,4 tri-substituted benzene ring and therefore the mass loss process begins with an endothermic effect. The corresponding mass loss would have been 56.8%. But according to Fig. 1, at 300 °C (the intersection of the two DTG_{max}) the determined mass loss is 44.6%. This means that the first thermodegradation process is not complete before the second one takes place, i.e., the exothermic thermo-oxidation. This scenario is also supported by the comparison of pure verapamil's U-ATR spectra, respectively, its char at 300 °C (see Fig. 3). For the V sample the significant peaks at 1239, 1141, 900–860, and 860–800 cm^{-1} are assigned to a 1,2,4 tri-substituted benzene ring [7]. On the char's spectrum these peaks are absent. Also the hypothese of the total thermooxidation as the second process is supported by the EG spectrum at 320 °C, where the major compounds are water vapor and carbon dioxide (see Fig. 4).

The thermal behavior of V under non-isothermal conditions was determined also in nitrogen atmosphere (see Fig. 5).

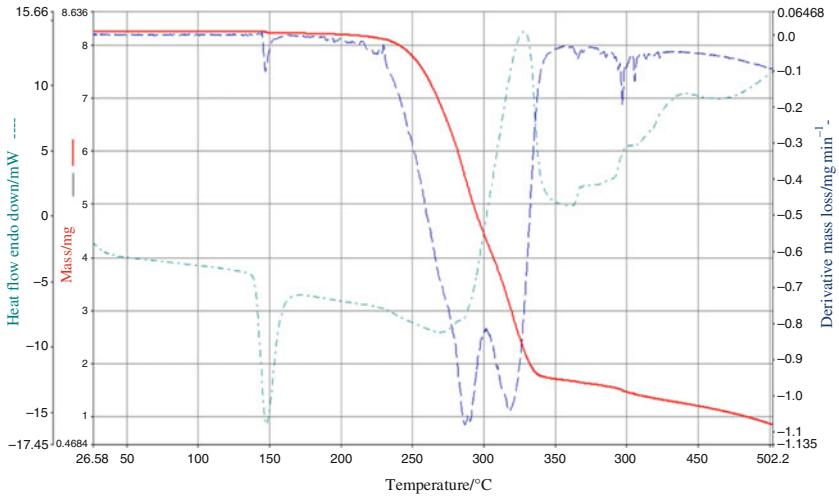


Fig. 1 TG/DTG/HF curves obtained for verapamil in air at a heating rate of 10 °C min^{-1}

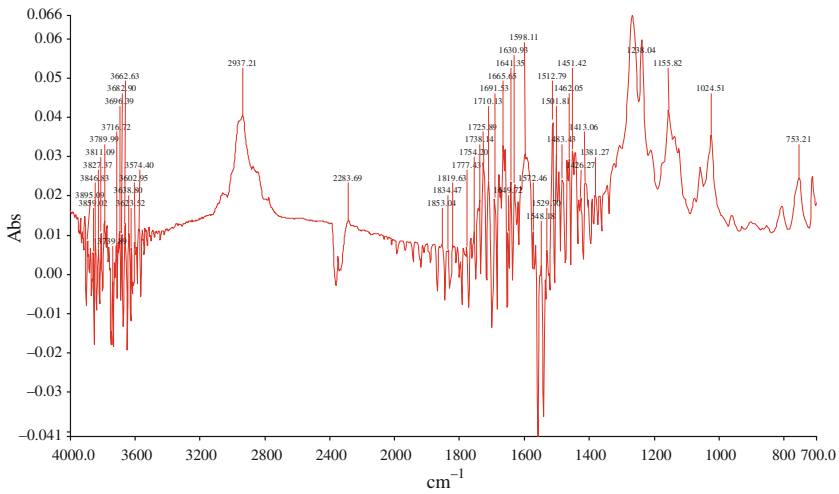


Fig. 2 Spectrum of evolved gases (in air) at 288 °C

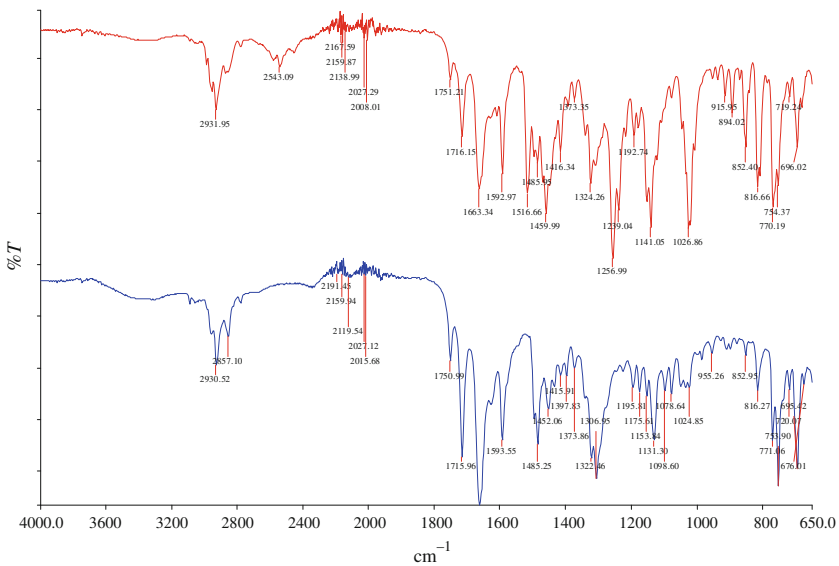


Fig. 3 IR spectra of I (−) and its char at 400 °C (−)by U-ATR technique

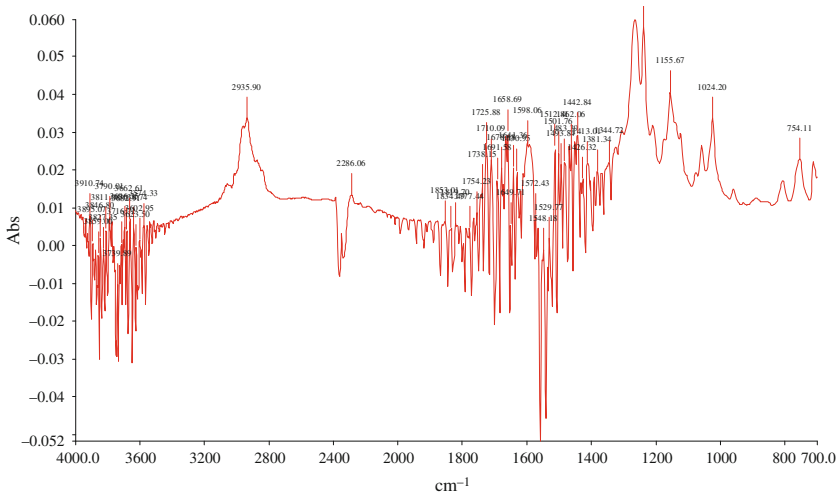


Fig. 4 Spectrum of evolved gases (in air) at 320 °C

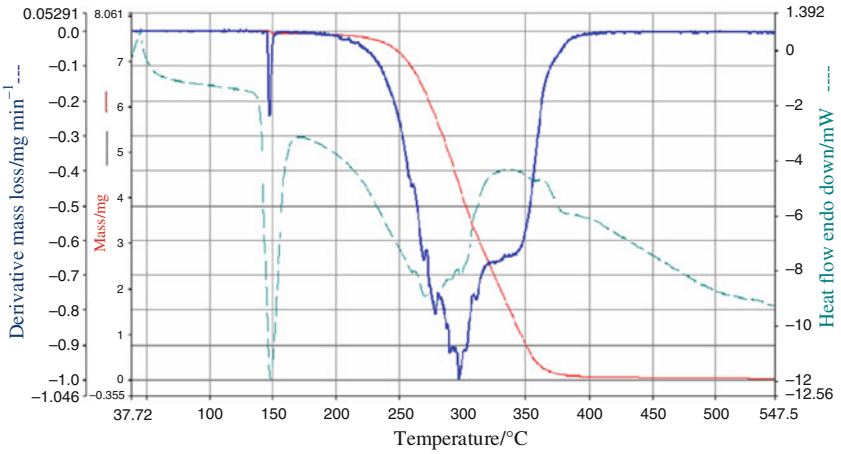


Fig. 5 TG/DTG/HF curves obtained for verapamil in nitrogen at a heating rate of 10 °C min^{-1}

The melting at 148 °C had a thermal effect of 41.7 kJ mol^{-1}, in a good agreement with the obtained data in air atmosphere.

The mass loss of 98% took place between 190 and 390 °C, with the DTG_{max} at 298 °C. The endothermic effect is 122 kJ mol^{-1} with the DTA_{max} at 279 °C. A difference between DTG_{max} and DTA_{max} was observed again, due to the high-endothermic effect. The suggested process is a thermodegradation especially with breaking the end phenyl groups. The arguments are brought by the presence in EG's spectrum of 3,4-dimethoxy-benzyl derivatives, respective of veratrylamine (see Fig. 6).

Thermoanalytical data for solid dosage forms

The TG/DTG/DTA curves for samples according to Table 1, drawn up in air at a heating rate of 10 °C min^{-1} are presented in Fig. 7. By inspecting these curves, no significant differences in comparison with pure V were observed. The samples with organic excipients, i.e., VM, VC, and VS, exothermic oxidations were observed by temperatures over 350 °C.

Kinetic analysis

The kinetic analysis was performed for the decomposition in air, taking to account process between 250 and 350 °C. The authors will consider the Process (I) with the DTG_{max} at 287.4 °C and the Process (II) with DTG_{max} at 318 °C.

The strategy of the kinetic analysis was relied on two principles:

- The recommendation of the ICTAC 2000 Protocol [8], i.e., thermoanalytical data obtained at several heating rates.
- The use and comparison of more than one data processing method, including at least one differential and one integral method.

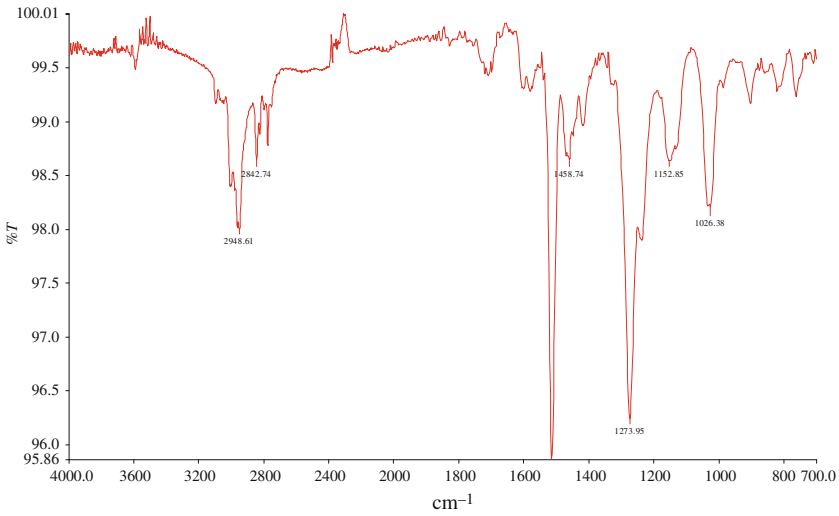


Fig. 6 Spectrum of evolved gases (in nitrogen) at 300 °C

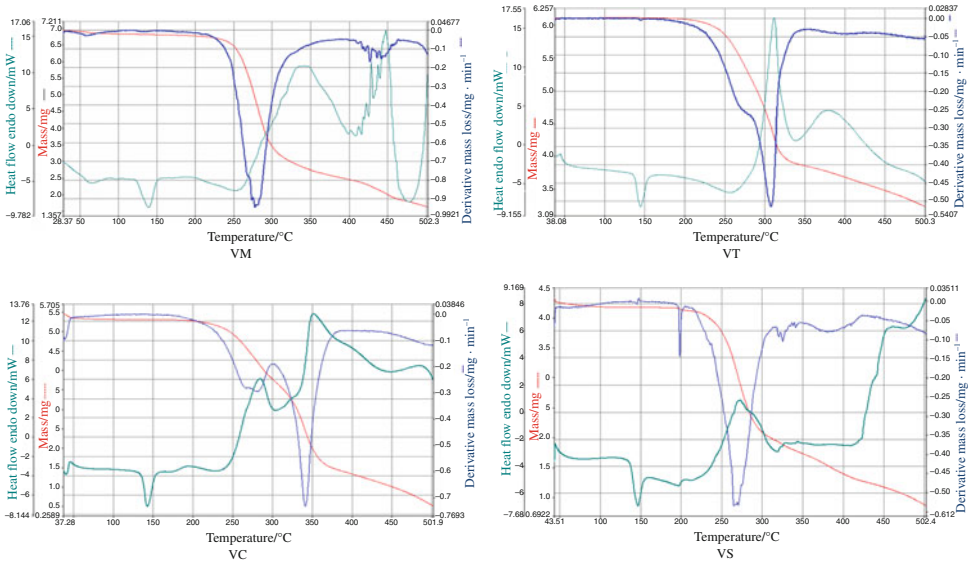


Fig. 7 TG/DTG/HF curves of the dosage form samples in air at 10 °C min^{-1} heating rate

Apparent complications seem to be the partial superposition of the two DTG peaks. But fortunately the heat effects were opposite so that the Heat flow curves were easily used by the data processing.

Starting from the generally accepted axiom that the reaction rate can be expressed as a product of two separate functions, i.e.,

$$d\alpha/dt = k(T) \cdot f(\alpha) \quad (1)$$

where t is time, T is temperature and f(α) is the reaction model.

(i) The Friedman's differential-isoconversional method (FR) [9].

For a single step process and a heating rate β, Eq. 1 becomes:

$$\ln(\beta \cdot d\alpha/dt)_{\alpha} = \ln[A \cdot f(\alpha) - E/RT] \quad (2)$$

when the Arrhenius equation was considered for $k(T)$.

At a certain conversion, the slope of the straight line of $\ln[\beta(d\alpha/dT)]$ versus $1/T$ gives the activation energy. Because the conversion function f(α) is not explicit, the Friedman's method is considered a "model free" method.

Owing to its simplicity and independence in respect to the kinetic model, this method is recommended for the beginning of whatever kinetic analysis.

According to Fig. 8 there is a significant variation of E versus α, this being a sign of a complex multi-step process.

(ii) The integral-isoconversional method of Flynn–Wall [10]–Ozawa [11] (FWO).

The integral form of Eq. 2 can be written:

$$\ln\beta = \ln A/[R \cdot g(\alpha)] - 5.331 - 1.052 \cdot E/R \cdot T \quad (3)$$

where $g(\alpha) = \int_0^{\alpha} [d\alpha/f(\alpha)]$ is the integral conversion function. In comparison with FR's method, this one takes into account the thermal history of the sample.

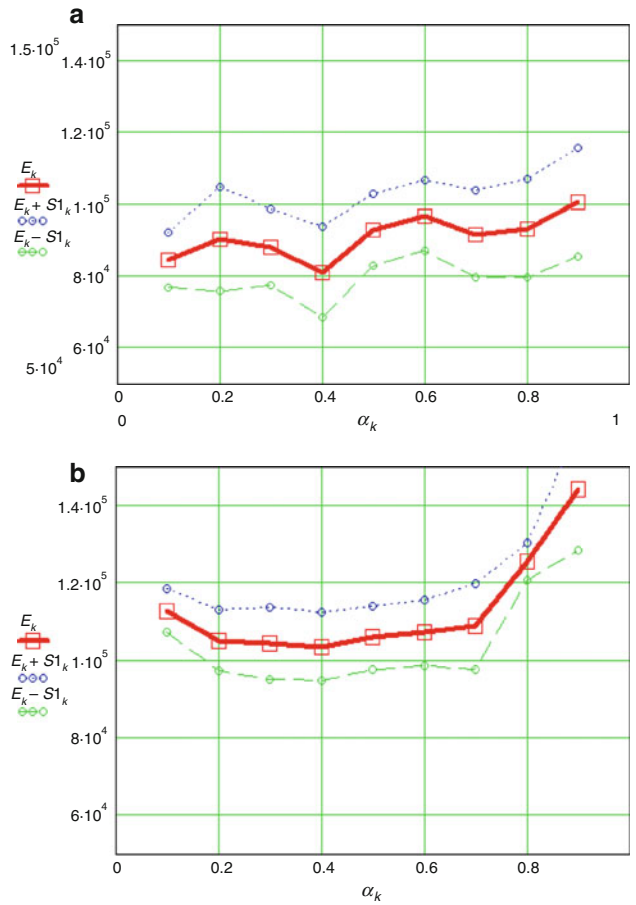


Fig. 8 E (J mol^{-1}) versus α diagram according to Friedman's method for **a** process I, **b** process II

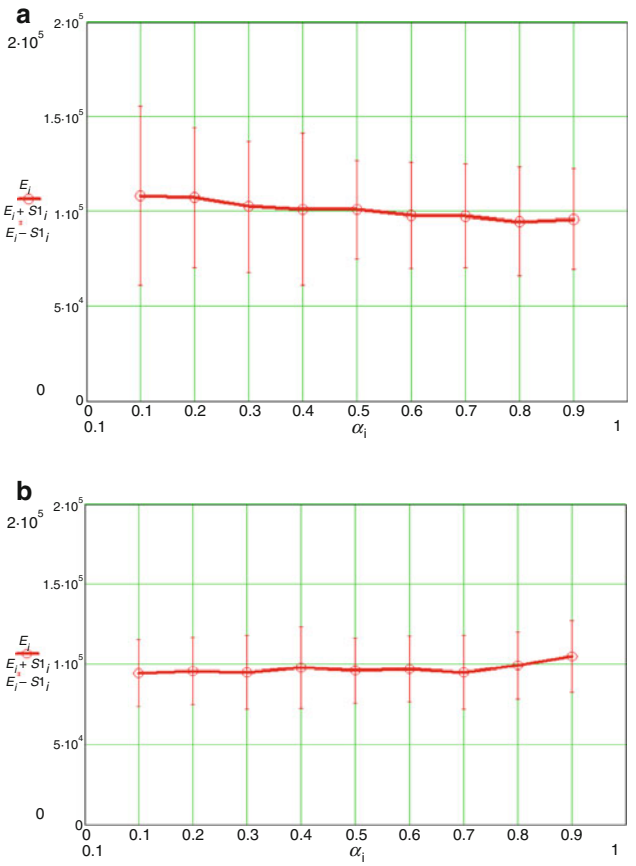


Fig. 9 E (J mol^{-1}) versus α diagram according to FWO method for **a** process I, **b** process II

According to the data in Fig. 9 there are monotonous variations of E versus α in the range of 20%, also a clear indication of a complex process.

(iii) The modified NPK method [12–16].

By the Non Parametric Kinetic method, the reaction rates $r = d\alpha/dt$ obtained at different heating rates are represented in a 3D coordinate system (r, T, α), according to Eq. 1. The modified version uses an appropriate interpolation algorithm to obtain a continuous reaction rate surface. This surface is then discretizated into a square matrix M, so that each element of this matrix is:

$$r_{i,j} = k(T_i) \cdot g(\alpha) \tag{4}$$

using a singular value decomposition (SVD) algorithm [17].

The matrix M was decomposed according to:

$$M = U(\text{diag.S})\ VT \tag{5}$$

A vector u_1 given by the first column of matrix U is analyzed in order to determine the conversion function, according to Šestak–Berggren [18] equation:

$$g(\alpha) = \alpha^m (1-\alpha)^n \tag{6}$$

A similar vector v_1, corresponding to V is checked for an Arrhenius type temperature dependence.

In this way the influence of T, respective α on the reaction rate are separated without any supplementary hypothesis.

If the decomposition process is a result of two or more simultaneous steps, it means that $r = \Sigma r_i$ and consequently the matrix M becomes:

$$M = \Sigma M_i \tag{7}$$

The contribution of each step to the observed process is expressed by the explained variance λ, so that $\Sigma\lambda_i = 100\%$.

This simple mathematical treatment allows an objective discrimination between two (or more) steps of a complex process.

The results of the data processing are systematized in Table 2. By inspecting the data in Table 2 it results that by both processes, one step has a major contribution, with more than 85% of the explained variance. So, a comparison of the mean value obtained by NPK method, $\overline{E} = \lambda_i \cdot E_i$

Table 2 Kinetic parameters by NPK method

Process	Step	λ/%	E/kJ/mol^{-1}	A/min^{-1}	Eq. 6	
					m	n
I	1	88.6	98.5	5.5×10^8	0	1
	2	11.4	111.0	1.5×10^{10}	0	1
II	1	85.2	111.0	1.3×10^9	0	1
	2	14.8	114.6	4.8×10^9	0	1

with the mean values of the activation energy obtained by FR, respectively, FWO methods will be interesting.

According to the data in Table 3, there are no significant inferences between the E values obtained by these three methods. Especially for the second, exothermic process, the values are rather the same. Also remarkable are the very near values by FWO and NPK methods, obtained for the first process.

By each kinetic method, the differences between the activation energy obtained for the first, respective second process are also not to high. This fact together with the thermoanalytical and EGA data discussed before suggest the following degradation mechanism: at beginning the molecular architecture is destroyed by breaking the C–C bond between the aliphatic middle group and the two aromatic rings. At a temperature around 300 °C a thermooxidation of these smaller structures is superposed on the first process.

Regarding the kinetic model, a first order reaction ($n = 1$) was expected for a reaction in melted state.

In a recent paper on thermal behavior of verapamil hydrochloride [19], the kinetic of its decomposition in nitrogen, under non-isothermal conditions was reported. A value of 230 kJ mol^{-1} for the activation energy is far from the mean values presented in Table 3. Therefore, some comments are necessary and useful:

- Nunes et al. [19] determined this value by means of a single kinetic method, FWO, not as a result of a real "kinetic analysis";
- The value reported was for particular conversions range (51–66%) even if the E versus α curve clearly demonstrate a complex process
- the observed phenomenon in nitrogen is a "thermodegradation", while in air a "thermooxidation" take place

Table 3 Mean values of the activation energy

Process	Mean value of E/kJ/mol^{-1}obtained by		
	FR	FWO	NPK
I	90.9	100.9	99.9
II	113.0	97.5	111.5

and is common that the activation energy for an oxidation process is significantly smalls in comparison with a thermodegradation process.

Consequently, no comparison is realistic between the E values reported in [19], respectively, in this article.

Conclusions

An extended study on the thermal behavior of verapamil and some of its dosage forms were performed.

The main thermal-induced process on pure verapamil was the melting and the thermodegradation. This last one is a complex phenomenon with two superposed processes: the first endothermic, the second exothermic.

In order to elucidate this complex thermodegradation, the thermoanalytical and evolved gas analysis data were corroborated with the data of the kinetic analysis and a reaction mechanism was suggested. This mechanism consists in an endothermic C–C bonds breaking superposed on an exothermic thermooxidation of the so obtained smaller structures.

By the solid dosage forms no significant interactions between the excipients and verapamil were observed until the beginning of thermodegradation of the last one.

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