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# Thermal analysis study of amlodipine as pure compound and in binary mixture

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**Abstract** Amlodipine is a very used selective calcium antagonist. The evaluation of thermal stability is crucial for the formulation setting of a solid dosage form. By heating in air under non-isothermal conditions, amlodipine presents two characteristic steps. More details were obtained using IR spectrometric data of the pure compound of the char, respectively, of the evolved gases at those temperatures. Data on a possible interaction between amlodipine and some excipients used in solid dosage forms were obtained by comparison of TG/DTG/DTA curves of amlodipine and of its mixtures with talc (considered thermally inert), magnesium stearate, starch and cellulose. No thermally induced interactions were observed. In order to obtain data for a believable Life Time Prediction a kinetic analysis was performed. The data of the first step of mass loss obtained at four heating rates (7, 10, 12, and 15 °C $min^{-1}$, respectively) were processed using at least three different methods. From these, the NPK method seems to be adequate because the separation between the temperature, respective the conversion dependent part of the reaction rate equation and the expression of the formal kinetic equation were obtained in a less speculative manner.

**Keywords** Amlodipine · Thermal behavior · Evolved gas analysis · Kinetics · NPK method

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## Introduction

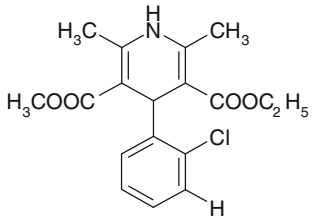
Amlodipine (see Scheme 1) is a dihydropyridine derivative of class II of $Ca^{2+}$ channel antagonists [1]. They block the L-type calcium ion channels [2]. In a recent study [3], amlodipine significantly reduced both systolic and diastolic blood pressure, improved the flow-mediated dilation, increased the HDL-cholesterol level and reduced the insulin resistance state. The dihydropyridine type pharmaceuticals showed their capacity to have an antihypertrophic effect [4].

Regarding the structure–activity relationships (SAR) in the series of 2,6-dimethyl-3,5-dicarboetoxi-1,4-dihydropyridine in vivo, some fruitful rules were established [5]:

- The substitution in position 4 increase the activity as follows: H < methyl < cycloalkyl < heterocycle < phenyl and substituted phenyl;
- The substitution in the position 4 ring increase the activity in the order ortho > meta ≫ para, but electron-attracting groups in para diminished the activity;
- The presence of the 1,4-dihydropyridine ring is essential, the oxidation to pyridine leading to loss of activity; also the presence of $N_1$–H bond is essential.

From these before mentioned SAR the stability of amlodipine, especially of the dihydropyridine cycle, against a thermooxidative degradation possess both practical and scientific significance. Also a possible interaction between the active substance and different excipients is relevant for the establishment of dosage forms.

The decomposition reaction of pharmaceuticals is important from both fundamental and practical viewpoints. In a recent article [6], dealing with the stability of amlodipine besylate, a duration of 4.5 months was necessary by the classical procedure, and the obtained data, at a single




**Scheme 1**

temperature, do not allow simulations for other temperature.

Knowledge on thermal behavior, especially the kinetics, leads to Life Time Prediction, essential for prediction of storage conditions as well as for technological processing. They also enable to get information on possible drug–excipient interactions.

Therefore, the application of hyphenated techniques like TG/DTG/DTA/EGA/UATR is of great importance in solving pharmaceuticals problems such these mentioned before. The evaluation of drug stability in solid state is usually made by analyzing their decomposition under isothermal or non-isothermal conditions, i.e., at different temperature and conversion degrees.

The aim of this study is to perform an extensive study on the thermal behavior of an active form of amlodipine and its binary mixture with talc (T), magnesium stearate (M), starch (S) and cellulose (C), excipients commonly used in solid dosage forms. A hyphenated technique for simultaneous TG/DTG/DTA/HF/EGA determinations was used.

## Experimental

The active form of amlodipine (A) was amlodipine maleate monohydrate (molecular mass 438.5 a.m.u.). The physical binary mixtures in 1:1 mass ratio were prepared by gently mixing at room temperature in an agate mortar.

The TG/DTG/DTA measurements were performed on a Perkin Elmer Diamond device, in dynamic air, respectively, nitrogen atmosphere (100 mL $min^{-1}$) at heating rates of 7, 10, 12, 15, and 20 °C $min^{-1}$.

For the heat effect determinations the DTA curves (in μV) were changed with the Heat Flow curves (in mW).

The EGA was performed with the gas chamber of a Perkin Elmer Spectrum 100 device. The IR spectra were drawn up at the maximums of the Gramm-Schmidt profile and the identification was carried out with the Sadtler Gas Vapor Library.

The FTIR spectra of different solid samples were obtained on the same spectrometer using the U-ATR technique.

## Results and discussions

Regarding the thermal behavior of the active compound in air, an example is presented in Fig. 1, and the most important data are systematized in Table 1.

There are two observable processes:

- The first one, between 175 and 220 °C, is a water loss from both hydrate and maleic acid. The calculated mass loss of this process is 8.2%, in a very good agreement with the experimental data (see Table 1). Also the data in Fig. 2 support this suggestion.
- The second one, developed on a large range (296–388 °C), is a thermooxidative degradation. According to data in Fig. 3, the oxidative degradation is mainly complete. The presence of small quantities of anisol-like compound accounts for a break of the C–C bond between the two rings (calculated mass loss 54%).

The differences between the $DTG_{max}$ and the $DTA_{max}$ are due to the heat effect. The gradient $(DTG_{max} - DTA_{max})/\Delta H$ is rather the same, 0.11, respectively, −0.09 °C mol $kJ^{-1}$.

In nitrogen the thermal behavior is not very different (see Fig. 4 and Table 1), excepting the heat effect. The first process in nitrogen, like in air, is the same degradation. The relatively large temperature range of the second process makes it necessary to draw up the FTIR spectra of the EG at more than one temperature, i.e., at 342, 382, and 405 °C (see an example in Fig. 5). From this spectra, species like five-ring anhydrides (1734–1739 $cm^{-1}$) and aromatic rings (C–H stretching at 2986–2988 $cm^{-1}$, C=NH at 2340–2350 and below 1560 $cm^{-1}$ ring CH deformations and C=C, respective C=N stretching) account for a deep degradation. Probably the degradation process, in nitrogen, began also with the breaking of the bond between the two rings. The whole process is endotherm. Certainly the exothermic effect in air is due to the thermooxidative degradation of smaller structures (for example maleic anhydride and substituted aromatic rings).

Taking into account that the pure active compound, i.e., amlodipine maleate monohydrate, was destroyed during the first process, a possible interaction with excipients was searched in the range 175–220 °C. According to data in Fig. 6, no such interactions (i.e. changes in the TG/DTG/DTA profiles) were observed.

### Kinetic analysis

An evolution from simple to more complicated methods and the use of isoconversional variant were the two conducting ideas of the kinetic analysis strategy. This will be applied to the first process, i.e., to the dehydration.

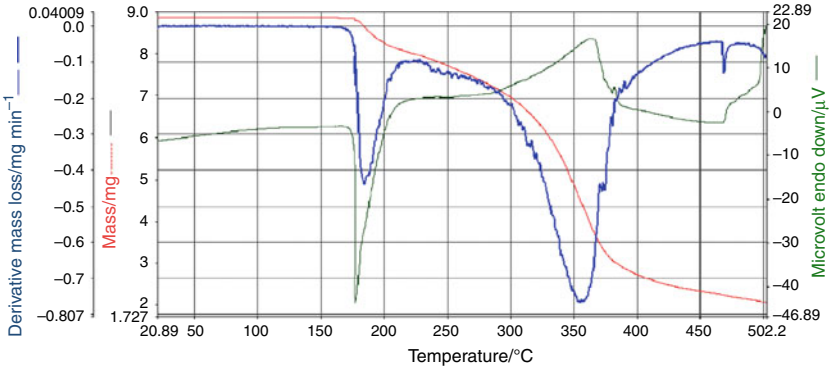



**Fig. 1** TG/DTG/DTA curves obtained for I in air at a heating rate of 10 °C $min^{-1}$

**Table 1** Synthetic data on amlodipine thermal behavior

| Atmosphere | Process | Mass loss/% | DTG max/°C | DTA max/°C | Heat effect $\Delta H$/kJ $mol^{-1}$ |
|---|---|---|---|---|---|
| Air | I | 9.0 | 184.7 | 177.5 | 63.5 |
| | II | 64.0 | 355.7 | 364.6 | −98.7 |
| Nitrogen | I | 9.9 | 179.4 | 185.0 | 73.7 |
| | II | 61.9 | 366.0 | 285.0 | 17.5 |

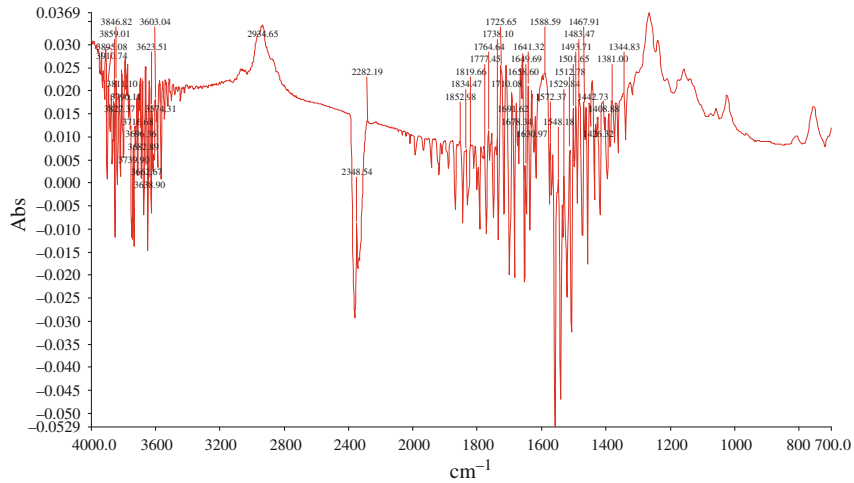



**Fig. 2** Spectrum of EG in air at 180 °C. Water vapors as main compound was detected

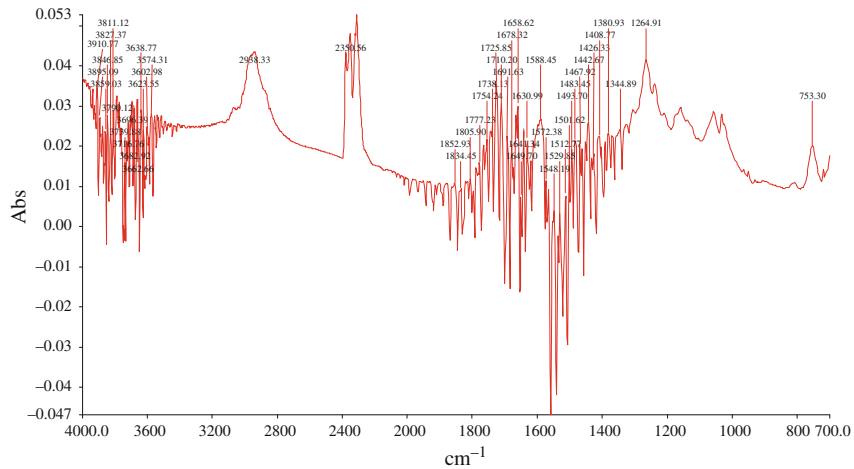



**Fig. 3** EG spectrum at 360 °C. Water vapors and carbon dioxide are the main compounds detected (also small anisole-like derivatives)

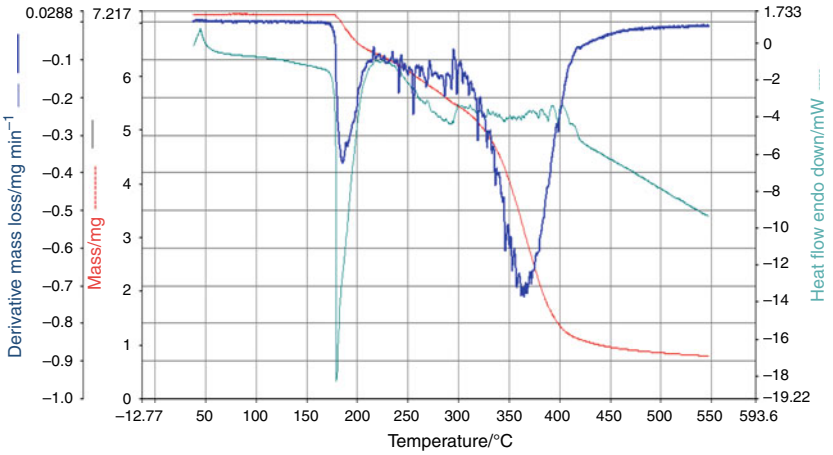



**Fig. 4** TG/DTG/HF curves obtained for I in nitrogen at a heating rate of 10 °C $min^{-1}$

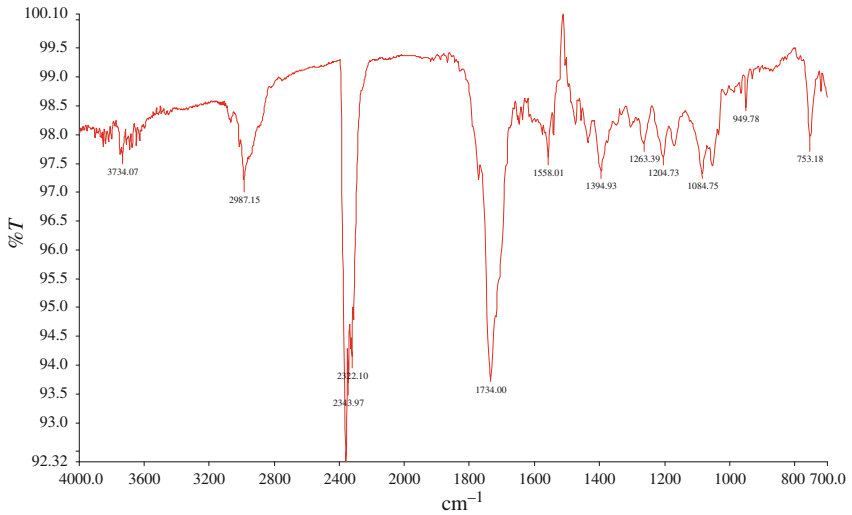



**Fig. 5** EG spectrum in nitrogen at 380 °C

At a constant conversion the differential form of the reaction rate can be written:

$$\ln\left[\beta(\mathrm{d}\alpha/\mathrm{d}T)_{\alpha}= \ln[Af(\alpha)\right] - E/RT \quad (1)$$

where $\alpha$ is the conversion degree, $\beta$ is the heating rate, $T$ is the temperature, $A$ and $E$ are the preexponential factor, respectively, the activation energy in the Arrhenius equation and $f(\alpha)$ is the implicit conversion function.

By a $\ln[\beta(\mathrm{d}\alpha/\mathrm{d}T)]$ vs. $1/T$ plotting the activation energy can be determined. This is the Friedman (FR) [7] method, considered "model free" method because $f(\alpha)$ is not explicitated.

An integral-isoconversional method is that of Flynn and Wall [8], and Ozawa [9] (FWO), based on the equation:

$$\ln\beta = \ln[A/Rg(\alpha)] - 5.331 - 1.052E/RT \quad (2)$$

where $g(\alpha) = \int_0^{\alpha} \mathrm{d}\alpha/f(\alpha)$ is the integral conversion function.

Considering for the same $\alpha_i$ the temperatures $T_i$ corresponding to different heating rates, a plot of the left member of Eq. 2 versus $1/T$ gives the value of the activation energy, also without an explicit form of $g(\alpha)$, i.e., a "model free" method.

The $E$ vs. $\alpha$ variation obtained by these two methods is depicted in Fig. 7. The variations are over the accepted 10% for a single step process. Also the shape of the curves, with a breaking point at $\alpha = 0.6$ accounts for a process with two steps.

In order to elucidate this hypothesis, the modified NPK method [10–15] was used. The TG/DTG experimental data are represented in a 3D coordinate system ($T$, $\alpha$, $\mathrm{d}\alpha/\mathrm{d}T$) and then interpolated in order to obtain a continuous surface of reaction rate. After partitioning a square matrix M is obtained, each element of this matrix being

$$m_{i,j} = k(T_i)g(\alpha_j) \quad (3)$$

Regarding our hypothesis of two simultaneous reactions, it means that each element $m_{i,j}$ and obvious the matrix M are the sum:

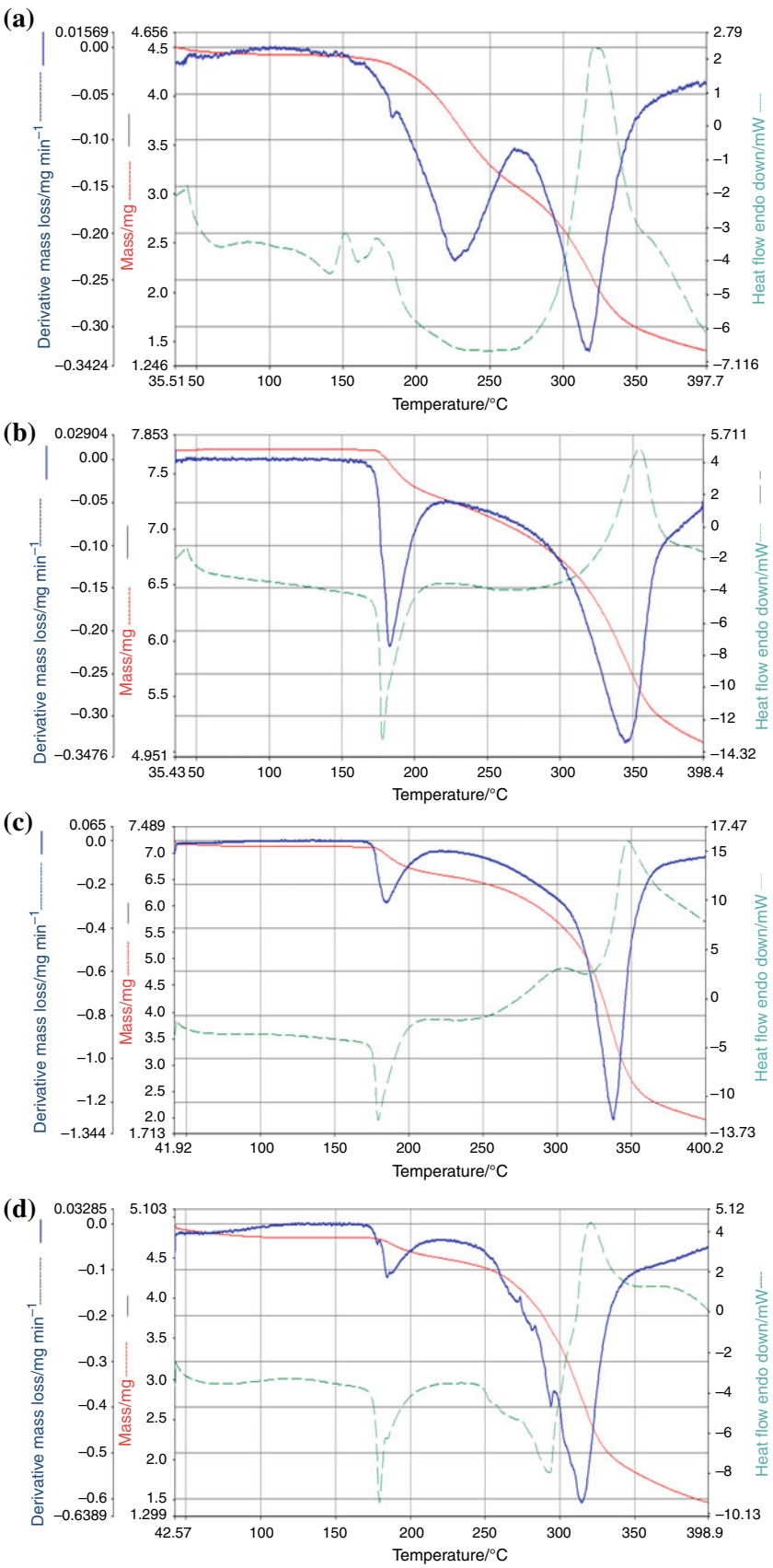



**Fig. 6** TG/DTG/HF curves for binary mixtures with **a** magnesium stearate; **b** talc; **c** cellulose; **d** starch

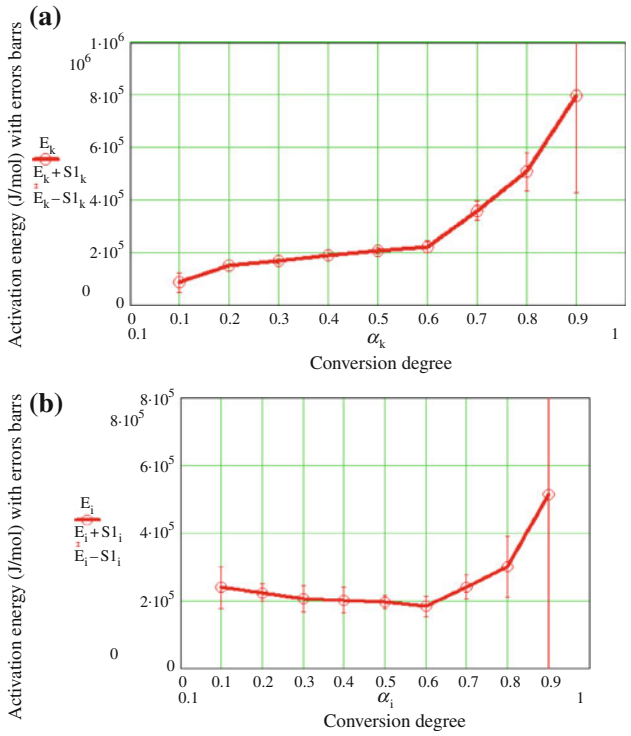



**Fig. 7** $E$ vs. $\alpha$ variation of the first process, obtained by FR (**a**), FWO (**b**) methods

$$M = M_1 + M_2 \tag{4}$$

In this way the observed process is separated into the corresponding steps, the contribution of each step being expressed by the explained variance $\lambda$, so that $\lambda_1 + \lambda_2 = 100\%$.

By applying the Singular Value Decomposition algorithm [16], a discrimination between the temperature, respectively, the conversion dependence of the reaction rate is possible. For the first one an Arrhenius model was searched, whereas for the conversion dependence the Sestak–Berggren equation [17] was suggested:

$$g(\alpha) = \alpha^m(1-\alpha)^n \tag{5}$$

The data obtained according to this method are systematized in Table 2. The $\lambda$-values account for a two-step process.

The EGA-FTIR data indicate a clear dehydration, but taking into account the initial compound, i.e., the amlodipine maleate monohydrate, two dehydration steps were possible.

**Table 2** Kinetic parameters by modified NPK method

| Step | $\lambda$/% | $E$/kJ mol$^{-1}$ | $A$/min$^{-1}$ | $m$ | $n$ |
|---|---|---|---|---|---|
| 1 | 73.2 | 117.5 | $2.5 \times 10^{12}$ | 0 | 0.1 |
| 2 | 26.7 | 210.0 | $5.0 \times 10^{22}$ | 0 | 0.1 |

Amlodipine hydrate → amlodipine + water (6)

Maleic acid → maleic anhydride + water (7)

The contribution of maleic acid to the total mass of the active compound is 26.5%, and that of amlodipine monohydrate is 73.5%. By inspecting Table 2, these values are in a very good agreement with the explained variance (or contribution) of the separate step. Together with the significant differences of the activation energy values, it leads us to consider the step 1 corresponding to Eq. 6, respectively, step 2 to Eq. 7. It is obvious that an intramolecular dehydration needs a higher activation energy in comparison with the loss of crystallization water.

## Conclusions

Amlodipine maleate monohydrate, as active compound of many calcium antagonist drugs, is a thermal sensitive molecular architecture. The first thermally induced process is dehydration.

An evaluated kinetic analysis, together with the EGA data allows establishing two simultaneous processes: a loss of crystallization water, respectively, an intramolecular dehydration of maleic acid.

Fortunately, these dehydration reactions are not influenced by the common excipients used in solid dosage forms.

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