Erythromycin-excipients compatibility studies using the thermal analysis and dynamic thermal infrared spectroscopy coupled with chemometrics

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Abstract

This study aims to characterize erythromycin (ERY) estolate by thermogravimetry analysis and differential scanning calorimetry. For such a purpose, compatibility testing has been conducted using binary mixtures of four excipients (magnesium stearate, sodium starch glycolate, povidone and mannitol). A comparison of simulated and experimental TG curves was made using Pearson's correlation coefficient so as to determine possible incompatibilities by the formation of volatile thermal degradation products. (r^2 of around 0.91 was found for mixtures of magnesium stearate and mannitol, i.e., there might be interactions.) Dynamic thermal FT-IR spectroscopy and multivariate curve resolution (MCR-ALS) were used to identify incompatibilities before the occurrence of mass loss observed due to the chemical decomposition found through the TG. Infrared pure profiles were obtained as a function of the temperature of each component, thus revealing that it is an important and promising tool for monitoring solid-state phase transformations. Thereby, this methodology confirms that ERY shows incompatibilities regarding magnesium stearate and mannitol, and compatibilities concerning povidone and sodium starch glycolate.

Keywords Erythromycin · Compatibility · Thermal analysis · Multivariate curve resolution

Introduction

A solid-state characterization of active pharmaceutical ingredients(API) is fundamental as a stage of preformulation, since data on their characteristics is particularly important to properly conduct a stability study. Characterization tests provide information about their chemical structure and identification, particle size and shape, crystallinity and polymorphism, melting point and thermal stability. Stability is influenced by factors which are directly related to pharmaceutical formulation, such as physicochemical properties of their components, dosage form, manufacturing process and packaging, as well as environmental factors as humidity,

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temperature and luminosity [1]. Thereby, these conditions should be monitored during a stability study in order to avoid changes in their therapeutical efficacy [2].

Another factor that is worth mentioning is a compatibility study on APIs with other formulation components otherwise known as excipients. Although these are pharmacologically inert substances, they can catalyze or react with APIs [3]. Such interactions may be strictly physical, in which the excipient presence may cause changes in drug polymorphism. Chemical interactions lead to degradation and, consequently, decreased API assay and increased amount of degradation products. All these interactions may compromise the quality of pharmaceutical formulation, which directly affects product efficacy and safety. Thus, API-excipient compatibility studies play an important role in the development of new pharmaceutical products [4]. Commonly, such studies are conducted using 1:1 m/m binary mixtures and evaluated using distinct analytical techniques. Among the most widely used techniques are thermal analysis (mainly differential scanning calorimetry (DSC) and thermogravimetry (TG) [5, 6], thermal analysis coupled with chemometrics [7, 8], Fourier transform infrared (FT-IR) spectroscopy [9] and X-ray diffraction [10–12].

Thermal analysis techniques are quite effective during preformulation stages, since they allow a rapid characterization of compound composition by using just small masses. Furthermore, FT-IR spectroscopy has been commonly used for pharmaceutical characterization, once spectral fingerprint provides specific structural information [13].

A few drawbacks of a holistic approach, e.g., while using FT-IR, are larger volume of spectral data and need for refined statistical tools. On the other hand, chemometrics is an important tool that allows analyzing multiple components over a complex dataset. It is also worth mentioning its advantages in thermal and infrared analysis at assessing multivariate data involving compatibilities and incompatibilities between APIs and excipients [14, 15]. A recent application using artificial neural networks (ANN) with a thermogravimetry analysis (TGA) dataset has been a favorable tool for preformulation studies [16]. Interesting enough, multi-curve resolution with alternating least squared (MCR-ALS) is a deconvolution method employed for assessing complex mixtures of components so as to find information about the number of compounds present in mixtures and their pure spectra [17].

Wherefore, the present work aimed to evaluate erythromycin (ERY) compatibility with four different excipients commonly used for solid formulation. ERY is a macrolide antibiotic used to treat skin and respiratory tract infections. Chemically, macrolides are lipophilic molecules consisting of a macrocyclic lactone with 14, 15 or 16 carbons attached to sugar molecules [18]. ERY is produced by biological fermentation of *streptomyces erythreus*, whose major product is erythromycin A [19, 20]. In pharmaceutical formulation, erythromycin estolate is the most commonly used form. It is a salt composed of erythromycin A propionate linked to lauryl sulfate. It is the most commonly marketed antibiotic, since it improves stability and absorption in acidic media [21]. Figure S1 (see supplementary materials) shows the chemical structure of ERY (a) and erythromycin estolate (b) with high molecular mass, i.e., 1056.397 g mol^{-1}.

This is the very first compatibility study about ERY. As APIs, excipients and mixtures have been investigated by thermal analysis (DSC and TG) and FT-IR coupled with a heating plate. In addition, FT-IR spectra were deconvoluted by a MCR-ALS analysis to confirm the results obtained from the thermal analysis.

Experimental

Materials and sample preparation

In this study, ERY was used in the form of erythromycin estolate salt purchased from Sigma-Aldrich (code E8630). For laboratory compatibility studies, binary mixtures of ERY were prepared by using pharmaceutical-grade excipients: magnesium stearate, sodium starch glycolate, povidone and mannitol (99% pure).

The components of binary mixtures were in the ratio of 1:1 (m/m), which were weighed by an analytical microbalance, transferred to microtubes and homogenized using a vortex tube shaker. Each mixture was prepared individually in triplicate, and their total mass was transferred to a crucible and then analyzed so as to avoid content uniformity issues. The samples have not been previously ground.

Methods

Solid characterization of ERY and compatibility studies with excipients

The TG (TG/DTA7300—SII Nano Technology, Japan) curves of erythromycin estolate, excipients and binary mixtures were obtained from the analysis of 3 mg of sample, conditioned in open aluminum crucibles at a heating rate of 10 °C min^{-1} and temperatures ranging from 30 to 600 °C in a synthetic air atmosphere at 50 mL min^{-1}.

The DSC (Calorimetric Cell DSC7020—SII Nano Technology, Japan) analysis was performed using 3 mg of sample placed in hermetically sealed aluminum crucibles in a synthetic air atmosphere at a flow rate of 50 mL min^{-1} and heating rate of 10 °C min^{-1} and temperatures ranging from 30 to 160 °C. This temperature range was selected due to being able to reach the melting point and avoiding sample degradation in the system. Indium standard (purity 99.99%; $T_{onset} = 156.4$ °C; $\Delta H_{fusion} = 28.7$ J g^{-1}) was used for temperature calibration.

The results from a thermal analysis of mixtures have been compared with data on the pure substances in order to observe possible incompatibilities by appearance, disappearance or modification of peaks and enthalpy changes in thermal curves.

The absorption bands of the drug's chemical structure were obtained by FT-IR (Nicolet iS50 FT-IR Infrared Spectrometer—Thermo Scientific, USA, and Pike Gladiator Technologies) in the range of 4000 to 600 cm^{-1}, 64 scans and 4 cm^{-1} resolution at 25 °C. In addition, ERY, excipients (magnesium stearate, sodium starch glycolate, povidone and mannitol) and their binary mixtures were also subjected to simultaneous thermal infrared analysis at temperatures ranging from 30 to 140 °C and heating rate of 2 °C min^{-1}. Their spectra were obtained at every 5 °C using the same FT-IR conditions of drug characterization.

Statistical and chemometric analysis

In order to improve the TGA results, an evaluation was performed using a simulated TG curve for each binary mixture produced by a mean of thermal profiles of pure components obtained from TG experimental curves [22]. A comparison of the similarity between simulated curves and experimental data has been carried out using Pearson correlation coefficient, represented by the letter r, which measures the linear correlation between two variables; its value ranges between $-1 \le r \le 1$. When $r = 0$, it means that there is no linear correlation between variables; thus, the mixture might be incompatible. When it is closer to 1 (negative or positive), there is a higher linear correlation between variables, thus indicating that the mixture may be compatible. The differences among samples evaluated by DSC have been determined through the ANOVA, in which $p < 0.05$ was considered significant according to the Scott–Knott test.

MCR-ALS is a chemometric method based on a raw data matrix ($\mathbf{X}$) of spectra which could be deconvoluted into the concentration profile and pure spectra of constituents, represented by matrices $\mathbf{C}$ and $\mathbf{S}^T$, respectively, and a residual matrix $\mathbf{E}: \mathbf{X} = \mathbf{C} \cdot \mathbf{S}^T + \mathbf{E}$. The method is optimized using initial guesses of spectra or concentration profile [23].

Since FT-IR data are in accordance with Lambert–Beer's law, the mixtures of ERY and excipients should present an individual absorbance average as a function of temperature. If incompatibilities should occur, new compounds will be detected, as well as an increase in the residuals of matrix $\mathbf{E}$. ERY and single excipients spectra measured as a function of temperature were considered standards of the MCR-ALS model.

The MCR-ALS analysis was carried out using MATLAB R2015a (Mathworks, Natick, USA). Full spectra (4000–600 cm^{-1}) and selected regions (720–930 cm^{-1} and 2812–3008 cm^{-1}, region I and II, respectively) were used to perform the MCR-ALS without preprocessing.

Results and discussion

Solid characterization of ERY

A thermal characterization of ERY is shown in Fig. 1a, b. The DSC curve (Fig. 1a) shows an endothermic event at approximately 100 °C, which is equivalent to mass loss in the TG curve (Fig. 1b) in the same temperature conditions, which can be attributed to dehydration and mass loss of 3.4% corresponding to a couple of water molecules (dihydrate). Afterward, another endothermic event is observed in the DSC curve ranging from 123 to 148 °C with T_{onset}
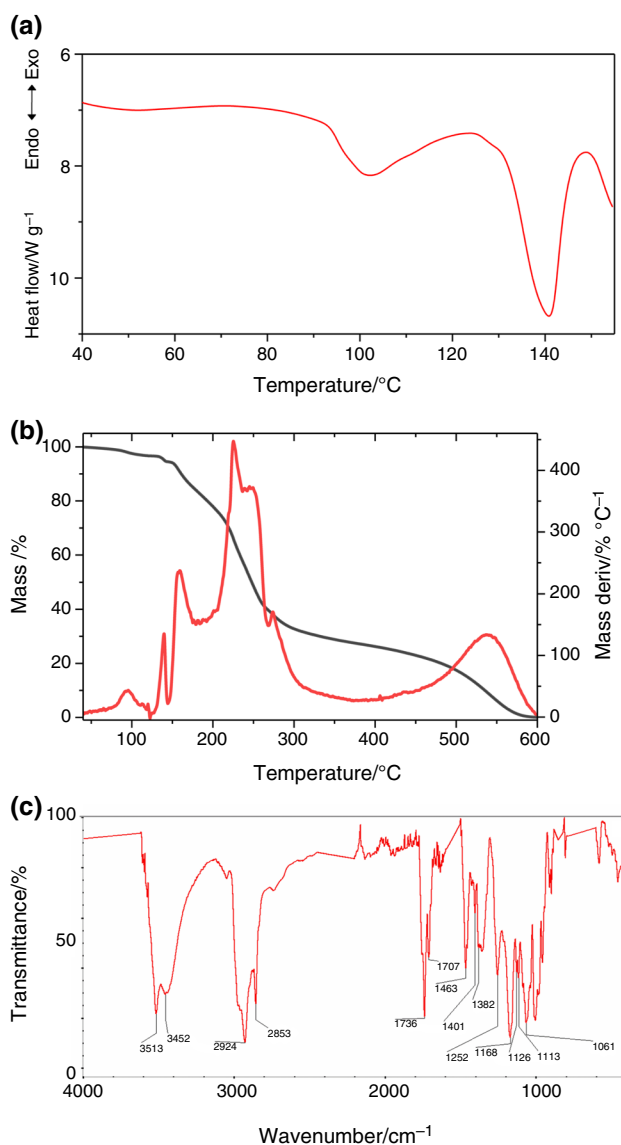

Fig. 1 **a** DSC and **b** TG/DTG curves of ERY and **c** infrared spectrum of erythromycin estolate

(peak start extrapolation temperature) at 130 °C, i.e., enthalpy of 45 Jg^{-1}. This event corresponds to standard melting and is followed by multiple mass losses during TG. As shown by Marian et al. [24] and Fujii et al. [25], the ERY is thermally stable up to 192 °C. In the DTG curve (Fig. 1b, in red), it can be observed the beginning of the largest mass loss event exactly at 193.3 °C. Up to that point, the losses noted on the TG curve at temperatures below 193 °C correspond to 20%, which refers to a theoretical value of 24% due to mass loss of estolate. Moreover, the losses are exactly as those reported in the literature.

Figure 1c shows the infrared spectrum of erythromycin estolate with the characteristic bands of functional groups, which are depicted in table S1. The spectrum was in agreement with data from the literature [26].

Table S1 (see supplementary materials) shows the infrared absorption bands of erythromycin estolate indicating the wave number and respective associated group.

ERY compatibility studies with excipients

Figure 2a compares the ERYDSC curve with the excipient curves. It can be observed that the excipients show no indication of a thermal event in the ERY melting range. Thus, for mixtures, changes in the temperature and enthalpy of the melting peak of ERY, as well as the appearance of thermal events, indicate some interaction between the drug and the excipient [27]. Figure 2b shows the DSC curves of binary
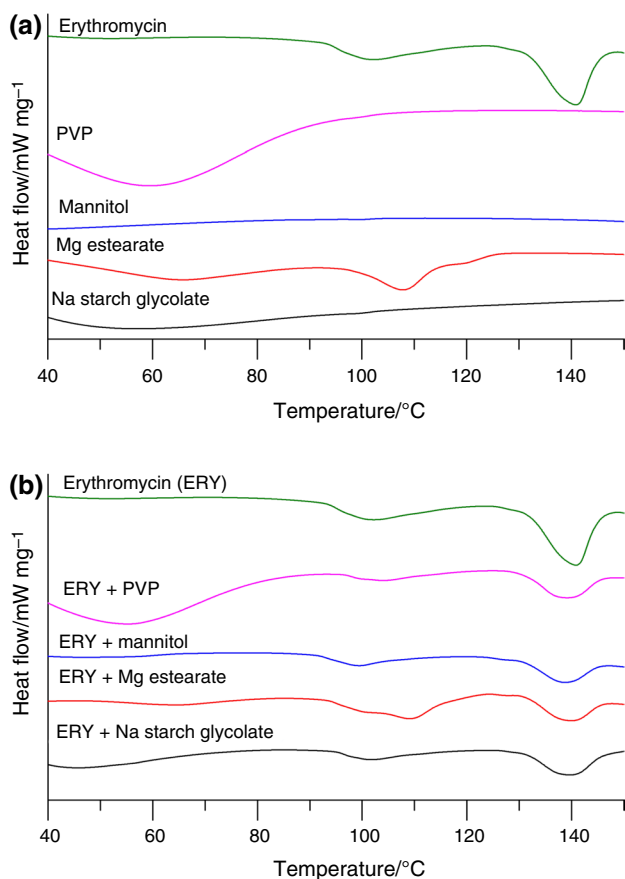

Fig. 2 **a** DSC curves of ERY and excipients and **b** DSC curves of ERY and mixtures

Table 1 DSC parameters of ERY and binary mixtures ($n=3$)

Sample	Mean $\pm$ SD[*]		
	ΔH_{fusion}/J g^{-1}	T_{onset} °C	T_{peak}/°C
Erythromycin (ERY)	45.0 ± 0.8^a	131.2 ± 0.1	140.8 ± 0.2
ERY + PVP	44.0 ± 2.0^a	130.9 ± 0.1	138.8 ± 0.2
ERY + Mannitol	33.8 ± 0.4^b	124.4 ± 0.3	138.8 ± 0.2
ERY + Magnesium stearate	39.1 ± 0.9^c	131.4 ± 0.1	140.0 ± 0.2
ERY + Sodium starch glycolate	48.0 ± 2.0^a	130.7 ± 0.1	139.6 ± 0.2

[*]Standard deviation

[a–c]Statistical class by Scott–Knott test

mixtures. Table 1 shows the melting enthalpy values of ERY in each mixture. The melting enthalpy values of ERY in binary mixtures with PVP and sodium starch glycolate were statistically the same as those of the pure drug according to the Scott–Knott Test. This means that these excipients are compatible with ERY. For mixtures of mannitol and magnesium stearate, these values were lower than expected, thus demonstrating an interaction between the drug and these excipients. Complementary analyzes were performed so as to evaluate the type of interaction (physical or chemical).

Table 1 shows the enthalpy of fusion (ΔH_{fusion}) of binary mixtures 1:1 (m/m) ERY + excipient ($n=3$).

Considering the same principle of DSC compatibility, a study involving binary mixtures of excipients with ERY by the TGA was performed in order to find significant changes in the thermal profile of active pharmaceutical ingredients/excipients when compared to the binary mixture. In this study, simulated or theoretical binary mixtures which were obtained by summing the thermal profiles of ERY and its excipient have been assessed to compare the results. Chemometric methods or Pearson correlation coefficient can be successfully used to evaluate similarities between experimental and theoretical profiles. For the purposes of simplicity, it was opted to use Pearson's. ERY TG curves, excipients, respective binary mixtures and simulated binary mixtures are shown in Fig. 3.

In Fig. 3a, starch glycolate (red curve, Starch) dehydration is observed up to 200 °C, whose mass loss was approximately 8%. From this temperature onward, the excipient starts to undergo a continuous decomposition process up to 450 °C, with loss of 70% of its initial mass. Its TG curve presented a very similar thermal profile to that of ERY alone, i.e., up to 150 °C; afterward, a thermal decomposition of ERY occurs; however, the curve remains with limited mass
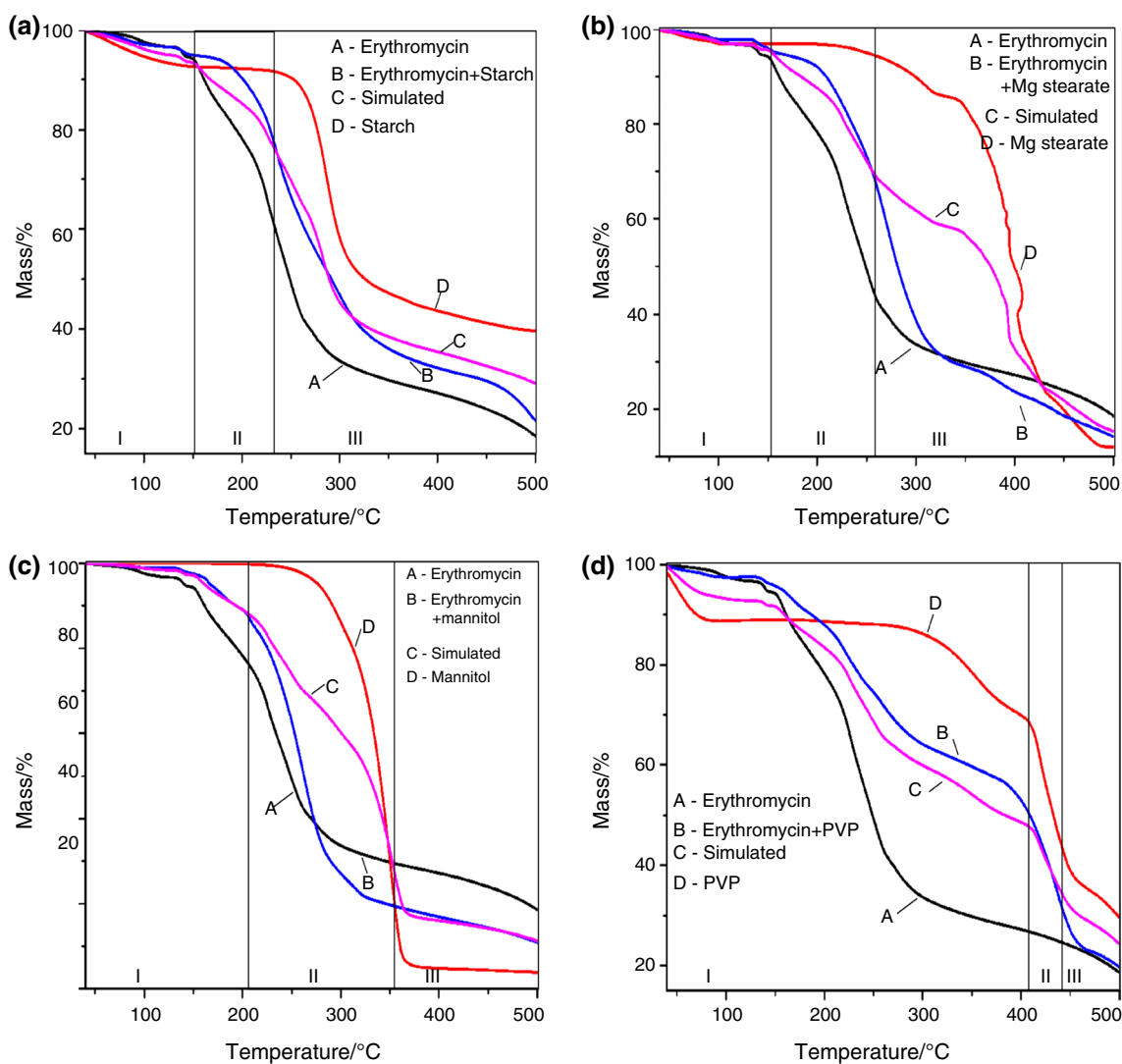
Fig. 3 TG curves of **a** ERY, starch glycolate and mixture, **b** ERY, magnesium stearate and mixture, **c** ERY, mannitol and mixture and **d** ERY, PVP and mixture

loss. By making a direct comparison with the simulated curve (pink curve, theoretical), there are basically three regions (I, II and III). In region I (from 40 to 150 °C), there is marked similarity between the curves. Between 150 and 240 °C, region II, the theoretical curve is below the experimental one, which suggests that there would be greater mass loss in the degradation region of ERY. Thus, it is suggested that starch glycolate had a protective thermal effect on ERY degradation. At 240 °C, region III, the similarity of the two curves occurs once more, since the most important degradation of ERY has already occurred in region II.

In Fig. 3b, the dehydration of magnesium stearate occurs up to 110 °C, with mass loss of approximately

3.3%. The excipient remains stable up to 200 °C, and then, a continuous decomposition process starts with mass loss of 88% up to 500 °C. When comparing the experimental binary mixture with the simulated binary mixture, the thermal profile can be classified into three regions (I, II and III). In region I (from 40 to 150 °C), there is great similarity between the curves. Between 150 and 260 °C, defined as region II, the simulated curve is well below the experimental one, suggesting a protective thermal effect of stearate, as in the previous example involving starch in this region. However, in the third region (ranging between 260 and 500 °C) the opposite occurs, i.e., the simulated curve is well above the experimental one, indicating that

there was further mass loss in the experimental curve due to a chemical interaction and formation of more volatile products.

In Fig. 3c, the thermal stability of mannitol is observed up to 210 °C and then its rapid degradation in a single segment up to 410 °C. By comparing the binary mixture is to the simulated one, the thermal profile can be separated into three regions (I, II and III). In region I, from 40 to 210 °C, there is marked similarity between experimental and simulated curves. Between 210 and 360 °C defined as region II, the simulated curve is above the experimental one, suggesting that mannitol and ERY react at high temperatures and form more volatile products than those that would exist in an isolated system. In region III (above 360 °C), the two curves precisely overlap exactly, thus revealing the absence of interaction.

In Fig. 3d, there is PVP dehydration up to 100 °C with mass loss of approximately 11.5%. The excipient remains stable up to 200 °C, and there is a continuous decomposition process soon afterward with loss of 71% of its initial mass at about 500 °C. When comparing the binary mixture to the simulated one, the thermal profile can be separated into three regions (I, II and III). In the first one, region I, from 40 to 410 °C, the simulated curve is always below the experimental one, revealing greater thermal stability. Between 410 and 440 °C defined as the second region, the curves overlap, thus indicating the absence of interaction. In the third region (between 260 and 500 °C), the opposite occurs, and the simulated curve is above the experimental one, which means that there was further mass loss in the experimental curve due to a chemical interaction and formation of more volatile products.

According to the Pearson correlation coefficient shown in Fig. 4, it is clearly possible to observe the distance from the ideal value ($r^2 = 1.00$), especially concerning the mixture of mannitol with magnesium stearate. These data confirm the interactions found by the DSC (Table 1), in which mannitol showed greater interaction, followed by magnesium stearate. PVP excipients
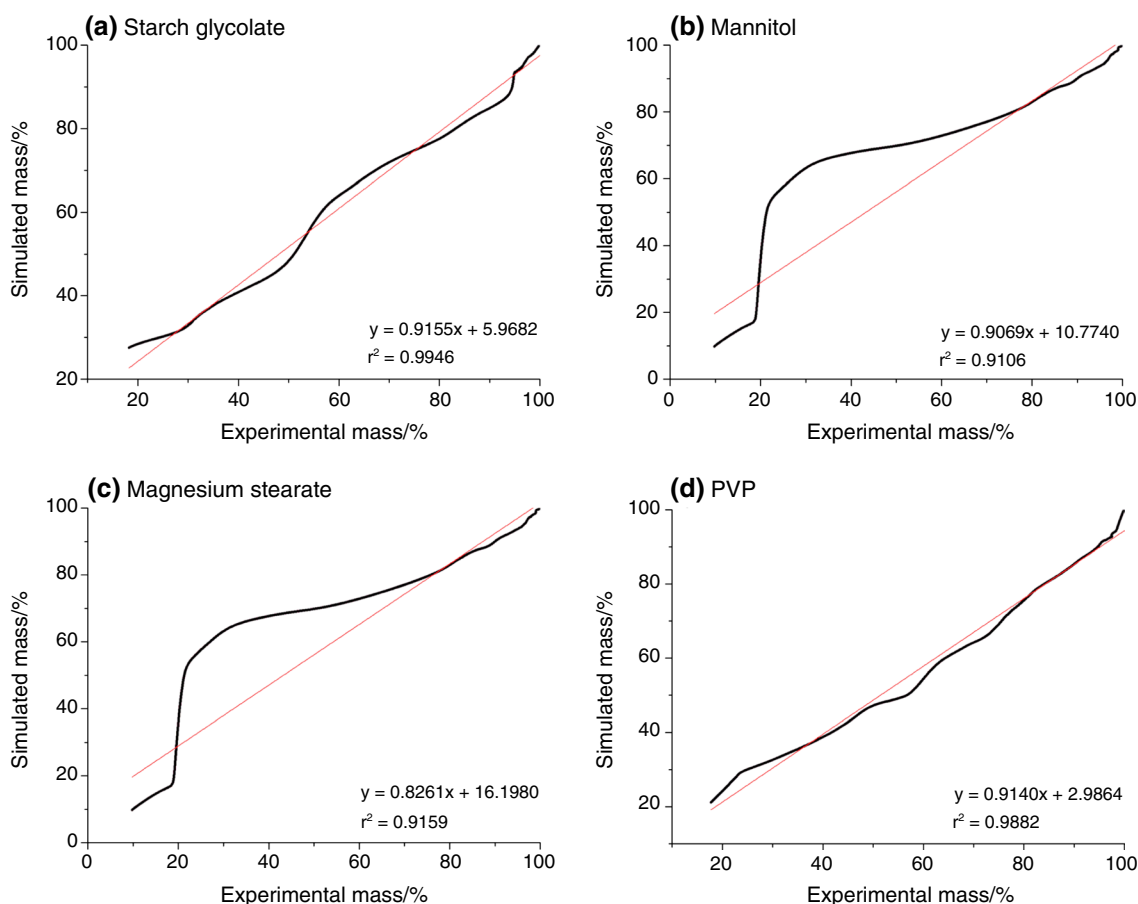

(a) Starch glycolate

$y = 0.9155x + 5.9682$
$r^2 = 0.9946$

(b) Mannitol

$y = 0.9069x + 10.7740$
$r^2 = 0.9106$

(c) Magnesium stearate

$y = 0.8261x + 16.1980$
$r^2 = 0.9159$

(d) PVP

$y = 0.9140x + 2.9864$
$r^2 = 0.9882$

Fig. 4 Correlation graphs of the mixtures, **a** starch glycolate, **b** mannitol, **c** magnesium stearate and **d** PVP
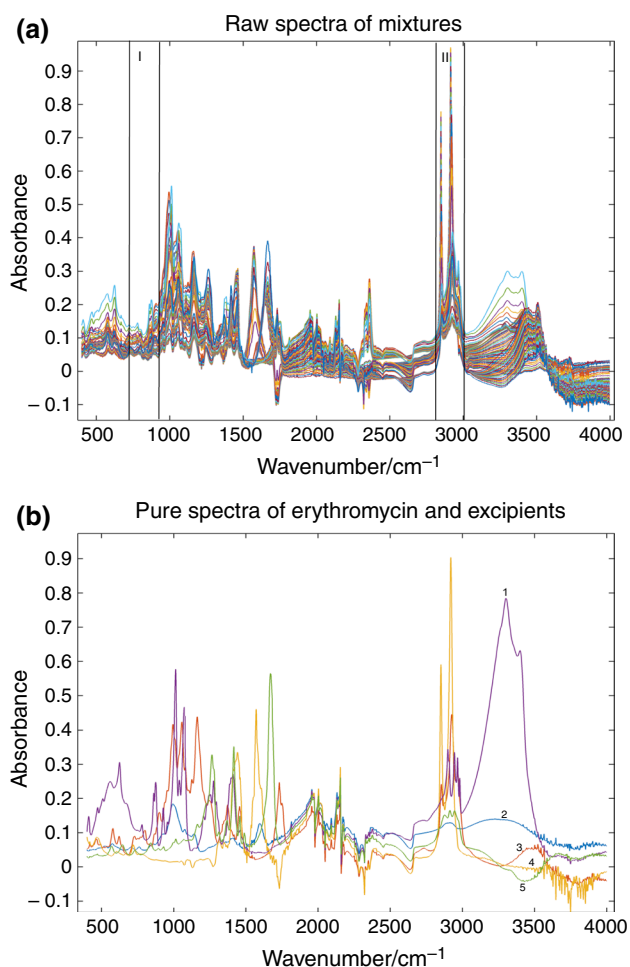
(a)

(b)

Fig. 5 a Experimental set of spectra data containing the mixtures ERY:starch glycolate, ERY:stearate, ERY:mannitol and ERY:povidone with temperatures from 30 to 140 °C. Fingerprint regions: 720 to 930 cm^{-1} (region I) and 2812 to 3008 cm^{-1} (region II). **b** Pure spectra dataset for each compounds at 140 °C, where: 1. mannitol, 2. starch glycolate, 3. ERY, 4. stearate and 5. povidone

and starch glycolate showed no interaction at high temperatures.

Infrared and chemometric analysis

Infrared spectra using heating mode of each single component (ERY and four excipients) and ERY + mixtures were obtained and processed using automatic baseline corrections, which were then divided into separated matrixes for the chemometric analysis. In an attempt to find new spectra species due to the formation of degradation products or other interaction substances, the principal components analysis (PCA) was used because it is one the most widely used techniques to estimate a ranking of species. It revealed the presence of only five different forms (ERY plus four excipients) present in the whole dataset. Figure 5a shows all the spectra data obtained during the infrared analysis with by heating each mixture of ERY with excipients (starch glycolate, stearate, mannitol and povidone).

In order to verify the occurrence of spectra outliers due to incompatibilities of ERY and excipients through continuous heating and monitoring, another chemometric analysis was carried out. MCR was performed using spectra profile of single components (ERY and excipients) as standard. Two continuous intervals of spectra variables (interval I: 720–930 cm^{-1}; interval II: 2812–3008 cm^{-1}) were selected, totaling 774 spectra variables. The choice of these regions is explained by the fact that it represents a stable temperature of the fingerprint region of ERY. Figure 5b shows the pure spectra obtained for each compound at 140 °C, used for deconvolution of the dataset.

By considering the application of MCR models for the deconvolution of spectra, some points must be taken into account, e.g., the nonnegativity of spectra with respect to concentrations and intensities, in order to assign meaning to measurements.

The spectra profiles produced for MCR-ALS were compared to pure spectra of the five substances. To avoid a strictly visual comparison, numerical Pearson's correlation coefficients were also calculated, resulting in 0.94, 0.98, 0.85 and 0.90 values for ERY:starch glycolate, ERY:povidone, ERY:stearate and ERY:mannitol, respectively. The developed MCR-ALS achieved over 96.20% of the explained variance. It is possible to verify higher Pearson correlation coefficients for the two first mixtures and lower coefficients for the last ones, which is in accordance with the experimental results obtained by the TGA (see Fig. 3) and Pearson correlation (see Fig. 4). This reveals that, at higher temperatures, there are interactions between ERY and mannitol and magnesium stearate.

In addition to the correlation results, the MCR-ALS concentration profile provided interesting information about the changes in ERY concentration through temperature, as shown in Fig. 6. It is possible to verify that the concentration profiles of mixtures. Fig. 6a, b present contrary behavior to temperature increase, indicating that there is no interaction between ERY and starch glycolate and povidone. Figure 6c, d indicate a possible interaction between ERY and stearate and mannitol, even before the temperatures indicated by the TGA.

The infrared measurements did not exceed 140 °C, because ERY melting occurs before this temperature and it was used to verify the possibility of interaction of ERY with excipients.

Fig. 6 Deconvoluted profile of concentration, **a** ERY:starch glycolate, **b** ERY:povidone, **c** ERY:stearate and **d** ERY:mannitol
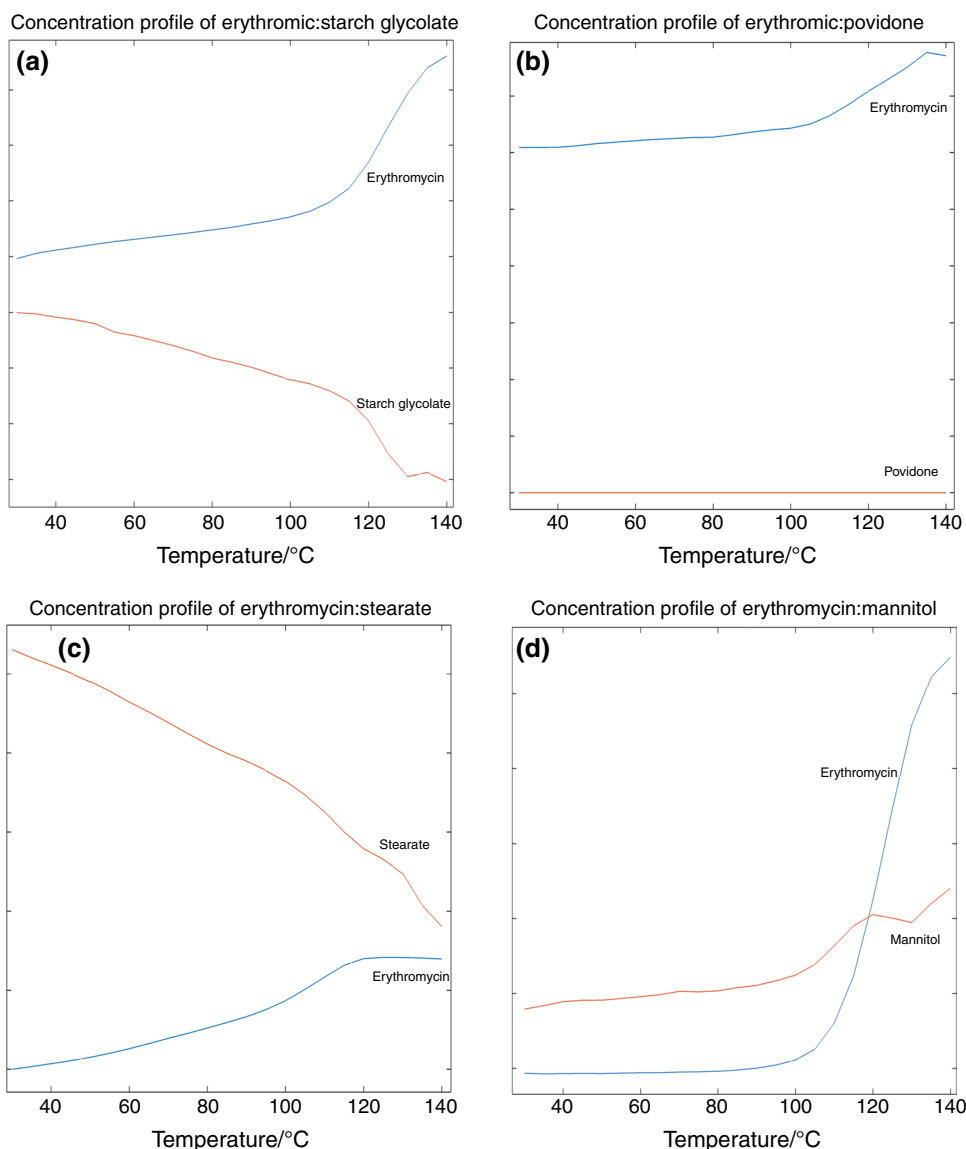
Conclusions

A compatibility study of ERY and its excipients was well conducted by a thermal analysis, and it reveals possible interactions of API with mannitol and magnesium stearate. This interpretation was facilitated while using TG curves (simulated and experimental) with a comparison of Pearson correlation coefficients.

FT-IR with a heating plate was also performed in order to seek spectral changes due to formation of new compounds generated by chemical incompatibilities. However, the PCA was not able to verify the incompatibilities that occur from temperature increase. On the other hand, the infrared analysis coupled with MCR-ALS allowed verifying the presence of five principal components (ERY and four excipients) of mixtures. It was not also able to identify the presence of

new degradation products. Nevertheless, the deconvolution of spectra allows recovering the pure spectrum and concentration profile as a function of temperature. Thus, the methodology enabled a verification of the variation of ERY concentration and its incompatibilities. Mannitol and magnesium stearate once more had a lower Pearson correlation coefficient. Thereby, it is possible to conclude that these excipients are not recommended for pharmaceutical formulation with ERY. Such a strategy provides qualitative (exact temperature at which incompatibility occurs) and quantitative (concentration profile) information about such interactions.

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