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Non-isothermal thermogravimetry as an accelerated tool for the shelf-life prediction of paracetamol formulations

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Abstract

In this work, non-isothermal thermogravimetric studies have been carried out on several paracetamol formulations with the aim to predict their shelf-lives under variable storage conditions. Specifically, paracetamol tablets of different brands have been investigated allowing to estimate their pharmaceutical quality by considering the specific drug stability. The proposed protocol is based on the kinetic study of thermogravimetric data by the combination of isoconversional procedures (Friedman and Kissinger-Akahira-Sunose (KAS) methods) and "Master plot" analysis. Accordingly, the kinetics of the paracetamol degradation is totally explored in terms of activation energy, pre-exponential factor and reaction mechanism of the drug decomposition. The obtained insights drive to simulate the decay time functions of paracetamol amount for the several pharmaceutical formulations. Interestingly, these simulations can be easily adapted to variable isothermal conditions providing the shelf-lives of the paracetamol tablets at different temperatures. The kinetic characteristics of the paracetamol degradation as well as the corresponding shelf-life values evidenced that the expiration date of the pharmaceutical products are significantly affected by the composition of the excipients. In conclusion, this work demonstrates that non-isothermal thermogravimetric analysis can be used as efficient and sensitive tool for the prediction of the shelf-lives of paracetamol formulations.

Keywords: Shelf-life, thermogravimetry; isoconversional methods, paracetamol.

1. Introduction

Pharmaceutical products are obtained as mixtures of active molecules and several excipients, which control the workability, the stability and the release properties of the formulations [1–3]. The actual shelf life of the active molecules represents a key parameter of the pharmaceutical quality of drug products [4,5]. Therefore, the accurate estimation of the drug shelf-life is challenging in the pharmaceutical technologies [6,7]. It should be noted that the shelf-life corresponds to the time after which the drug loses its properties and it cannot perform its function efficiently because of decomposition or structural changes, which depend on several factors, including dehydration, oxidation and microbial spoilage [8]. The shelf-life determination of the drugs can be conducted by accelerated degradation conditions avoiding to study the entire real-time decomposition [9,10]. As reported in a recent review [11], acceleration studies on the chemical degradation of several materials can be performed by thermal analysis and calorimetry techniques. In this regard, thermogravimetry represents a powerful method to estimate the oxidative stability of vegetable oils [12] and to predict the life time of polymeric materials used in technological applications [13–15]. Within pharmaceutics, thermogravimetric analysis was used to determine the shelf-life of vitamin C under both inert and oxidative conditions [16]. Moreover, thermogravimetry was employed to investigate the thermal stability of drug molecules encapsulated into polymeric nanoparticles [17,18], cyclodextrins [19,20] and inorganic mesoporous materials [21–28]. The influence of the excipients in the shelf-life of the active molecules plays a crucial role in the development of pharmaceutical formulations. Any unintended variations of the inherent nature and physicochemical characteristics of the excipients could lead to potential instabilities in the formulations [29,30]. In addition, both physical and chemical interactions between drugs and excipients can affect the stability [31] as well as the porosity of the pharmaceutical products [32]. Literature reports that the excipients can significantly alter the properties and functionalities of paracetamol. As examples, the presence of povidone could generate severe allergy [33], while excipients containing trehalose and melibiose affect the crystallization of the drug molecules [34]. The degradation of paracetamol can be influenced

by several processes, such as peroxymonosulfate activation reactions [35] and catalytic actions of iron oxide nanostructures [36] or black TiO_2 as photocatalysts [37]. The thermal stability of paracetamol depends on the polymorphs of the drug molecules [38] as well as on the presence of impurities in the pharmaceutical products [39].

In this study, the thermal degradation of various paracetamol tablets from different brands was investigated by thermogravimetry. In particular, thermogravimetric experiments were conducted at variable heating rate to explore the kinetics of paracetamol degradation through non isothemal isoconversional methods. As reported in literature, different isoconversional procedures are suitable to study the kinetic aspects of the polymer decomposition in nanocomposite materials [40–43], polymer blends [44,45], ionic liquids [46,47] and bioactive molecules [16,48,49]. Here, Kissinger-Akahira-Sunose (KAS) and Friedamann methods were employed as non-isothermal and model-free procedures providing the activation energy of the degradation processes without any assumption on the reaction mechanism [50]. Consequently, they are widely used in kinetic studies of thermal decomposition of macromolecules [51–54]. Furthermore, the Master plot analysis was employed to determine the mechanism of the paracetamol degradation allowing to estimate the shelf-life of the pharmaceutical products.

2. Materials and methods

2.1 Materials

Several paracetamol tablets from different pharmaceutical companies were analyzed. Prior to their analysis by thermogravimetry, the tablets were treated in an agate mortar to obtain homogeneous powder samples. The properties of the paracetamol formulations are listed in Table 1.

Table 1. List of paracetamol formulations

Sample ID	Country	Excipients	Excipients (wt%)
US	United States of America	Carnauba wax Polyvinylpyrrolidone PEG Sodium CrosCarmellose Stearic Acid Hypromellose Jelly Sodium Starch Glycolate	11.85
IT 1	Italy	Potato starch Magnesium stearate	6.72
BR	Brazil	Polyvinylpyrrolidone Polyvinylpyrrolidone Sodium Starch Glycolate Starch Stearic Acid Polyvinyl Alcohol Macrogol Talc Titanium Dioxide	12.29
RO	Romania	Corn Starch Povidone K30 Colloidal silica Anhydrous Magnesium Stearate Talc	16.25
RU	Russian Federation	Potato starch Polyvinylpyrrolidone (low molecular weight) Stearic Acid Magnesium stearate	9.17
IT 2	Italy	Microcrystalline Cellulose Pregelatinized Starch Stearic Acid Sodium CrosCarmellose Polyvinylpyrrolidone	4.9

2.2 Methods

Thermogravimetric experiments were performed by using a Q5000 IR apparatus (TA Instruments) under inert atmosphere. To this purpose, the measurements were conducted under nitrogen flows of

25 and 10 cm^3 min^{-1} for the sample and the balance, respectively. The weight of each sample was ca. 5 mg. The temperature calibration was carried out using the Curie temperatures of several standards (cobalt, nickel and their alloys) as reported elsewhere [51,54]. To determine the kinetics of degradation, the tests were carried out by heating the sample from room temperature to 400 °C at variable heating rates (β). In detail, heating rates of 2, 5, 10, 15 and 20 °C min^{-1} were selected. The preliminary analysis of the thermogravimetric curves provided the following parameters: 1) residual mass at 400 °C (RM_{400}); 2) onset temperature (T_{onset}); 3) decomposition temperature (T_{max}) taken at the maximum of the first order derivative curves of mass loss to temperature (DTG curves). Kinetic analysis of the thermogravimetric data was conducted by using KAS and Friedman methods in order to determine the activation energies (E_α) of the paracetamol degradation at variable conversion degree (α), which was calculated as $(m_0 - m)/(m_0 - m_\infty)$ being m_0 the initial mass, m the mass at time t e m_∞ the residual mass. Both isoconversional procedures were employed within the α range between 0.1 and 0.9. Finally, the thermogravimetric results were investigated through the Master plot analysis driving to the determination of the shelf-life of the paracetamol formulations.

3. Results and Discussion

3.1 Thermal degradation under nitrogen atmosphere.

Thermogravimetric analysis is a powerful method to investigate the degradation of materials under controlled atmospheres upon a given heating ramp. The thermal stability of composites [55], polymers [56] and pharmaceuticals formulations [57] can be evidenced by comparing the thermogravimetric curves in terms of T_{onset} and residual mass values. This strategy is typically successful and it endows comparisons and assessments when systematic changes in internal/external parameters are targeted. As an example, Figure 1 shows the thermogravimetric curves at variable heating rate for the BR sample. Supporting Information shows the thermogravimetric curves collected for the other paracetamol tablets as well as the DTG curves at variable heating rates for the BR formulation.

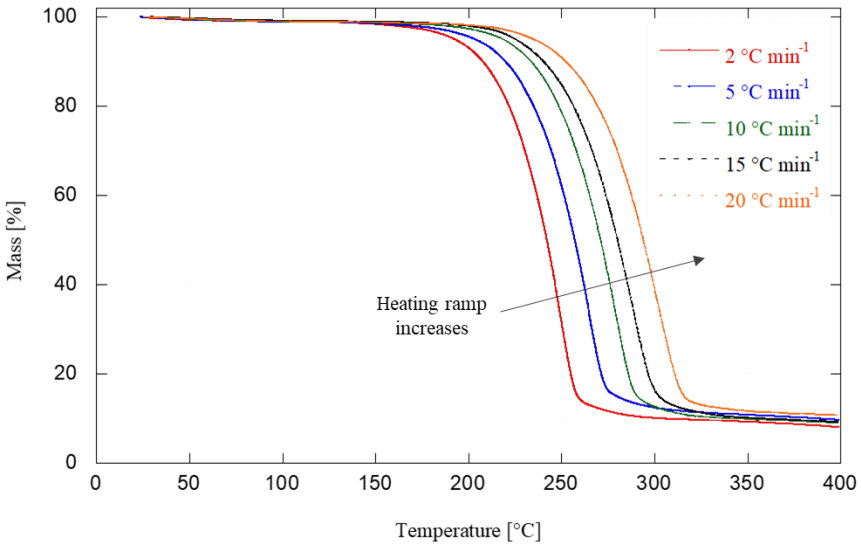

Fig. 1. Thermogravimetric curves of BR sample obtained at variable heating rates.

As a general result, the thermogarvimetric curves evidenced a mass loss within the temperature range between 150 and 320 °C due to the paracetamol degradation. It should be noted that the increase of the heating rate shifts the paracetamol decomposition to larger temperatures. For a quantitative comparison of the several paracetamol formulations, we calculated the values of T_{max}, T_{onset} and residual mass at 400 °C for each sample by considering the heating rate of 10°C min^{-1} (Table 2).

Table 2. Therrmogravimetric parameters of the paracetamol formulations obtained at β of 10 °C min^{-1}.

Sample ID	T_{max} [°C]	T_{onset} [°C]	RM_{400} [%]
US	271 ± 3	232 ± 2	3.28 ± 0.03
IT 1	281 ± 3	246 ± 2	3.79 ± 0.03
BR	279 ± 3	241 ± 2	9.10 ± 0.09
RO	274 ± 3	235 ± 2	7.87 ± 0.08
RU	262 ± 3	228 ± 2	8.12 ± 0.08
IT 2	264 ± 3	231 ± 2	6.03 ± 0.06

We observed that the paracetamol tablets possess different T_{onset} and T_{max} values within intervals of ca. 20 °C. These results highlight that the amount and the composition of the excipients can affect

the thermal degradation process of paracetamol. The variations of the residual masses at 400 °C (Table 2) reflects the different chemical composition of the excipients. In particular, we estimated larger RM_{400} values for the tablets containing inorganic excipients, which decompose at temperatures higher than 400 °C. Similar observations were detected for levothyroxine formulations [58]. The comparison of the thermogravimetric results obtained from a single heating ramp represents a preliminary analysis, which cannot drive to quantitative conclusions on the shelf-life differences among the paracetamol formulations. To this purpose, a further and deeper analysis of the thermogravimetric data is necessary. In this regard, we determined the kinetic parameters of the paracetamol degradation in the different tablets by using non isothermal isoconversional methods.

3.2 Isoconversional methods and kinetic parameters.

Thermogravimetric curves at variable heating rates (β) were analyzed by isoconversional procedures (KAS and Friedman methods) with the aim to investigate the kinetics of the paracetamol degradation in the different pharmaceutical formulations.

Friedman differential method [59] is based on the following equation

$$ln\left(\beta \frac{d\alpha}{dT}\right)_{\alpha,i} = \ln[f(\alpha)A_\alpha] - \frac{E_\alpha}{RT_{\alpha,i}} \quad (1)$$

where $d\alpha/dT$ is the first derivative of α respect to temperature, $f(\alpha)$ is a function of the extent of conversion, A is the pre-exponential factor, R is the gas constant and T is the absolute temperature. The subscript i refers to the various heating rates. On this basis, $T_{\alpha,i}$ corresponds to the temperature with a certain extent of conversion under a selected heating rate. E_a values at different α were obtained from the slope of the ln (β dα/dT) vs 1/T plots.

On the other hand, KAS approach [60] is an integral isoconversional procedure, which can be expressed as

$$ln\left(\frac{\beta_i}{T_{\alpha,i}^2}\right) = Cost - \frac{E_\alpha}{RT_\alpha} \quad (2)$$

According to equation 2, E_α values at different α can be calculated from the slope of $\ln(\beta/T^2)$ vs $1/T$ plots. The E_α vs α trends obtained by both Friedman and KAS method are presented in Figure 2.

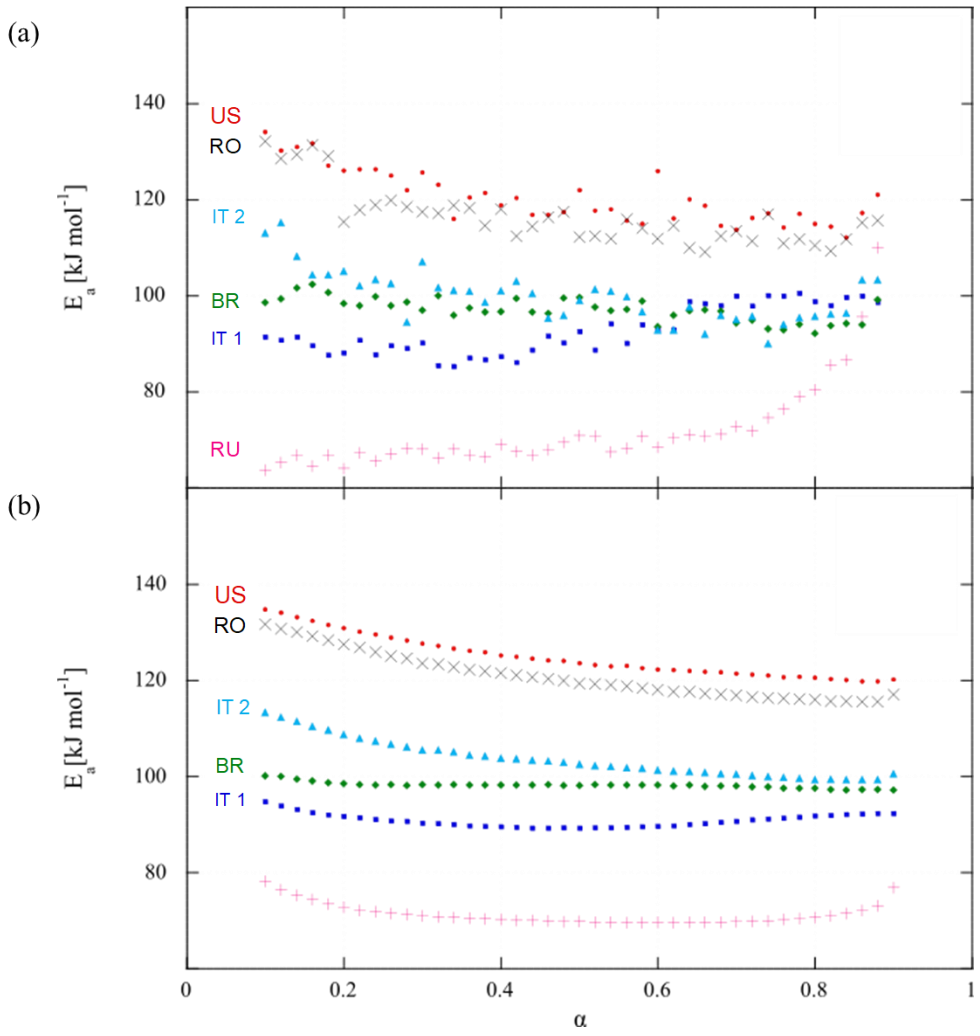

Fig. 2. Activation energy as a function of the conversion degree obtained from Friedman (a) and KAS (b) methods.

Based on the ICTAC recommendations [61], the activation energy can be considered constant within the whole conversion degree range for all paracetamol formulations being that the difference between the maximum and minimum values of E_α is less than 20-30% of the average E_α value. On this basis, we can state that the paracetamol degradation is a single stage process. The averaged activation energies obtained from both procedures are presented in Table 3.

Table 3. Average activation energies obtained from Friedman and KAS methods.

Sample ID	Friedman [kJ mol^{-1}]	KAS [kJ mol^{-1}]
US	120 ± 12	124 ± 8
IT 1	93 ± 16	90 ± 16
BR	97 ± 22	98 ± 22
RO	117 ± 7	121 ± 7
RU	71 ± 10	72 ± 12
IT 2	100 ± 6	105 ± 6

We observed that KAS and Friedman methods provided similar average activation energies highlighting the robustness of both integral and differential isoconversional procedures in the kinetic analysis of paracetamol degradation. It should be noted that the activation energy reflects the thermal stability of the drug molecules. The estimation of the activation energy values represents the first step in the kinetic analysis of the thermogravimetric data. Notwithstanding, the determination of the full kinetics path is necessary for any shelf-life prediction. With this in mind the Master plot method developed by J. Malek [62] was used to determine the reaction mechanism. To this purpose, the function z(α) was calculated by using the following equation

$$z(\alpha) = f(\alpha)g(\alpha) = \left(\frac{d\alpha}{dt}\right)_{\alpha} T_{\alpha}^{2} \quad (3)$$

The experimental values of z(α) are plotted as a function of α and compared to the theoretical master plots reported in literature [61]. As an example, the experimental z(α) vs α plot for the IT2 tablet is provided in Figure 3. We observed that a maximum is reached at α equals to ca. 0.75.

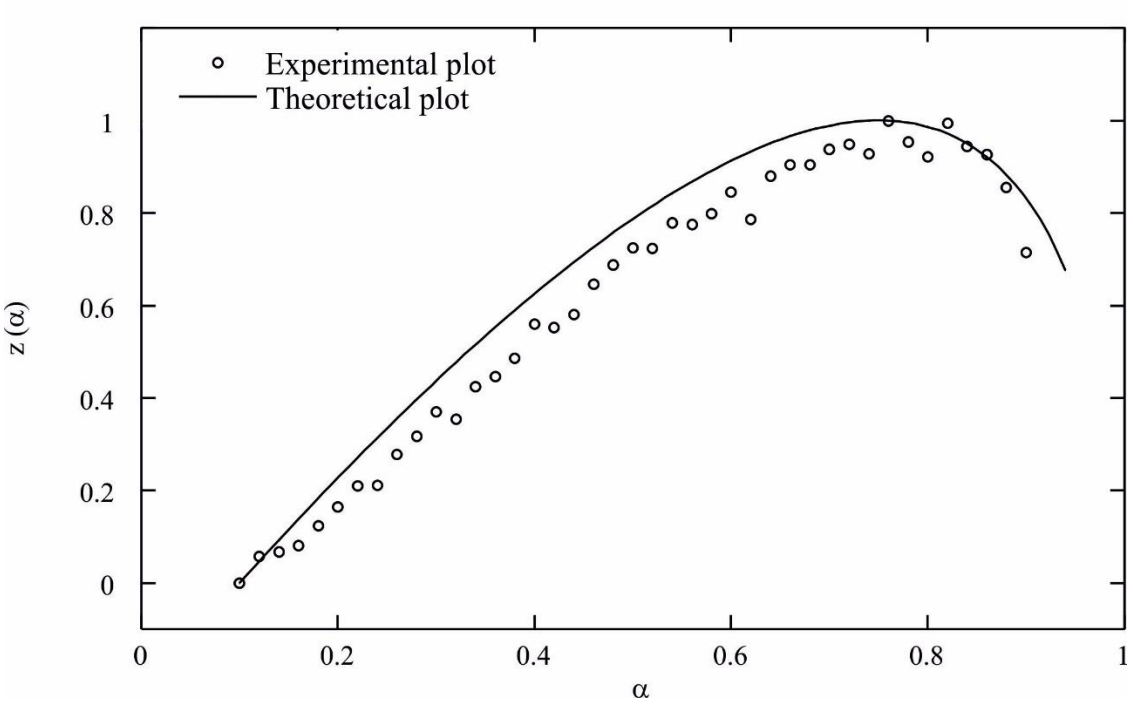

Fig. 3. "Master plot" analysis for the IT2 sample presented as z(α) vs α plots (experimental and theoretical). The theoretical z(α) vs α plot is based on the R2 mechanism. The coefficient of determination (R^2) between experimental and theoretical curves is 0.985.

Similar z(α) vs α trends (see Supporting Information) were detected for the other paracetamol formulations. According to literature [61,63], the obtained z(α) vs α plots can be ascribed to the R2 mechanism (contracted cylindrical geometry) for the paracetamol degradation. As shown in Figure 3, the experimental z(α) vs α plot for the IT2 sample is properly described by the theoretical z(α) vs α function based on the R2 model. We estimated the goodness of the fit between experimental and theoretical curves by the determination of the coefficient of the determination (R^2). We observed that the R^2 value is 0.985 for the IT2 sample. Supporting Information shows that R2 model is proper for the description of the z(α) vs α trends for all the paracetamol formulations. The R^2 values range between 0.958 and 0.982 highlighting that the data analysis by R2 model is accurate. As a general result, we estimated lower R^2 values by fitting z(α) vs α plots with different theoretical models. Accordingly, we can state that R2 is the best kinetic model for the description of the paracetamol degradation. It should be noted that R2 model assumes that the degradation starts at the surface. The

degradation rate is affected by the resulting interface reaction progress from the surface toward the centre [64]. Based on R2 model, f(α) can be expressed as

$$f(\alpha) = 2(1-\alpha)^{\frac{1}{2}} \quad (4)$$

Based on the activation energies (Table 3) and taking into account that all the tablets present the same degradation mechanism, US and RU samples can be considered the most stable formulations, while RU sample presents the slightest resistance to the thermal degradation of paracetamol.

According to the R2 mechanism, the pre-exponential factor (A) of the paracetamol decomposition can be determined by fitting the experimental data with the following equation

$$y(\alpha) = \left(\frac{d\alpha}{dt}\right)_{\alpha} exp\left(\frac{E_0}{RT_{\alpha}}\right) = A\ 2(1-\alpha)^{\frac{1}{2}} \quad (5)$$

where E_0 represents the average activation energies (Table 3) determined from the isoconversional procedures. As evidenced in Table 4, the pre-exponential factor of the paracetamol degradation is significantly dependent on the specific pharmaceutical formulation. The latter can be related to different amounts and composition of the excipients containing in the paracetamol tablets.

Table 4. Pre-exponential factor values obtained from Friedman and KAS methods.

Sample ID	A [s^{-1}] (Friedman method)	A [s^{-1}] (KAS method)
US	$(151 \pm 5) \cdot 10^8$	$(280 \pm 9) \cdot 10^8$
IT 1	$(46 \pm 5) \cdot 10^5$	$(28 \pm 3) \cdot 10^5$
BR	$(110 \pm 3) \cdot 10^5$	$(130 \pm 3.3) \cdot 10^5$
RO	$(35.0 \pm 1.1) \cdot 10^8$	$(94 \pm 3) \cdot 10^8$
RU	$(15 \pm 6) \cdot 10^3$	$(16 \pm 7) \cdot 10^3$
IT 2	$(110 \pm 4) \cdot 10^6$	$(31.0 \pm 1.0) \cdot 10^7$

The determination of the pre-exponential factors, activation energies and the reaction mechanism allowed us to completely describe the kinetics of the paracetamol degradation. These findings can be exploited to predict the shelf-life of paracetamol tablets under variable storage conditions.

3.3 Shelf-life prediction

Based on the calculated kinetic parameters, we can estimate the time (t_α) required to achieve a certain degree of degradation under isothermal conditions. Specifically, t_α can be can be calculated by the following equation:

$$t_\alpha = \frac{g(\alpha)}{Aexp(-\frac{E}{RT_0})} \quad (6)$$

where T_0 is the fixed temperature, while g(α) is a function dependent on the specific reaction mechanism. According to the R2 mechanism, g(α) can be expressed as [61]

$$g(\alpha) = 1 - (1-\alpha)^{\frac{1}{2}} \quad (7)$$

Equations 6 and 7 allowed us to determine the simulated t_α vs α curves for the paracetamol formulations. It should be noted that the kinetic parameters calculated from KAS method were used. As examples, Figure 4 shows the t_α vs α functions for BR sample at three different temperatures (4, 25 and 40 °C).

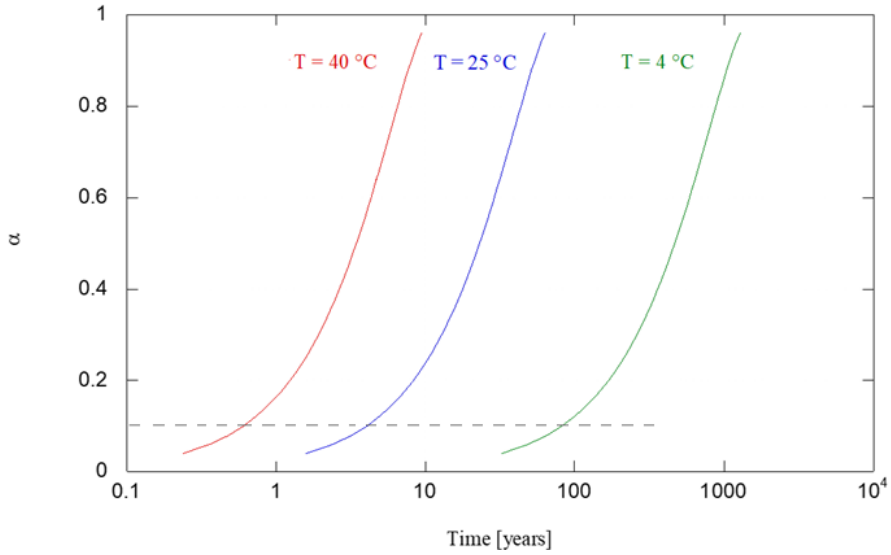

Fig. 4. Simulated t_α vs α curves for BR sample at 4, 25 and 40 °C. The functions were determined according to equations 6 and 7. Dotted line represents $\alpha = 0.1$.

As reported in literature [65,66], the shelf-life of pharmaceutical products can be defined as the time required for the drug to degrade more than 10% of its original amount. Accordingly, we estimated the shelf-life of paracetamol formulations by determining the t_α values at $\alpha = 0.1$. As shown in Figure 4, the shelf-life at variable temperatures can be easily detected from the simulated t_α vs α curves. Figure 5 illustrates the shelf-lives of the paracetamol tablets under variable temperatures (4, 25 and 40 °C), which mime different storage conditions of the pharmaceutical products. The corresponding t_α values are presented in Supporting Information. Note that the reported values refer to the KAS method.

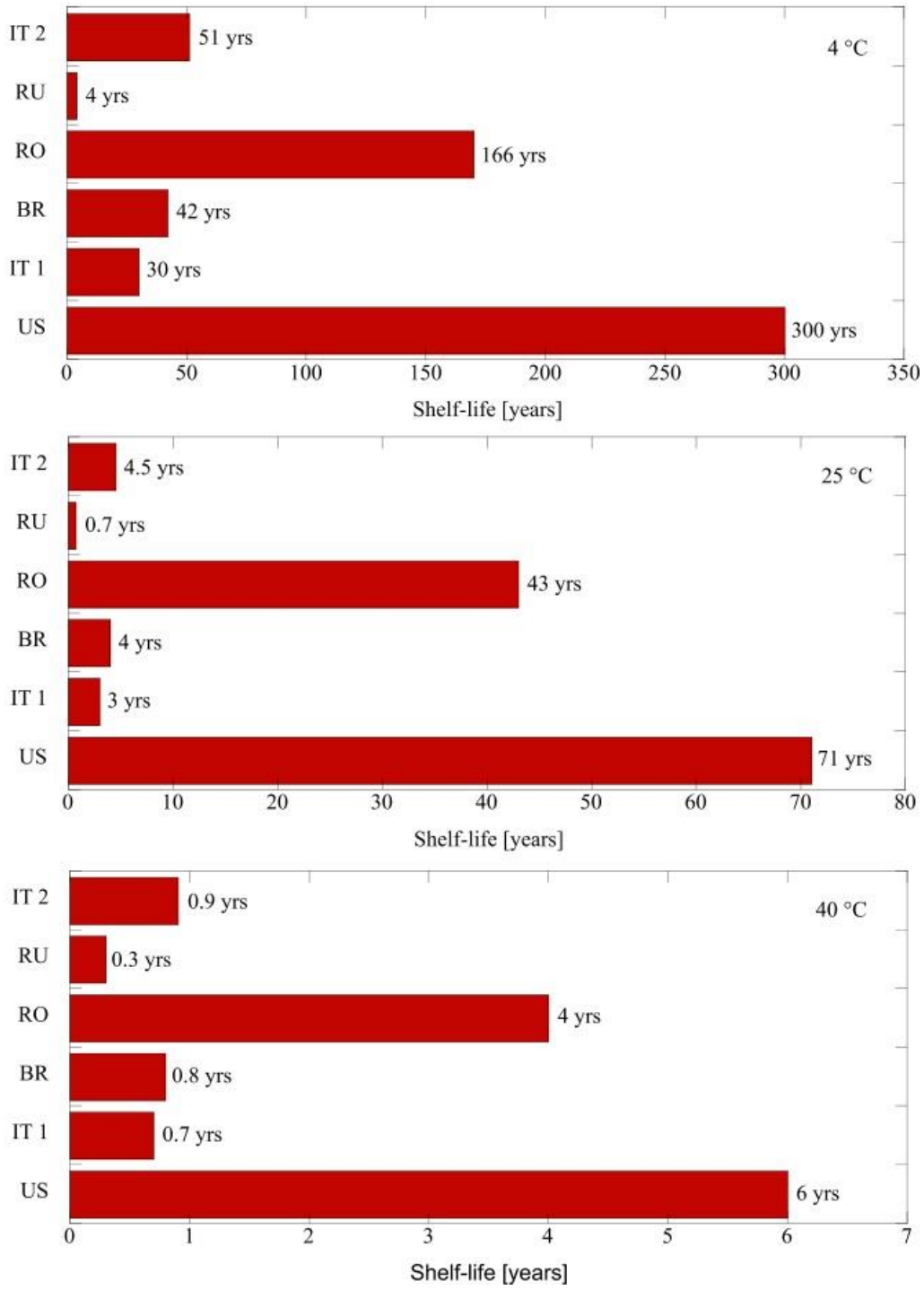

Fig. 5. Shelf-lives of paracetamol formulations at 4, 25 and 40 °C. The data were determined by the simulations of t_α vs α functions obtained using the kinetic parameters from KAS method.

Comparing the six paracetamol formulations, the estimated shelf-lives show the same trend of the activation energies. The latter is consistent with the paracetamol degradation mechanism (R2), which is equivalent for all the tablets. As expected, the temperature increase determines a significant

reduction of the shelf-life for all the samples. We detected that US and RO formulations exhibits larger stability compared to the other formulations. Comparing the data at 40 °C, we calculated shelf-lives of 4 and 6 years for RO and US samples. On the other hand, RU tablet exhibited shelf-lives of 8.4 and 3.6 months at 25 and 40 °C, respectively. These values are shorter with respect to the normal shelf-lives stated by the manufacturers. The products from Italy and Brazil evidenced similar characteristics with shelf-lives in the range 36-54 months at 25 °C. It should be noted that the calculated results are obtained by thermogravimetric experiments conducted under nitrogen flows. Therefore, the shelf-lives presented in Figure 5 can be considered for tablets stored in inert atmosphere. The obtained results can be used to evaluate the pharmaceutical quality of the investigated products as well as the preferential storage conditions for the different formulations. Within this, the storage of the RU tablet in the refrigerator at 4°C (shelf-life of 48 months) could guarantee similar characteristics (in terms of efficacy and the safety) of other paracetamol formulations (IT1, IT2, BR) stored at room temperature.

4. Conclusions

We propose non-isothermal thermogravimetry as accelerated tool to estimate the shelf-life of paracetamol tablets. Specifically, the study was conducted on commercial formulations produced from various pharmaceutical industries worldwide. The protocol consists of three steps: 1) preliminary analysis of the thermogravimetric curves at a fixed heating ramp; 2) kinetic analysis of thermogravimetric data collected at five variable heating rates in order to totally describe the kinetics of paracetamol decomposition for all the tablets. In this regard, activation energies and pre-exponential factor values were successfully estimated from isoconversional procedures (Friedman and KAS methods) and “Master plot” analyses, respectively; 3) simulations of the decay time functions of paracetamol at variable temperatures (4, 25 and 40 °C). We observed that the formulation produced in Russian Federation possesses the lowest stability. In particular, we calculated shelf-lives of 3.6, 8.4 and 48 months at 4, 25 and 40 °C, respectively. The American formulation exhibited the

largest stability with shelf-lives of ca. 1 order larger with respect to those of the Russian sample. The formulation produced in Italy and Brazil evidenced intermediate shelf-lives, which range between 36 and 54 months at storage temperature of 25 °C. The different stability of the paracetamol is related to peculiar composition of the excipients in the formulations. It should be noted that the mentioned results were calculated in inert atmosphere without any stress inputs in terms of humidity variations and light and/or oxygen exposure.

In conclusion, this work evidenced that kinetic studies by non-isothermal thermogravimetry are suitable to determine the shelf-lives of paracetamol tablets under accelerated conditions. The proposed protocol might be adapted to investigate the quality of pharmaceutical products under variable storage conditions.

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Supporting Information: Thermogravimetric curves at variable heating rates for US, IT1, IT2, RO and RU tablets. Differential thermogravimetric curves at variable heating rates for BR, US, IT1, IT2, RO and RU tablets. Master plot analysis (presented as experimental and theoretical $z(\alpha)$ vs α plots) for BR, IT1, US, RO and RU tablets. Shelf-life values calculated at 4, 25 and 40 °C for all paracetemol formulations.

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