



# Talc concentration effect on shelf life of acetaminophen tablets

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Received: 30 November 2022 / Accepted: 12 July 2023 / Published online: 9 August 2023  
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## Abstract

Excipients in pharmaceutical formulations are inactive ingredient from the biological point of view, but they have a key role in the preparation, and they can alter the stability of the active principle. In this work, we prepared acetaminophen tablets with different amounts of talc as excipient and the thermal stability was deeply investigated by thermogravimetric studies. Isoconversional analysis by Kissinger–Akahira–Sunose method and “Master plot” analysis have been successfully employed to describe the kinetics of degradation under inert atmosphere, and the shelf lives have been calculated as a function of the talc content. The shelf-life values as well as the activation energy, which is the dominant factor, evidenced that the inorganic filler enhances the drug degradation to a certain extent and that the composition dependence has a peculiar trend reflecting the particle cluster formation at a critical concentration value. An effort of physico-chemical explanation for this behaviour is put forward by a simple geometrical model from the microparticle-size analysis to predict the critical talc concentration.

**Keywords** Thermogravimetry · Isoconversional methods · Acetaminophen · Talc

## Introduction

Drug formulations are carefully designed as mixtures of the active compound and excipients [1]. Typically, the nature and composition of excipients change between companies that produce a given drug formulation. Although the excipients should not alter the biological activity of the drug, they have a role in the production process (workability of the mixture) as well as in the stability of the active ingredients that is responsible for the shelf life of the final product [2–5].

Thermoanalytical methods are relevant in the characterization of pharmaceuticals providing a straightforward approach to the degradation kinetics of composites under several controlled environmental conditions such as inert and oxidative gases [6–9]. Thermogravimetry was employed for the characterization of hybrid composite materials, and the inorganic fillers can have a key influence on the thermal behaviour as catalytic or stabilizing agents in the degradation process [10–15].

It is reported that excipients could lead to instabilities in the formulations with a significant reduction in the shelf life [16, 17]. The literature reports that iron oxide nanostructures or black TiO<sub>2</sub> has a catalytic action towards acetaminophen degradation, and therefore, their uses as excipients should be considered with particular care; notwithstanding, these inorganic particles can be considered for the drug degradation in environmental remediation [18] [19]. Talc is a promising filler in polymer-based composites [20–22], adsorbent [23] and excipient in pharmaceutical formulations [24].

In this study, the thermal degradation of acetaminophen/talc formulations with different compositions was investigated by thermogravimetry at variable heating rate and isoconversional methods. The mechanism of degradation and the effect of the inorganic filler will be interpreted to the light of the particle dispersion into the composites.

## Experimental

### Materials

Acetaminophen (> 99.0%, Mw = 151.16 g mol<sup>-1</sup>) and talc (3MgO·4SiO<sub>2</sub>·H<sub>2</sub>O, Mw = 379.27 g mol<sup>-1</sup>, 325 mesh) were Sigma products.

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## Sample preparation

The tablets of acetaminophen and talc were obtained by mixing the powders in an agate mortar to obtain homogeneous samples for ten minutes. Afterwards, the tablets were obtained by processing ca. 250 mg of each sample under 10 tons for 20 min by means of a Manual Hydraulic Press 15 T (*Specac*). The talc mass per cent (Ct) was systematically varied from 0 to 13%.

## Methods

Thermogravimetric experiments were performed by using a Q550 apparatus (Discovery series—TA Instruments) under  $N_2$  flow. The mass of each sample was ca. 10 mg. The heating rates ( $\beta$ ) were selected at 2, 5, 10, 15 and 20  $^{\circ}C\ min^{-1}$  from room temperature to 400  $^{\circ}C$ . KAS was used for the isoconversional kinetic analysis of the thermogravimetric data. Finally, the Master plot analysis was used to define the kinetics model and the determination of the formulation shelf life.

Digital optical microscope (*Digitus*, DA-70351) was used for talc particle-size analysis. ImageJ software was used for the determination of particle-size distribution.

## Results and discussion

### Thermal degradation under nitrogen atmosphere

Figure 1 shows some examples of TG results on different samples. We detected that the mass loss up to 150  $^{\circ}C$  is insignificant for all tablets with variable amount of talc,

highlighting that the water content is negligible. Mostly, the mass loss occurs between 160 and 350  $^{\circ}C$  due to the acetaminophen degradation. The talc addition generates an increase in the residual mass after the degradation step, and it slightly promotes the sample volatilization at lower temperature. It should be noted that filling organic materials with inorganic microsize particles can have both a stabilization and even a catalytic effect on the thermal degradation [25–28].

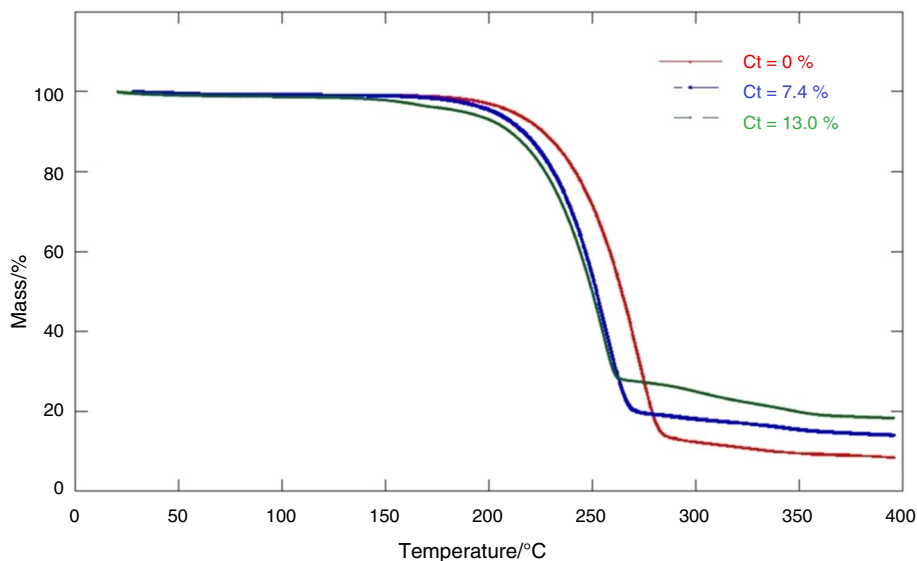
The thermogravimetric curves collected at variable talc content have been compared quantitatively at a given heating ramp by means of the following parameters: (1) residual mass at 400  $^{\circ}C$  and (2) decomposition temperature ( $T_{max}$ ) taken at the maximum of the first-order derivative curves of mass loss to temperature. The  $T_{max}$  value shows a decrease up to 4% of talc content being constant for larger concentrations of the inorganic filler (Fig. 2), whilst the residual mass shows a linear trend as it is typically reported for other organic–inorganic composites [29]. Similar observations were reported for levothyroxine formulations [30]. It should be noted that the obtained findings are confirmed at each investigated heating ramp.

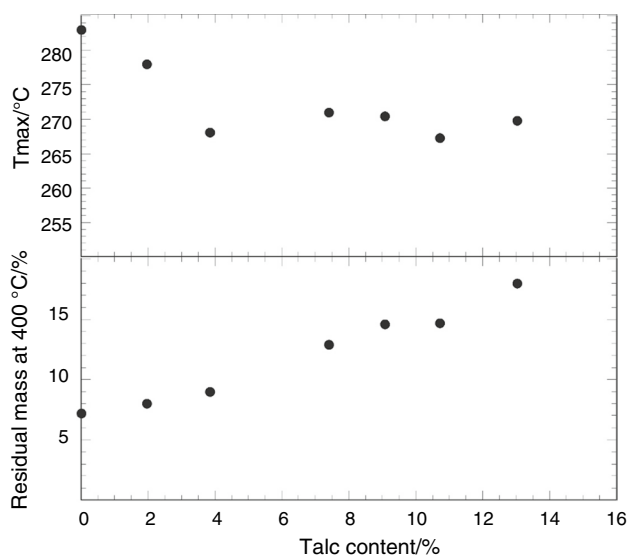
The analysis of single heating ramp TG results cannot provide a comprehensive point of view on the thermal stability of the formulations and in particular to the talc content effect. To this purpose, a complete kinetic investigation through non-isothermal isoconversional methods is more appropriate.

### Isoconversional methods and kinetic parameters

Thermogravimetry and isoconversional methods represent powerful tools to estimate the stability of materials like vegetable oils [31, 32] and polymers [33–35] in various

**Fig. 1** Examples of thermogravimetric curves at variable talc content and  $\beta = 5\ ^{\circ}C\ min^{-1}$





**Fig. 2** Decomposition temperature ( $T_{max}$ ) at the maximum of DTG and residual mass at 400 °C as a function of the talc content. Data refer to  $\beta = 5$  °C min<sup>-1</sup>

technological applications as well as in pharmaceuticals [36–38]. Figure 3 shows an example of the thermogravimetric curves at variable heating rate. As expected, a single step of mass loss is observed within the temperature range between 160 and 350 °C. This is confirmed by the DTG curves (Fig. S1 in Supplementary Information), which evidenced the presence of a single peak.

The isoconversional methods (KAS) have been used to determine the activation energy as a function of the conversion degree ( $\alpha$ ) [39] and it turned out that the obtained values are consistent and constant with the conversion degree for all the samples. The averaged activation

energies from KAS are presented in Fig. 4 as functions of the talc content. The addition of talc to acetaminophen generates a decrease in the activation energy value; nevertheless, the trend evidenced a minimum when the talc content is ca 7%. These results likely indicate that a catalytic effect at the talc surface enhances the drug degradation, and this effect is attenuated when the filler concentration overcomes a certain value.

It should be noted that the activation energy values reflect the thermal stability of the acetaminophen, but the evaluation of the pre-exponential factor and reaction mechanism have to be considered for a proper evaluation. Therefore, the Master plot method [40] was used to determine the reaction mechanism. Namely, the function  $z(\alpha)$  was calculated (Eq. 1) as a function of  $\alpha$  and compared to the theoretical curves [39]

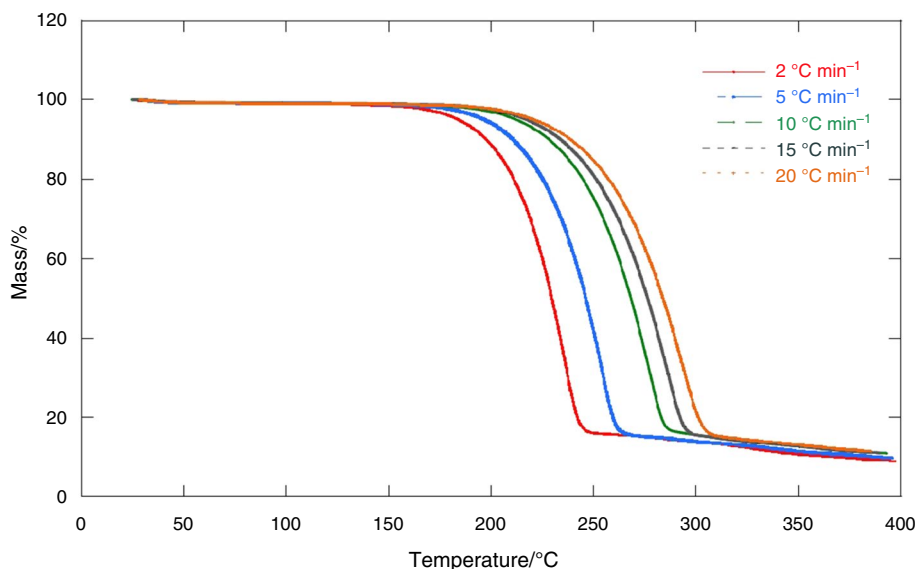
$$z(\alpha) = \left( \frac{d\alpha}{dt} \right)_{\alpha} T_{\alpha}^2 \quad (1)$$

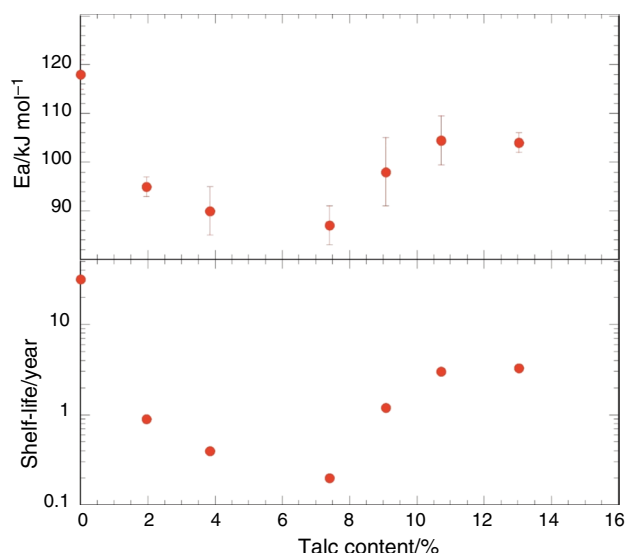
where  $d\alpha/dt$  is the first derivative of  $\alpha$  respect to time and  $T_{\alpha}$  is the temperature at a given  $\alpha$  value. As Fig. 5 shows, the experimental  $z(\alpha)$  function has a maximum at  $\alpha \approx 0.75$  that together with the shape analysis indicates that the degradation mechanism follows a contracted cylindrical geometry (R2 mechanism), and therefore, the  $f(\alpha)$  can be expressed as

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

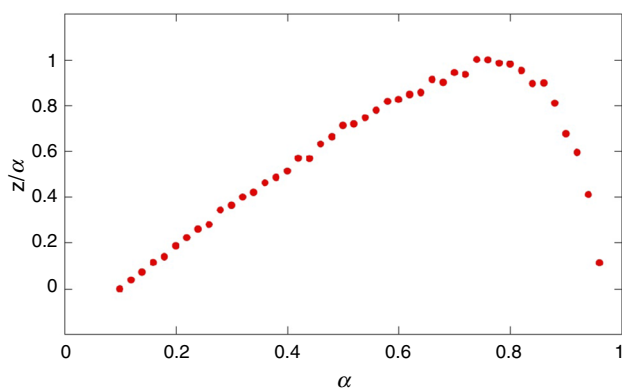
The same conclusion can be drawn for all the investigated samples at variable talc content, highlighting that talc does not alter the degradation path of acetaminophen. This result is also consistent with the findings for several commercial formulations based on acetaminophen with a wide range of excipients [4].

**Fig. 3** Examples of thermogravimetric curves at variable heating ramp and talc content of 3.85%

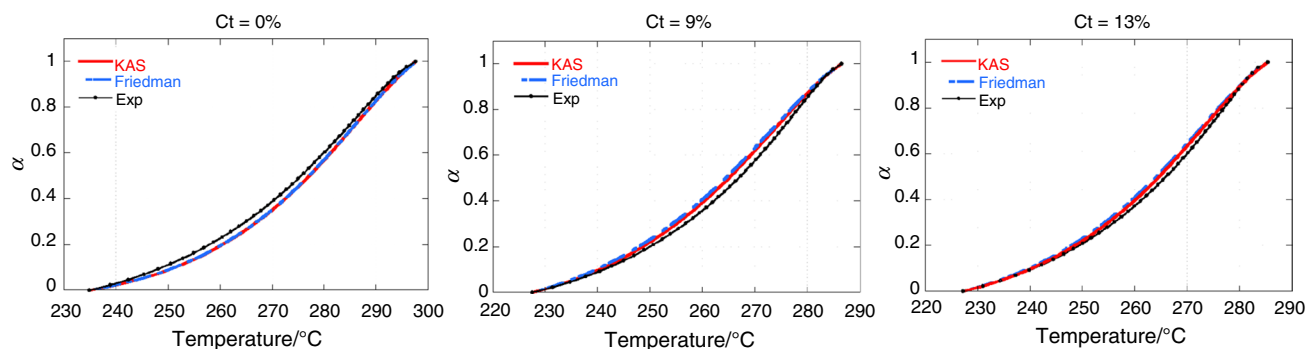




**Fig. 4** Activation energy for the acetaminophen degradation and shelf life calculated at 25 °C and conversion of 10% as a function of the talc content. Data refers to results from KAS analysis



**Fig. 5** Example of “Master plot” analysis for acetaminophen degradation



**Fig. 6** Comparison of experimental conversion degree curves (Exp) with those simulated using KAS and Friedman models for a heating rate of 10 °C min<sup>-1</sup> in the case of acetaminophen, acetaminophen with talc content of 9% and acetaminophen with talc content of 13%

As soon as the mechanism is identified, the pre-exponential factor ( $A$ ) of the decomposition can be determined by fitting the experimental data with the following equation:

$$\left(\frac{d\alpha}{dt}\right)_{\alpha} \exp\left(\frac{E_a}{RT_{\alpha}}\right) = A2(1 - \alpha)^{\frac{1}{2}} \quad (3)$$

where  $E_a$  represents the averaged activation energies from the isoconversional analysis. The obtained  $A$  values are in Supplementary Information. The accuracy of the kinetic results was verified by comparing the experimental conversion curves with those obtained by simulation. Figure 6 shows some examples of the conversion curves as a function of temperature.

The presented curves (Fig. 6) are related to the sample of acetaminophen and acetaminophen with talc content of 9 and 13% at a heating rate of 10 °C min<sup>-1</sup>. The simulations were carried out by employing Eq. 4 [41]:

$$\left(\frac{d\alpha}{dt}\right)_{\alpha} = A \exp\left(-\frac{E_a}{RT_{\alpha}}\right) f(\alpha) \quad (4)$$

The obtained results demonstrate that both Friedman and KAS models accurately simulate the overall evolution of the conversion degree as a function of temperature, regardless of the specific sample under investigation. In general, the simulations generated by both models exhibit a good agreement with the experimental data, thereby confirming the reliability and consistency of the implemented modelling procedure.

The full description of the kinetic parameters, namely the activation energy, the pre-exponential factor and the reaction mechanism, endows to the estimation of the shelf life under inert storage atmosphere. Accordingly, the shelf life of drug formulations is typically calculated as the time ( $t_{10\%}$ ) that correspond to 10% of degradation, namely at  $\alpha = 0.1$  [42, 43].

For a contracted cylindrical geometry (R2 mechanism),  $t_\alpha$  can be calculated as [39]

$$t_\alpha = \frac{1 - (1 - \alpha)^{\frac{1}{2}}}{A \exp\left(-\frac{E_a}{RT_0}\right)} \tag{5}$$

Figure 4 reports the shelf-life values calculated at 25 °C as functions of the talc content. The obtained trends agree with the activation energy findings, demonstrating that this is the dominant factor in the investigated systems.

### Microscopic interpretation

The thermal properties of composites filled with inorganic particles are typically enhanced compared to the organic material. The influence of inorganic nanofillers is discussed in terms of barrier effects towards both mass and heat transports or catalytic effects [25, 44–46]. In general, the resistance to thermal stabilization is mainly due to a barrier effect towards the mass transport of the volatile products. In the investigated system, the talc addition has a destabilization effect on the acetaminophen thermal degradation. That observation may reflect the catalytic effect of the talc surface; this hypothesis can be verified through the effect generated by the increase in the concentration, considering that above the concentration that represents the contact distance between the particles, the further increase in the talc content does not increase the available surface, but actually, it generates a reduction in the free surface provided that particles clusters are obtained.

To determine a critical volume fraction of the particle, the particle size has to be determined. Therefore, the talc particles have been imaged by optical microscopy and the distribution function of the particle diameter was fitted to

a Gaussian distribution that evidenced an average value of 38 μm (Fig. 7).

By assuming a simple cubic model of spherical particles of radius  $R$  at a given volume fraction ( $\phi$ ), the distance between particles ( $L$ ) can be calculated as [47]

$$L = R \left[4\pi/(3\phi)\right]^{1/3} \tag{6}$$

By considering the density values of talc (2.82 g cm<sup>-3</sup>) and acetaminophen (1.26 g cm<sup>-3</sup>), the dependence of  $L$  with talc content is provided in Fig. 8.

The contact distance, corresponding to the average particle diameter, is approached at a talc concentration of ca. 8%. This finding highlights that the minimum in the thermal stability evidenced by the activation energy vs talc content trend is nearly coincident with the critical composition required for a contact between particles. Therefore, the catalytic degradation of acetaminophen at the talc surface is enhanced up to a concentration that allows particle dispersion, whilst further addition generates a decrease in the

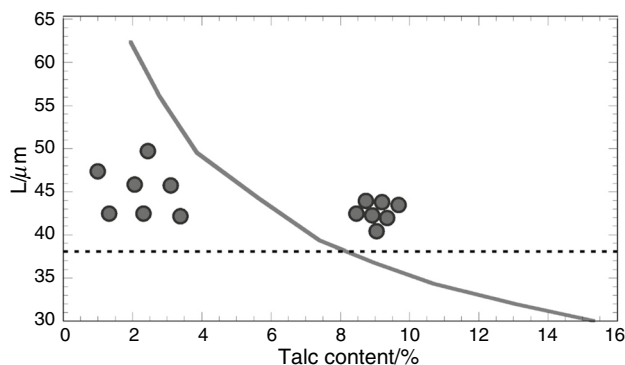


Fig. 8 Particle distance as a function of their concentration in the formulation. Dotted line represents the talc particle diameter

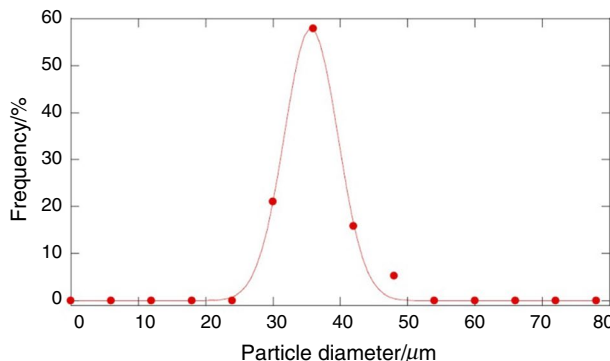
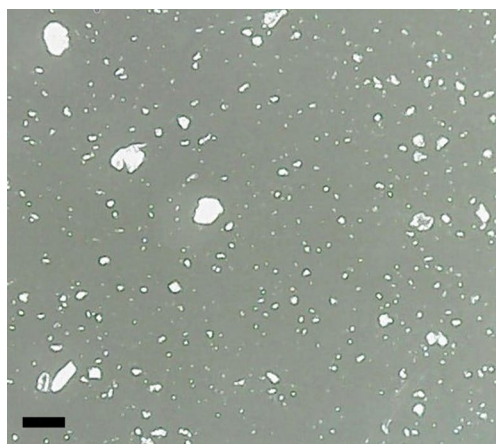


Fig. 7 Optical micrograph of talc- and particle-size distribution obtained by the analysis of 200 particles. Scale bar is 100 μm



available surface due to contact between particles, and therefore, the catalytic degradation is less pronounced.

## Conclusions

Thermogravimetric experiments have been carried out in acetaminophen filled with variable amounts of talc as excipient. The degradation temperature shows a decrease up to a critical talc content, whilst the residual mass after the degradation shows a linear trend that correlates with the content of inorganic particles into the formulations.

Kinetic studies by non-isothermal thermogravimetry evidenced that the shelf lives of acetaminophen/talc formulations are dependent on the composition with a non-monotonic behaviour that is dominated by the activation energy contribute. The degradation mechanism of acetaminophen is not influenced by the talc content, but an enhanced degradation is attributed to the surface interaction. The key role of the interface is further highlighted by the calculated particles contact distance that evidences the possibility of talc-cluster formation at the excipient concentration corresponding to the minimum of the thermal stability.

It should be noted that shelf life corresponds to the time after which the formulation cannot perform its function efficiently, and therefore, additional factors including oxidation and microbial damage can play a role that is differently influenced by the excipient content, and therefore, further studies should be devoted to this direction.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10973-023-12389-6>.

**Acknowledgements** The work was financially supported by FFR 2023 project and University of Palermo.

**Authors' contribution** MMC was involved in investigation, data curation and writing—original draft preparation. GC was responsible for writing—reviewing and editing and validation. GL took part in conceptualization and supervision. SM contributed to funding acquisition and resources.

**Funding** Open access funding provided by Università degli Studi di Palermo within the CRUI-CARE Agreement.

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