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Original scientific paper

Non-Isothermal Degradation of Vitamin C by Simultaneous Thermogravimetric and Differential Thermal Analysis

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Abstract: The non-isothermal degradation process of Vitamin C (Galenika, Serbia) was investigated by simultaneous thermogravimetric and differential thermal analysis (TG-DTA), in the temperature range from an ambient one up to 650°C. The scope of presented work is toward stability of active pharmaceutical substance – ascorbic acid and calculation of all relevants kinetics parameters: activation energy (Ea), pre-exponential factor (A) and half-time ($t_{1/2}$) for stability assesment in explored formulation. It was established that the degradation proceeds through five degradation stages (designated as I, II, III, IV and V), which involve: the dehydration, the melting of ascorbic acid, as well as the decomposition of excipients present: microcrystalline cellulose, D-glucose, carboxymethylcellulose, magnesium stearate , lactose and corn starch. During thermal degradation, all excipients increase their thermal stability and some kind of solid-solid and/or solid-gas interaction occur. The kinetic parameters and reaction mechanism was determined for the II stage, where decomposition of ascorbic acid happened using powerfull kinetic software KINETICS05. Two approaches were used: isoconversional and modell fitting method. It was concluded that degradation of ascorbic acid is best described with N-th order model with Ea= 139.550kJ/mol, A= $1.9689 \cdot 10^{13} s^{-1}$ and n=1.2132.

Keywords: vitamin C, kinetics, non-isothermal, thermogravimetry.

Introduction:

Vitamins are essential micronutrients which are very different in chemical structure and biological activity and physico-chemical properties. They decompose under the influence of heat, light, moisture and oxidation process. The combination of these influences can lead to very complex behavior of substances (Byrn *et al* 1999). Products containing vitamins are often subjected to thermal treatment in the preparation or storage, so it is very important to have information on their thermal stability. The stability of vitamins to heat, oxidation, light exposure is a topic of great practical interest. Thermal stability can be significantly improved by the addition of auxiliary components, excipients, which can very effectively protect vitamins from thermal decomposition. Further more, the selection of a suitable carrier in order to increase the thermal stability is a very topical issue (Sazan *et al* 2013, Corvis *et al* 2013, Li *et al* 1998, Wang *et al* 2013). One of the most reliable way to get an insight into the thermal stability of the preparation, is a method of thermal analysis (Brown *et al* 1998, Brown 1980). The potential applications of thermal analysis in the pharmaceutical industry is wide in terms of physicochemical studies (Ford *et al* 1989, Girone al 2008, Stodghill *et al* 2010, Plano *et al* 2013, Zhang *et al* 2013). These methods include the characterization and specification of active ingredient or auxiliary and provide analysis relating to quality control and stability studies. In the solid state, the temperatures required for thermal degradation at a measurable rate are generally far higher than the temperatures existing, even locally, during photolysis (Tønnesen *et al* 1991), so the mechanisms of thermal and photo-chemical degradation can be expected to differ. On the other hand, it is well known that at high temperature the chemical reactivity of drug active components, both pure and in the mixture, can be

modified, thus leading to uncontrollable reactions with consequent dangerous situations. For this reason, it is important to determine the thermal stability (i.e. the temperature range over which a substance does not degrade with an appreciable rate). Moreover, kinetic study is useful to determine the most probable mechanisms and the kinetic parameters. There are numerous studies on stability of ascorbic acid. Vitamin C is a water-soluble vitamin , also known as an antioxidant. It is unstable and decomposes under the influence of air (oxidized), light, ions Fe , Mn and Cu (Muratović *et al* 2013). Vitamin C degradation is accelerated at high temperature, and decomposes at 190°C . All the presented mechanism of ascorbic acid degradation are quite complex, there are about 200 different products reported in the literature so far. Upon literature review degradation of ascorbic acid was investigated by different methods: HPLC and spectrophotometry (Jingyan *et al* 2013), GC-MS (Vernin *et al* 1998) TG (Lerdkanchanaporn *et al* 1996). Information about degradation products containing vitamin C are very interesting and useful in terms of safety and efficacy of food and medical products .

In the present study, we focused our attention on the thermal stability of the active component (ascorbic acid) in the commercial pharmaceutical tablet formulation (Vitamin C - Galenika) by elaborating data of the corresponding TGA and DTA curves referring to the thermal degradation from a kinetic point of view. Furthermore, in this paper, special attention was given to the role of presented excipients for the stability determination of the dosage form and the evaluation of *shelf-life* values, in order to prepare the most ideal optimization procedure for the storage of pharmaceutical preparations. Pharmaceutical preparations (Giron *et al* 1986) provide the means by which pharmaceutically active substances or drugs can be supplied to the body, so that both the physiological considerations concerning the means of application (oral, cutaneous, sub-cutaneous, rectal, etc.) and the physico-chemical properties of the drug are suitable. A pharmaceutical preparation consists of the actual drugs or the active ingredients (fillers, additives, etc.), all of which must be present in the right proportions.

Materials and methods

The SDT 2960, simultaneous TG-DTA thermobalance manufactured by TA Instruments (109 Lukens Dr, New Castle, DE 19720-2765, USA) was used to examine the non-isothermal degradation of Vitamin C (Galenika, Serbia).

The vitamin C powder samples were heated at a rates of β = 5, 10 and 20 ^{o}C min^{-1} and the flow rate of the purging gas (Air) was 100 mL min^{-1}. The samples were heated in the temperature range from an ambient one up to 650°C. The loading amount was 2.0 ± 0.1 mg. A black residue was left in the pan, which was assumed to be carbon.

Vitamin C was provided by pharmaceutical company Galenika, Serbia. Each tablet contains 500 mg of ascorbic acid. The tablets are round with flat surface and faceted edges, almost white to pale yellow.

In addition to the active ingridient (ascorbic acid) the other excipients are as follows: microcrystalline cellulose (disintegrant), D-glucose (filler), carboxymethylcellulose (disintegrant), magnesium-stearate (lubricant), lactose (filler) and corn starch (binder).

Software KINETICS05 - Lawrence Livermore National Laboratory (LLNL), Livermore, CA

Kinetics analysis

Kinetic analysis of a degradation process is traditionally expected to produce an adequate kinetic description of the process in terms of the reaction model and the Arrhenius parameters using a single-step kinetic equation (Brown *et al* 1980):

$$\frac{d\alpha}{dt} = k(T)f(\alpha) \tag{1}$$

where t is the time, T the temperature, α the extent of conversion and $f(\alpha)$ the reaction model. The temperature dependence of the rate constant is introduced by replacing $k(T)$ with Arrhenius equation, which gives:

$$\frac{d\alpha}{dt} = A\exp\left(-\frac{E_a}{RT}\right)f(\alpha) \tag{2}$$

Kinetic analysis of TG data for degradation process was done by means of software KINETICS05. Software Kinetics05 provides different kinetics model. The models are divided in two sections: model free method (isoconversional models) and model fitting method (phase boundary models and nucleation growth models). Each model was tested on obtained TG data. In order to choose the best model, we followed the agreement between experimental and calculated data, as well as some statical data (RSS_1-sum of squares of weighted normalized rate residuals and RSS_2- sum of squares of weighted normalized cumulative residuals). The best agreement is when RSS_1 and RSS_2 have the lowest value.

Expended Friedman method belongs to isoconversional methods, which were find very helpful in non-isothermal solid state kinetics (Burnham *et al* 2007). Isoconversional methods provide us information of variation of Ea with conversion of extent during the course of reaction.

$$\ln\left(\frac{d\alpha}{dt_\alpha}\right) = -\frac{E_\alpha}{RT_\alpha} + \ln\{A_\alpha f(\alpha)\} \tag{3}$$

The modified Coasts-Redfern method (Kissinger *et al* 1957, Li *et al* 1997) is a multi-heating rate application of the Coast-Redfern equation, resulting in a model-free isoconversional approach, similar to that of Friedman one. It is based on the equation:

$$\ln\left[\frac{\beta}{T^2(1-2RT/Ea)}\right] = -\frac{Ea}{RT} + \ln\left(-\frac{AR}{Ea\ln(1-\alpha)}\right) \tag{4}$$

To use this equation, at a selected common value of conversion degree for different heating rates, the left-hand side should be plotted vs. $1/T$, giving a family of straights lines of slope $-E_\alpha/R$, while the intercept with vertical axis presents the pre-exponential factor A. If the values of E_α varies with the variation of α, the results should be interpreted in terms of multi-step reaction mechanism. The Friedman method (Kissinger *et al* 1957) applies to any thermal history while the modified Coast-Redfern applies only to a constant heating rate. Where t_α, T_α, E_α and A_α are the time, temperature, apparent activation energy and pre-exponetnial factor, respectively at conversion α. $-E_\alpha/R$ and $\ln\{A_\alpha f(\alpha)\}$ are the slope and the intercept with vertical axis of the plot of $\ln(d\alpha/dt_\alpha)$ vs. $1/T_\alpha$. The Kissinger method (Li *et al* 1997) is a isoconversional special case of determing A and Ea at a fixed conversion. In the method plot $\ln(\beta/Tmax^2)$ vs. 1/Tmax is made for the series of experiments at different heating rates β. The slope of such plot is –Ea/R.

$$\ln\left[\frac{\beta}{T_p^2}\right] = \ln\left(\frac{AR}{E_a}\right) - \frac{E_a}{RT_p} \tag{5}$$

Extended Prout-Tompkins model describes nucleation-growth processes in solids. Burnham (Burnham *et al* 2007) modified originally prout-Tomkins model, introducing the exponents m and n different then one.

$$\frac{d\alpha}{dt} = k(1-\alpha)^n\left(1-q(1-\alpha)\right)^m \tag{6}$$

Parameters m and n are adjustable in order to give the best fit between experimental data and theoretical model. The coefficient q is a fixed parameter and its value is 0.99. This model is applicable to a wide range of solid-state processes involving the nucleation and growth. If n=0 and m=1, equation 3 has the limit of linear chain-branching model. If n=1 and m=0 it has the limit of a first-order reaction. When is m=n=1 equation presents standard Prout-Tompkins model.

Upon obtaining the proper kinetic triplet (Ea, A and f(α)) it is possible to evaluate the stability parameter. Stability testing is a routine procedure performed on drug substance and products at various stages of the product development. Accelerated stability testing at high temperatures and humidities is used in order to determine the type of decomposition of products which may be found after long-term storage. Testing under less rigorous conditions is used to determine a products *shelf life* and expiration dates. The major aim of pharmaceutical stability testing is to provide assurance that the product will remain at an acceptable level during storage in pharmacy. From the known Arrhenius parameters (E and A) and the mechanism of degradation it is possible to calculate the *shelf-life*. This parameter is defined as degradation time required reaching decomposition at specific conversion degree level and at given operating temperature, according to the following equation:

$$t_\alpha(T_j) = \frac{f(\alpha)}{A\exp\left(-\frac{E}{RT_j}\right)} \tag{7}$$

Results and discussions

Thermal analysis of ascorbic acid

TG and DTA curves of vitamin C tablets are presented in Figure 1 and Figure 2. From TG curve it is possible to evaluate decompositon steps, along with corresponding mass loss for each phase, as well as, temperature range in which decomposition step occurs.

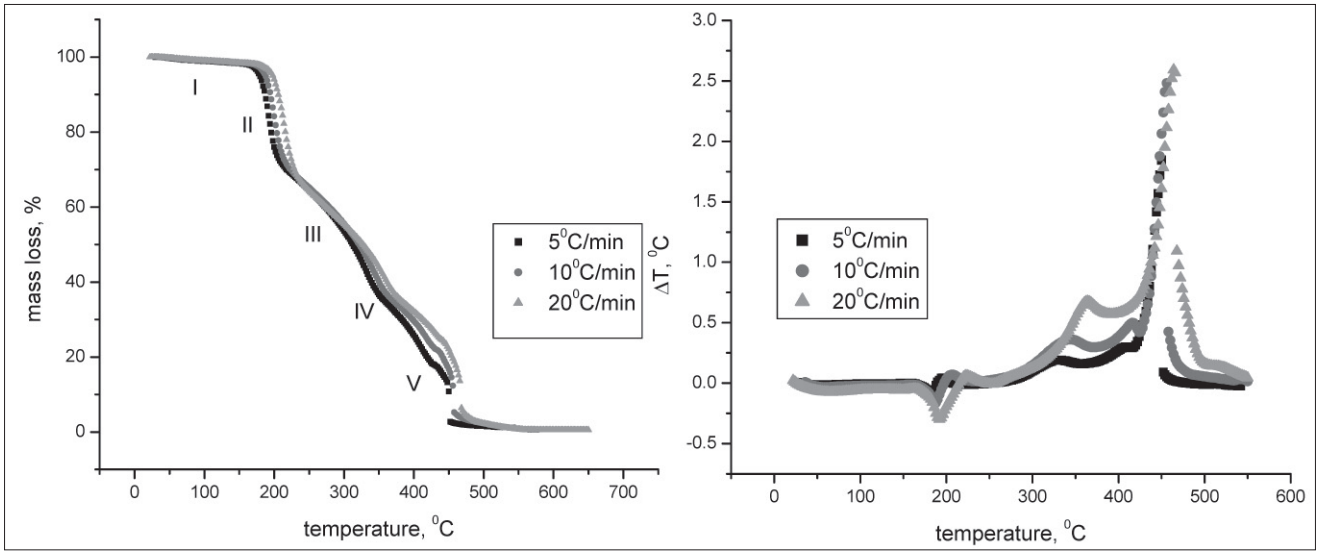

Figure 1. and Figure 2. TG curve (left) and DTA curve (right) of decomposition of ascorbic acid in air atmosphere with β = 5, 10 and 20°C/min

Table 1 summarised all the relevant data from TG and DTA curve for each heating rate employed. Data for T_i (initial temperature), T_f (final temperature), T_{max} (tempearature where reaction reach its maximum) and Δm (mass loss) are presented for each phase of degradation for all heating rates employed.

We can conclude that degradation of ascorbic acid and its excipients in air is presented through five phases, where I phase correspond to loss of moleculas of water (polymer hydratation). Some of excipients may contain a high content of water (such as corn starch), but different percentage. Moisture, as well as heat can accelarate reaction of degradation. Process of hydratation is presented as a broad endothermic peak at DTA curve. Starting from II phase decomposition process of ascorbic acid and melting of excipients occur. The most excipients in investigated formulation are stable up to 300°C (magnesium stearat - 349°C, microcrystalline cellulose - 330°), but degradation of lactose and D-glucose should be expected in range of 150-170°C. Second well defined endothermic peak goes in favor of excipients melting. Above 300°C two parallel processes exit, carbonisation and charcoal combustion. Charcoal combustion above 420°C is so intense that affects investigated sample so much, that the temperature of samples is getting higher than heater temperature.

Table 1. Reaction phase of ascorbic acid degradation with temperatures and mass loss

β (°C/min)	*Reaction phase*	*Ti (°C)*	*Tmax (°C)*	*Tf (°C)*	*Δm (%)*
	I	30	75.67	146	98.31
	II	146	193.26	232	67.62
5	III	232	309.03	360	34.56
	IV	360	398.87	432	17.61
	V	432	450.35	542	1.19
Average		**240**	**285.44**	**342.4**	**43.86**
β (°C/min)	***Reaction phase***	***Ti (°C)***	***Tmax (°C)***	***Tf (°C)***	***Δm (%)***
	I	36	83	152	98.39
	II	152	201.46	242	66.54
10	III	242	320.74	376	34.03
	IV	376	408.14	436	21.52
	V	436	456.36	578	0.61
Average		**248.4**	**293.94**	**356.8**	**44.22**
β (°C/min)	***Reaction phase***	***Ti (°C)***	***Tmax (°C)***	***Tf (°C)***	***Δm (%)***
	I	22	164.67	192	96.54
	II	192	215.82	252	63.92
20	III	252	332.42	390	33.74
	IV	390	417.35	440	24.58
	V	440	466.3	650	0.4894
Average		**259.2**	**319.31**	**384.8**	**43.8539**

In this paper the main focus in decompositon process of Vitamin C tablet is on ascorbic acid degradation which developes in II phase. In order to evaluate thermal stability of ascorbic acid, as pharmaceutical active ingredient, it is important to obtain all the relevant kinetics parameters for II phase of degradation. The first step is to construct conversional curves for II stage of decomposition process under investigation.

The original mass loss vs. temperature plots obtained at constant heating rate were transformed into conversion degree(□) vs. temperature curves by means of the equation

$$\alpha = \frac{m_0 - m_t}{m_0 - m_f} \tag{7}$$

where m_t represents the mass of the sample at arbitrary time t (or temperature T), whereas m_0 and m_f is the mass of the sample at the beginning and at the end of the process, respectively.

The α-T curves for different heating rates are shown in Figure 3. The results indicate that degradation process does not occur below 150 ^{0}C (at □ = 5 ^{0}Cmin^{-1}). Upon construction of calibration curves we can proceed with kinetics analysis by means of KINETICS05 software which provides two approaches: isoconversional and model fitting method.

Results of isoconversional approach which describes changes of activation energy with conversional degree are presented in Table 2, along with some statistical data provided by kinetics software. As one can see, there is a good agreeement between Ea obtained by Friedman and Coats-Redfern isoconversional method, while Kissinger method gave a higher value.

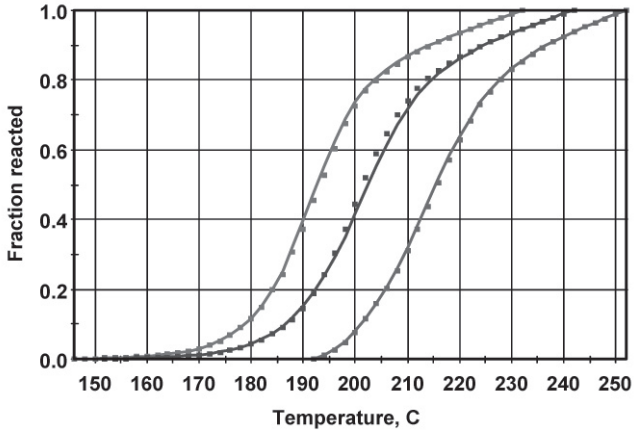

Figure 3. Conversional curves α = f(T) for II phase of ascorbic acid degradation

Table 2. Kinetics parameters for II degradation phase of ascorbic acid by isoconversional methods

Model	A (s^{-1})	E (kJ/mol)	RSS$_1$	RSS$_2$
Friedman	4.28 E+10	89.007	2.00E-01	1.14E-02
Coats-Redfern	6.08 E+08	82.53	-	-
Kissinger	1.74 E+09	114.73	-	-

Expanded Friedman method showed a very good fit, which was confirmed by Figure 4a, 4b, 4c and 4d. Following graphs given by Friedman method show variation of absolute reaction rate with time, temperature and conversional degree (fraction reacted). As one can see, there is an excellent agreement between used Friedman model and experimental data. With higher heating rate employed, absolute reaction rate is getting higher value, leaving curves with the same shape.

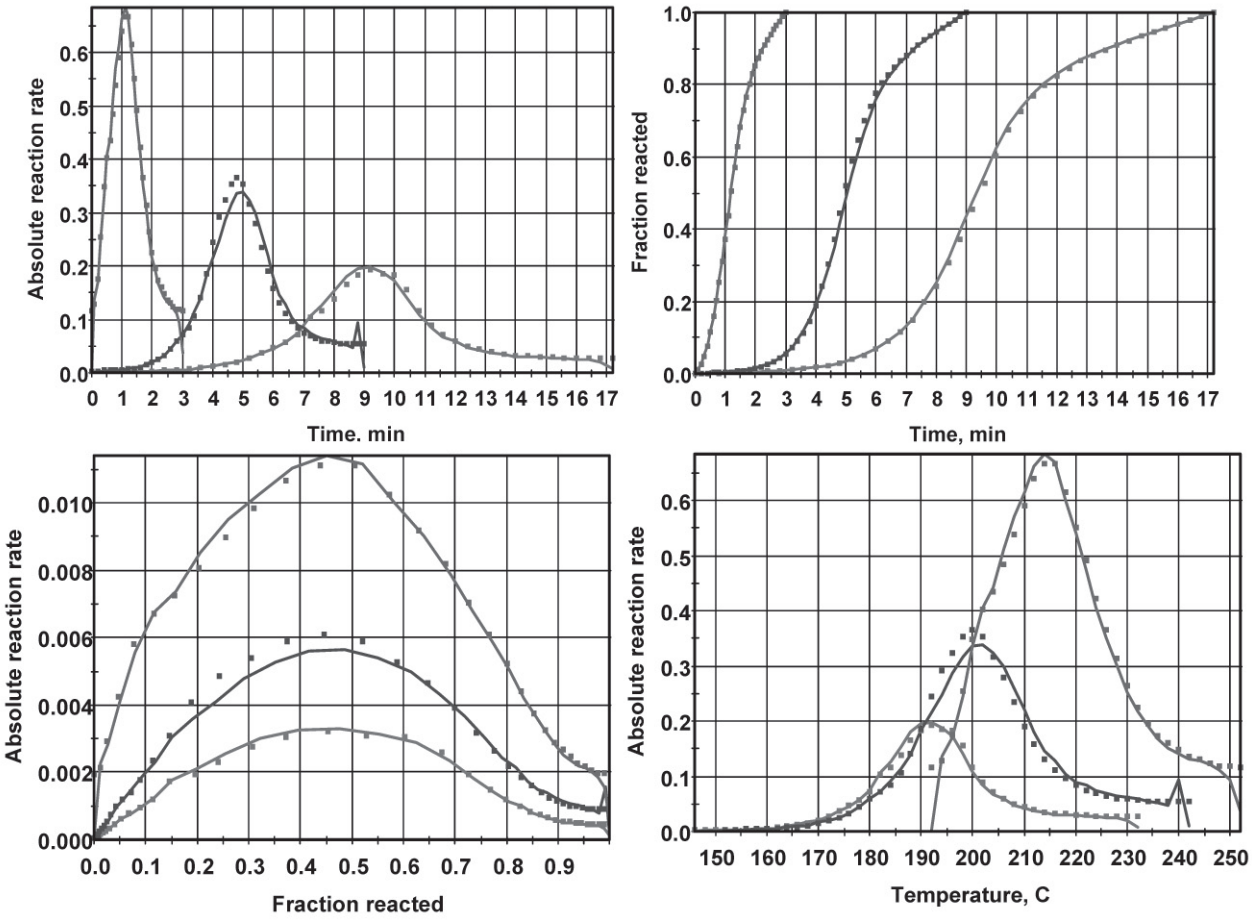

Figure 4. Degradation of II stage of Vitamin C obtained by expanded Friedman method

Figure 5 presents variation of Ea (solid line) and lnA (dashed line) with conversional degree (α) obtained by Friedman method, which presume n=1. In general, if Ea vary with conversional degree a lot, we can exclude a single step process. So, we can conclude that degradation of ascorbic acid in II stage of process under investigation is a very complex one. Vyazovkin *et al* suggested that if value of Ea rises with higher conversioanl degree, there is some parallel reaction in the process. We can see, that starting from α = 0.5, Ea shows such behaviour, which can be attributed to the decomposition of lactose and D-glucose.

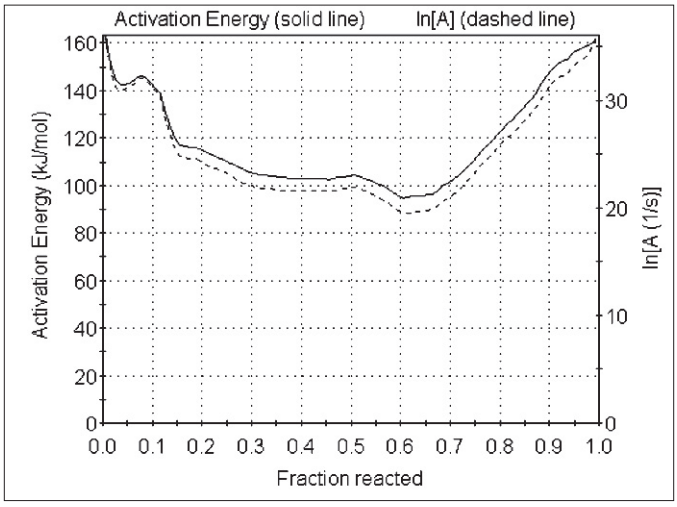

Figure 5. Dependence of Ea (left axis) and lnA (right axis) with conversional degree – II phase of degradation of ascorbic acid

Upon obtaining results for E and A with isoconversional approach, model fitting method was further used. Two models, N-th order model and Nucleation and growth model gave the best agreement between experimantal data and theoretical models by model fitting approach. Results are presented in Table 5. Since a slighty better agreement is obtained for N-th order model, we will use f(α) that corresponds to that N-th order model for further calculation and prediction of *shelf-life* according to equation 7.

Table 5. Kinetics parameters for II degradation phase of ascorbic acid by model fitting methods

Model	A (s^{-1})	E (kJ/mol)	n	m	RSS_1	RSS_2
N-th order	1.97E+13	139,550	1.21E+00	-	2.44E+00	2.05E-01
Nucleation and growth	1.28E+14	134,929	3.56E+00	1.23E+00	4.91E+00	2.82E-01

Calculated *shelf-life* ($t_{0.1}$, $t_{0.5}$ and $t_{0.9}$) for 25, 50, 75 and 100°C are in Table 6. As expected, temperature has a great impact on the decomposition of ascorbic acid and this is confirmed by data in Table 5. The percentage α = 10% ($t_{0.9}$) is often selected to calculate a shelf life, since it is often considered the reference percent of a drug degraded the *shelf-life* value at a fixed temperature, usually 25°C. Stability of ascorbic acid is quite high at 25°C, but it lowers rapidly with higher temperature employed. This confirms that ascorbic acid is rather unstable and heat sensitive substance. But it should be pointed out, even though ascorbic acid is heat sensitive, its thermal stability is quite improved in mixture with presented excipients.

Table 6. Estimation of *shelf-life* for degradation of ascorbic acid

Shelf-time	25°C	50°C	75°C	100°C
$t_{0.1}$	310.65 years	3.968 years	826 hours	32.412 hours
$t_{0.5}$	2193.7 years	27.89 years	5775 hours	226.008 hours
$t_{0.9}$	4466.92 years	56.846 years	11769 hours	459.9 hours

Conclusions:

Thermal analysis methods are very useful and powerfull tool for thermal stability assesment of substances. Thermal degradation od vitamin C was explored. By performing detailed kinetic analysis, Friedman method (isoconversional approach) and N-th order model (model fitting method) gave the best agreement between TG data and KINETICS05 models. Vitamine C is rather unstable and heat sensitive substance, but during thermal degradation, all excipients increase their thermal stability and thermal stability of ascorbic acid. It was established that the presented excipients show a different bahavior from that of the pure materials.

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