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Drug shelf life estimation by non-isothermal treatments in DSC: specific surface area effect

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ABSTRACT

Isothermal methods for determining the stability of drug products are expensive and require a lot of time, non-isothermal ones are fast, require little sample and other resources; they allow to estimate the shelf life by considering the solid state chemical kinetics and can be used at an industrial level like alternative stability method. Samples of acetylsalicylic acid produced in different years by the same manufacturer, were submitted to a variable heating rate in a differential scanning calorimeter; the non-isothermal method of Kissinger allowed calculating the activation energy and the pre-exponential factor of the degradation. The dimensions of crystalline raw material particles were determined, smaller specific surface area involves a longer shelf life. The application of the non-isothermal Kissinger method allows the rapid determination of the remaining shelf-life of acetylsalicylic acid and to detect differences in activation energy possibly related to variations in composition, production process or storage. Considering the inverse relationship between Specific Surface Area and remnant shelf life; crystallization step should be carefully controlled to obtain crystals of 16 mm^{-1}.

Keywords*: Shelf life; Non-isothermal methods; Kissinger method; Differential scanning calorimetry; Specific Surface Area.*

1. INTRODUCTION

The traditional methods for determining the shelf life of drugs are isothermal and require long periods of time for their execution [1,2]; has basis on the kinetic theory of reactions in the liquid and gaseous state, emphasize the factors influencing the reaction rate of homogeneous systems such as temperature, pressure and composition, and leave aside those characteristic of heterogeneous systems as the transport of matter between phases and the mode of interaction between them [3].

The dynamics of industrial production require that decisions regarding stability should be taken quickly without neglecting the safety, efficacy, and quality inherent in medicines; therefore, rapid, sensitive and safe methods are needed to calculate the shelf life of raw materials and pharmaceutical forms [4,5,6,7]. The use of non-isothermal techniques, like differential scanning calorimetry, reduces the time required, from months or years to a few days. Besides, it can be used for purity determination, compatibility studies, polymorphism, eutectic melt determination, phase diagram determination and for the drug delivery system analysis [8,9].

Non-isothermal methods for determining the velocity of material deterioration appeared in the late 1950s as a result of the wide development of thermal analysis [10,11]. These studies involve the treatment of samples at one or more heating rates (β) to investigate the effect of temperature on the course of the reaction [12,13]; in comparison with isothermal methods, kinetic parameters are calculated from data obtained from the measurement of weight loss (thermogravimetry), loss/gain of heat or changes in temperature of the thermal event (differential scanning calorimetry) [14,15], these methods save time and samples.

The Kissinger method, applied in the present work, allows estimating the activation energy, in processes of physical or chemical nature, from data obtained at several non-isothermal tests conducted at constant heating rates [16], $\beta = dT/dt > 0$. The rate of reaction (c), depends on temperature (T) and conversion (α), and is the product between kinetic constant (k), which is a function of temperature of reaction [17], and f (α), a function of the conversion which is temperature independent [16].

$$c = d\alpha/dt = k(T)\, f(\alpha) \quad (1)$$

The kinetic constant is a function of the reciprocal of the temperature [16]:

$$k = A\, e^{(-Ea/RT)} \quad (2)$$

There, A is the pre-exponential factor, Ea is activation energy, R the universal gas constant, and T is the temperature in absolute scale [16].

The rate of reaction at constant heating rate as a function of temperature has a maximum [18], a peak temperature (Tm) for which $dc/dT=0$ and $d^2c/dT^2 < 0$. The variation of $f(\alpha)$ at the peak is a negative constant, $q = (df/d\alpha)_m < 0$; under the before mentioned condition, Kissinger demonstrated that [16]:

$$\beta\, Ea/R\, T_m^2 = -q\, A\, e^{(-Ea/RTm)} \quad (3)$$

Kissinger´s method does not require any modelistic assumption to calculate activation energy; it is not an isoconversional method because the activation energy is not obtained as a function of the degree of conversion, rather it is assumed that this parameter is constant [19]. According to it, the displacement of the temperature (Tm) at which the maximum in the exothermic reaction curve occurs, varies with the heating rate (20), the equation that describes it, is:

$$\ln(\beta/T_m^2) = \ln(AR/Ea) - Ea/(RT_m) \quad (4)$$

Kinetic parameters, Ea and A, are obtained plotting $\ln(\beta/T_m^2)$ versus $1/T_m$ for experiments with different heating rates [21].

Those parameters allows to calculate the shelf life (t_D): the time necessary to reach a percentage of degradation (D) at a given temperature [21].

$$t_D = [-\ln(1-(D/100))] / A\, e^{(-Ea/RT)} \quad (5)$$

This paper presents the shelf life estimation of acetylsalicylic acid (ASA) as a raw material using variable heating rate in DSC as an alternative to the traditional methods [22]. For this purpose, we started quantifying the acetylsalicylic acid and its main degradation, salicylic acid (SA), present in raw material produced by the same manufacturer in different years. Binary mixtures of ASA/SA were prepared in order to simulate a degree of degradation and to compare with the results of the raw materials. The kinetic parameters, activation energy, and pre-exponential factor were calculated using the Kissinger method from the maximum temperature (*Tm*) of the thermal event determined by DSC; with those parameters, the remaining shelf life of the samples was determined.

2. EXPERIMENTAL SECTION

2.1. Materials. Acetylsalicylic acid and salicylic acid were obtained directly from the only local manufacturer DAN QUÍMICA C.A. The analytical reagents and excipients available in the laboratory were not treated or modified prior to their use.

2.2. Quantification of acetylsalicylic acid and salicylic acid by HPLC. Mobile phase formed by KH_2PO_4 pH 2.25 buffer and acetonitrile HPLC in a 75:25 ratio was vacuum filtered using a 0.45 um PTFE membrane. For the standard, 32.5 mg of acetylsalicylic acid was weighed into a 10 ml volumetric flask; 0.5 ml of acetonitrile was added, stirred and diluted to volume with mobile phase. In another 25 ml volumetric flask, 10.8 mg of salicylic acid was weighed, 0.5 ml of acetonitrile was added, stirred and diluted to volume with mobile phase. 1 ml of standard solution of acetylsalicylic acid was transferred to 10 ml volumetric flask, then 0.225 ml of standard salicylic acid solution was added and the solution was diluted to volume using mobile phase. The acetylsalicylic acid concentration was 0.325 mg/ml and 0.00975 mg/ml for salicylic acid. For the raw material sample, 32.5 mg ASA were weighed into a 10 ml volumetric flask, 0.5 ml of acetonitrile was added, stirred up to complete dissolution and diluted to volume with mobile phase. A 1 ml aliquot of the prepared solution was taken and diluted to 10 ml with mobile phase in a volumetric flask. Both, samples and standards, were filtered through a 0.22 um PTFE filter before being injected into a Dionex Ultimate 3000 HPLC equipped with a DAD detector at a wavelength of 235 nm. The column, a Zorbax Eclipse XDB-C8 4.6mm ID x 5cm x 3.5um, was maintained at 30°C, the flow of the mobile phase was 0.8 ml/min, the injection volume was 10 µL and the autosampler temperature was 5°C. The runtime was 8 minutes; the ASA peak appears at 2.3 minutes and the SA peak at 3.5 minutes.

2.3. Preparation of ASA/SA binary mixtures. A solution of 0.5 mg/ml of salicylic acid in ethyl ether [23] was prepared. To form mixture 1, 1.95 g of ASA crystals were spread in a Petri dish, 0.4 ml of the salicylic acid solution was distributed dropwise, the mixture was homogenized for 3 minutes and allowed to dry at room temperature; for binary mixtures 2 and 3, treatment the same process was repeated but adding 1.2 and 4.4 ml of SA solution.

2.4. Kinetic parameters of ASA in raw material and binary mixtures ASA/SA determined in DSC. The calibration mode was selected in TA DSC Q2000 – 1705 to perform the cell constant and temperature test using indium standard and aluminum capsules, one of them containing 7 mg of standard and the other empty to be used as reference. Both capsules were placed on the calorimeter platform and heated from 90 to 300 °C at a rate of 10 °C/min using an ultrapure nitrogen atmosphere at a flow rate of 25 ml/ min.

For determination of Tm, the aluminum capsules were weighed and closed containing approximately 5 mg of sample, each capsule was subjected to its respective heating rate: 5, 10 or 20 °C/min, from 90 to 300 °C using a nitrogen atmosphere at a flow rate of 25 ml/min. From the obtained thermogram, the values of Tm were determined from the maximum point of the degradation peak, each measurement was performed in triplicate.

2.5. Quantification of ASA and SA in aluminum capsules. The residual content in the aluminum capsules after the non-isothermal treatment was analyzed by HPLC: 10.8 mg of Compound B standard [24] was weighed into a 25 ml volumetric flask, 0.5 ml of acetonitrile was added, stirred and diluted to volume with mobile phase. The same procedure was followed for compounds D, E and F [24]. 1 ml of standard ASA solution was taken and placed in a 10 ml volumetric flask, 0.225 ml of standard SA solution was added, as well as 0.225 ml of each standard solution of related compounds; then was stirred and diluted to volume with mobile phase. The final concentration of standards was 0.00975 mg/mL.

For sample preparation, the aluminum capsule containing the residue was placed in a 10 ml volumetric flask, 1 ml of acetonitrile and 5 ml of mobile phase was added, sonicated for 10 minutes and finally diluted to volume with mobile phase. Samples and standards were filtered through a 0.22 µm PTFE membrane. The only difference of the chromatographic conditions previously described is that the mobile phase used was KH_2PO_4 pH 2.25 buffer and acetonitrile in ratio of 60:40.

2.6. Determination of particle size of ASA crystals by microscopy. ASA crystals from the different batches were placed on slides and observed on the inverted microscope AMScope with the 4X lens; AMScope software was used to measure them.

3. RESULTS SECTION

3.1. Quantification of Acetylsalicylic acid and salicylic acid by HPLC. In order to obtain a representative difference in the content of ASA and SA, the batches of raw material were selected according to their manufacturing time. Table 1 shows that, although the amount of active ingredient does not vary significantly, the percentage of salicylic acid does, thus differentiating the samples according to the level of degradation.

The composition of the binary mixtures was selected based on the percentages of ASA and SA found in the raw material of different

manufacturing dates, in order to simulate a degree of degradation and to compare with the results of the raw materials.

Table 1. Quantification of ASA and SA in raw material (RM) and binary mixtures.

	Age, months	% ASA	% SA
RM 1	15	97,26	0,037
RM 2	24	97,50	0,053
RM 3	51	96,33	0,131
Mixture 1	-	98,76	0,055
Mixture 2	-	97,27	0,062
Mixture 3	-	98,86	0,093

3.2. Kinetic degradation parameters of ASA and binary mixtures ASA/SA determined in DSC. The treatment of acetylsalicylic acid by DSC in non-isothermal conditions allowed to define the peak of degradation between approximately 160 and 230 °C [25]; because this is a kinetic process, the degradation temperature and the peak limiting temperatures are shifted depending on the heating rate [26], so the set range involves the lower limit of a DSC curve at 5˚C/min (Lw) and the upper limit of a curve at 20 °C/min (Up), as seen in Figure 1a.

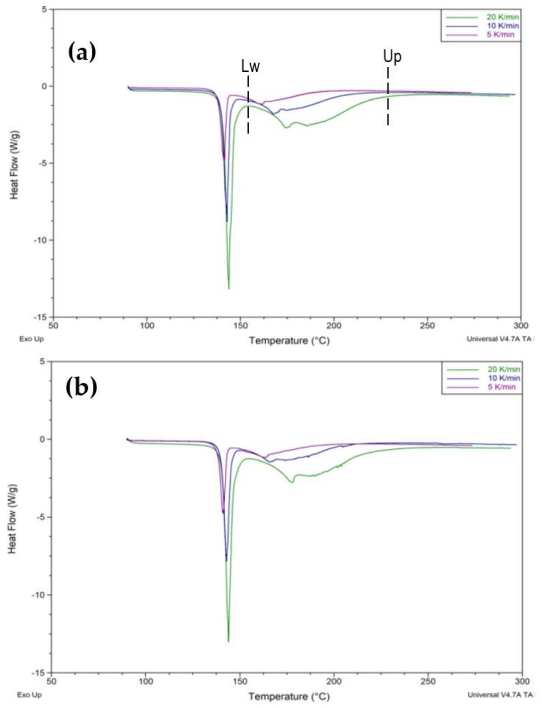

Figure 1. DSC thermograms of ASA (a) RM 1; (b) Mixture 2; (Lw) Inferior limit y (Up) Superior limit of degradation peak.

The Kissinger method or kinetic peak displacement method is based on the significant effect of heating rate on the maximum reaction temperature [26] (Figure 1). Table 2 shows the mean, standard deviation (SD) and the relative standard deviation (RSD) of *Tm* obtained from the triplicate tests in DSC.

As the velocity is doubled, the Tm values increase by about 10 °C, this ratio is maintained for all samples; the review of articles on the application of isoconversion methods to active principles such as acyclovir or zidovudine, with values for Δ*Tm* of 15 and 12 °C [27], would suggest that the relationship between β and *Tm* is characteristic of each raw material.

Table 2. Temperature of the maximum in degradation peak at different heating rates.

β [°C/min]	RM 1		RM 2		RM 3	
	Tm ± SD [°C]	RSD [%]	Tm ± SD [°C]	RSD [%]	Tm ± SD [°C]	RSD [%]
20	192,83 ± 1,32	0,69	193,36 ± 0,65	0,34	189,72 ± 2,83	1,49
10	183,07 ± 1,40	0,76	183,91 ± 0,92	0,5	181,83 ± 1,72	0,94
5	172,08 ± 2,13	1,24	174,29 ± 3,90	2,24	170,30 ± 1,57	0,92
	Mixture 1		Mixture 2		Mixture 3	
20	193,10 ± 0,41	0,21	193,32 ± 4,32	2,24	193,63 ± 4,33	2,23
10	182,59 ± 0,13	0,07	185,35 ± 2,28	1,23	180,95 ± 1,73	0,96
5	170,12 ± 2,83	1,67	175,30 ± 0,34	0,19	172,12 ± 2,34	1,36

From the adjustment of the velocity data and *Tm* to the equation (4) and the resulting plot ln (β/T_m^2) versus $1/T_m$ the kinetic parameters of Arrhenius were obtained; from the slope b = -Ea⁄R the activation energy was calculated and, replacing this value in the intercept a = ln (AR⁄Ea), the pre-exponential factor [21].

The kinetic parameters obtained from the regression are shown in Tables 3 and 4, where, the dependence of the preexponential factor of the activation energy is reflected [19]; the isoconversion methods involve a dependent calculation that agrees with the fact that to reach and surpass an energy barrier a certain number of effective molecular collisions are needed [17].

Table 3. Degradation of kinetic parameters for ASA (RM).

		RM 1	RM 2	RM 3
Activation energy	[KJ/mol]	107,43 ± 5,38	118,57 ± 2,12	112,54 ± 14,39
Pre-exponential factor	[min^{-1}]	1,29 x 10^{12}	2,46 x 10^{13}	5,98 x 10^{12}
Degradation constant (25°C)	[min^{-1}]	1,94 x 10^{-7}	4,15 x 10^{-8}	1,15 x 10^{-7}
Remanent shelf life, t_{95}	[months]	2,73	14,14	2,71

These parameters characterize the degradation kinetics of each sample and show a marked difference between them, this is more clearly reflected in the degradation constant calculated from Arrhenius equation and in the time required to reach a degradation of 5 %.

For RM 2, with the highest values of Ea and A, it is necessary that approximately 14 months elapse to come out of specification, compared to RM 1 and RM 3 which require 2.7 months. For the most recent ASA (RM 1), the remaining shelf life is similar to the oldest one; this fact cannot be attributed only to the amount of SA present, but also to factors related to the synthesis, storage, and transportation of samples.

Table 4. Degradation of kinetic parameters for binary mixtures

		Mixture 1	Mixture 2	Mixture 3
Activation energy	[KJ/mol]	95,67 ± 6,51	125,41 ± 10,35	102,91 ± 9,99
Pre-exponential factor	[min^{-1}]	5,38 x 10^{10}	1,48 x 10^{14}	3,84 x 10^{11}
Degradation constant (25°C)	[min^{-1}]	9,32 x 10^{-7}	1,58 x 10^{-8}	3,59 x 10^{-7}
Remanent shelf life, t_{95}	[months]	0,96	33,69	2,54

The binary mixtures (Table 4) follow a similar trend to raw material, the intermediate value of %SA (Mixture 2) was the most stable; considering that the three mixtures were prepared under the same conditions and with the same ASA batch, the highest

stability can be attributed to the existence of an optimum value of α (% SA) at which the rate of degradation is minimal; as it is known, for solid state reactions, Ea may vary with the progress of the reaction [19].

In order to establish a relationship between kinetic parameters of the naturally degraded ASA and those of the artificial mixtures, the activation energies were compared by simple ANOVA, since the assumptions of sample independence, normal distribution, and homogeneity of variances are satisfied.

Since the p-value was 0.6371 ($p \geq 0.05$), we established that there was no statistically significant difference between activation energy of raw material and binary mixtures. Figure 2 shows confidence intervals at 95% for the Ea average.

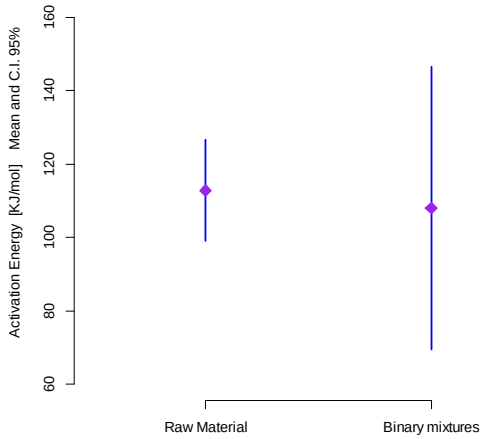

Figure 2. Activation energy for raw material and binary mixtures.

According to the previous analysis and to generalize the behavior of the studied samples, the Arrhenius diagram (Figure 3) was plotted; the existence of a point (isokinetic point) through which the lines of all the samples cross, implies that both raw materials and binary mixtures follow similar degradation kinetics.

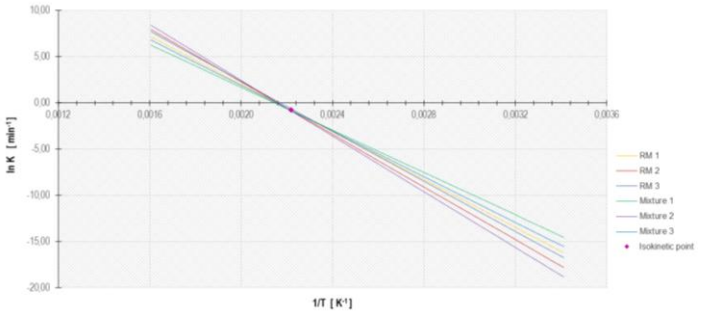

Figure 3. Arrhenius diagram for raw material and binary mixtures.

Isokinetic point represents the temperature (T_{iso}=177.67 °C) at which the rate of degradation is the same for all samples, K_{iso}=0,4659 ± 0,2474 min^{-1}; considering that the value of T_{iso} is inside the limits of degradation peak, is it possible to use equation (4) to calculate β_{iso}, that is, the required heating rate in the non-isothermal treatment (β_{iso} =7,17 ± 0,88 °C/min) in which *Tm* is equal to T_{iso}.

3.3. Quantification of ASA and SA in aluminum capsules. To verify the assumption, in the Kissinger method, that the reaction order is 1 [20], the chromatographic analysis of the residue contained in the aluminum capsule from the binary mixtures was performed; the ASA concentration after heat treatment at all speeds was 0.0814%, representing a conversion degree of 99.92%, eliminating the possibility that the variation of the kinetic parameters is due to incomplete degradation in the DSC and involve another reaction model.

Considering that the amount of salicylic acid found in the residue (0.0161%) is lower than the initially quantified, it could be suggested the simultaneous formation of 2-(acetyloxy) benzoic anhydride 2-hydroxybenzoic anhydride, product of thermal reaction between ASA and SA [28], indicating that the variation of the "effective" activation energy, occur not only as a function of α and the heterogeneous nature of the solid sample [19], but also by the contribution of the activation energy corresponding to other processes of chemical degradation involved.

3.4. Determination of the dimensions of ASA crystals by microscopy. The complex behavior of the kinetic parameters may involve physical processes related to the shape and the particle size of the samples [29], so the dimensions of the ASA crystals of the three raw materials were determined.

Figure 4. ASA crystals: (a) RM 1; (b) RM 2 and (c) RM 3.

The area, volume and exposed surface for the degradation in each raw material are presented in Table 6.

Table 6. Specific Surface Area of ASA.

	A[1], mm²	V[2], mm³	SSA[3], mm⁻¹
RM 1	1,58	0,099	17,85
RM 2	1,88	0,139	15,99
RM 3	1,58	0,100	17,20

[1] Area, [2] Volume, [3] Specific Surface Area

If a solid-state reaction occurs at surfaces, larger particles, which have a lower specific surface area, will be less reactive than smaller particles [19], this explains how RM 2 with less area available for the reaction also has a lower rate of degradation.

The different probability density for particle sizes, estimated through nonparametric Gaussian kernels (Figure 5), also help to explain the different degradation rates. Different samples of the same material may have different imperfection distributions. Therefore, no two solid samples are identical, although they may be similar [30]. This changes the degradation kinetic profile of RM 2 and once again it is different from the others.

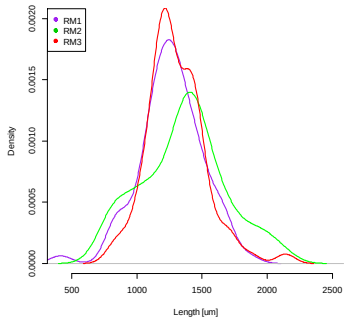

Figure 5. Particle size distribution of ASA

For further studies, the size and shape of the crystals should be carefully controlled, for example by recrystallization and/or sieving, to determine their influence on the kinetic parameters; in the same way the effect of relative humidity should be included in the study.

4. CONCLUSIONS

The non-isothermal variable heating rate method of Kissinger in DSC is a fast tool for estimating the remnant shelf life in raw material; and is sensitive enough to detect activation energy differences possibly related to variations in composition, production process or storage. For analyzed samples of ASA, an inverse relationship between Specific Surface Area and remnant shelf life was found; crystallization step should be carefully controlled to obtain crystals of 16 mm^{-1}.

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