Hindawi
Journal of Nanomaterials
Volume 2018, Article ID 3047178, 7 pages
https://doi.org/10.1155/2018/3047178

Review Article

Drug Nanoparticle Stability Assessment Using Isothermal and Nonisothermal Approaches

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Received 30 April 2018; Revised 18 July 2018; Accepted 30 July 2018; Published 28 August 2018

Academic Editor: Victor M. Castaño

Many drugs are administered in the form of liquid-dispersed nanoparticles. Frequently, one of the overlooked aspects in the development of this drug delivery system is the loss of efficacy and the degradation of the carried drugs. Estimating the shelf life of drug products implies the storage of samples under controlled conditions of temperature and humidity for different periods, ranging from months to years, delaying decisions during development, manufacturing, and commercialization. Adapting well-known isothermal and nonisothermal methods to nanoparticles would allow correlating kinetic parameters obtained in a single mathematical model and predicting the shelf life faster than traditional methods. Unlike the traditional approaches, the isoconversional method (i) considers drug products as heterogeneous systems, without a unique kinetic order, (ii) establishes a maximum percentage of degradation, (iii) assumes the same kinetics for all processes regardless of the conditions, and (iv) includes the influence of humidity by a modification of Arrhenius equation. This method serves in calculating the kinetic parameters and shelf life derived from them, in a few weeks. In the same way, nonisothermal treatments allow obtaining these parameters by differential scanning calorimetry. Samples are subjected to different heating rates to establish the temperature at which the thermal decomposition event occurs and, thus, to calculate in a few days the activation energy and the preexponential factor using the Kissinger method. But this approach has limitations: the isoconversional method does not consider crystalline state of the sample, while nonisothermal method ignores the effect of the storage conditions. Processing nanoparticles for isothermal and nonisothermal treatments would allow accurate and fast prediction of the drug-loaded nanoparticle shelf life correlating parameters obtained using a single mathematical model. The accuracy of the prediction would be assessed by comparison of estimated shelf life versus data coming from traditional stability studies.

1. Introduction

1.1. Nanoparticles as Drug Carriers. Nanotechnology offers different solutions in the development of new therapeutic strategies for the treatment of diseases where traditional solutions have already failed. As an important specific application, nanomedicine emerged, this is a new science with diverse therapeutic possibilities for the development of new treatments [1].

Many drugs are frequently supplied in the form of nanoparticles dispersed or not in a liquid for consumption. These particles have diameters in the range of one to several hundred nanometers and are presented in colloidal forms. Poorly soluble drugs that have an average particle size between 200 and 600 nm are stabilized in suspension by surfactants and/or polymers in a dispersion media. In crystalline nanosuspensions, the drug is maintained with a decreased particle size and an increased surface area leading to a higher rate of dissolution [2] and thus better bioavailability. Nanoparticles intended for oral administration are often presented in nanosuspensions, commonly transformed into a solid paste to prevent sedimentation, cremation, and crystal growth. This facilitates drug administration, patient comfort, and medication compliance [2].

One of the main problems of nanoparticles in suspension is the great difference that they present in the saturation

solubility and the concentration gradient that can give rise to Ostwald maturation (small crystal dissolution to increase size of larger crystals). The process of producing nanoparticles can lead to (i) a crystalline or amorphous product, (ii) a mixture of both, or even (iii) a disordered phase. Amorphous nanoparticles are prone to particle growth due to Ostwald maturation; on the other hand, it can be highly unstable in the presence of small amounts of crystalline particles. In addition, the high surface energy of these particles triggers agglomeration of the drug crystals. These phenomena can be controlled by the addition of various additives to ensure adequate stabilization. The main function of the stabilizer is to coat the drug particles to prevent Ostwald maturation and agglomeration of the nanosuspension and to achieve a physically stable formulation by providing a steric or ionic barrier. Suitable wetting of drug particles as well as their electrostatic and steric stabilization by excipients is necessary to produce stable nanosuspensions [3, 4].

As it happens for many other nanoparticles of different natures, the industrial production of pharmaceutic nanoparticles is also carried out through two basic approaches: (i) bottom-up, upstream process and (ii) top-down, downstream process. The first consists of controlled precipitation or crystallization to make nanoparticles of desired size from the molecular state, while the latter technologies consist of mechanical wear of large drug powder into smaller particles. The relationship of production process in the stability of nanoparticles is not yet completely clarified, but it is highly probable that processes requiring high levels of mechanical energy, like top-down ones, affect the most.

To improve nanoparticle bioavailability, it is of prime importance to control their extent of dispersion and, therefore, an encapsulation process is required. In this respect, drug nanoparticles can be straightforwardly encapsulated in the presence of polymers, surfactants, and both. These polymeric nanoparticles have been extensively investigated in both pharmaceutical and medical fields because their subcellular size and biocompatibility with tissue and cells can serve in controlling their release properties in vivo. The most common methods to elaborate polymeric nanoparticles are based on solvent-based encapsulation such as selective nanoprecipitation in the presence of surfactants. It is now clear that the stability of heterogeneous particulate systems depends on the number of components. As the number of components increases, greater is the possibility of negative interactions of a physical or chemical type with deleterious effects over the stability of the particle.

Most of the characterization processes are performed in nanoparticle dispersions. These analyses are carried out in a very similar way to traditional studies, where the particle size, appearance, color, odor, and related impurities are analyzed. In addition, dispersion is also evaluated for zeta potential, crystalline state, dissolution, and *in vivo* efficacy. For an electrostatically stabilized nanodispersion, a suitable zeta potential is above +30 mV or below −30 mV and for a static and electrostatic stabilization, it must be above +20 mV and below −20 mV. Dynamic light scattering (DLS) is a fast and sensitive method, especially for determining particle sizes that are in the nanometer range, requiring only a small amount of particles. Therefore, it is very suitable for routine measurements and development of early formulation, when only small amounts of API are available [5].

1.2. Stability Test for Drug Delivery Systems. Determining the stability of a pharmaceutical compound in the form of nanoparticles is critical in terms of safety and efficacy. These tests serve to recommend ideal storage conditions and to establish the effect of out-of-specification results or deviations on the manufacturing process. This will ultimately affect the safety, efficacy, or quality of a drug in the short term, medium term, or long term.

There are different stability tests to determine the shelf life of pharmaceutical forms. Official guidelines—such as those recommended by *International Conference of Harmonization, ICH Q1A (R2), Stability Testing of New Drug Substances and Products* (2003)—describe an isothermal process, where the sample is subjected to constant temperature and humidity conditions for a minimum period of 12 months in the case of long-term studies and 6 months for accelerated studies in order to determine the decreasing content of active principle during degradation, as well as changes in other parameters specific to the performance of the product such as degradation products, dissolution test, and appearance.

Traditional stability methods are based on the application of mathematical models that come from the kinetic theory of gases to wide variety of liquid, semisolid, and solid drug products. These tests are applied at different stages of drug product life cycle. In early stages, extreme conditions of temperature and humidity are investigated, not only to identify the degradation products that can be found in long-term storage but also to select the most promissory drug candidates. Other studies are also carried out a posteriori under less severe conditions to predict the shelf life of products.

In addition to these tests, real-time stability tests are performed over long periods (months to years). During these studies, the evolution of the degradation process is measured sampling at different time points. The reliability of data interpretation can be increased by including a batch of reference material, the characteristics of which have already been established.

In accelerated stability tests, samples are subjected to relatively high temperatures in order to cause an increase in degradation rate, in an attempt to reduce the time necessary to take decisions over safety, efficacy, and quality of medicines. These methods are used to predict drug shelf life or for comparison with alternative formulations. The most used is Arrhenius method, which determines the variation of the kinetic constant as a function of temperature; its application requires knowing the kinetic order of reaction.

1.3. Kinetics in Heterogeneous Drug Delivery Systems. The study of the rapidity of physical and chemical transformations is of great importance, since it has uses in many fields of industry, pharmacy, or chemistry, both in its processing conditions and in the storage of raw materials and products.

Most pharmaceutical nanoparticulated systems are highly complex and not homogeneous at molecular or atomic levels,

so approaches based on gas kinetic theory which assumes that each reactant molecule is surrounded mostly by vacuum probably are not the best. The transformations of substances in such systems comprise changes in physical state, crystallization, melting, solubility, chemical reactions, etc. that can be thermally stimulated by heating or cooling processes. The speed and form to which they are transformed are determined by the kinetic characteristic of the system [2].

The classical method of assessing pharmaceutical stability has three main problems that must be considered: First, a mathematical model that attempts to match the kinetics of solid substances must be created. The second element to be considered is the effect of relative humidity on the reaction kinetics, and the third lies essentially in the time required to perform the determination of stability [6].

From the classical perspective, chemical reactions can be fitted into a mathematical model with a certain kinetic order. Nevertheless, this approach may be appropriate when dealing with homogeneous systems, such as chemical reactions that occur in gaseous or liquid solution where the intensity at which the reaction takes place is a function of the total molecules present in the volume occupied by the system, in other words, the kinetic equations are expressed as a function of the concentration of the reactants. In the case of a heterogeneous system, a substance that reacts with an external agent is not mixed at the molecular level, and the reactants should be represented as individual phases, which interact at the interface. In pharmaceutical forms, the active pharmaceutical ingredient (API) may exist in several states, which may be modified as changes in temperature occur in the system. Parallel to the physical transformation, processes of chemical degradation can develop, which also modify the structure of the API and even of excipients. In such scenario, mathematical expressions describing the rate of degradation will be only approximated.

In the evaluation of the reaction kinetics in heterogeneous systems, the only concentration of importance is at the reaction interface, which cannot be quantified in a practical way; for this reason, the way of monitoring the development of the reaction is measuring the degree of conversion (α) of the reagent or the product [7]. Considering the above, the kinetics of transformation can be represented by

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

where α is the magnitude of the chemical or physical conversion, t is the time, T is the temperature, $f(\alpha)$ is the reaction model, and $k(T)$ is the proportionality constant whose value depends on temperature and is defined by Arrhenius equation:

$$k(T) = Ae^{-E_a/RT}, \tag{2}$$

where A is the collision factor, E_a is the activation energy, R is the constant proportionality of the ideal gas, and T is the system's temperature.

The degree of transformation can be defined in different ways, either as a decrease in the amount of the substance of interest or in the generation of a decomposition compound.

$$\alpha = \frac{\Delta C}{C_0}. \tag{3}$$

For the purposes of the present study, α is considered to be

$$\alpha = \frac{C_0 - C}{C_0}, \tag{4}$$

where α corresponds to the extension of change in a specific parameter of interest, the amount of degraded substance for example; in this particular case, C_0 is the initial concentration of substance and C is the amount of substance measured at time t [8].

For homogeneous systems, the chemical kinetics of reactions can be classified as first, second, and third order; in heterogeneous systems, models should be developed to describe the phenomena of kinetic transformation, and three main types of kinetic behaviors are identified and represented by isothermal curves α versus T: acceleration, deceleration, and linear sigmoidal.

In acceleration models, the degree of conversion α increases with time; on the contrary, in the deceleration models, the conversion rate decreases over time; sigmoidal ones share the characteristics of both and represent autocatalytic process. The three types of kinetics can spread on dozens of heterogeneous reaction models. Frequently, experimental data do not fit any model, or if it does, it will fit one of them at the beginning of the process and other at the end. The challenges increase when model fitting is performed on experimental data obtained in a nonisothermal run at a single heating rate, β [9].

To overcome this complexity, the isoconversion paradigm was developed: it allows the calculation of the Arrhenius equation constants, without the need to determine the order of the reactions.

1.4. Isoconversional Methods. The isoconversion is a methodology created by Kujirai and Akahira in 1925, who studied the decomposition of materials under isothermal conditions, allowing them the determination of the activation energy as a function of mass loss; in 1948, Dakin proposed some kinetic models in the decomposition of complex materials; and, in the 1950s, instrumentation was generated that allowed the study of materials under nonisothermal conditions.

Modern methods maintain the principle of isoconversion through flexible integration procedures for the determination of activation energy. Moreover, it has been observed that the activation energy obtained from the free models is independent of the heating rate, but certain studies indicate that there would be dependence of the heating range.

The kinetic isoconversion methods are based on the elimination of the reaction model from kinetic calculations. The principle states that the rate of conversion, under certain environmental conditions, depends solely

on temperature. For the experimental determination, it is necessary to establish a specification (broken line in Figure 1), an acceptation limit to which the samples must not reach, in a determined time, in order to remain safe and effective.

In plotting degradation versus time, the shape of the curve would be the same at different temperatures, being more pronounced at elevated temperatures and with a tendency to look like a straight line as the temperature decreases [10]. From Figure 1, it can be said that the lines $k1$ and $k2$ start from zero as the origin and can be described by

$$ki = \frac{\alpha i}{ti}. \tag{5}$$

If the degradation value α is the same for the lines $k1$ and $k2$, one has to

$$k1t1 = k2t2. \tag{6}$$

It is possible to calculate the value of the kinetic constants based on a fixed degradation limit, regardless of the shape of the curve. Thereby, a sample submitted to intense conditions of temperature and humidity will reach a predetermined limit in a specific time. The isoconversion stability test uses some samples as maintained at different temperature and humidity conditions, in order to determine the values of the kinetic constants at different temperatures [6, 11, 12]. Unlike the gaseous or solution state kinetics, where the molecules react according to a reaction order, in nonhomogeneous systems, the molecules are arranged in multiple unbalanced states, characterized by their variable mobility, where each one can react to form products under their own kinetics. The kinetics of the set of states or phases is complex. In this situation, the isoconversion method is advantageous for the determination of degradation kinetics because it only considers the time to reach the specification [13]. There are some types of isoconversional methods.

Standard isoconversion method uses the logarithm of the exponential relation between degradation and time of the Arrhenius Equation, for data of an isothermal process, of the function $g(\alpha)$, which expresses the degree of conversion.

$$\ln g(\alpha) = \ln A - \left(\frac{E_a}{RT}\right) + \ln t. \tag{7}$$

Friedman's method is a differential method expressed as

$$\ln\left(\frac{d\alpha}{dt}\right) = \ln A f(\alpha) - \left(\frac{E_a}{RT}\right). \tag{8}$$

Ozawa Flyn and Wall, who applies to data from nonisothermal process:

$$\log g(\alpha) = \log\left(\frac{AE_a}{R\beta}\right) + \ln p(x), \tag{9}$$

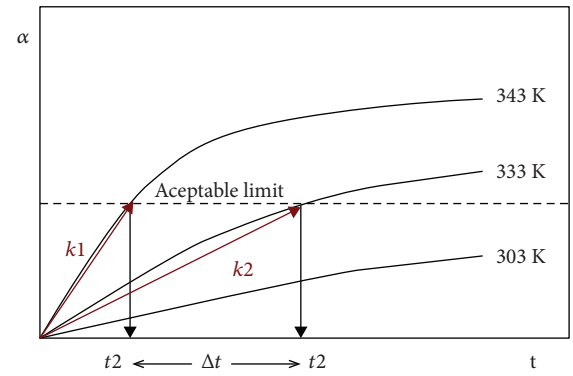

Figure 1: Relation between the degree of conversion and the time at different temperatures (graph based on [9]).

where $p(x)$ is the integral function of Arrhenius, x is equal to E_a/RT, and $\beta = dT/dt$ [2].

1.5. Moisture Effect. Moisture has a significant effect on the stability of the pharmaceutically active ingredient even if the reactions do not involve water molecules. As the temperature increases, the water content in the atmosphere for a given relative humidity value increases; however, the water activity depends only on the relative humidity (% RH) value [14]. One of the main effects of the relative humidity value is the loss or addition of water molecules of hydration in the crystalline forms of the active principle; in certain cases, this loss of water of hydration can result in the complete transformation of the API to the amorphous state, which may present a higher instability than the crystalline forms. For a given temperature, the effect of moisture on the kinetic constant can be represented by the following equation:

$$\ln k = B(\%\mathrm{RH}) + C. \tag{10}$$

This expression is called moisture sensitivity equation, where B and C are constants. The value of B usually ranges from 0.00 to 0.09; for example, under conditions of 10% RH, B will have a value of 0.00, and under conditions of 75% RH, B would have a value of 0.09.

1.6. Combining the Effect of Temperature and Relative Humidity. The combination of Arrhenius equations and moisture sensitivity [6] gives an equation that considers the effects of temperature and humidity on API stability.

$$\ln k = \ln A - \left(\frac{E_a}{RT}\right) + B(\%\mathrm{RH}). \tag{11}$$

This equation states that the rate of degradation, or kinetic constant, depends on temperature and relative humidity.

Because the equation has 3 constants A, E_a, and B and two independent variables, the minimum number of experiments required to solve the equation is three, being necessary to increase the number of points to improve the accuracy of the measurements [13]. In most studies, two to three weeks may be suitable to determine the shelf life of a product under

environmental conditions. Some authors suggest considering the variation of 5°C and 5% of RH for 14-day assay.

These measurements can be used to estimate the isoconversion time in each condition. (1) First, draw a line through the data to find the intercept with the limit specification. (2) The two points closest to the specification limit can be used to interpolate or extrapolate the time to reach the specification. (3) A single point closest to the specification can be used to determine $k = \alpha/t$.

To determine the relationship between the variables with the degradation, two methodologies can be used: (1) transform the Arrhenius equation to the linear form and determine the constants by least squares regression and (2) make a least squares fit in the exponential form.

1.7. Accuracy of Accelerated Isoconversion Stability Studies. The determination of the value of the constants in the corrected Arrhenius equation for moisture is associated with an imprecision value from the measurements. In addition, extrapolation is required in the axes of temperature and humidity, incorporating another imprecision factor. Applying an error propagation procedure in the corrected Arrhenius equation is mathematically complicated; instead, an approximation is used by simulation. The approach used is the Monte Carlo method, which provides variations at each temperature and relative humidity, within a certain range, and makes a least squares fit with all possible combinations. In the application of the simulation with the Monte Carlo method, a normal distribution and its standard deviation are assumed. The process comprises 5000 simulations, in order to build confidence limits for kinetic parameters [15]. In the development of the isoconversion stability test, it is necessary to consider the following: (i) the precision of the analysis will affect the accuracy of the shelf life, the improved result may increase the number of repetitions, but in many cases, it will not be necessary. (ii) Greater extrapolation in the magnitude of % RH or temperature generates a greater error of the predictions, (iii) for certain API's, broad extrapolations provide an acceptable determination. (iv) Conditions of low humidity levels and high temperatures can cause problems if physical changes are generated, such as dehydration and changes of crystalline forms.

1.8. Nonisothermal Methods. As previously stated, stability tests provide information on how the quality of an API, excipient, or drug delivery system changes as a function of time under the influence of environmental factors such as temperature, humidity, and light, in order to establish the shelf life of the compound and propose the best storage conditions.

The factors influencing the reaction rate of homogeneous systems, such as temperature, pressure, and composition, do not include factors characteristic of heterogeneous systems such as the matter transport between phases and the mode of interaction between these phases.

This leads to the use of standard methods to determine small changes in drug concentration, which have low sensitivity and therefore require the previous dissolution of the solid product, causing distortions in the test as a result of the acceleration of the decomposition process when the compound is solvated.

Applying a nonisothermal treatment by differential scanning calorimetry would reduce the analysis period from months or years to a few days and reduce the problems related to the evaluation of heterogeneous systems.

In order to do that, some points have to be issued. First, it is necessary to create a mathematical model that could adjust to the kinetics that develops in condensed phases; the second element to be considered is the effect of the relative humidity on the reaction kinetics, and the third one is the necessary time to carry out the determination of the stability.

The traditional kinetic models state out that their postulates on the concentration monitoring as a function of time consider the system as homogeneous and accept the loss of precision by assuming a zero-order model for all reactions.

For heterogeneous systems, kinetic studies monitor the degraded fraction, α, as a function of time and reaction order models are much more varied than for liquids. To deal with the large number of models involved, isoconversional methods have been developed, which do not need to consider the reaction model, focusing instead on the failure time or shelf life, t_α, i.e., the time during the substance, which undergoes decomposition as a result of the conditions under which it is stored, is kept within acceptable limits.

The kinetic parameters of a decomposition reaction can be estimated using differential scanning calorimetry (DSC).

If a sample is subjected to different heating rates, β, in DSC, the maximum decomposition temperatures T_m increase as β increases.

According to Kissinger's method, if $\ln(\beta/T_m^2)$ is plotted as a function of the inverse of T_m, the activation energy of the reaction, E_a, can be determined from the slope of the line.

$$\ln\left(\frac{\beta}{T_m^2}\right) = a - b\left(\frac{1}{T_m}\right). \tag{12}$$

In which

$$a = \ln\left(\frac{AR}{E_a}\right), \qquad b = \frac{E_a}{R}. \tag{13}$$

Once E_a is known, the value of A can be estimated by the expression:

$$A = \beta\left(\frac{E_a}{RT_m^2}\right)\exp^{(E_a/RT_m)}. \tag{14}$$

The values of the decomposition rate constant, k, can be calculated for a reference temperature, T, by

$$\log k = \log A - \left(\frac{E_a}{2.3RT}\right). \tag{15}$$

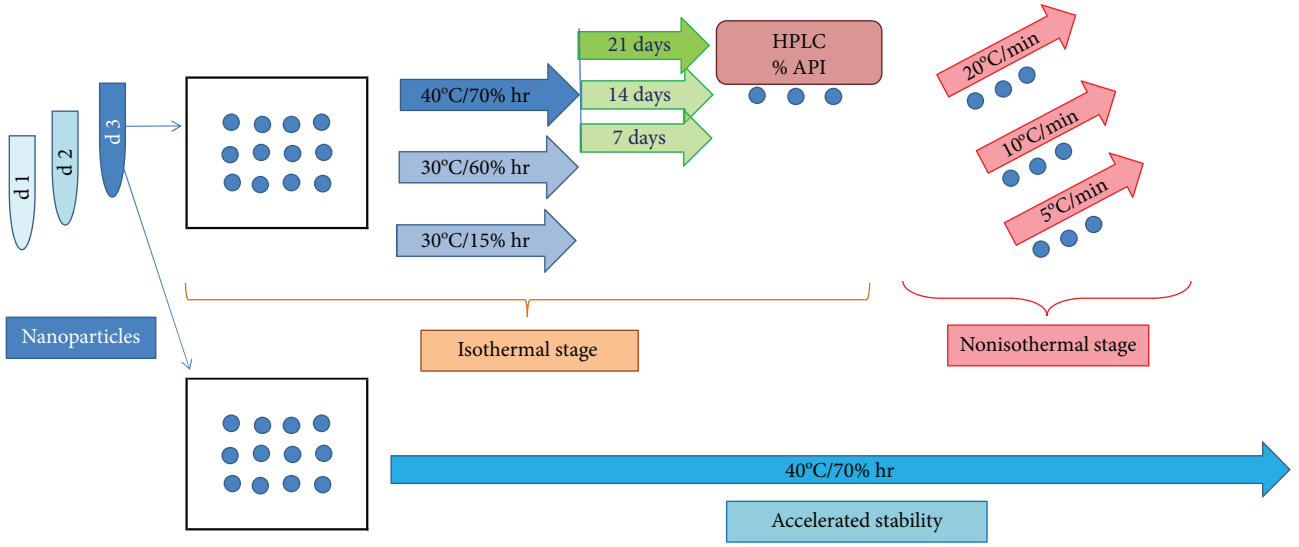

Figure 2: Schematic representation of methodology combining isothermal isoconversional and nonisothermal approaches for the assessment of shelf life in nanoparticles.

Low E_a values would imply a lower energy barrier to be overcome for degradation to occur and, therefore, less stability; low values of k would indicate longer times until the substance comes out of the specification by decomposition.

The shelf life of a drug delivery system is the period during it remains under the acceptable limits, for example, an API content $\geq 95\%$ (or a value of $\alpha = 0.05$); it can be calculated by

$$t_\alpha = \frac{-\ln\left(1 - (\alpha/100)\right)}{Ae^{(-E_a/RT)}}, \quad (16)$$

where the reference temperature, T, is 298.15 K (25°C) [16].

The kinetic parameters and the shelf life time are used to compare API from different batch, manufacturer, time, or storage conditions and make inferences about their stability and decomposition progress. In the case of drug delivery systems, decisions can be made about which formulation has the greatest stability or whether a formulation in the process of development is similar or not to a market one, of known stability.

The validity of the predictions of shelf life must be verified because the calculations are made by assuming that (i) the reactions are of first order; (ii) the values of the kinetic parameters are similar for the temperatures in the study range; and (iii) the effect of moisture is not significant. Studies that propose new methods of analysis or that provide specific information on an active principle such as kinetic parameters and degradation pathways are very useful in the pharmaceutical industry because they can save resources, as well as guarantee the safety, quality, and effectiveness of medicines.

Thermal analysis techniques such as differential scanning calorimetry (DSC) allow the characterization and identification of physicochemical changes in the solid state of different compounds, thus streamlining the process of preformulation and development of drugs and substances of pharmacological interest. Its use is not limited solely to the determination of purity, polymorphs, solvates and hydrates, melting point, and component quantification but also allows the characterization of the surface properties of powders, such as humectants, adsorbents, and surface energy, thus constituting a useful tool in decision making in the case of problems related to the production process.

Another advantage of using a nonisothermal method is that it is not based on any assumptions about the reaction mechanism and thus does not require any prior knowledge of the initial concentration of the API, which eliminates the prolonged reaction times and storage requirements required by conventional techniques.

It also allows the saving of money, labor, and amount of drug used and decreases the generation of waste, which even lowers the cost of the drug, making it more accessible for the population.

Finally, by combining isothermal isoconversional and nonisothermal method, their individual limitations could be overwhelmed, allowing a faster and accurate shelf life estimation that could be contrasted against data obtained from accelerated or long-term stability studies. This proposal is schematized in Figure 2.

1.8.1. Isothermal Stage. Nanoparticles should be weighted in 18 open aluminum capsules for DSC; all the capsules of the same type of nanoparticle (d1, d2, or d3) are placed in specially designed supports, subjecting the nanoparticles to the established humidity and temperature conditions (3 different conditions). Keep the nanoparticles to the selected conditions during the selected time (3 storage times). Quantify by HPLC the amount of API remaining in 3 capsules at 7, 14, and 21 days.

1.8.2. Nonisothermal Stage. For T_m determination, submit the remaining 9 capsules of isothermal stage at three different

heating rates (3 capsules for each speed). Calculate the kinetic parameters for the isothermal and nonisothermal methods.

1.8.3. Accelerated Stability Study Stage. Another set of 12 samples will be subjected to 40°C and 75% RH in accelerated traditional stability study. Samples will be taken at 1, 2, 3, and 6 months and analyzed for API content.

Using the API remaining quantity in each sample, corresponding to each temporal point, elaborate confidence hyperbola to establish the shelf life.

The accuracy of the estimated shelf life will be assessed by comparison with long-term stability data. A mathematical model to predict shelf life stability should be established.

2. Conclusions

The development of a fast and reliable method to assess shelf life nanoparticles by isothermal and nonisothermal methods allows to calculate its kinetic parameters and to establish a mathematical model to estimate its shelf life.

The accuracy of mathematical model could be assessed by comparison of predicted shelf life versus results coming from long-term stability studies.

Isothermal isoconversional methods and nonisothermal treatments could allow the establishment of mathematical predictors of stability with less uncertainty than traditional approach for nanoparticles.

Conflicts of Interest

The authors declare no competing financial interests.

Acknowledgments

This work was supported by IDIVAL INNVAL17/11.

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