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REVIEW

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Systematic strategies for degradation kinetic study of pharmaceuticals: an issue of utmost importance concerning current stability analysis practices

Dhiraj Bhangare[†], Niraj Rajput[†], Tarang Jadav, Amit Kumar Sahu, Rakesh K. Tekade and Pinaki Sengupta[*]

Abstract

Degradation kinetic study ascertains the shelf life of drugs under different environmental conditions. It can facilitate the prediction of specific critical factors that can affect the quality of pharmaceuticals during storage. To date, general systematic strategies for performing degradation kinetics of drugs have not been discussed in any literature. Moreover, no regulatory guideline is available on the degradation kinetic study of pharmaceuticals. Owing to this, the kinetic behavior of drugs is not being analyzed uniformly. This article provides a detailed insight into degradation kinetic approaches including criticality in selecting different variables for the study. Factors that can affect the quality of degradation kinetic study data have been critically discussed. In addition, a systematic strategy to perform degradation kinetic study with advanced degradation models has been discussed. This article will be helpful for the researcher working in the field of stability analysis and guide to select a logical path for determining the kinetic behavior of drugs. High-quality degradation kinetic data through the properly designed study will help to establish accurate storage conditions of pharmaceuticals. This article is unique and novel of its kind and would have a significant contribution to the field of stability analysis.

Keywords: Degradation kinetics, Practical approaches, Advanced models, Stability, Pharmaceuticals

Introduction

Stability of pharmaceuticals is a critical quality attribute (CQA) and an integral part of the pharmaceutical drug development program. The term stability primarily refers to a drug's ability to maintain its chemical nature, strength, and efficacy within pharmacopoeial limits. Stability also includes considerations regarding shape and size, palatability, uniformity of content, dissolution rate, suspendability, resistance to microbial growth, and, most importantly, therapeutic effect without significant increases in toxicity during its shelf life (Jain et al. 2011; Tapkir et al. 2021). Stability of pharmaceutical products can be determined by assessing their quality with a variety of environmental factors such as relative humidity, light, and temperature. Stability testing of pharmaceuticals is important to describe product's safety, quality, and efficacy, as well as to determine its shelf life. Degradation of a pharmaceutical product includes a variety of chemical reactions initiated by different factors including pH, temperature, and light. It is important to study the kinetic behavior of these reactions to generate predictive data for the calculation of shelf life of pharmaceutical products (Pokar et al. 2020b; Sahu et al. 2021; Sharma et al. 2021). The term degradation kinetic refers to the study of the rate of drug degradation. Data obtained from the degradation kinetic study can be used to generate a better

*Correspondence: psg725@gmail.com
[†]Dhiraj Bhangare and Niraj Rajput have contributed equally to this work
National Institute of Pharmaceutical Education and Research-Ahmedabad (NIPER-A), An Institute of National Importance, Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India, Gandhinagar, Gujarat 382355, India

understanding of the mechanism behind drug degradation. Moreover, it also helps to suggest better packaging and storage conditions for pharmaceuticals to improve their shelf life (Pokar et al. 2020a).

Stability testing can be carried out under accelerated conditions such as temperature and humidity to enhance the rate of pharmaceutical degradation for obtaining stability data in a short period. In the literature, various degradation kinetics models have been reported by the researchers and many of them have already been applied to basic systems such as drug crystals or API. Study of drug degradation kinetic in its solid form is significantly more complex due to the overlapping of one or more degradation reactions at a time. However, the initial decrease in potency is largely due to pharmaceutical stability issues which depends on order of their degradation kinetics. Sometimes, residual moisture present in drug substances and drug products can lead to a large number of solid-state reactions (Zhou et al. 2017). Degradation kinetics generally involves the degradation of a drug under various stress conditions. Different kinetic variables can be subsequently utilized to evaluate the order of drug degradation through the best-fitted line model based on regression coefficient. Thereafter, various kinetic parameters such as rate constant, half-life ($t_{1/2}$), time taken for 10% degradation (t_{90}), and activation energy (Ea) required to initiate the degradation reaction are determined. The t_{90} data are used to interpret shelf life of the pharmaceuticals and to establish their expiration date (Oliveira et al. 2016).

It is important to study the degradation kinetics of pharmaceuticals to ascertain their shelf life under different environmental conditions. Evaluation of degradation rate under different stress conditions reveals the CQAs of drug stability. The primary objective of this review article is to provide a detailed insight into the degradation kinetics of pharmaceuticals. In this review, conventional and advanced approaches including individual steps employed in drug degradation kinetic study have been explained. In addition, criticality in selecting different variables for degradation kinetics for generating better drug stability data has been discussed. Factors that can affect the quality of degradation kinetic study data have been critically discussed. Moreover, systematic strategies to perform degradation kinetic study with advanced degradation models have been described.

Stability of pharmaceuticals

Physicochemical properties of drug substances and drug products can get altered during their use, storage, and transport. The significance of instabilities that occur in drug products are primarily described by stability of drug products. Pharmaceuticals may generate toxic substances because of unfavorable environmental factors like moisture, temperature, pH, light, and air. This affects the quality, efficacy, and other properties of drugs. For instance, Fanconi syndrome is caused due to the toxicity of epianhydrotetracycline, a degraded product of tetracycline. Pharmaceutical stability can be defined as the potential of a drug substance or drug product to resist any change in its physical, chemical, biopharmaceutical, and microbiological property with respect to change in environmental factors (temperature, light, humidity, etc.). Pharmacological stability can be defined as the ability of a pharmaceutical product to preserve its original pharmacological effect to the same extent throughout its shelf life. Toxicological stability can be defined as the ability of a drug product to resist any increase in its toxicity during shelf life. Physical stability means that the physical characteristics of the pharmaceutical product, such as size, shape, hardness, appearance, brittleness, and particle size, stay unchanged over its shelf life. Abrasion, vibrations, and temperature variations are the main causes of physical shape change. These characteristics must be maintained throughout the medication development and shelf-life processes. The drug efficacy and safety are ensured by stability and maintained throughout the production, formulation, packing, and storage stages (Yoshioka and Stella 2000). Table 1 summarizes different types of pharmaceutical stability and their requirements. Precipitation, sorption, and leaching are examples of physical instability. Chemical stability indicates the absence of any change in the chemical constituent of the drug product. Drug products can experience chemical degradation by

Table 1 Different types of pharmaceutical stability and its requirement

Sl. nos.	Types of stability	Stability problems	Stability requirements
1.	Physical	Precipitation, sorption, leaching, color change	Physical appearance, palatability, uniformity
2.	Chemical	Reduction in active concentration of API	Chemical integrity and labeled strength
3.	Microbiological	Microbial growth	Sterility, no microbial contamination
4.	Toxicological	Toxicity	No increase in toxicity
5.	Therapeutic	No therapeutic activity	Drug action does not change on storage

various reactions like oxidation, hydrolysis, and photolysis. Such chemical reactions can lead to reduction in the concentration of the active ingredient present in a formulation. Moreover, it may cause formation of unwanted degradation products. Microbial stability is related to the sterility of drug substances or products and the absence of contamination with any microorganism in them. Microbial growth in drug products can compromise the safety of products and may lead to serious unwanted effects. Toxicological studies are performed to check the development of any toxic compounds because of the degradation of pharmaceuticals (Rehman et al. 2020).

Kinetics of drug degradation

Degradation kinetic study is crucial because it affects the stability of pharmaceuticals throughout the stages of product development and testing. With the help of proper storage conditions, reduction in the rate of their degradation reaction can be possible. This ensures the stability of pharmaceuticals throughout their shelf life (Rehman et al. 2020; Denisov et al. 2003).

Order of drug degradation reaction

Order of degradation reactions of pharmaceuticals is generally categorized as zero, first, and second order. Knowledge of the order of drug degradation can help pharmaceutical scientists to establish shelf life and optimum storage conditions for drug substances and drug products. Table 2 denotes different orders of degradation reaction and formulas for calculating kinetic parameters.

First-order degradation reaction

Most pharmaceutical products are found to get degrade through first-order reactions. The reaction rate of first-order degradation of drugs under different environmental conditions can be determined through a decrease in the initial concentration of the drug with time. Hence, degradation reaction rate is proportional to a decrease in the initial concentration of the drug as a function of time. Equation 1 denotes the formula for the rate of drug degradation through a first-order reaction. A negative sign denotes a decrease in the initial concentration of the drug as a function of time.

$$r = -\frac{\mathrm{d}[A]}{\mathrm{d}t} = k_1[A] \tag{1}$$

where A designates the concentration of a drug, k_1 designates the first-order rate constant, and t denotes the time.

It has been established that the degradation of imidapril hydrochloride under hydrolytic (acid/base catalyzed) conditions follows first-order degradation kinetics (Stanisz and Regulska 2013). Another example describing first-order degradation includes the thermal decomposition of meropenem a beta-lactam antibiotic when exposed to a higher temperature (70, 80, and 90 °C) for 335, 295, and 95 days, respectively. The degradations were found to follow first-order degradation kinetics (Mendez et al. 2006).

Second-order reaction

Rate of second-order drug degradation reaction mainly depends on the concentration of the drug substance and stressor. Equation 2 indicates the rate of drug degradation through a second-order reaction.

Table 2 Different orders of degradation reaction and formulas for calculating kinetic parameters

Order of degradation reaction	Kinetic parameters			Example	References
	Rate equation	Half-life	Shelf life		
Zero-order	$R = \frac{-\mathrm{d}[A]}{\mathrm{d}t} = k_0$	$t_{1/2} = [A]_0/2\,k$	$t_{0.9} = 0.1[A]_0/k_0$	Hydrolysis of atorvastatin Electrochemical degradation ceftriaxone	Ahmad et al. (2006), Ahmad and Vaid (2011), Aulton and Taylor (2007), de Haro Moreno and Salgado (2012), Jain et al. (2011), Oliveira et al. (2013), Robnik et al. (2019), Shubha and Sushma (2015) and Tutunaru et al. (2021)
First-order	$R = \frac{-\mathrm{d}[A]}{\mathrm{d}t} = kA$	$t_{1/2} = \ln(2)/k$	$t_{0.9} = 0.105/k_1$	Oxidation of butacaine Oxidation of benzocaine hydrochloride Hydrolysis of atorvastatin Thermal and photodegradation of ceftazidime	
Second-order	$\mathrm{d}[A] = \frac{-k[A]^2}{\mathrm{d}t^2}$	$t_{1/2} = 1/k[A]_0$	$t_{0.9} = (0.11/k)\,[A]_0$	Photodegradation of formamethylflavin in acidic solution Thermolysis of formamethylflavin, hydrolysis of esters in alkaline solution	

R, rate of reaction; k, rate constant; A, concentration

$$\frac{d[A]}{dt} = -k_2[A]^2 \quad (2)$$

where k_2 designates second-order rate constant and A designates concentration of the drug. Photodegradation of formamethylflavin in acidic solution, thermolysis of formamethylflavin, hydrolysis of esters in alkaline solution reported to follow second-order degradation reaction (Ahmad et al. 2006; Ahmad and Vaid 2011; Aulton and Taylor 2007). Degradation of trans-lutein (carotenoids) via isomerization into cis-lutein under ultrasonic waves was reported to follow second-order degradation kinetic at 30–50 °C temperature (Song et al. 2015).

Zero-order reaction

In zero-order kinetic, degradation reactions do not depend on the concentration of the drug and stressor. Equation 3 denotes the rate of zero-order drug degradation reactions. Zero-order reactions mainly include rearrangement or radical-mediated cleavage of chemical bonds under photolytic and oxidative stress conditions.

$$r = -\frac{d[A]}{dt} = k_0 \quad (3)$$

where A designates concentration of the drug and k_0 denote rate constant for zero-order degradation reaction and t denotes the time. Ultrasonic degradation of diclofenac under acidic (pH = 3) oxidative condition at higher concentration (40–80 mg/L) occurs through zero-order degradation kinetic (Naddeo et al. 2010). Another example includes the degradation of atorvastatin an antilipemic drug under basic hydrolytic conditions that follows a zero-order rate of degradation (Oliveira et al. 2013).

Pseudo-zero-order reaction

The main principle of pseudo-zero-order kinetics is that the drug concentration is kept constant throughout course of reaction. Therefore, degradation rate does not depend on the concentration of the drug at saturation. Pseudo-zero-order reactions are mainly seen in solid dosage forms and suspensions. Degradation kinetic study of pharmaceutical formulation such as tablet or capsule containing API sometimes represents mixed order of degradation due to overlapping effect of more than one degradation mechanism. During the degradation phase, overall degradation kinetic of the drug follows a zero-order rate. However, first-order degradation kinetics can also be observed. Equation 4 denotes the formula for the calculation of rate of pseudo-zero-order reaction, where A denotes the concentration of reactant and k_1 is the pseudo-zero-order rate constant.

$$\frac{d[A]}{dt} = -k_1[A] \quad (4)$$

Interaction between the drug and moisture present in the drug product leads to degradation of drug via pseudo-zero order. The presence of moisture causes the system to act as a suspension, and the increased concentration of solid drug makes it pseudo-zero order, and drug degradation to be linear with time. Equation 5 describes the mixed order behavior of pseudo-zero-order reaction, where $[A]_s$ denotes solubility of drug due to moisture present in the system, [A] denotes concentration of the drug, k_0 denotes zero-order rate constant, and k_1 is the first-order rate constant.

$$k_1[A] = k_1[A]_s = k_0 \quad (5)$$

Bhasker et al. reported a study on the degradation of dacarbazine (antineoplastic agent) in an aqueous solution. As per the study, photolytic degradation of dacarbazine was found to be accelerated in light at lower concentration (0.05 mg/ml) and there was a reduction in the overall degradation rate above 0.05 mg/ml concentration. This was attributed to the absorption of light by the degradation product at higher concentrations. Therefore, photolysis of dacarbazine was shown to follow pseudo-zero-order kinetics (Shetty et al. 1992).

Pseudo-first-order reaction

It only happens when one of the reactants is in a higher concentration or held constant in comparison with another substance. Therefore, rate of reaction is determined by only one reactant although both the reactants are present. In such a situation, no significant effect of the second reactant on the concentration change during the degradation reaction is observed. Degradation of ascorbic acid and hydrolysis of aspirin follows pseudo-first-order reaction (Alibrandi et al. 1996; Uddin et al. 2002). Andrea et al. have reported a study on degradation kinetics of heat-stable oxytocin formulation. As per the study, hydrolytic degradation of oxytocin at lower pH (~2) follows pseudo-first-order degradation kinetics (Hawe et al. 2009).

Parameters for degradation kinetics

Rate constant, activation energy, half-life, shelf life, and mean kinetic temperature are the primary parameters measured in degradation kinetics. Rate constant can be defined as a proportionality constant that is seen in the rate law. Rate constants are mostly independent of concentration and sometimes depend on other factors, mainly temperature. Activation energy can be defined as the lowest amount of energy needed to start any kind of chemical reaction. It is the energy gradient between

reactants and state of activation. The lower the activation energy, the faster is the reaction rate. Arrhenius equation ($k = Ae^{-Ea/RT}$) can be employed for the calculation of activation energy. Half-life of a reaction is the time taken by the reactant to reach 50% of its initial concentration. It is used in pharmaceuticals to predict the concentration of drugs over a specific time. It plays a key role in degradation of the drug during stability study. Formula for the calculation of half-life for different orders of reactions is mentioned in Table 1. Shelf life is the time during which the pharmaceutical product is predicted to be stable and remains fit for its intended use under specified storage conditions. Shelf life of pharmaceuticals can be estimated by using mean kinetic temperature. The idea of mean kinetic temperature is utilized to ensure that real-time storage circumstances do not have a direct impact on the drug's stability and shelf life. This is mostly because degradation rate constants are temperature sensitive. It may be evaluated following the procedures described in USP and FDA. The USP method calculates the mean kinetic temperature by averaging the temperatures measured over one year. Hayne's equation, which is a variation of the Arrhenius equation, is used to calculate 52 data points in this approach (Bajaj et al. 2012).

Arrhenius equation and its use in degradation kinetics

Arrhenius regression equation is the most commonly used mathematical model for the assessment of stability of the drug during different types of stability studies. It helps to establish a relation between temperature and rate constant to estimate shelf life of a drug substance and drug product during developmental phase. With the help of this method, the effect of temperature and catalyst on chemical stability and decomposition can be established. Equation 6 denotes Arrhenius equation, where A denotes frequency factor, T designates for temperature (kelvin), Ea is the activation energy require to start degradation reaction in J mol^{-1}, k is a rate constant of any order reaction as a function of absolute temperature, and R denotes Gas constant (R = 1.987 Cal mol^{-1} K^{-1}).

$$k = Ae^{-E_a/RT} \tag{6}$$

Arrhenius equation is most important to predict the stability of drug at room temperature, higher than or lower than the room temperature (Bajaj et al. 2012).

Factors affecting quality of degradation kinetic data of pharmaceuticals

Degradation kinetics of pharmaceuticals can be affected by several factors including pH, temperature, medium used for degradation kinetic study (solvent, dielectric constant, and ionic strength), intensity of light exposure, and excipients (Fig. 1). These factors individually and/or synergistically can affect the quality of data generated from the degradation kinetic study of pharmaceuticals. For generation of good quality kinetic study data, it is important to study the individual effect of each variable on the rate of degradation. An overlapping effect of variables can make the interpretation of kinetic data more complicated. Simultaneous effect of variables can change the rate as well as the order of degradation reaction which can further lead to false positive data. Among all these factors, temperature used for degradation kinetic study is one of the most important factors which can directly affect the rate of degradation. It is important to control and carry out degradation kinetic at logical temperatures to provide optimum degradation of the drug. An increment in temperature often impacts the order of degradation reactions. A 10 °C increase in temperature can double the reaction rate with the same activation energy. This increase in reaction rate is mainly due to an increase in numbers of meaningful collision of molecules with right orientation above activation energy level. Degradation kinetic can also be affected by the type of solvent used for performing degradation kinetic study of pharmaceuticals. Iqbal et al. had reported the linear increase in the degradation of riboflavin (vitamin B2) to form two major degradation products formylmethylflavin and lumichrome with an increase in polarity of solvent under photolytic conditions (Ahmad et al. 2015).

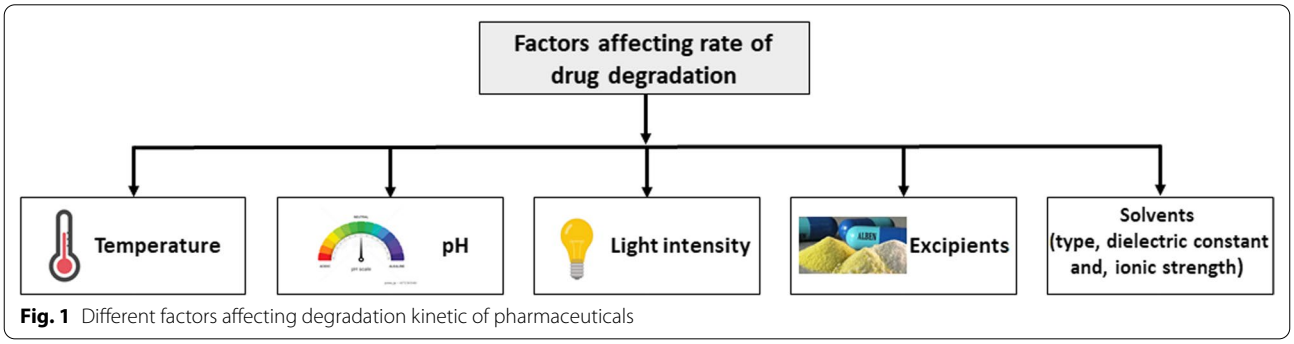

Fig. 1 Different factors affecting degradation kinetic of pharmaceuticals

Dielectric constant and ionic strength of the medium can also sometimes affect the rate of drug degradation. pH is another important variable for degradation kinetic study. The rate of hydrolysis of ester and amide-containing drugs is greatly affected by pH of the medium in which degradation is supposed to happen. Barbosa et al. had reported a study on effect of pH on the rate of hydrolysis of nitazoxanide (NZN), a broad-spectrum antiparasitic and antiviral drug (Barbosa et al. 2020). They found an increase in the rate of hydrolysis of NZN at neutral and slightly alkaline pH. Excipients present in the drug formulation can also influence the rate of degradation of drug substances. Natasa et al. had studied the impact of different excipients on the degradation of solid-state olanzapine an antipsychotic medication. Olanzapine is reported to be sensitive to light and moisture (Djordjević Filijović et al. 2015). They found an increase in the formation of hydrolytic degradation product in the presence of lactose monohydrate when used as a filler in tablet formulation. Their study concluded that hydrolysis of olanzapine was excipient mediated. Degradation kinetics of pharmaceuticals can be studied by considering individual factors based on their impact to generate good quality kinetic data for a better understanding of drug stability which can help to develop a stable formulation and to improve the shelf life of the drug.

Systematic strategies to perform degradation kinetics

Degradation kinetic requires the selection of different kinetic variables including pH, temperature, stressor concentration, excipient type and quantity, ionic strength, and radiation intensity. This study is performed to evaluate the rate of drug degradation under different environmental conditions such as hydrolytic (acid, base, and neutral), oxidative, photolytic, and thermolytic stress conditions. Figure 2 shows general steps to perform degradation kinetic study of drug substances and drug products. Selection of variables for degradation kinetic study is a crucial step as it can provide information regarding rate-limiting factors for each degradation reaction. To study the degradation kinetics of a drug under hydrolytic conditions, different variables including temperature, light, and pH of the reaction mixture can be used. It is important to consider one variable at a time to evaluate the effect of an individual variable on the kinetic of drug degradation reactions. Selection of multiple variables simultaneously to study degradation kinetics can provide false positive or false negative data due to overlapping effects of multiple variables at a time. The study of degradation kinetic is carried out by using different selected variables, and the data are plotted as a percentage of drug remaining vs time. From this graph, the best-fitted line can be obtained to determine the order of reaction based on the regression coefficient value of each graph with an individual variable. The data obtained from this graph can be used to calculate different kinetic parameters such as degradation rate constant (k), $t_{1/2}$, and t_{90}. The activation energy for the reaction can be calculated based on the Arrhenius equation. Table 3 denotes different examples of drugs with their degradation mechanism and order of degradation.

Vasantakumar et al. have studied the degradation kinetic of butacaine sulfate by sodium chlorobenzenesulfonamide (CAB) in the presence of perchloric acid at 303 K. This reaction shows first-order kinetics, as the substrate showed fractional order dependence, but it did not depend on perchloric acid. Measure of elements of the reaction was found to be 1:3 and the oxidation product formed was recognized. The degradation kinetics by oxidation was studied at different temperatures, and activation parameters have been assessed (Vasantakumar 2008).

Shubha et al. have reported a study on oxidation of a local anesthetic benzocaine hydrochloride with the help of sodium n-halo-p-toluene sulfonamide in the perchloric acid medium at 303 K. As per the study, oxidative degradation of benzocaine hydrochloride was found to follow first-order degradation kinetics. When the dielectric constant of the medium decreased by the addition of methanol, the rate of reaction was increased. The rate of reaction was not affected much with the variation in ionic strength and the addition of p-toluene sulfonamide. The reaction has been studied at various temperatures, and activation parameters were established. Measure of elements of the reaction was found to be 1:1 and the degradation product formed by oxidation was identified by using spectral analysis (Shubha and Sushma 2015).

Oliviera et al. investigated the mechanism of atorvastatin degradation in acidic and basic environments. It was found to be the first-order kinetics in acidic environments and zero-order kinetics in basic conditions, which are less stable when examined in acidic medium. The rate constant for degradation in acidic medium was found to be 1.88×10^{-2} s^{-1}, suggesting first-order kinetics. On the other hand, rate constant for degradation in the basic medium was found to be 2.35×10^{-4} mol L^{-1}, indicating zero-order reaction and the drug was less stable in acid media (Oliveira et al. 2016).

Berge et al. studied the kinetics and degradation mechanism of cefotaxime sodium in a pH 0–10 solution at 25 °C. HPLC was employed for analysis of the samples to find out the rate of degradation reaction, which revealed pseudo-first order under the drug concentration. According to the research, hydrogen ion, solvolysis, and hydroxide ion catalysis improved the rate of degradation kinetics

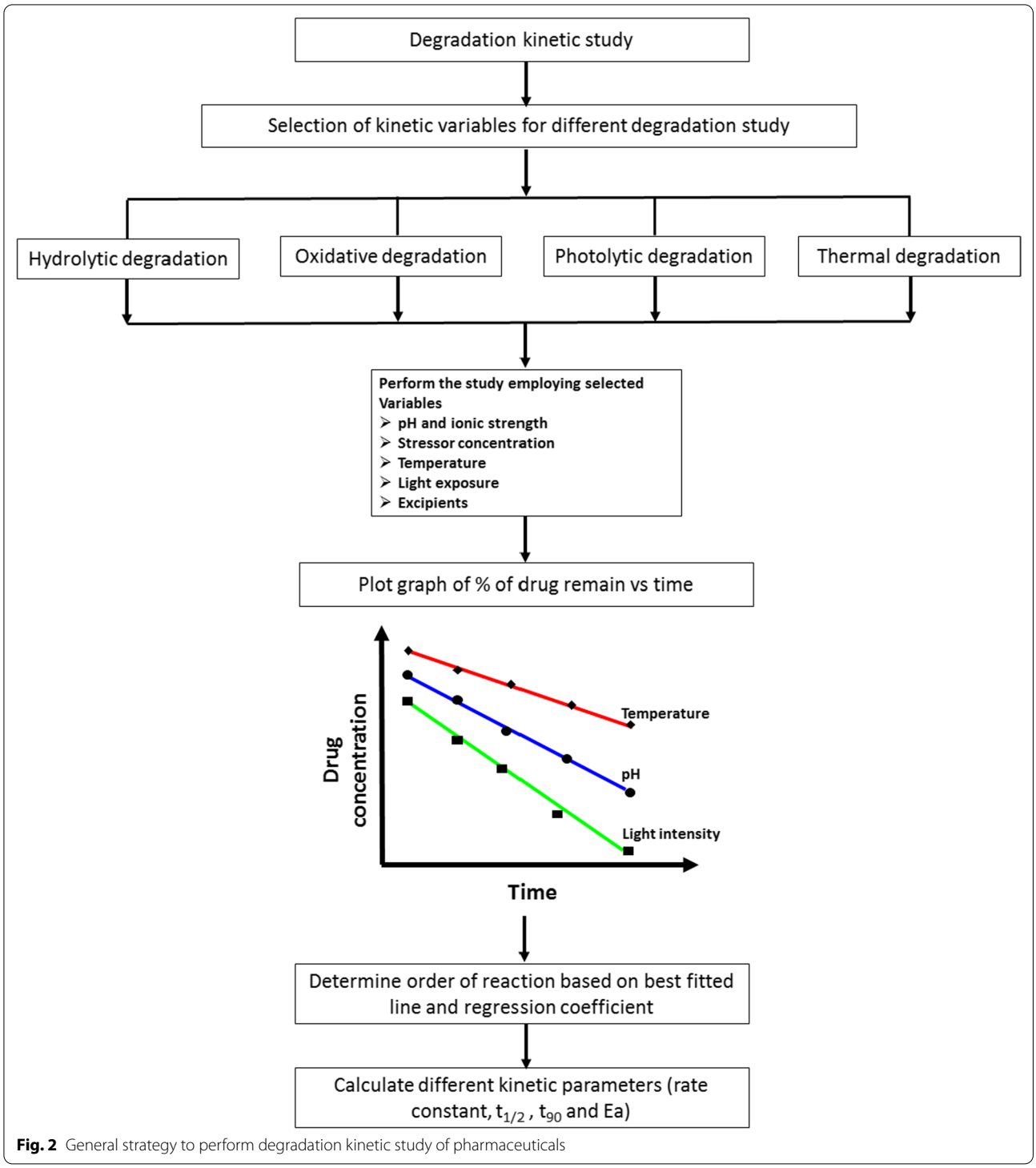

Fig. 2 General strategy to perform degradation kinetic study of pharmaceuticals

substantially. The pH rate profile at 25 °C showed that cefotaxime had the best stability between 4.5 and 6.5. In an aqueous solution, cefotaxime degraded by two concurrent reactions, namely C-3 position de-esterification and β-lactam cleavage (Berge et al. 1983).

Hashimoto et al. reported degradation kinetic study of moxalactam in an aqueous medium by employing HPLC method of sample analysis. Separate pH profile rates for degradation and epimerization were calculated at 37 °C and in the pH range of 1.0–11.5. A constant

Table 3 Degradation mechanism and order of degradation of different drugs

Sr. nos	Name of drug	Reaction type	Variables	Order of degradation	References
1.	Bedaquilline	Hydrolysis	pH	First-order reaction	Agrahari et al. (2015), Atkins et al. (1986), de Haro Moreno and Salgado (2012), Haleem et al. (2006), Hashimoto et al. (1984), Lerner et al. (1988), Oliveira et al. (2013, 2016), Paczkowska et al. (2015), Rajput and Vanavi (2021), Tutunaru et al. (2021), Vaucher et al. (2010) and Zhao et al. (2019)
2.	Tenofovir	Hydrolysis Oxidation	pH, H_2O_2	First-order reaction	
3.	Cefotaxime	Hydrolysis of the lactam ring	UV, pH, temperature	Pseudo-first order	
4.	Ceftriaxone	Electrochemical oxidation of thiazole side chain (R1-CONH-)	Electrolysis, temperature	First-order reaction Zero-order reaction	
5.	Amoxicillin	Hydroxylation of β lactam ring	pH, temperature	Pseudo-first-order reaction	
6.	Moxalactam	Hydroxylation of β lactam ring	pH, temperature	Pseudo-first order	
7.	Telithromycin	Oxidation Photolysis	UV light, H_2O_2	First-order reaction	
8.	Azithromycin	Ester hydrolysis	pH, temperature	Pseudo-first order	
9.	Erythromycin	Ester hydrolysis	Concentration, ionic strength, buffer concentration, pH, temperature	Pseudo-first order	
10.	Cefozopran	Amide hydrolysis	Temperature, humidity	First-order reaction	
11.	Ciprofibrate	Acid hydrolysis	pH, temperature	First-order reaction	
12.	Ceftazidime	Amide hydrolysis	pH, temperature	First-order reaction	

ionic strength of 0.5 was maintained. The measurement of both epimers (R and S) of moxalactam was shown to degrade with pseudo-first-order kinetic with simultaneous epimerization. Degradation with hydroxide ion and hydrogen was affected due to phenolic group dissociation at the side chain. The degradation profile of moxalactam has represented the lowest degradation rate constant within pH range 4–6 (Hashimoto et al. 1984).

Vaucher et al. employed a UV lamp at a wavelength of 254 nm and a power of 15 watts to photodegrade telithromycin in a chamber with internal mirrors. Coated tablets were used to make telithromycin solution and placed in the quartz cell. They carried out the oxidation reaction by mixing the telithromycin solution with 3% hydrogen peroxide. The rate constant of degradation and the kinetics parameter including order of reaction was calculated. Degradation of telithromycin displayed first-order kinetics under the experimental conditions. There was no peak in the chromatograms of the placebo solutions, neither in the telithromycin retention time nor in the degradation products. Therefore, excipients did not affect the kinetics of this drug. Temperature in the photodegradation chamber was kept below 30 °C at all times during the photodegradation process (Vaucher et al. 2010).

Zhao et al. studied amoxicillin degradation kinetic in an aqueous medium. Amoxicillin was found to get degraded by active persulfate under oxidative conditions. Each time, the drug was found to obey pseudo-first-order degradation kinetics. When the energy of activation was 126.9 kJ mol^{-1} and the temperature of the reaction was varied from 35 to 60 °C, the reaction was matched with the Arrhenius equation. When the initial concentration of persulfate, reaction temperature, concentration of chlorine, and concentration of humic acid were high, the degradation efficiency was improved (Zhao et al. 2019).

Moreno et al. studied thermal and photodegradation kinetics of ceftazidime and the dependability of microbiological assay for it. During stress process, degradation of the antibiotic was found to follow first-order reaction kinetics. In an aqueous solution, ceftazidime showed extensive degradation when it compared with solid state (de Haro Moreno and Salgado 2012). Paczkowska et al. studied the degradation process of Cefozopran with the help of HPLC by employing a DAD detector. Total two DPs were identified when analyzed with Q-TOF mass spectrometer. They investigated the effect of relative humidity and temperature on stability of cefozopran. The degradation kinetic profile of solid-state cefozopran hydrochloride was found to obey first-order reaction where the rate of drug degradation reaction depends on the concentration of the drug. (Paczkowska et al. 2015).

Degradation kinetic study of pharmaceuticals employing advanced models

Many advanced degradation models have been developed to perform forced degradation studies by employing mixed effects of different stressors. This advancement in degradation study requires the study of degradation kinetic data to evaluate deviation from normal degradation kinetic of drug substance and drug product.

Autocatalytic kinetic of hydrolysis

Autocatalytic process generally involves modification in the reaction kinetic of many chemical reactions including

degradation of pharmaceuticals. The basis of change in chemical kinetics includes the formation of a product that can further increase or decrease the rate of drug degradation reaction. Antheunis et al. have developed a mathematical kinetic model to describe and predict the rate and extent of degradation of different polyester molecules including polycaprolactone (PCL), poly (4-methyl caprolactone), polylactide, and the copolymer poly (D, L-lactide-co-glycolide) by autocatalytic hydrolysis in an aqueous medium. This model helps to calculate the degradation rate of polyesters by plotting a decrease in molecular weight as a function of time. The model considers autocatalytic effect of carboxylic acid on the hydrolysis of polyesters to predict degradation rate. It describes the formation of carboxylic acid as a product of hydrolysis of polyesters which further catalyze this hydrolysis process by decreasing pH of the media up to 2. Sudden decrease in pH leads to more degradation and faster decrease in molecular weight which further affect the kinetic of this hydrolytic reaction and increase the rate of degradation (Antheunis et al. 2009).

Oxidation/reduction models

Advanced oxidative degradation uses oxidizing agents with UV exposure to degradation system followed by generation of highly reactive radicals which increases the rate of oxidative degradation of the drug. Rosenfeldt et al. studied the effect of UV radiation on oxidative degradation kinetics of endocrine-disrupting compounds such as ethynyl estradiol, bisphenol, and estradiol by exposing hydrogen peroxide stressed compound to ultraviolet radiation. They have reported that the addition of hydrogen peroxide to UV exposed samples accelerates oxidative degradation of compounds. The change in drug degradation caused by hydrogen peroxide addition is because when hydrogen peroxide was added, the primary mechanism of endocrine-disrupting chemical destruction changed to hydroxyl radical-mediated accelerated oxidation. This mechanism results in the creation of highly reactive species, such as $OH^{\bullet}$ radicals, which appear to react rapidly with endocrine-disrupting compounds. Several endocrine-disrupting compounds are destroyed by chemical oxidation using different oxidative metal stressors including TiO_2, chlorine, potassium permanganate, and ozone-based photocatalysis. The UV absorption spectrum of chemical pollutants and contaminating agents denoted a higher degradation rate after the addition of hydrogen peroxide to generate a harsh oxidative system which lead to an increased rate of degradation (Rosenfeldt and Linden 2004).

Oxidation by using Fe(II) activated bisulfate

Wang et al. employed advanced oxidation techniques including Fe (II)-activated bisulfite (BS) to degrade diclofenac from wastewater. Degradation mechanisms was studied concerning Fe(II) dose, bisulfite concentration, initial pH, reaction temperature, and dissolved oxygen. Fe(II)/BS had a better removal rate of diclofenac than Fe (II)/persulfate, and its degradation followed a pseudo-first-order kinetic model. The best pH for diclofenac decomposition was 4 due to the morphology of Fe(II) and bisulfite. Excess Fe (II) or bisulfite inhibited diclofenac degradation as an SO_4 scavenger, but higher initial Fe (II) or bisulfite concentration enhanced diclofenac degradation. Although dissolved oxygen did not influence diclofenac elimination in the range of 4.6–8.3 mg L^{-1}, it was found to be an important factor in promoting the conversion of SO_3 to SO_3. Based on the enhanced diclofenac degradation with rising temperature, the activation energy of this process was found to be 120.75 3.43 kJ mol^{-1}. As per the radical scavenging studies, SO_4^{-}, $HO^{\bullet}$, and other reactive species contributed 71.1%, 24.6%, and 4.3% to diclofenac degradation in the Fe(II)/BS system, respectively. UPLC-Q-TOF–MS was used to detect nine transformation products. The suggested degradation pathways of diclofenac were hydroxylation, dehydration, decarboxylation, dichlorination, and formylation (Wang et al. 2019).

UV-activated persulfate model

Xian Lu et al. demonstrated the effect of different degradation processes that were evaluated using three different approaches, namely direct UV irradiation, persulfate (PS) oxidation alone, and UV/PS combination. It was found that there was a considerable increase in the degradation of diclofenac under the impact of UV/PS. After 60 min of irradiation, direct UV photolysis removed 75% of the material. With a rate constant of 3.9104 s^{-1}, the degradation was found to be followed a pseudo-first order (Lu et al. 2017).

Oxidation by UV-activated sulfate radical

The removal efficiency of trimethoprim in the UV-activated persulfate system was investigated by Luo et al. (2021). By employing a pseudo-first-order reaction kinetic model, degradation behavior of trimethoprim in UV-activated persulfate was studied. Because of the poor molar absorptivity and quantum yield of trimethoprim at 254 nm, direct photolysis was slower. The degradation rate was increased dramatically with the addition of H_2O_2 and persulfate. In the UV-activated persulfate model, the SO_4 radical plays a major role in the degradation reaction. In the presence of a UV-activated persulfate system, the model built by them can assess and elaborate

the effect of natural organic matter, persulfate concentration, and chloride ion on trimethoprim degradation. The pseudo-first-order rate constant for trimethoprim was increased with an increase in persulfate concentration. On the other hand, rate constant was decreased in the presence of chloride (Lu et al. 2017).

Oxidation by sonoelectrochemical degradation

It is a technique that uses electrochemistry and ultrasound as the main source instead of any additional chemicals. Shestakova et al. investigated the sonoelectrochemical technique among the advanced oxidation process. The main purpose of this study was to establish the sonoelectrochemical degradation of formic acid and to optimize its parameter involved in formic acid degradation. The results were then compared with other existing advanced oxidation processes (Shestakova et al. 2016).

Mixed oxidation catalysis

Wols et al. investigated UV/H_2O_2-based mixed oxidation catalysis, which is a well-known method for degrading organic micropollutants. The degradation of organic micropollutants in UV/H_2O_2 reactors was predicted using a computational fluid dynamics model combined with an advanced kinetic model. It takes into account the fluence rate, hydraulics complex photochemical reactions in the water matrix, and interactions between these processes. The compound was degraded with the help of UV photolysis, carbonate radicals, and $HO^{\bullet}$ radicals. In pilot-scale UV/H_2O_2 reactors, pharmaceutical degradations were monitored and shown under various operating settings. Their study concluded that temperature affects the decomposition of organic micropollutants during mixed oxidation catalysis (Wols et al. 2015).

Photoassisted Fenton reagent-based model

Kušić H et al. employed Fenton-type (Fe^{3+}/H_2O_2, Fe/H_2O_2 Fe^{2+}/H_2O_2) and photoassisted processes (UV/Fe/H_2O_2, UV/Fe^{3+}/H_2O_2, and UV/Fe^{2+}/H_2O_2) for the degradation of phenol as a model organic pollutant in wastewater. They looked at the entire kinetic model that described phenol degradation. Their analytical models anticipated the degradation of phenol and the generation of main oxidation byproducts such as catechol, hydroquinone, and benzoquinone. In this study, the mineralization kinetics of the phenol solution was predicted using advanced oxidation. Additional reactions that describe the removal of Fe from the catalytic cycle through the creation of ferric complexes and their regeneration triggered by UV light are included in the well-known Fenton and photo-Fenton chemical reactions. HPLC analysis and total organic carbon content measurements were employed to examine phenol breakdown kinetics. The procedures used were successful in removing all phenols by degradation (Kušić et al. 2006).

Thermal degradation

Vieira et al. studied thermal degradation kinetics of ascorbic acid by using two mathematical models in replication to regenerate experimental conditions and data. With the help of linear regression, all kinetic parameters were identified on the logarithmic curve of experimental data. The mathematical model was used to estimate the loss of ascorbic acid and to study the degradation kinetics of ascorbic acid. Quantification of ascorbic acid was performed with UHPLC-MS/MS. The degradation parameter was determined using data after fitting in linearized equations, and the final result showed fast degradation with a low activation energy value. Because of the low average error achieved, both of the generated kinetic models may be employed to represent the deterioration rate. To achieve isothermal heating and prevent air oxidation, samples were put in screw cap tubes with a diameter of 1 cm. In a dry block heater, thermal deterioration was tested in triplicate at 50 °C, 70 °C, and 90 °C temperature (Vieira et al. 2000).

Acid hydrolysis and photolysis under near-UV light in the presence of TiO_2

Kwiecien et al. investigated two mechanisms of roxithromycin degradation under near-UV irradiation to perform acidic hydrolysis and photocatalytic degradation of drug by TiO_2 photosensitizer. Silica gel F254 precoated aluminum TLC plates with mobile phase composition of ammonia–acetone–methanol 25% (0.1:14:1, v/v/v) was used for analysis of acidic degradation samples. Dense spots of drug and its degradation products was observed. HPLC was used to track photocatalytic degradation experiments by using TiO_2 as a stressor. The results revealed that both ways of roxithromycin degradation are quite effective. The Langmuir–Hinshelwood theory for photocatalytic microheterogeneous systems governs the kinetics of first-order photocatalytic degradation reactions. For elucidating the structure of degradation product under photocatalytic and acidic conditions, UPLC-MS/MS technique was used. The structure was proposed based on its fragmentation pattern (Kwiecień et al. 2014).

Accelerated degradation by ferrous/chloride ions

Mao et al. established the mechanism and degradation kinetics of ibuprofen and sulfamethoxazole. The study showed that reactive chlorine species had a major role in the degradation of ibuprofen at pH 3. Fe(IV) was not found to be the main contributor in degradation reaction because of the low reaction rate between Fe and the

targeted compound. In the acidic conditions, degradation of the pharmaceuticals was facilitated. Chlorine showed significant degradation of sulfamethoxazole, but showed negligible effect on the degradation of ibuprofen. The reactive species like $OH^{\bullet}$, Fe(IV), and reactive chlorine species showed a major contribution to the degradation of the drugs (Mao et al. 2021).

Boron-doped diamond electrode mediated electrochemical oxidation

Loos et al. reported a study assessing the degradation kinetics using a boron-doped diamond electrode for electrochemical oxidation. In their research, electrochemical oxidation was carried out for selected drugs, namely iopromide, sulfamethoxazole, 17-ethinylestradiol, and diclofenac, in simulated wastewater and hospital effluent wastewater. The degradation kinetics follows pseudo-first-order reaction kinetics in all experimental conditions. The result showed that sulfamethoxazole, 17-ethinylestradiol, and diclofenac degraded rapidly, but the degradation of iopromide was significantly slower in simulated wastewater and real wastewater. The activation energy was calculated based on the reaction rate constant at different temperatures (Loos et al. 2018).

Computation-based kinetic models

Computation-based kinetic modeling is gaining more attention to predict the degradation behavior of pharmaceutical products under defined stress conditions which can help to understand the effect of individual variables on degradation rate kinetics. The study of degradation kinetic employing a computation-based model helps to predict different kinetic parameters such as rate constants, activation energy (Ea), and mean kinetic temperature which provide a better understanding of the degradation kinetic behavior of the drug. While employing computation-based models to study drug degradation kinetics, initial experimental data are required to predict the effect of the individual variable on the rate of drug degradation. The success of computation-based prediction of kinetic parameters mainly depends on the quality of initial data generated from different experiments. Blaž et al. reported a study on computation-based kinetic model to assess the degradation kinetic behavior of complex solid dosage form employing saxagliptin as a model drug (Robnik et al. 2019).

Conclusive remark and authors' opinion

Stability evaluation of drugs is an important and integral part of the drug development program. Stability of pharmaceuticals can be evaluated by exposing the drug to various stress conditions. The main aim of stability studies includes generation of information regarding different degradation products formed during accelerated and long-term stability studies. The study is employed to identify the structure of degradation products formed. Degradation kinetic data immensely help in the optimal formulation development, determination of proper storage conditions, selection of container closure system, drug-excipient interactions anticipation, better stabilization of the drugs, and accurate prediction of shelf life. Pharmaceutical stability encompasses the ability to resist change in the quality of drug substances and products during their storage when exposed to a variety of environmental conditions. Assessment of the kinetic behavior of drug degradation is important to establish its shelf life and to determine the rate at which drug substance or product gets deteriorate. Degradation kinetic data can be used to establish optimum packaging and storage conditions for improving the shelf life of a drug.

Unfortunately, general strategies to perform drug degradation kinetic are not extensively reported in the literature. This article discusses various aspects of the degradation kinetic study of pharmaceuticals in detail and provides general strategies to evaluate drug degradation kinetics. Selection of kinetic variable is an important factor in degradation kinetic study to provide proper information on various rate-limiting factors for different degradation reactions. It further helps to understand the detailed mechanism behind drug degradation and the effect of various factors on drug degradation kinetics. To establish accurate degradation kinetic data, there should be a clear understanding of various advanced kinetic models and related critical quality attributes. Different computation-based kinetic models are available to study the degradation kinetics of pharmaceuticals. Several researchers reported individual studies on the degradation kinetics of drugs. However, to date, systematic strategies for performing degradation kinetics of drugs have not been discussed in any literature. Moreover, there is no regulatory guideline to guide the researcher on performing the degradation kinetic study of pharmaceuticals. Owing to this, the kinetic behavior of drugs is not being analyzed by researchers in uniform manners. Therefore, it is an utmost need to generalize the process of degradation kinetic study. It is highly recommended to consider one-factor-at-a-time approach to assessing the impact of each environmental parameter on the degradation reaction of drugs. This will avoid overlapping effects of multiple variables at a time. Degradation kinetic data generated after employing the selected variables need to plot as a percentage of drug remaining vs time. Thereafter, the regression coefficient of the best-fitted line should be considered to determine the order of reaction for individual variables. Identification of the actual order of degradation reaction is essential to ensure the accuracy

of the shelf-life calculation of a product. However, various advanced experimental approaches and mathematical models available nowadays can also be considered to evaluate the mixed effects of different stressors on the order of degradation reaction. In conclusion, high-quality stability data should be generated through properly designed degradation kinetic studies to ensure improved stability of pharmaceuticals by establishing their accurate storage conditions.

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DB, NR, TJ, and AKS carried out data curation, formal analysis, and visualization, and wrote the original draft. RT was involved in conceptualization, visualization, and writing, review, and editing. PS took part in conceptualization, project administration, supervision, visualization, and writing, review, and editing. All authors read and approved the final manuscript.

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