Chemical Kinetics and Its Applications in Drug Stability

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Abstract

The study of chemical kinetics is very crucial as it plays a significant role in drug stability, which has direct impact on storage and release characteristics of drugs. Various kinds of instabilities occur that lead to the degradation of drugs. Drug degradation is of different types including physical, chemical, and biological degradation. This chapter presents an overview of chemical kinetics and a brief introduction of rate of reaction and its types. The following text also provides detailed information about the physical and chemical factors that affect the rate of reactions. The types along with various mechanisms through which degradation occurs are also included in this chapter.

Keywords

Chemical kinetics · Rate of reaction · Drug stability · Drug degradation

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3.1 Introduction

Kinetics deals with rate of reactions, and chemical kinetics includes the study of rate of chemical reactions. It is the rate of conversions of reactants through various mechanisms into final products [1]. Chemical kinetics are described by different mathematical models which then serve as tools for scientists and chemists to control and understand a variety of chemical reactions. In chemical reactions, there is the breakage of bonds present in reactants, followed by the formation of new bonds to form the product [2]. Reactions can occur fast and slow, and chemical kinetics measure this rate that either reactions precede at a slow or faster pace. Other than providing information about the speed of reaction, it also provides detail about the mechanism of reaction including knowledge about each step in the reaction process. Mechanism of reaction is the step-by-step process through which a reaction occurs. A mechanism provides information about all the stages of a chemical reaction [3].

3.2 Rate of Reaction

It is the speed at which the reactants (initial) are converted into products (final). Every reaction has two rates:

1. The rate at which the reactant declines
2. The rate at which the final product appears

If we consider two species X as initial reactant and Z as final product,

$$X \rightarrow Z$$

This reaction can be expressed either as disappearance of X or as appearance of Z. This rate of chemical reaction can be expressed as a change in concentration of reactants in respect of time [4]. As the rate of reaction is related to the concentration of reactant that decreases with respect to time, the dimension must be of concentration which is moles per liter second or moles per liter minute. Rate of reaction for the above equation would be:

$$\text{Rate} = -d(X)/d(t)$$

where d(X) is the speed at which reactants change into products and is negative because reactants decrease.

$$\text{Rate} = +d(Z)/d(t)$$

where $d(Z)$ is the speed at which the product appears and is positive because the concentration of products increases with respect to time.

Mathematical equation that relates concentration of species with that of time is called as rate law or rate equation.

3.2.1 Types of Rate of Reactions

Depending on the velocity, rate of reactions is classified as slow and fast rate of reactions.

3.2.1.1 Fast Reaction Rates

Reactions that occur at a faster pace are fast reaction. Example of fast reactions includes burning [3].

3.2.1.2 Measuring Fast Reactions

Some reactions occur instantaneously, and therefore, special techniques are required in order to measure such reactions. There are two major difficulties that occur in fast reactions: the first is it is difficult to measure initial time accurately and second is the time in which quantity of substance is measured is comparable with half-life of reaction. In order to cope with these complications, flow, pulse, and probe methods are used. The basic principle in pulse and probe method is that a short pulse is directed to a chemical system, which is then followed by a probe, which gives spectroscopic data of what happened after the initial pulse. In flow methods, two different solutions or gases are added in the mixing tube, and then the mixture will flow along the tube. Concentrations of reactants and products are then measured along the tube by different spectroscopic methods which correspond to different reaction times [2].

3.2.1.3 Slow Reaction Rates

Reactions that occur at a low speed have slow reaction rates. Example of reactions that have slow rate is disintegration of a plastic bottle in sunlight [3].

3.2.1.4 Measuring Slow Reactions

To measure slow reactions, the best approach is to alter reaction conditions like an increase in temperature. For instance, if the temperature of a mixture containing hydrogen and carbon is increased up to 500 °C, the reaction will occur rapidly in this condition, and reaction rate can be studied [2].

3.3 Factors That Affect the Reaction Rate

Factors affecting the rate of reaction are classified into physical and chemical factors, which are then further classified as follows:

3.3.1 Physical Factors

3.3.1.1 Surface Area

Surface area is the area of space available for reaction. This term is most significant in solid state of matter. Solids have a definite shape, and therefore limited sites are

available for the atoms or molecules of solids to react with other reactants. However, when solids are crushed into powders, surface area increases and hence the rate of reaction, as more atoms collide with reactant [4].

3.3.1.2 Concentration of Reactants

To predict the rate of chemical reactions, the reaction theory is used according to which reaction occurs when reactant molecules come closer and collide. If the proportion of reactants is more, there will be an increased concentration of reactant particles moving together; hence, more collisions will occur; resultantly, the rate of reaction will be increased [4].

3.3.2 Chemical Factors

3.3.2.1 Temperature

The measurement of average kinetic energy of molecules or atoms in the system is called as temperature. Temperature has impact on all chemical reactions, and depending upon an increase or a decrease of temperature, this change can either be positive or negative. For example, degradation and evaporation of solutions and samples slow down at low temperature, and these phenomena get four times slower while storing solutions and samples at a temperature of 4 °C. For every 10 °C increase in temperature, the reaction rate will be doubled for most of the chemical processes [5]. Temperature is directly proportional to the kinetic energy of molecules or atoms in a system, and therefore, when the temperature of the system is increased, the collisions to overcome the activation energy will also be increased. Activation energy as described by Swedish Scientist Svante Arrhenius in 1889 is the minimum energy required by reactants to initiate a chemical reaction [6]. When the temperature of a system is increased, the following two factors occur:

1. More intense collisions
2. Greater frequency of collisions

As the intensity of collision of molecules within the system increases, the rate of reaction also increases. For example, the rate of reaction of enzymes Maxatase and Alcalase was higher at 45° C and lower at 37° C, when pH of the medium is 8.2. When activation energy is calculated, it appears that the higher the temperature, the higher is the rate of reaction and the lower is the activation energy [7].

3.3.2.2 pH

pH of a medium can have a significant impact on the stability of a drug. More than tenfold change in the reaction rate constant results in only 1 pH unit shift. For calculating optimum pH for stability of drugs in solution, drug versus reaction rate profiles are constructed [8].

3.4 Applications of Chemical Kinetics in Drug Stability

Chemical degradation of pharmaceutical products is a common phenomenon in our everyday lives. Careful storage of non-sterile pharmaceutical products and manufacturing and storage of sterile drugs are some examples that are totally based on knowledge about chemical kinetics of pharmaceutical products. From both economical and safety points of view, it is very crucial for pharmacists to have thorough knowledge about chemical kinetics [9]. Kinetics plays a basic role in the development and evaluation of drug substances by analysis of inhibitory mechanisms. Kinetics is applied in enzymology on routine basis in order to determine the inhibition mechanism and to check the relative efficacy and efficiency of various inhibitors. Chemical kinetics has multiple applications in designing a pharmaceutical product ranging from drug manufacturing characteristics to its action inside the body.

3.4.1 Stability of Drug Products

Rate process is the one that leads to incompatibility and inactivation of drugs which occurs by the breakdown of drug substances into less active or unwanted metabolites. The various ways through which a pharmaceutical drug product can degrade are briefly explained in Sect. 4.5. By proper storage of drug products, it is possible to reduce the rate of these reactions, hence maintaining the stability of drug products throughout their shelf life.

3.4.2 Pharmacokinetics of Drug

It includes absorption, distribution, and elimination of drug through metabolism inside the body. All of these mechanisms involve chemical kinetics.

3.4.3 Dissolution of a Drug

Rate process involves the conversion of solid drug molecules into an aqueous solution of drug substance.

3.4.4 Chemical Kinetics and Drug Stability

For designing any pharmaceutical drug product, the most significant factor is its stability. For a drug to show its pharmacological activity, it is very crucial that it is stable in formulation form until used for the intended purpose. Several forms of instabilities occur that impair the activity of the pharmaceutical drug product, which is the cause of rejection of drug. First of all, chemical decomposition of the drug may

lead to a decrease in the quantity of an active drug present in the pharmaceutical dosage form. Second, during the process of decomposition, a toxic product may form which can cause adverse effect. Moreover, instability of product may lead to reduction in therapeutic efficacy of the drug. Other than this, instability can also affect physical appearance of drugs such as cracking or creaming of emulsions or breaking or mottling of tablets. Such changes may not affect the pharmacological activity, but patients will not compromise over the unpleasant appearance of pharmacological dosage forms. In addition, sometimes the drug substance itself does not degrade, but the excipients in the formulation may get degraded affecting the therapeutic activity of drugs. The following are the drug degradation pathways.

3.4.5 Chemical Degradation Pathways of Pharmaceutical Drug Product

Chemical degradation of a product occurs through the following mechanisms, which have been summarized in Fig. 3.1.

3.4.5.1 Photodegradation

It is the process in which drugs and excipient molecules are degraded by light. Exposure of drugs to a photolytic source, i.e., a source emitting radiation between

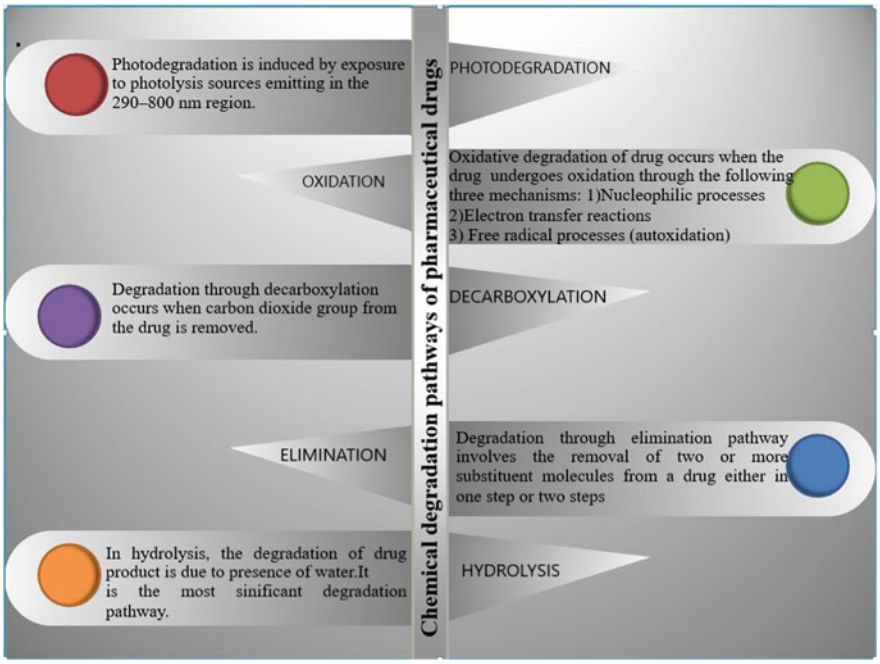

Fig. 3.1 Chemical degradation pathways of pharmaceutical drug product

290 and 800 nm, results in photodegradation. Multiple sources of light emit radiations in this range, for instance, fluorescent lamps, metal halide lamps, sunlight, and some indoor lighting sources. If a molecule absorbs light, its electronic configuration changes to an excited state. Electrons present in the outermost shell are susceptible ones as they are least firmly bounded electrons. Photolysis is a consequence of the absorption of light, or radiation energy, allowing for quantum restrictions by a molecule A, to produce an unstable excited-state species, and the energy can be lost either by a radioactive mechanism in which the energy is given in the form of fluorescence or by a radiation-less mechanism. These mechanisms can be physical or chemical in nature. The physical decay results in the loss of energy in the form of heat or by collision with other molecules [10].

In the pharmaceutical industries, photostability studies of pharmaceutical products are carried out to ensure the safety, potency, and efficacy of formulated drugs during manufacturing, throughout shelf life and upon administration. Photostability studies are an integral part of drug development because the presence of light can affect the drug characteristics if the drug is photosensitive. For example, when the photostability of flunitrazepam was measured, it was investigated that flunitrazepam shows a drop of more than 60% in concentration when stored in light, after 8 h, though no such change was seen in samples that were kept in the dark [11, 12].

3.4.5.2 Oxidation

Oxidative reactions are somewhat common drug degradation pathways. Oxidation is a loss of electrons or an increase in the oxidation state.

$$\text{Reduced form} \leftrightarrow \text{Oxidized form} + \text{ne-}$$

For example, the aqueous solution of ascorbic acid (vitamin C) degrades in aerobic conditions, and the molecule is then oxidized into dehydroascorbic acid [13], as shown in Fig. 3.2.

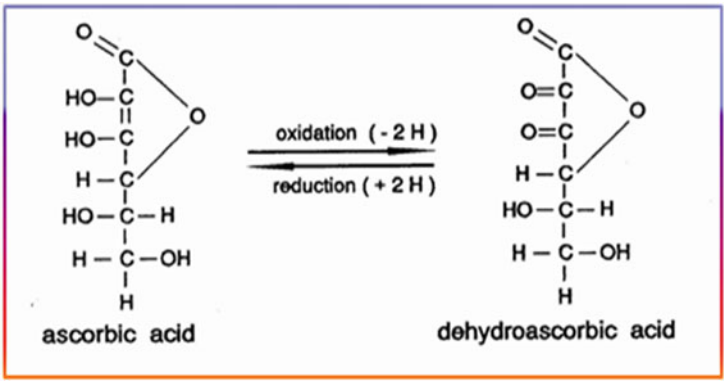

Fig. 3.2 Oxidation of ascorbic acid

After hydrolysis, oxidation is the most significant drug degradation pathway. But because of complex nature of oxidative reactions, despite their significance in stability of drugs, the studies related to them have not been well developed [14]. Organic compounds undergo oxidation mainly through one of these mechanisms:

3.4.5.3 Nucleophilic/Electrophilic Process

Oxidation might be related to nucleophilic displacement reactions as oxidative addition reactions include the attack of a nucleophile on carbon by metal [15]. Oxidative addition reactions and electrophilic reduction reactions are among the most significant transformations in organometallic chemistry [16]. This process mostly occurs between organic reactants and metal peroxides.

3.4.5.4 Electron Transfer Process

This process includes chemical reactions that involve the transfer of electrons. In this type of oxidation, molecule undergoing the oxidation process loses electron; however, the molecule that gains electron undergoes the process of reduction. Basically, electron is transferred from a donor having low affinity to a molecule that is being reduced. This reaction is often catalyzed by metals (transition metals). This process is quite simple; however, this can be made complex by the system in which it occurs [14].

3.4.5.5 Autoxidation

Autoxidation is a complex oxidation mechanism that proceeds through a free radical chain process. It is a common degradation mechanism for unsaturated fats, but a number of drugs containing carbon-carbon double bonds also undergo oxidation. Free radical chain process has three main steps [17]. At first, there is formation of free radical by photochemical or thermal breakdown of an R-H bond. The first step is catalyzed by metal ions such as Ni21, Cu21, and Fe31. In propagation step, molecular oxygen is added to the free radical. In the rate-determining step or RDS, the peroxyl radical extracts the hydrogen atom from R-H bond to produce another R• radical. The rate of rate-determining step depends on how strong the CH bond is which is being breached. Last is the termination step, in which the chain reaction is cleaved when two free radicals react with each other to form non-radical products. Thiols after oxidation can form acid, disulfides, sulfonic acids, and sulfenic acid through various mechanisms such as autoxidation, electron transfer reactions, and nucleophilic processes [14].

3.4.5.6 Elimination

The removal of one or more than one substituent molecules from a drug either in a single step or multiple steps is called elimination. For instance, synthetically made antitumor drug trimelamol (N2,N4,N6-trimethylol-N2,N4,N6-trimethylmelamine) gets degraded when hydroxymethyl groups were removed from its structure. To evaluate the kinetics of this reaction, HPLC was used [18]. Bimolecular reaction or

E2 reaction is one which consists of a single-step mechanism, however unimolecular or E1 reactions have two-step mechanisms.

3.4.5.7 Decarboxylation

Removal of a carbon dioxide group from a compound is called as decarboxylation; it is not a common phenomenon. Drugs containing carboxyl groups in their structure are susceptible to degradation through the process of decarboxylation under some circumstances. Antibiotics containing carbonyl group specifically on the beta carbon of a carboxylate anion or a carboxylic acid undergoes beta-Keto decarboxylation. For instance, this type of decarboxylation occurs in these antibiotics: carbenicillin sodium, ticarcillin sodium, carbenicillin free acid, and ticarcillin free acid. A major example of this reaction is 4-aminosalicylic acid which after decarboxylation, in aqueous medium, is converted into 3-aminophenol, as shown in Fig. 3.3. In alkaline medium, the drug is in ionized form, and therefore this reaction is faster in acidic medium.

Decarboxylation does not have to be a photochemical degradation. Few carboxylic acids, for instance, p-aminosalicylic acid, undergo decarboxylation by loss of CO2 from the carboxyl group. Decarboxylation of p-aminosalicylic acid has been shown to be a rate-controlling proton addition followed by rapid decarboxylation [19].

3.4.5.8 Hydrolysis

Hydrolysis includes degradation of drug product due to presence of water. A large number of drug products are prone to lyses in the presence of water. Esters and amides are the two most prominent functional groups that are susceptible to hydrolysis on storage. The hydrolysis of these groups occurs due to nucleophilic attack on carbonyl carbon resultantly cleaving carbon, nitrogen, and carbon-oxygen bond [20]. Examples of drugs that have ester functional group and undergo hydrolysis are aspirin, cocaine, procaine, etc. Examples of drugs that have amide functional group and undergo hydrolysis are acetaminophen, chloramphenicol, and indomethacin [21].

3.4.6 Physical Degradation of Pharmaceutical Drug Product

Physical degradation of product occurs through the following mechanisms, also shown in Fig. 3.4.

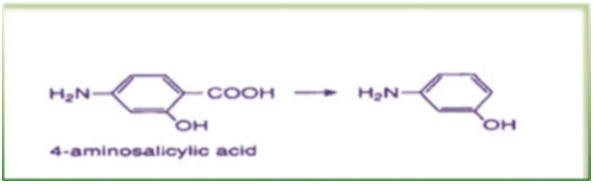

Fig. 3.3 Decarboxylation of 4-aminosalicylic acid into 3-aminophenol

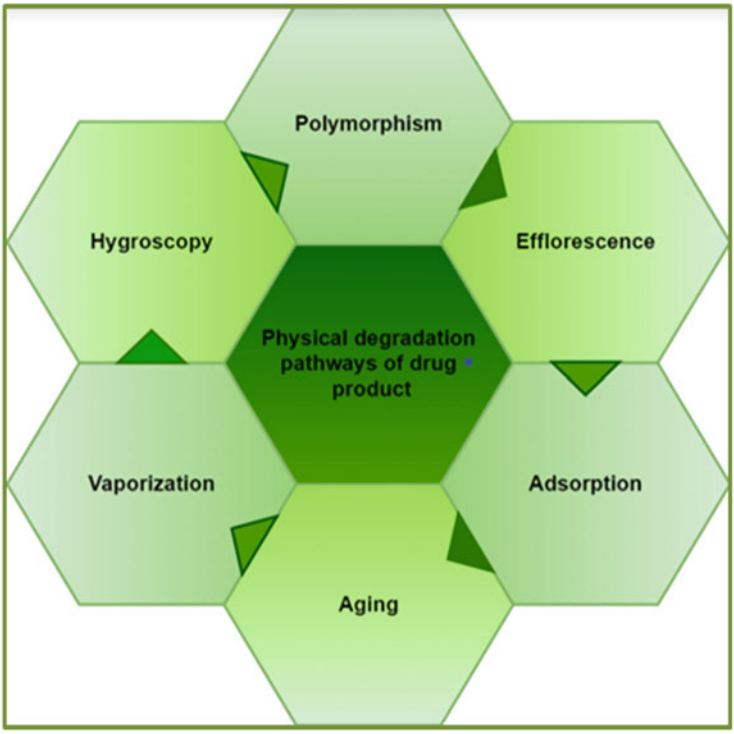

Fig. 3.4 Physical degradation pathways of drug product

3.4.6.1 Polymorphism

The term "polymorphs" is used for different crystalline forms of the same compound, and these forms occur when there is a change in pressure, relative humidity, and temperature. Examples of drugs that show phenomenon of polymorphism include formaldehyde and aminopenicillins [21].

3.4.6.2 Efflorescence

It is a phenomenon in which a drug product loses water, and resultantly the concentration of drug in the product increases. For example, solution loses water and becomes supersaturated [21].

3.4.6.3 Adsorption

While storing drugs, plastic material is mostly used especially in primary packaging and is occasionally used for administration of a drug product. During this period of direct contact of a plastic with the drug product, adsorption of drug may occur resulting in drug loss. For instance, 40% of quinidine gluconate is lost when the drug is administered with a traditional polyvinyl chloride IV administration set [8].

3.4.6.4 Hygroscopy

It is a phenomenon in which drug product absorbs water from environment or surroundings and resultantly the drug deteriorates. For example, powders deteriorate under moist storage conditions [21].

3.4.6.5 Vaporization

Volatile compounds, for instance, camphor, volatile oils, ethers, and ketones, can escape from formulation through the process of vaporization, which results in drug loss affecting the efficacy of the product. Therefore, such products are needed to be placed in a tightly close container with temperature considerations [8].

3.4.6.6 Aging

Aging is the process in which the physical and chemical properties of the active substances and excipients present in the drug change. It is the most interesting phenomenon in physical degradation of drug product but occurs rarely. It affects the dissolution and disintegration characteristics of the dosage form [8]. For example, in aminophylline suppositories, melting time increases from about 20 min to more than 60 min after storing at 22° C for 24 weeks' period. This increase in melting time resultantly decreases the drug bioavailability [22].

3.4.7 Microbiological Degradation of Pharmaceutical Drug Product

Microorganisms are adaptable to a huge range of conditions and therefore possessed a risk for the pharmaceutical drug products. Deterioration of drug product due to the presence of microorganisms can make the product harmful for human use or can have adverse effects on the properties of drug product. Contamination of a product by microorganisms affects both the quality and safety of drug product. A microbial control strategy should have to be employed, and therefore thorough information about the microbe entry points in a process along with potential of microbial contamination of medium, buffers, and drug product is required [23].

3.5 Conclusion

The speed at which reaction occurs is termed as rate of reaction, and the study of the rate of reaction is known as chemical kinetics. Reactions can progress both at a faster and slower pace, and there are multiple factors affecting these rates. Among various chemical and physical factors, the most important factor is temperature; every 10 °C increase in temperature can double the speed of reaction; therefore, temperature should be carefully monitored and maintained according to the product specifications. Chemical kinetics plays a significant role in drug design, development, and manufacturing, to ensure stability of drug. Drug instability leads to drug degradation which ultimately results in loss of drug activity. Drugs can be degraded by microbes and also by physical and chemical pathways. Chemical pathways of

drug degradation are most prevalent, and the majority of drugs degrade through chemical mechanisms.

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