Role of Kinetic Models in Drug Stability

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Abstract

Kinetic models are studied to determine their role in stability and release kinetics of drugs. The mathematical models that have been widely used are zero-order kinetic model, first-order kinetic model, Higuchi model, Korsmeyer-Peppas model, and Hixson-Crowell model. Although they have vast applications, there are some factors that may effect on mechanical, physical, pH, relative humidity, and presence of solvents. Several types of drugs are being fitted in zero-order and first-order kinetic models, while a polymeric matrix system containing drugs is preferably fitted in Higuchi model, Korsmeyer-Peppas model, and Hixson-Crowell model. In this chapter, we have briefly discussed in detail the role of these aforementioned kinetic models in the stability of various types of drugs and their dosage forms.

Keywords

Zero-order kinetic model · First-order kinetic model · Higuchi model · Korsmeyer-Peppas model · Hixson-Crowell model

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11.1 Introduction

Chemical kinetics deals with the changes in chemical properties of drug and any substance over time and is mainly related to the rate of changes. It is interpreted as rate of reaction in which concentration **c** is changed with respect to time *t* (indicated mathematically as d*c*/d*t*). Factors that are mainly involved in the rate of reaction are concentration of reactants, temperature, catalysts, and various environmental conditions [1]. Information and description of different types of reactions including their mechanisms can be shown through kinetic models. Various types of reactions particularly the Michaelis-Menten reaction, mass action, and some other parameters like the catalytic constant (*k*cat), maximal rate of reaction (*V*max), and Michaelis-Menten constant (*k*m) can be described by kinetic models [2]. These mathematical models express the relationship between the variables and parameters, which helps the researcher to demonstrate the ideas about the process under research [3].

Stability of drug plays an important role in drug efficacy and its activity. Study of drug stability using different kinetic models has been developed in order to explain the course of reaction mathematically. For this purpose, stability studies are conducted that ensure that the drugs lie within the range of acceptance criteria and are unaffected by environmental or non-environmental factors that may involve in causing instability of drugs. Factors primarily involved in instability of drug are taken into account as they can cause loss in quality and efficiency as well as increase and/or decrease in concentration of drug in dosage form and also lead to decomposition and degradation of it. These types of instabilities may occur during shelf-life and transportation of drugs. Chiefly, three types of drug stabilities are considered to be maintained during such conditions, i.e., physical, chemical, and microbiological [4].

11.2 Types of Stability of Drugs

Three types of drug stabilities are considered to be maintained during such conditions, i.e., physical, chemical, and microbiological. Their detailed description has been discussed in the following subsections:

11.2.1 Physical Stability

Physical stability includes stability of physical properties of the drug in terms of its organoleptic characteristics, change in its appearance, size and shape of particle, content uniformity, and pH. These physical alterations are reasonably due to vibration, abrasion, and temperature variation. The abovementioned physical characteristics are necessary to be maintained throughout stages of drug development and shelf-life [5, 6].

11.2.2 Chemical Stability

The changes occurring in chemical constitution of drug formulation are referred to as chemical instabilities. Chemical reactions going down in pharmaceutical product are mainly hydrolysis, oxidation, photolysis, solvolysis, oxidation, reduction, and racemization. Such variations lead to loss of therapeutic activity and efficacy of active pharmaceutical ingredient (API) and also generation of toxic products. Liquid dosage forms are more prone to chemical degradation than solid dosage forms [5].

11.2.3 Microbiological Stability

Microbiological stability of drugs includes the stability of drug formulation in respect to its sterility, i.e., free from any microbial contamination (bacteria or fungi). The safety of drug product could be compromised in case of any microbial growth especially in semi-solid drug products and liquid dosage forms due to the presence of water or moisture. Microbiological instability can be controlled in these formulations by adding preservatives or antimicrobial agents [5]. To identify about the type and cause of instability, forced degradation studies are executed in order to understand the stability behavior of an active pharmaceutical ingredient. With the help of these studies, information related to degradation pathways of drug products can be obtained [7]. Types of these studies are shown in Table 11.1.

11.3 Kinetic Models

Kinetic models are employed to study the abovementioned stabilities in pharmaceutical drug products. After gathering data through various experimental procedures, an appropriate model is appointed in order to evaluate their stability behavior [8]. These models then manifest the results of data being fitted in these models, by the help of their respective equations. The most commonly used kinetic models in drug stability and drug release are:

Table 11.1 Types of stability studies

Type of study	Storage conditions	Time duration
Long term	25 °C ± 2 °C and 60% RH ± 5% RH or 30 °C ± 2 °C and 65% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C and 65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C and 75% RH ± 5% RH	6 months

11.3.1 Zero-Order Kinetic Model

In zero-order kinetic model, the rate of reaction is independent of the concentrations of reactants; thus, the rate will be represented as:

$$\text{Rate} = \frac{\mathrm{d}[A]}{\mathrm{d}t} = k[A] = k$$

where A represents the reactant and k is a zero-order rate constant.

11.3.2 Role

- Mostly osmotic pump delivery system and transdermal delivery system and matrix system for drugs with low solubility follow zero-order kinetic models [9].
- The stability study of powder for injection and reconstituted sample of third-generation cephalosporin, ceftazidime, was conducted. Stress conditions like temperature and ultraviolet and visible radiation were applied to study their kinetics of degradation. For reconstituted sample and powder for injection, zero-order and second-order kinetic models were utilized to explain the degradation phenomena of ceftazidime [10].
- Thermal stability of drug that is used in the treatment of diabetes mellitus, i.e., metformin hydrochloride (1,1-dimethylbiguanide hydrochloride), was studied by using kinetic models. This drug was exposed to temperatures 30, 40, 50, and 70 °C in aqueous medium. The gathered data was treated by Arrhenius, zero-order, and first-order kinetics. It was evaluated that thermal degradation of metformin followed zero-order kinetics and decomposed up to 10% in 208 h [11].
- The level of scopolamine in plasma after the application of transdermal patch on the skin was anticipated through theoretical model of transdermal drug delivery system. The drug released from this system followed zero-order kinetics. The rate constant of zero-order kinetics in this type of system is related to the diffusional characteristics of scopolamine [12].
- An erodible device which maintains the constant surface area with respect to time was used in order to measure the release kinetics of amoxicillin. The prediction made by using this device elicited that amoxicillin follows zero-order kinetics apparently from the planar surface of tablet [13].

11.3.3 First-Order Kinetic Model

This model is widely used in the stability studies of pharmaceutical products. In this first-order kinetic model, the rate of reaction is directly proportional to the concentration of the reactants:

$$\text{Rate} = \frac{dC}{dt} = -Kt$$

The time at which the concentration of reactants decreases to 50% from its original concentration is referred to as the half-life denoted as $t_{1/2}$. The half-life of first-order kinetics can be determined by these formulas:

$$t_{1/2} = \frac{\ln 2}{k}$$

$$t_{1/2} = \frac{0.693}{k}$$

11.3.4 Role

- The porous matrices in dosage forms that contain water-soluble drugs follow first-order kinetics, as their release is proportional to the concentration of drug [14].
- Degradation profiles of drugs like metronidazole, tetracycline, and famotidine can be determined with the aid of these kinetic models. This triplicate therapy is used in the treatment of *Helicobacter pylori*-associated peptic ulcer. The stability and compatibility of these drugs in different states were studied which were exposed to mild to extreme conditions. It was concluded that the degradation profiles of these drugs follow pseudo-first-order kinetics [15].

11.3.5 Higuchi Model

This model was proposed in 1963 by Higuchi to explain the release kinetics of drugs from the matrix system. Model expression is given by the equation:

$$Q = A[D(2C - C_S)C_S \quad t]^{1/2}$$

where "Q" represents the quantity of drug released in time t per unit area A, "C" represents the drug initial concentration, Cs is solubility of drug in the media, and diffusivity of molecules (diffusion coefficient) is denoted by "D" in the matrix. The simplified form of this model is represented as:

$$Q = K_H\sqrt{t}$$

The above equation demonstrates the direct relationship between cumulative quantity of drug released and square root of time. The proportionality constant or Higuchi constant, i.e., K_H, can be obtained by the slope of graph that has some physically realistic and specific meaning.

11.3.6 Role

- The equation derived by Professor Takeru Higuchi facilitates quantification of release of drug from different dosage forms, for example, release of finely dispersed drug from thin ointment film under sink conditions.
- Kinetic models are used in the in vitro stability studies of different pharmaceutical dosage forms. For example, aspirin-magaldrate double-layer tablets were compared with marketed Ascriptin® and Aspro®. They were stored at different temperatures for specified period of time. The best fitted model to study the stability was first-order kinetic model when storage temperature was 70 °C and Higuchi model when storage temperature was 50 °C and 60 °C with the time period of 50 days. The result of this study showed that the presence of alkaline moieties in aspirin-magaldrate double-layer tablets reduced the shelf-life and increased the rate of decomposition of aspirin [16].

11.3.7 Korsmeyer-Peppas Model

Korsmeyer et al. and Peppas explained the phenomena of release of drug from polymeric system. They also formulated an equation for the analysis of Fickian and non-Fickian release of drugs through polymeric delivery system that may be either swellable or non-swellable matrix. The mechanism of release of drug can be found after fitting first 60% drug release data in Korsmeyer-Peppas model. The following equation represents Korsmeyer-Peppas model:

$$Mt/M_{\alpha} = kt^{n}$$

The fraction of drug released at time t is designated as Mt/M_{α}, where k is the release rate constant and n is the release exponent [17]. The value of n characterizes the release mechanism of drug as shown in Table 11.2.

Table 11.2 Drug release mechanism according to Korsmeyer-Peppas model

Mechanism of drug transport	Release exponent (n)	Mechanism of drug release	Rate as f(t)
Quasi-Fickian diffusion	$n < 0.5$	Non swellable matrix diffusion	t^{n}
Fickian diffusion	0.5		$t^{0.5}$
Anomalous (non-Fickian transport)	$0.5 < n < 1.0$	For both diffusion and relaxation (erosion)	t^{n-1}
Case II transport	1.0	Zero-order release	Independent of time
Super case II transport	Higher than 1.0	Relaxation/erosion	t^{n-1}

11.3.8 Role

- Korsmeyer-Peppas and Higuchi models are the best kinetic models for the evaluation of stability of advanced drug delivery systems, as these models not only describe the in vitro release of drug from the matrix system but also explain the stability behavior. The compatibility between drug-polymer, content of drug, and encapsulation efficiency was studied in intravaginal mucoadhesive microspheres of tenofovir disoproxil fumarate (TDF). Accelerated stability study was followed to conduct that research [18].

11.3.9 Hixson-Crowell Model

Hixson-Crowell cube root model is employed for those systems in which the surface area and diameter of the drug matrix change with time. Hixson and Crowell in 1931 discovered that regular area of a group of particles is proportional to the cube root of its volume. The relationship established by Hixson-Crowell is described by the following equation:

$$W_0^{1/3} - W_t^{1/3} = K_{\mathrm{HC}t}$$

The initial amount of drug at time 0 is represented as "W_0," the amount of drug remaining in the pharmaceutical dosage form at time "t" is represented as "W_t," and Hixson-Crowell constant is denoted as "K_{HC}" which describes the surface-volume relationship [19].

11.3.10 Role

- Hixson-Crowell model was applied to study the efficient release of an anti-schizophrenic drug haloperidol by using vehicle cysteamine hydrochloride protected carbon dots. Under standardized conditions, haloperidol followed the Hixson-Crowell model, i.e., constant release of drug was attained for more than 40 h [20].
- The accelerated stability was conducted on regioselective floating tablets of atenolol and lovastatin, and their degradation profiles were obtained as well as release kinetics. It was evaluated that atenolol followed mixed pattern of kinetic models, among which Hixson-Crowell was present [21].
- A study was carried out to understand the role of various polymers on drug release kinetics of losartan potassium oral controlled release tablets. In that study, through Hixson-Crowell model, a good correlation was obtained. This showed

that the release of drug was affected by the change in surface area of the solid dosage form [22].

11.3.11 Merits and Demerits of Kinetic Models

We have described the merits and demerits of the aforementioned kinetic models in Table 11.3.

Table 11.3 Merits and demerits of kinetic models

Kinetic model	Merits	Demerits
Zero-order kinetic model	It is used to explain dissolution of drugs in many different types of pharmaceutical modified release dosage forms	This model cannot be utilized for all types of pharmaceutical dosage forms
	It helps to describe the release kinetics of drugs in transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic system	
First-order kinetic model	This model describes the dissolution of drugs which are water soluble present in porous matrices	First-order kinetic model is not always applicable to controlled drug delivery system
Higuchi model	Higuchi model is very easy to use in spite of the complex mass transport process	Due to the occurrence of many advanced kinetic models, the Higuchi equation could be confused with other equations while implementation or study of release kinetics of drugs [23]
	This type of model helps in understanding the release of drug mechanism from controlled drug delivery systems, e.g., transdermal patches, matrix tablets, etc. where water-soluble drug is being incorporated	
Korsmeyer-Peppas model	This type of model aids in linearization of data obtained from the release profile of several formulations of microcapsules or microspheres	The researcher while using this model could get confused when explaining the release pattern of drugs
	This model describes the Fickian and non-Fickian release pattern of drugs	
Hixson-Crowell model	This model is applied to those pharmaceutical dosage forms in which the dissolution of drugs takes place in planes parallel to drug surface, when the dimension of tablet diminishes proportional to the initial geometrical form with respect to time	It is complicated to use and understand in some cases

11.4 Factors Influencing the Rate of Kinetics in Kinetic Models' Selection

11.4.1 Mechanical Factors

The rate of transformation from one type of compound to similar or different type of compound can be significantly increased due to trituration and compression [24].

11.4.2 Physical Factors

The rate of kinetics can be affected by solubility and racemization of chemical compounds.

11.4.3 Relative Humidity

In the presence of moisture, transformation of both polymorphs to monohydrate form could be occurred.

11.4.4 Effect of Solvent

The presence of solvent vapors like dichloromethane can have significant effect on the rate of transformation.

11.4.5 pH

Acidic and alkaline pH affect the rate of kinetic reaction. The effect of pH either causes an increase or a decrease in the rate [25].

11.5 Conclusion

Kinetic models assist in describing the stability behavior with the help of stability studies as well as release patterns of drugs from different pharmaceutical dosage forms. The most common and simple models used are first-order and zero-order kinetic model. Higuchi model, Korsmeyer-Peppas model, and Hixson-Crowell model have a large implementation in the study of drug polymeric matrix system.

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