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Drug Release Kinetics and Mathematical Models

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ABSTRACT

The drug release from dosage form plays an important role in therapeutic activity. Various factors can affect the rate of drug release from the dosage form. Understanding the rate and amount of drug release from pharmaceutical formulations requires a solid understanding of drug release kinetics and mathematical models. By predicting the behavior of drug delivery systems, these models aid in assuring its efficacy and safety. The mathematical models include the zero-order release model, First order release model, Higuchi model, Hixson-Crowell model, Korsmeyer Peppas model, Baker and Lonsdale model, Weibull equation model, Hopfenberg model, Gompertz model, Regression model, Gallagher-Corrigan model.

Keywords: Release kinetics; Controlled release; Diffusion; Dissolution; Erosion; Mathematical modeling.

INTRODUCTION

In the drug release process, the active drug undergoes pharmacokinetic parameters, including ADME, showing pharmacological action. The process involves studying the drug release rate, mechanism, and the factors that can affect drug release.

Factors Affecting Drug Release

1. **Drug-related factors**

a] Solubility of the drug

b] Drug content

c] Molecular weight

d] Particle size and shape

2. **Formulation variables**

a] Formulation geometry

b] Formulation variables

3. **Polymer-related factors:** Increases in polymer proportion cause the gel to become more viscous, which lengthens the diffusional path. Consequently, the rate of drug release falls and the diffusion coefficient drops [1, 2].

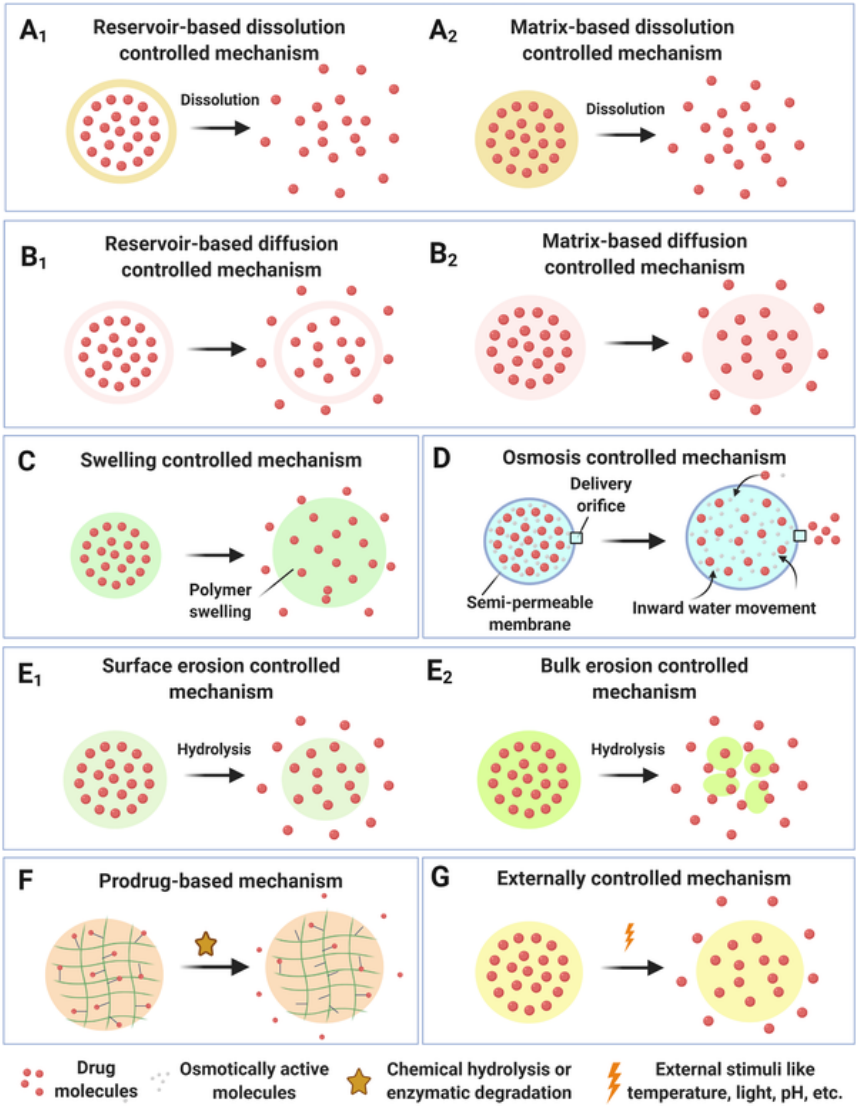

Figure No: 01-Drug release mechanism:

Mathematical models:

Zero order release model:

It describes the process of a medicine being released continuously from a drug delivery regardless of concentration. The following equation can be used to depict medication dissolution from dosage forms that do not break down and release the drug gradually:

$$Q_t = Q_O + k_o t$$

Where,

Q_t = Amount of drug dissolved (or) released in time "t".

Q_O = Starting dosage of the medication in the mixture (Generally Q_O= O)

k_o = Zero order release constant

t= Time

Graphical representation:

X-axis: Time

Y-axis: cumulative amount of drug release.

Applications:

1. **Tablets with extended release:** For extended release tablets, where a medication is meant to be delivered gradually over an extended period of time to maintain therapeutic drug levels and reduce dose frequency, zero order release works well.

2. **Transdermal Patches:** Zero-order kinetics can be used to mimic the consistent medication levels in the blood stream that these patches release through the skin at a constant rate.

3. **Implantable Device:** To guarantee a constant release rate, drug implants intended for long- term release, such as hormone therapy (or) contraceptive implants, frequently adhere to zero-order kinetics.

4. **Intraocular Implants:** Drugs used in eye treatments, such as glaucoma medications, benefit from zero-order kinetics since they help keep the drug concentration in the eye steady.

5. **Infusion systems:** Zero order kinetics can be used to mimic the steady medication release that occurs in some intravenous infusion systems [3,4].

First order release model:

Drug release from polymeric films can be effectively described by a first-order kinetic model, suggesting that the drug release mechanism is concentration dependent. With decreasing concentration gradient overtime, the amount of medication release reduces.

$$\textbf{Log } C_t = \textbf{log } C_o - Kt / 2.303$$

Where,

Log C_t= concentration of drug in solution at time‘t’.

Log C_o= initial concentration of drug.

K= first order rate constant.

T= Time

Graphical representation:

X-axis: Time

Y-axis: Log cumulative of % drug remaining.

Applications:

1. **Immediate- release tablets& capsules:** since the drug is rapidly released from the dosage form and its concentration swiftly drops in the gastrointestinal tract, these formulations frequently exhibit first order kinetics.

2. **Drug solutions:** first- order kinetics can be frequently used to approximate the release of medications when they are provided in liquid form, such as oral solutions (or) intravenous injections. It is used to estimate the release, especially if the drug concentration falls with time.

3. **Matrix systems:** if the drug is gradually diffusing out as the concentration gradient lowers, some matrix-type controlled-release systems, where the drug is spread inside a polymeric matrix, may display first-order kinetics.

4. Elastomeric Pumps: Insulin pumps are examples of devices that are used for regulated drug deliver; If the rate of drug distribution dependent on the drugs decreasing concentration with in the device, then the device may display first-order kinetics [3].

Higuchi model

Higuchi (1961) presented the first example of a mathematical model intended to explain drug release from a matrix system.

$$Q = K_H t^{1/2}$$

Where,

Q= Amount of drug released.

K_H= Higuchi dissolution constant.

T= Time

Graphical representation:

X-axis: Square root of time

Y-axis: Cumulative percentage of drug release

Applications:

1. Matrix Tablets: these are tablets with a homogenous drug distribution inside a polymeric matrix, used in controlled- release formulations. The Higuchi model uses matrix diffusion to forecast the drugs release profile over time.

2. Hydrophilic polymer matrices: The Higuchi model can be used to predict release rates in these systems, such as those that use hydrophilic polymer like Hydroxyl propyl methylcellulose (HPMC), when the drug diffuses through the swelling matrix.

3. Controlled- Release Microspheres: To comprehend and regulate profile of drug containing microspheres (or) microcapsules distributed in a polymer matrix, the Higuchi equation can be utilized as a model.

4. Semisolid Systems: I f diffusion plays a major role in regulating release, ointments, creams and gels containing a drug dispersed in a gel matrix can also be examined using Higuchi model.

5. Implantable Drug delivery systems: The Higuchi model is frequently used top asses drug- loaded implants (or) devise that release the medication through diffusion from a matrix [5].

Hixson- Crowell model:

In systems where the medication is released from a matrix (or) solid dosage form, the Hixson- Crowell model is very useful for studying drug release kinetics when the geometric shape of the dosage form affects the drug release this model is helpful in understanding how drugs release rate varies over time**.**

$$Q_t^{1/3} = Q_O^{1/3} - K_t$$

Where,

Q_t= Remaining amount of drug in pharmaceutical formulation at a time 't'

Q_O= Initial amount of drug

K= Dissolution rate constant

Graphical representation:

X-axis: Time

Y-axis: Cube root of drug percentage remaining

Applications:

1. **Matrix Tablets:** When a drug is placed in a solid polymeric matrix, the model is frequently used to examine how the drug releases from the tablet. It aids in comprehending how, overtime the matrix erodes (or) dissolves and affects the drug release rate.

2. **Controlled Release formulations:** The Hixson-Crowell model can explain the kinetics of drug release and assist in creating formulations with desired release profiles for controlled- release systems where the medicine is released gradually.

3. **Spherical and Cylindrical dosage forms:** The concept is especially helpful for spherically (or) cylindrical dosage forms, like beads (or) cylinders, because the geometric shape of the dosage form might affect how quickly the drug release its effects.

4. **Drug release mechanism studies:** By illuminating how modifications to formulation (or) processing conditions impact the release kinetics, the Hixson-Crowell model helps researchers investigate the release mechanisms. This can be very helpful for improving medication delivery systems.

5. **Erosion- Controlled systems:** The model assists in estimating the rate of erosion and comprehending how it affects drug release in formulations where the erosion of the dosage form is the primary mechanism controlling drug release.[6].

Korsmeyer- Peppas model:

In drug release kinetics, the Korsmeyer- peppas model is frequently employed to explain how a drug releases from a polymeric matrix understanding release mechanisms from a system where drug release requires swelling (or) diffusion occurs in a polymer matrix is made easier with the use of this model.

$$M_t/M_\infty = kt^n$$

Where,

M_t= Amount of drug released at time 't'.

M_∞= Total amount of drug available for release.

K= Release rate constant.

n= Release exponent.

Graphical Representation:

X-axis: Log Time

Y-axis: Log cumulative percentage of drug release.

Applications:

1. **Matrix Tablets:** This type of tablet in which the medication is distributed across a polymer matrix, is used to forecast and regulate drug release. This model aids in matrix design and polymer selection to produce desirable release characteristics.

Hydrophilic polymers: used in systems using hydrophilic polymers, like hydrogels, that swells and releases the medication by erosion (or) diffusion.

2. Formulation development:

- **Optimization:** Offers insights in to how medications, to polymer type, concentration and formulation factors impact drug release rates, which aids in the optimization of formulation parameters.

- **Mechanism Understanding:** Guides formulation modifications by helping to determine the predominant release mechanism (diffusion, erosion) based on release exponent.

3. Evaluation of Release profiles:

- **Comparative studies:** These studies compare the release profiles of various formulations in order to analyze the effects of processing (or) formulation changes on drug release.

- **Quality control:** Aids in evaluating the dependability and consistency of medication release from commercial goods is tests related to quality control.

4. Development of Advanced drug delivery systems:

- **Nano particles and micro particles:** Systems in which pharmaceuticals are encapsulated, hence offering valuable insights in to the release kinetics from these carriers.

- **Polymeric micelles and vesicles:** These complex carriers which can display a variety of release behaviors are used to investigate release form.

5. Predicting in-vivo behavior:

- **In-vitro to in-vivo correlation:** Help to forecast the potential translation of in-vitro release characteristics to in-vivo medication release. [7].

Baker- Lonsdale model:

This model, which explained the drug release from spherical matrices, was created by Baker and Lonsdale using the Higuchi model.

$$f= 3/2 [1-(1- M_t/M_\infty)^{2/3}] - M_t/M_\infty= Kt$$

M_t/M_∞= Fraction of drug release.

K= Release rate constant.

Graphical Representation:

X-axis: Time

Y-axis: Fraction of drug release (M_t/M_∞)

Applications:

The Baker-Lonsdale model aids in the prediction of drug release kinetics from spherical matrix system when applied to spherical matrices. Drug loaded beads, microcapsules (or) spherical tablets are examples of these spherical matrices [8, 9].

Weibull model:

Langer Bucher included a broad empirical equation for the dissolution (or) release process, which weibull had first proposed in 1951. Drug dissolution and release from dosage forms can be described using the weibull equation, which describes the cumulative fraction of drug 'm' in solution at time 't'.

$$m= 1- exp [-\{(t- T_i)\}/a]$$

Where,

a= Scale parameter (time dependence)

b= Shape parameter (shape of dissolution curve)

T_i= Location parameter (time before action of release process)

Graphical Representation:

X-axis: Time

Y-axis: Cumulative percentage of drug release.

Applications:

1. **Predicting drug release profiles:** The Weibull model fits a range of dissolution profiles, which enables researchers to forecast a drug's temporal release understanding and creating controlled release formulations are aided by this.

2. **Comparing formulations:** To compare various drug formulations (or) batches according to their release characteristics, such as rate and extent of drug release, dissolution data must be fitted to the Weibull model [10].

Hopfenberg model:

Hopfenberg created a mathematical model to correlate the release of drugs from polymers whose surfaces erode with time, provided that the surface area stays constant.

$$M_t/M_\infty = 1-[1-K_o t/cLa]$$

Where,

K_o= Zero order rate constant

cL= Initial drug loading

a= Half thickness of system

n= exponent

M_t/M_∞= Fraction of drug release

Graphical Representation:

X-axis: Time

Y-axis: Cumulative fraction of drug release

Applications:

1. **Predicting drug release from reservoir systems:** In reservoir type drug delivery systems, a drug is enclosed in a matrix (or) core and encircled by a polymeric membrane. The Hopfenberg model is useful for forecasting release from these types of systems.

2. **Analyzing matrix systems:** This aids in comprehending the release kinetics of drugs dispersed with in a polymer matrix found in matrix tablet (or) beads [3].

Gompertz model:

A less complex exponential model called the Gompertz model is frequently used to describe the in-vitro dissolution profile.

$$X_t = X_{max} \exp[-\alpha e^{\beta \log t}]$$

Where,

X_t= Percent dissolved at time t divided by 100

X_{max}= maximum dissolution

α= Undissolved proportion

β= dissolution rate per unit time.

Graphical Representation:

X-axis: Time

Y-axis: X

Applications:

1. **Characterizing drug release profiles:** The Gompertz model can be used to characterize pharmaceuticals with complex release patterns, such as those that exhibit a release phase after an initial log phase. This is because the model is good at fitting sigmoidal dissolution curves.

2. **Designing controlled release formulations:** when a precise release rate (or) pattern is required, researchers can create controlled release formulations that accomplish specified release profiles by using the Gompertz model to analyze dissolution data [3].

Gallagher- Corrigan model:

Compounds of diffusion and degradation are frequently used conjunction to assess drug release from biodegradable polymeric drug delivery devices polymer breakdown and drug release happen simultaneously. A sigmoidal shape is typically observed in drug release patterns in these systems. An equation that represents the percentage of medicine released from a biodegradable polymeric system is the Gallagher- Corrigan model. Drugs that are not attached to the drug matrix exhibit an initial bursts effect, and subsequent gradual release is regulated by matrix erosion, as represented by the Gallagher- Corrigan equation

$$F_t = f_{tmax}.(1-e^{k_1 t})+(f_{tmax}-f_B).(e^{k_2.t-k_2 t_{2max}}/1+e^{k_2 t-k_2 t_{2max}})$$

Where,

f_t = fraction of drug released at time't'.

f_{tmax}= maximum fraction of drug released during process

f_B= fraction of drug released during 1st stage

k_1=first order constant

k_2= kinetic constant for 2nd stage of release process- matrix degradation.

Graphical representation:

X-axis: Time

Y-axis: Fraction of drug release

Applications:

1. Modeling biodegradable system: Since release rates are influenced by both drug diffusion and polymer degradation in biodegradable polymeric systems, the Gallagher- Corrigan model is extended to explain the complex release patterns frequently seen in these systems.

2. Predicting release over time:

Assists in forecasting the changes in the drug release profile that occur with the degradation of the polymer matrix. For formulations meant to offer controlled (or) longer release, this is essential [13, 14].

Regression model:

Regression models are statistical instruments employed to comprehend the correlation between variables. These models aid in the prediction of medication behavior and efficacy in pharmaceutics.

Importance: drug release characteristics can be better understood quantatively with the use of regression analysis its assists in determining the variable that affects pharmacokinetics and bioavailability.

Types:

1. Linear regression

2. Logistic regression

3. Polynomial regression

$$Y = \beta_0 + \beta_1 x + €$$

The term regression is represented as R^2

R^2 is the word used to describe coefficient of determination in regression analysis in pharmaceutics according to one or more independent variables this statistical measure shows how effectively a model explains the variability of a dependent variables.

R^2 has several users in pharmaceutics including:

1. Dissolution profile analysis: R^2 is a measure of models goodness of fit that describes how a drug releases from a formulation over time the model appears to suit the experimental dissolution data quite well if the R^2 value is high.

2. Stability studies: R^2 can be used to examine how changes in drug stability parameters over time relate to one another to list out it facilitates comprehension of how well a stability model forecast a drug's deterioration overtime [15].

Graphical representation

For simple linear regression

X-axis: time

Y- axis: drug release percentage

Conclusion:

The application of mathematical modeling to medication administration has great promise for stream lining the development and assessment of new products as well as aiding in the comprehension of intricate pharmaceutical dose forms. The goal of choosing appropriate model is to guarantee the study's efficacy.

References:

1. G.L. Flynm, S.H. Yalkowsky, T.J. Roseman, "Mass transport phenomena and models: theoretical concepts", J pharm Sci. 63(4): 579-510 (1974).
2. J.W. Skoug, M.V. Mikelson, C.N. Vignron, N.L. Stemm, "Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release". J Cont. Rel. 2:227-45 (1993).
3. D. Suvakanta, P.N. Murthy, N. Lilakanta, C. Prasanta, "Kinetic Modeling on drug release from controlled drug delivery systems". Acta Poloniae Pharmaceutical. 67(3), 217-223 (2010).
4. C.G. Varles, D.G. Dixon, C. Steiner, "Zero-order release from biphasic polymer hydrogels", J. Cont. Rel. 34: 185-192 (1995).
5. T. Higuchi, "Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices", J. pharm. Sci. 52, 1145- 1149 (1963).
6. A.W. Hixson, J.H. Crowell, "dependence of reaction velocity upon surface and agitation (1) theoretical consideration", Ind. Eng. Chem. 23, 923-931 (1931).
7. R.W. Korsmeyer, N.A. Peppas, "solute and penetrant diffusion in swell able polymers. III. Drug release from glassy poly (HEMA-co-NVP) copolymers", J. Cont. rel. I (2): 89-98 (1984).
8. R.W. Baker, H.S. Lonsdale, in controlled release of biologically active agents, Tanquary A.C., Lacey R.E. Eds., Plenum Press, New York 1974.
9. A.J. Shukla, J.C. Price, "Effect of drug (core)particle size on the dissolution of the theophylline from microspheres made from low molecular weight cellulose acetate propionate", Pharm. Res. 6: 418-421 (1989).
10. F. Langenbucher, "Linearization of dissolution rate curves by the Weibull distribution", J. Pharm. Pharmacol. 24: 979-981 (1972).
11. S. Cohen, T. Yoshika, M. Lukarelli, L.H. Hwang, R. Langer, "controlled delivery systems for proteins based on poly (lactic/glycolic acid) microspheres", Pharm. Res. 8(6): 713-20 (1991).
12. S. Wilbert, P. Viness, P.D. Michal, M.V. Alvaro, V. Sandy A.K. Riaz, "Experimental Design for the Formulation and Optimization of Novel Cross linked Oilispheres Developed for In Vitro Site-Specific Release of Mentha piperita Oil", AAPS Pharm. Sci. Tech. 5(I): 18 (2004).
13. J. Balcerzak, M. Mucha, "Analysis of Model Drug Release Kinetics from Complex Matrices of Polyactide-Chitosan", Progress on Chemistry and Application of Chitin and Its Derivatives, Volume XV, 2010; 117-126.
14. M. Arezou, H. Mobedi, H. Mahdavi, "A Comparative Study of Progesterone and Lidocaine Hydrochloride Release from Poly (L-lactide) Films", Pharm. Sci. 21:77-85 (2015).
15. Myatt. G.S., & Wallis, W. A. (2015). Using Regression Models for Pharmaceutics. Pharmaceuticals statistics, 14(5), 263-270.

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