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Statistical Moment Theory and Non-Compartmental Analysis

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Abstract

Mathematical model a numerical classification of the biological framework and utilized to state quantitative connections. A pharmacokinetic compartment is a numerical idea that portrays a space in the body that medication seems to possess These models just mediate the test information and permit an experimental equation for the assessment of medication focus with time. A non-compartmental model is a pharmacokinetic model that does not involve the consequence of a definite compartment model is called a Non-compartment model. This approach is based on the consequence that the drugs or substances created in a metabolic process follow direct kinetics, which is the basis that this approach can be functional to any compartment model. The non-compartmental analysis gives an elective strategy to portraying drug pharmacokinetics without appointing a specific compartmental model to the medication.

Key Words: Non-Compartmental Model, the Non-Compartmental Analysis Statistical Moment Theory, the Non-Compartmental Analysis, Types of Models

Introduction

Mathematical Model

It is a numerical clarification of the biologic framework and is utilized to state quantitative connections. An assortment of numerical amounts, tasks, and relations along with their definitions are called numerical models and they ought to be sensible and pragmatic. Speculation that utilizes numerical terms to compactly depict quantitative connections is known as a model. (Howlett,)

Pharmacokinetic Models

A pharmacokinetic compartment is a numerical idea that portrays a space in the body that medication seems to possess. It does not have to relate to a particular anatomical space or physiological volume. A theory that uses numerical terms to depict quantitative connections is a pharmacokinetic model.

Compartmental Models

A gathering of tissues with the comparative bloodstream and medication fondness is known as a compartment which is a physiologic or anatomic zone. The compartment is the traditional and comprehensively utilized way to deal with the pharmacokinetic portrayal of medication. These models just mediate the test information and permit an experimental equation for the assessment of medication focus with time.

Non-compartment Model: A pharmacokinetic model that not involving the consequence of a definite compartment model is called a Non-compartment model. This process is based on the consequence that the drugs follow direct kinetics, which is the keystone that this technique can be applied to any compartment model. The non-compartmental pharmacokinetic process allows detailed pharmacokinetic analysis without hangout to

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curve fitting, complicated computers, or monotonous numerical equations. (Howlett)

The Noncompartmental Analysis

Non-compartmental investigations give an elective strategy to portraying drug pharmacokinetics without appointing a specific compartmental model to the medication. Albeit this technique is often viewed as model-free, there are yet a couple of suspicions and key considerations that should not be disregarded. This methodology is, therefore, better alluded to as "non-compartmental" as it expects to be a "model" in that, among other things that will be inspected underneath, the PK needs to be direct and the terminal stage must be log-straight. (Wright, 1994)

The primary assumption is that direct pharmacokinetics is shown by the medication being referred to or we can say that openness increments in extent with increasing portion and PK boundaries are stable with time. A second critical supposition is that the drug is disposed of from the body carefully from the pool in which it is being estimated, for example, the plasma. All wellsprings of the medication are immediate and special to the estimated pool is the last assumption of this methodology.

The AUC foreseen for compound plasma focuses is the essential proportion of in general compound openness following intravenous or extravascular organization. The AUC is generally assessed by the direct or log trapezoidal strategies or a mix of both. (Wright, 1994)

The direct trapezoidal technique to estimate AUC over 2 adjoining time durations, t_1 and t_2 ($AUCt_1\_t_2$, the sphere of a trapezoid between t1 andt2), should be accomplished on a linear scale as follows:

$$AUCt_1\text{-}t_2 = \frac{(t2-t1)\,.\,(C2+C1)}{2}$$

The subsequent equation is used by the log trapezoidal method:

$$AUCt_1\text{-}t_2 = \frac{(t2-t1)\,.\,(C2-C1)}{\ln(C2\,/\,C1)}$$

The non-compartmental approach is based on the statistical moment's theory.

Statistical Moment Theory

The statistical moment is a mathematical explanation of a different assignment of data. Measurable minutes decided from a lot of focus time data imply a check of the real second or the authentic likelihood thickness work (PDF) that explains the veritable association between obsession and time. (Riegelman & Collier, 1980)

Explanation

The non-compartmental model includes the assortment of exploratory insights following a solitary portion and depends on the statistical moment hypothesis which gives an unmistakable method to consider time-related changes in visible occasions. A perceptible occasion is viewed as the general occasion achieved by the constitutive components included. The non-compartmental strategy does not require the suspicion of a particular compartment model for one or the other medication or metabolite. Truth be told, this strategy can be utilized in any compartmental model if direct pharmacokinetics is assumed.

The time course of drug concentration in plasma can generally be viewed as a statistical distribution curve. The general representation of statistical moment is as follows.

$$\mu_m \text{ warm}^{th} \text{ moment} = \int_0^\infty t^m f(t).\, dt \text{ --------}$$

Equation 1

where probability density function is represented by f(t), time by t and m is the M^{th} moment.

Irrespective of the routes of administration the first two statistical moments are as follows:

When m=0, substituting m=0 then the equation 1 will become

$$\mu_o = \int_0^\infty f(t).\, dt$$

Where μ_o is called as zero moment

Similarly, substituting m=1 in equation 1, then the first moment will be given as

$$\mu_1 = \int_0^\infty t^1 f(t).\, dt$$

The mean of the distribution is defined by the first moment.

If the time course of drug concentration in plasma is regarded as a statistical distribution curve, then. (Riegelman & Collier, 1980)

$$MRT = \frac{AUMC}{AUC}$$

MRT is referred to as the mean residence time.

AUMC is the area under the first-moment curve and is given by $\int_0^\infty C(t).dt.$ AUMC is achieved from a plot of the product of plasma concentration and time (i.e.C.t) in opposition to time from zero to infinity.

AUC is regarded as the area under the zero-moment curve and is given by $\int_0^\infty C.dt.$ AUC is attained from a plot of plasma drug concentration in opposition to time from zero to infinity.

$$MRT = \frac{\sum_{i=1}^{m} n_i t_i}{N}$$

The moments defined above can be computed by numerical integration using the trapezoidal rule from concentration-time data following drug administration.

Area of the trapezoid can be calculated by the formula: 1\2 ($C_{n-1} + C_n$) ($i_n - t_{n-1}$)

AUC i.e., area under the curve = ∑ (Area of trapezoids)

ESTIMATING AUC & AUMC

For samples until the last observed concentration

$$AUC_{t1\text{-}t2} = \frac{(t_2\text{-}t_1).C_1+C_2}{2}$$

$$AUMC_{t1\text{-}t2} = \frac{(t_2\text{-}t_1).t_1.\ C1+t2.C_2}{2}$$

And for the last observed sample and infinity($t_2=\infty$)

$$AUC_{tlast\text{-}\infty} = \frac{C_{last}}{\lambda}$$

$$AUMC_{tlast\text{-}\infty} = \frac{t_{last}.\ C_{last}}{\lambda} + \frac{C_{last}}{\lambda^2}$$

A c_{last} is the last observed concentration at time at last, λ is the slope of the terminal phase of the plasma drug concentration-time profile on a semi-log scale i.e., log(concentration) versus time. (Purves, 1992)

Mean Residence Time

The average amount of time spent by the drug in the body before its elimination from the body is referred to as MRT.

$$MRT = \frac{\text{Total residence time for all drug molecules in the body}}{\text{Total number of drug molecules}}$$

Figure 1: AUC and AUMC Plots. (McGlynn, McDonnell, Stewart & Seibert, 2002)

$$MRT = \frac{AUMC}{AUC} = \frac{\int tx\ C.\ dt}{\int C.\ dt}$$

The time for 63.2% of drug eliminated when administered via IV bolus injection is generally represented by MRT. It is like plasma elimination half-life, t1/2, i.e., 50% elimination. Like half-life, MRT is also a function of booth distribution and elimination. (Mcglynn, Mcdonnell, stewart & Seibert, 2002)

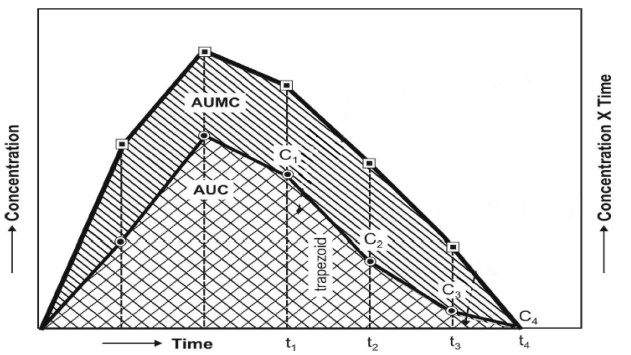

Figure 1: Time vs Concentration and Time vs Concentration x time curves

- For intravenous bolus dose $MRT = \frac{1}{k10}$
- In non-compartmental terms, $MRT = \frac{1}{k}$

Where k is constant and is equal to the ratio of clearance to Vss and Vss is referred to as the volume of distribution at steady state

Plasma elimination half-life can be given by $t_{\frac{1}{2}} = \frac{0.693}{k\ 10}$

$$t_{\frac{1}{2}} = 0.693\ MRT$$

MRT is used for the comparison e.g.:

Constant rate of infusion: $MRTiv = MRTinst - \frac{T}{2}$

Where T is the duration of infusion

Drug Absorption

After different modes of administration, the differences in mean residence time (MRT) are known as Mean Absorption Time.

$$MAT = MRTni - MRTiv$$

- MRTni is the mean residence time of the drug by non-instantaneous route, h
- MRTiv is the mean residence time of the drug by intravenous bolus injection.

This equation is also used for IM injection.

$$MAT = \frac{1}{Ka}$$

Absorption half-life can be given by $t\frac{1}{2} = \frac{0.693}{ka}$

Absorption half-life, $t\frac{1}{2} = 0.693MAT$

When zero-order is followed by absorption then,

$$MAT = T/2$$

Where T is the time over which absorption takes place

- MAT can be utilized for the comparison of dosage forms. (McGlynn, McDonnell, Stewart & Seibert, 2002)

Pharmacokinetic Parameters in Noncompartment Model

Drug Clearance

After iv bolus administration, $Cl = \frac{Dose\ iv}{AUC}$

At steady state after constant rate intravenous infusion

$$Cl = \frac{k_o}{Css}$$

Where the rate of infusion is given by Ko and Css is the steady-state concentration

By applying extraction ratio >> Cl=Q(ER) (Niederalt et al.,)

Apparent Volume of Distribution

Vss gives the volume of distribution at steady-state independent of elimination.

Vss =i. v dose (AUMC)/(AUC)

If the drug is given by constant rate intravenous infusion

$$V^{ss} = \frac{\text{Infused dose (AUMC)}}{(AUC)^2} - \frac{\text{Infused dose x } \tau}{2(AUC)}$$

$$V^{ss} = \frac{k_0 \times \tau\ (AUMC)}{2(AUC)^2} - \frac{k_0\,\tau^2}{2(AUC)}$$

Where Ko is the rate of infusion and π is the duration of infusion

Steady State Plasma Drug Concentration

The Css is a function of the effective rate of dosing and total body clearance of the drug in a patient.

$$\text{In continuous infusion } C_{ss} = \frac{k_o}{Cl}$$

$$\text{In multiple dosage regimen } \overline{C} = \frac{AUC^{ss}}{\tau}$$

At a steady state, the average plasma drug concentration is given by C,

Predicting the Time to Steady State

- The time needed for the drug to attain a steady state, i.e.,99%, takes 6.65 half-lives.
- In the extravascular route (or prolonged-release drug products), the time needed to reach ss takes longer than estimated by biological half-life.
- In multicompartment disposition, the time needed to achieve ss is shorter than that estimated by terminal half-life.

In case noncompartmental models, when the drug is administered repetitive or recurring dosing, fss

$$f^{ss} = \frac{AUC_0^{\ t}}{AUC}$$

AUC is the area under the curve in a single dose.

Bioavailability

Bioavailability can is defined as the fractional dose of a dosage form that reaches systemic circulation.

In the case of I.V bolus injection, bioavailability is referred to as unity (=1)

Bioavailability (F) of a dosage form can be given as

$$\text{Absolute bioavailability, } F = \frac{AUC\ oral\ Div}{AUCiv\ Doral}$$

Relative bioavailability, Fr may be expressed by comparing the zero moments of a product with a standard product.

Physiological-Based Pharmacokinetic Model

These are the mathematical models describing "The movement & disposition of the drug in the body based on blood flow to organ and spaces of organs that are penetrated by the drug". (Reineke, Li & Avgoustakis, 2012)

These models are explained on the following basis.

- Known physiology and anatomy of humans and other animals.
- Incorporates anatomical, physiological, and physicochemical data.

These models portray the creature as a bunch of tissue compartments interconnected by blood (plasma) stream. These models conquer a couple of

the constraints of customary compartmental models. Fig 2 is the speculation of this methodology. All physiological compartments should be remembered for the model. (Jones & Rowland-Yeo, 2013)

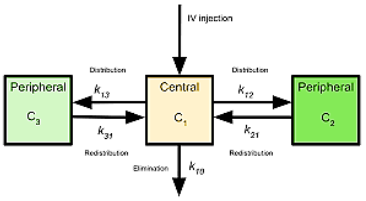

Figure 2: Physiological Pharmacokinetic Model. (Reineke, Li & Avgoustakis, 2012)

Physiological Pharmacokinetic Model Development

A separate compartment is formed by each organism's system.

The drug is disseminated homogenously. (In C versus t)

- The drug is distributed instantaneously.
- For that reason, the compartment is "very much blended" and the centralization of the medication going into and emerging from an organism in harmony with the conc. of the medication in that organ. (Parrott & Lave, 2008)

Thus, partition coefficient or equilibrium constant can be found from the conc. of the drug in the tissue compared to the conc. in the blood.

Barriers that is present between compartments (physiological systems):

- Transfer relies upon the pace of blood course through the physiological compartment.
- Every compartment has an unmistakable leeway rate.
- That is the reason it is compulsory to determine the pace of the bloodstream in each.
- Tissue or organ framework in the model.

Drug

- Elimination is just from certain compartments that are indicated in the model, for instance, kidneys and liver.
- No reversible restricting of the medication to the tissue is noticed.

Types of Model

1. Blood flow limited model.
2. A physiological pharmacokinetic model with binding.
3. Membrane limited model. (Yoshida, Budha & Jin,)

Blood Flow Limited Model

In this model, the drug is blood flow is limited. Arterial blood carries the drug to the organs whereas venous blood carries the drug away from the organs.

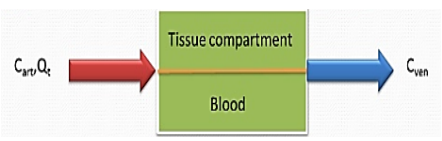

Figure 3: Non-eliminating tissue organ. (Holdford, Huang & Zheng, 2010)

The uptake of drugs into the tissues is fast, and a constant ratio of drug concentration between the organ and the venous blood is rapidly established. This ratio is called the tissue/blood partition coefficient. (Holdford, Huang & Zheng, 2010)

The magnitude of the partition coefficient can differ depending on the type of tissue and the drug. E.g., There is a high partition in adipose tissue for lipophilic drugs. (Sager, Yu, Ragueneau-Majlessi & Isoherranen, 2015)

The rate of blood flow to the tissue is represented as Q_t (ml/min), and the rate of change in the drug conc. w.r.t time within a given organ is represented as:

$$\frac{d(V_{tissue}C_{tissue})}{dt} = Q_t(C_{in} - C_{out})$$

$$\frac{d(V_{tissue}C_{tissue})}{dt} = Q_t(C_{art} - C_{ven})$$

Where arterial blood drug conc. is given by C_{art} and the venous blood drug conc.by C_{ven}. Blood flow is expressed by Q_l and represents the volume of blood flowing through an organ or tissue per unit of time.

If the drug uptake takes place in the tissue, the incoming conc. C_{art} is higher as compared to the outgoing venous conc., $C_{ven.}$ In this model the drug conc. in the blood leaving the tissue and the drug conc. within the tissue are in equilibrium and C_{ven} can be estimated from the tissue/blood partition coefficient. Using the above equations:

$$\frac{d(V_{tissue}C_{tissue})}{dt} = Q_t\left(C_{art} - \frac{C_{tissue}}{P_{tissue}}\right)$$

This eq. describes the drug conc. in a **non-eliminating tissue or organ group**. For tissue organs in which the drug is eliminated, parameters that represent drug elimination from the liver and kidney are added to account for drug removal through metabolism or excretion. The rate of drug elimination may be explained for different tissues or organs. (Edginton & Joshi, 2011)

$$\textit{Muscle: } \frac{d(V_{MUS}C_{MUS})}{dt} = Q_{MUS}\left(C_{MUS} - \frac{C_{MUS}}{P_{MUS}}\right)$$

$$\textit{Adipose tissue: } \frac{d(V_{FAT}C_{FAT})}{dt} = Q_{FAT}\left(C_{FAT} - \frac{C_{FAT}}{P_{FAT}}\right)$$

$$\textit{Skin: } \frac{d(V_{SKIN}C_{SKIN})}{dt} = Q_{SKIN}\left(C_{SKIN} - \frac{C_{SKIN}}{P_{SKIN}}\right)$$

The mass balance for the rate of change in the conc. of the drug in the blood, the pool is given by:

$$\frac{d(V_bC_b)}{dt} = \underbrace{Q_{MUS}\left(\frac{C_{MUS}}{P_{MUS}}\right)}_{\text{(muscle)}} + \underbrace{Q_{LIV}\left(\frac{C_{LIV}}{P_{LIV}}\right)}_{\text{(liver)}} + \underbrace{Q_{KID}\left(\frac{C_{KID}}{P_{KID}}\right)}_{\text{(kidney)}}$$

$$+ \underbrace{Q_{SKIN}\left(\frac{C_{SKIN}}{P_{SKIN}}\right)}_{\text{(skin)}} + \underbrace{Q_{FAT}\left(\frac{C_{FAT}}{P_{FAT}}\right)}_{\text{(adipose)}} + \underbrace{Q_{LU}\left(\frac{C_{LU}}{P_{LU}}\right)}_{\text{(lung)}} - \underbrace{Q_bC_b}_{\text{(blood)}}$$

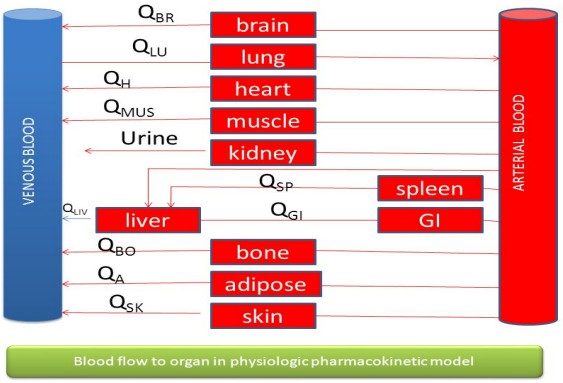

Figure 4: Example of blood flow to organs in a physiologic pharmacokinetic model. (Parrott & Lave, 2008)

Physiological Pharmacokinetic Model with Binding

It expects stream confined medicine allocation without drug limiting to either plasma or tissues while various prescriptions are bound to a variable degree in plasma/tissues. Prescription limitation ought to be immediate with most physiological models.

$$[C_b]_f = [C_t]_f$$
$$[C_b]_f = f_b[C_b]$$
$$[C_t]_f = f_t[C_t]$$

Where, blood-free drug fraction is represented by **fb**, tissue-free drug fraction by **ft**, total drug conc. in tissue by **Ct** and total drug conc. in the blood by **Cb**. **Pt which** is the Partition ratio of the tissue drug conc. to that of the plasma drug conc. is given by,

$$\frac{f_b}{f_t} = \frac{[C_t]}{[C_b]} = P_t$$

By accepting straight medication limiting and fast drug equilibration, the free medicine partition in the tissue similarly as blood may be joined into the section extent and the differential conditions. These conditions look like those besides that free medicine focus. are traded for Cb. Medication leeway in the liver should happen just inside the free medication. General mass balance of different tissues is expressed as: (Poulin & Theil, 2000)

$$\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t(C_{art} - C_{ven})$$

$$\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t\left(C_{art} - \frac{C_t}{P_t}\right)$$

$$\frac{d(V_{tissue} C_{tissue})}{dt} = Q_t\left(C_{art} - \frac{C_t f_t}{f_b}\right)$$

The impact of restricting medication appropriation is a huge factor in interspecies contrasts in pharmacokinetics. Now and again, creature information may anticipate dispersion in people by thinking about the distinctions in medication restricting. (Nestorov, 2003)

Diffusion Limited Model or Membrane Limited Model

In this, the cell layer fills in as an impediment for the medicine, which steadily infiltrates by scattering. Since the circulation system is very brisk and medicine invasion is moderate, a prescription conc. the tendency is made between the tissue and the venous blood. The rate-confining development of medicine spread is dependent on the invasion across the cell film rather than the circulation system. (Sander, 2000)

Physiological Pharmacokinetic Model Incorporating Hepatic Transporter- Mediated Clearance

Important roles are played by drug carriers in the ADME measures and ought to be represented in PBPK models. Anticipating human medication attitude is troublesome during drug advancement. Anyway, drug transport might be a basic cycle in Medication aura in the body to such an extent that without a sensible portrayal of transport measures in the body, model exactness might be inadequate.

Watanabe et al describe a model with hepatobiliary emission mediated using carriers, organic anion-transporting polypeptide (OATP) 1B1, and multi-drug fighting-related proteins (MRP) 2, for the HMG-CoA reductase inhibitor drug, pravastatin. The liver is a complex organ intimately connected to drug transport and bile-movement. Compartment concepts are needed to track the mass of drug transport in fine structures as shown in the figure. Human liver microsomes are used to help predict the metabolic clearance of drugs in the body.

The PBPK model with pravastatin is used to interpret the conc-time profile of metabolites in the blood plasma and the body parts using parameters related to the body functions, subcellular fractions, and metabolite dependent parameters. The principle was that first, sub-cellular fractions were attained by the comparison of living in a whole living organism or outside the living organism parameters in mice. After that **in-vitro human parameters** were extrapolated in vivo using sub-cellular fractions gained in rats. Then a one-compartment open model was selected to demonstrate the chemical reactions of a drug to its primary, secondary, and tertiary metabolites. (Bouzom, Ball, Perdaems & Walther, 2012)

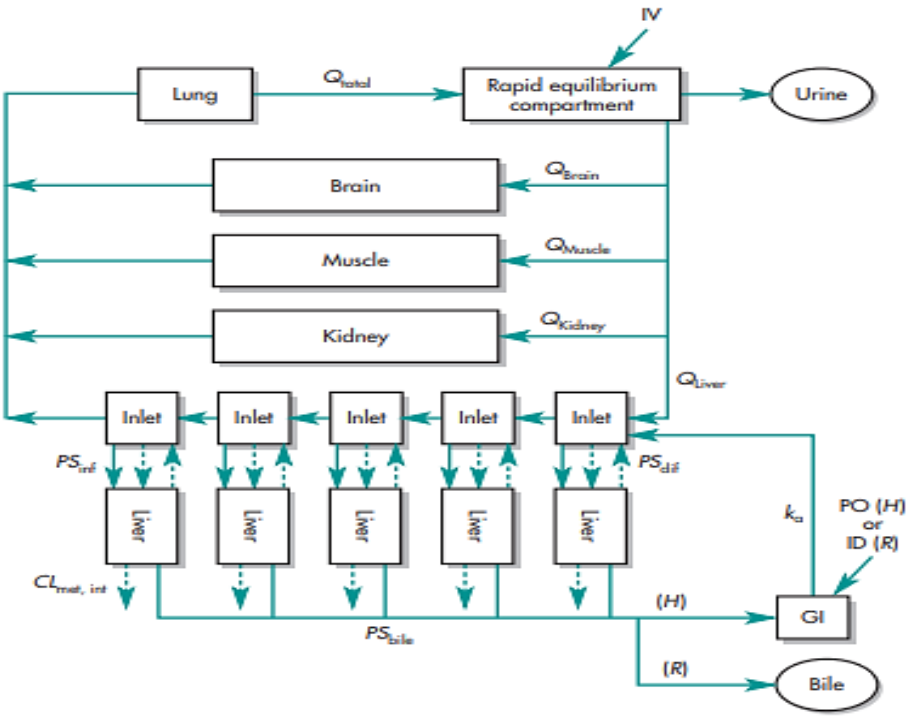

Figure 5: Prediction of the conc-time profile of pravastatin with the help of a Schematic figure of the PBPK model. The liver section has been partitioned into five compartments to mimic the spreading model. (Espié, Tytgat, Sargentini-Maier, Poggesi & Watelet, 2009)

Advantages

1. Ideally, give the main explanation of the time classes of the drug conc. in any tissue or organ.
2. They also provide entrance to the blood concentration of chemicals or their metabolites particularly at the part of their action.
3. In the end, they as well assist in interruption and extrapolation of knowledge.

Disadvantages

1. The comprehensive data of physiological, biochemical, and physicochemical processes are not accessible from one resource which will direct to some uncertainty in establishing a trusty source of correct data.
2. The researcher of this modeling process must recognize the functionally and the pharmacologically underlying principle following the model and must be responsive that this modeling besides its probable profit with a variety of accomplishment does not offer the eventual result and there ruins a scarcity of potential example that confirms that this method is as superior in clinical put into practice as in hypothesis.
3. Arithmetical assessment of insecurity and inconsistency is more difficult.
4. Model progress and accomplishment require suitable skills. (Bouzom, Ball, Perdaems & Walther, 2012)

Table 1. Comparison of Compartment and Non-Compartment Models (Wang, Kim, Quinney, Zhou & Li, 2010)

These need a detailed hypothesis to meet the data.	No need hypothesis for the model.
Curve setting of investigational statistics using computers. It is a monotonous way.	Simple algebraic equations are used. No curve fitting and not thus no use of computers.

Applicable to both linear as well as nonlinear pharmacokinetics.	Only appropriate to direct pharmacokinetics
C1 - time cycle is considered as terms of exponents.	C1 – time cycle is cogitated as an arithmetical division.
They are effective l for many of the conditions, though assumptions of modeling are involved.	Mainly useful for the applications of clinical pharmacokinetics, bioavailability, and bioequivalence studies.

Table 2. Advantages & Disadvantages of Compartmental Versus Noncompartmental Population Analyses (wang, kim, quinney, zhou & li, 2010)

	Advantages	Disadvantages
Non-compartmental Analysis	-simple and fast to perform -No special software is required -Robust and easily reproducible	-Need rich sampling -Makes suppositions regarding linearity
Compartmental Population Analysis	-Can be executed with rich or sparse data -Can be carried out using data from heterogeneous sources or special populations -Can deal with both linearity and nonlinearity	-Requires experienced analyst -Time-consuming and labor-intensive -Software is not user-friendly

Advantages

1. A by-product of the PK parameter is simple, due to uncomplicated numerical equations.
2. A mathematical cure remains identical, for medicine, handover first-order kinetics is followed by discharge.
3. Drug propensity kinetics require not to be illustrated comprehensively.

Disadvantages

1. Data regard plasma drug concentration-time outline is stated as a typical.
2. Commonly, not reliable for telling the time duration of the drug in the human body.
3. Is useable just for direct pharmacokinetics.

Conclusion

A numerical model a mathematical characterization of a natural system and used to state quantitative associations. A collection of mathematical sums, undertakings, and relations alongside their definitions are called mathematical models and they should be even minded. A pharmacokinetic compartment is a mathematical thought which depicts space in the body which a drug appears to have. Compartmental models are social affairs of tissues with near circulatory system and medicine affection is known as a compartment which is a physiologic or anatomic zone. A non-compartmental model is a pharmacokinetic model that does not include the suspicion of explicit compartment model is known as a Non-compartment model. This policy is related to the understanding that the drugs follow direct energy, which is the premise that this procedure can be applied to any compartment model. Beats a portion of the downsides related to old-style compartment displaying. The non-compartmental investigation gives an elective procedure to depicting drug pharmacokinetics without naming a particular compartmental model to the prescription. The statistical moment theory is a numerical clarification of a separate appropriation of information. arithmetical moments determined as of a bunch of concentration-time information stand for a gauge of the actual moment or the genuine probability density function which clarifies genuine connection sandwiched between fixation and time. Important roles are played by drug carriers in the ADME measures and ought to be represented in PBPK models. Anticipating human medication attitude is troublesome during drug advancement. Anyway, drug transport might be a basic cycle in medication aura in the body to such an extent that without a sensible portrayal of transport measures in the body, model exactness might be inadequate.

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