Second Edition

Controlled and Novel Drug Delivery

CHAPTER

1

Biopharmaceutical and Pharmacokinetic Considerations

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INTRODUCTION

The field of biopharmaceutics studies the effects of a drug's physicochemical characteristics, dosage form, and route of administration on the rate and degree of drug absorption into the bloodstream. A series of processes that take place prior to a drug's therapeutic response is used to describe the significance of the drug substance and product on absorption and *in vivo* distribution of the drug at its site of action. The patient takes the drug in its dosage form through oral, intravenous, subcutaneous, transdermal, etc. routes of administration. The drug is then released from the dosage form in a manner that is predictable. After that, a portion of the drug is absorbed from the site of administration into the body, surrounding tissue, or both (as with oral dose forms). The drug eventually reaches its site of action. When the concentration of drug at the site of action approaches or exceeds the minimum effective concentration (MEC), a pharmacologic response occurs.

A drug's relative bioavailability is evaluated by administering it to the subject through different routes and comparing their pharmacological, clinical and toxic response. Comparison of the therapeutic efficacy of different products can be used to assess the variation in drugs' bioavailability. A drug administered is therapeutically effective, harmful, or has no apparent effect at all depends on the nature of the drug molecule, the method of delivery, and the formulation of the dosage form (Shargel et al. 2012). This chapter discusses the scientific basis for the design and development of controlled and novel drug delivery systems aided by the knowledge of biopharmaceutics. The impact of the drug design on the pharmacokinetics of a drug and methods to assess its parameters, and factors affecting them are also discussed in detail.

BIOPHARMACEUTICAL CONSIDERATIONS

Physicochemical Nature of the Drug

Particle Size and Surface Area

The factor of particle size and surface area are inversely related to each other. The smaller the particle size, the larger its surface area, and so the higher its rate of dissolution and faster will be the absorption. Micronization can serve as a mechanism to increase the rate of dissolution of poorly soluble non-hydrophobic drugs, provided that particle size is reduced below 0.1 μm, which increases its intrinsic solubility

(Fincher 1968). Micronization has been used for dose reduction and to increase the absorption efficiency of drugs like carvedilol, griseofulvin, and spironolactone (Liu et al., 2015). For hydrophobic drugs like chloramphenicol, griseofulvin, nitrofurantoin, and tetracycline decreased solubility is exhibited by micronization, due to the reduction of effective surface area, due to the reaggregation of particles—either electrically induced, or due to the development of excessive surface free energy, or due to the air adsorption onto the particles. Particle size reduction could significantly increase the rate of dissolution and bioavailability of cilostazol crystals and its NanoCrystal® (Jinno et al., 2006). In case of novel drug delivery system like nano- and microparticles it has been proved that adhesive strength, target surface retention and nonspecific localization is decreased in spherical shaped particles if the particle size is increased. It was studied that in particle size >500 nm, the margination towards wall is affected by the gravitational force while when the particle size is <500 nm, the particles shows Brownian movement. The modelling study done by Decuzzi et al. proved that the particle size of 20–200 nm is critical for drug delivery systems like micelles, liposomes, polymeric particles etc (Sen, 2016; Decuzzi et al., 2007).

Particle size reduction might not be desirable when:

- Sustained effect is required.
- Drug exhibits undesirable GIT effects—gastric irritation, ulceration, nausea, e.g. NSAIDS, nitrofurantoin.
- Drug does not possess gastric stability and will undergo degradation in gastric environment (erythromycin, penicillin G) (Sandri et al., 2014).

Molecular Size and Diffusivity

For drugs to be passively absorbed, their molecular weight should be in the range of 100–400 Dalton. According to Graham's Law "rate of diffusion is inversely proportional to the square root of molecular size of thedrug", with an exception of Cyclosporin A, which has a molecular weight of 1200 Daltons. Pore transport can be a potential mechanism of transportation of low molecular weight drugs (≈100 Daltons) and those having particle size less than pore diameter, and which possess hydrophilicity, e.g. sugars, water, urea (Chillistone and Hardman, 2008; Brodin et al., 2010).

In the case of controlled release drug delivery formulations (CRDDS), where drug has to pass through matrix for its release, any molecule above 500 Daltons is released even more slowly. High molecular weight drugs like proteins and peptides are often considered unsuitable for controlled/sustained drug delivery as they have such low diffusion coefficient that they become difficult to quantify. Molecular weight of 150–400 Daltons has a diffusion coefficient of ranging from 10^{-6} to 10^{-9} cm^2/s and is deemed fit for formulating a CRDDS (Indurkhya et al., 2018).

Lipophilicity (log P)

Optimum lipophilicity (K*o/w* in 1–2 range) of a drug is a prerequisite for partitioning of the drug in lipoidal membrane and thus absorption, but it should also possess good aqueous solubility so as to facilitate good dissolution, which also necessitates the absorption. Therefore perfect HLB balance is desired for optimum bioavailability. Lipophilicity is evaluated by partition coefficient (K*o/w* or P). Unionized drugs tend to possess better lipophilicity than ionized drug and so exhibit better permeation across the biological membrane:

$$Kd = \frac{D_{org}}{D_{aq}} \quad \text{(Eq. 1.1)}$$

where, Kd = partition coefficient, D_{org} = Drug concentration in organic phase (n-octanol). D_{aq} = Drug concentration in aqueous phase (pH 7.4 buffer) (Di and Kerns 2016; Liu et al. 2011).

Passive transportation of a drug depends on: (Kramer, 1999)

- Molecular size,
- Lipophilicity (log P),
- Polarity-determined by total number of H-bond acceptors and donors.

Lipinski rule of 5 states that oral absorption might be poor if any 2 of these are greater than the specified values: (Waring, 2010)

- Molecular weight ⩽500
- Lipophilicity (log P) ⩽5
- Number of H bond donors ⩽10
- Number of H bond acceptors ⩽5

Solubility

Saturation solubility is a chemical equilibrium achieved between dissolved and undissolved excess solid compounds. The amount of drug in a solution under standard conditions of pressure and temperature, which is chemically in equilibrium with the excess undissolved solid, is known as its saturation solubility (Shahrin, 2013).

Intrinsic or absolute solubility is a *static* term and is defined as the maximum amount of drug dissolved in 1 mL of solvent (fixed composition) under standard conditions of pH and temperature. Dissolution rate, on the other hand, is a *dynamic* process and is the amount of drug that went into the solution, under standard temperature, and pH conditions.

There is a correlation between solubility and pH of the GI environment, which has an effect on absorption. Acidic drug solubilizes more in the alkaline environment of the intestine and forms a soluble salt, and vice versa for the basic drug. The solubility of such drugs can be modified by the addition of an acidic or basic excipient. For example, aspirin solubilization can be enhanced by an alkaline buffer addition. Also, buffering agent if added is made to be released slowly, so as to avoid immediate release of drugs (Martinez and Gordon, 2002; Serajuddin, 2007). For a drug to be prepared as CRDDS it should have the lowest solubility limit of 0.1 mg/mL. The mechanism for achieving controlled release, the appropriate mechanism to use depends on a drug's solubility; for example, some diffusional systems are inappropriate for drugs with poor water solubility. The dissolving rate controls, how well drugs whose solubility profile is poor are absorbed. These drugs are consequently viewed as poor candidates for such CRDDS since the controlled release mechanism will not be able to manage the absorption process (Indurkhya, 2018) **(Table 1.1)**.

Stability

The drug might be rendered unstable either during shelf life or in GIT, reducing its bioavailability, which might be due to its interaction with other formulation components (API or excipient) or due to its degradation and formation of unabsorbable

TABLE 1.1: Solubility criteria as per Indian Pharmacopoeia	
Descriptive term	***Parts of solvent required per part of solute***
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	>10000

or therapeutically inactive product. The pH of the solvent has a huge impact on drug stability (Loftsson, 2014). Stability of the drug plays the vital role in the designing of any dosage form. Various novel drug delivery systems have been prepared to enhance the chemical and physical stability of the drug.

Drugs unstable in GI environment are not suitable for CRDDS. Salt formation of a drug enhances its aqueous solubility and stability, but on contrast salt of weak acid is precipitated in the gastric pH, hindering its absorption. Gastric instability of penicillin G worsens its bioavailability. Prodrugs can also be formed to increase the stability of labile drugs and thus increase their bioavailability. Presystemic metabolism and colonic flora-mediated biotransformation might also reduce the bioavailability of a drug (Serajuddin, 2007) (Li et al. 2005). To protect the drug from acidic pH of stomach it could be coated with acetate phthalate and methacrylate-based polymers. Also, pepsin, which is responsible for the degradation of ingested protein gets inactivated at pH above 4. So, it could be deactivated by raising the stomach pH above 4 by pH-increasing buffer (Alqahtani et al., 2021).

Polymorphism and Solvates

Polymorphism is the phenomenon of the existence of a drug in different crystalline forms, referred to as polymorphs. Polymorphs exhibit similar chemical characteristics but different physical, thermodynamic and kinetic properties. Drugs like barbiturates, corticosterone acetate, riboflavin, and chloramphenicol palmitate exhibit polymorphism. Different polymorphs exhibit different physical properties- solubility, hardness, density, and melting point. Polymorphs can either be enantiotropic or monotropic. Stable polymorphs possess the least energy and thus least aqueous solubility, and the highest melting point; whereas metastable polymorphs, have higher energy, higher solubility, and lower melting point but have a tendency to convert to the stable form. Change of a crystal form to another may produce manufacturing problems, for example, cracking of tablet or resistance of granules towards compression. Metastable forms are more desirable in formulation due to their higher solubility and bioavailability (Saifee et al., 2009). In chloramphenicol palmitate B polymorph out of forms A, B, C exhibits maximum bioavailability (Censi and Piera, 2015).

Amorphous solids have no long-range order, or internal crystal structure like that of crystalline solids known as super cooled liquids, having the highest solubility, even more than the metastable polymorph, e.g. Phenobarbitone, Chloramphenicol palmitate, corticosterone acetate. Anhydrous Ampicillin exhibits a faster dissolution

Dissolution

It is the closest indicator of bioavailability and efficacy and is thus used as an *in vitro* parameter for IVIVC. Dissolution tests are performed so as to ensure that the release from tablet/capsule is close to 100% to prove its bioequivalence with the marketed formulation and to ensure batch-to-batch uniformity in drug release, and efficacy.

The rate of dissolution and rate of permeation are the critical steps determining the bioavailability of a drug. For hydrophobic drugs, dissolution is a rate-limiting step e.g. spironolactone, and griseofulvin. Hydrophilic drugs on the other hand exhibit permeation rate-limited absorption. Also, the maximum dose to be absorbed is directly related to intrinsic solubility. Drugs have been classified on the basis of solubility and permeability in BCS classification. Dissolution rate is a dynamic process, defined as the amount of drug that goes into the solution, under standard temperature, pH conditions (Balaji, 2014; Jain et al., 2015)

The process of solubilization of a solute into the solvent is defined as dissolution and is a process where mass transfer from the drug from the solute surface into the bulk liquid media occurs. Various theories and models proposed for dissolution are:

- Film theory/Diffusion layer model
- Surface renewal theory/Danckwert's model/Penetration theory
- Limited solvation theory/Double barrier/Interfacial barrier model

Physicochemical properties (particle size, wettability, salt form, polymorphism), of a drug and dosage form (formulation and excipient-related aspects), are the parameters controlling the rate of dissolution and thus absorption rate. The aqueous solubility of a drug does not pose bioavailability problems if it is >1% (Shahrin, 2013).

Factors affecting the rate of dissolution include physicochemical nature of API, formulation type, nature of solvents, nature of the excipients, and method of manufacturing. Dissolution tests are used for bioavailability prediction and for discriminating the formulation factors affecting bioavailability.

Noyes and Whitney equation of rate of dissolution:

$$\frac{dC}{dt} = \frac{D}{h} \times A \times \left(C_s - C\right) \qquad \text{(Eq. 1.2)}$$

where dC/dt = rate of dissolution at time t, A = drug particle surface area, D = diffusion rate constant, S = stagnant layer drug concentration, C = bulk solvent drug concentration, h = stagnant layer thickness (Sandri, 2014).

Effect of Excipients and Dosage Form

Excipients are inert components, also called inactive pharmaceutical ingredients (IPI), added to a dosage form to facilitate its acceptability, functionality, and uniformity and also ensure its bioavailability, and stability. Excipients have a huge impact on the bioavailability of drugs and should be chosen appropriately (Golightly et al., 1988).

In making any CRDDS, excipients play the primary role. This includes excipients like suspending agents, which slow down the pace at which drugs dissolve from suspensions by increasing the viscosity of the drug vehicle. When used in excessive quantities, tablet lubricants like magnesium stearate may reject water and hinder dissolution. Shellac in particular will crosslink as it ages, slowing the pace of breakdown. However, surfactants might have an unpredicted impact on how drugs dissolve. Low

surfactant concentrations lower the surface tension and speed up drug absorption, but high surfactant concentrations tend to cause the drug to form micelles and slow down absorption. Large drug particles dissolve more slowly than smaller ones because they have a lesser surface area. High tablet compression may be the cause of poor tablet disintegration in absence of enough and appropriate disintegrant.

For rendering a drug to dissolve rapidly, excipients capable of changing the pH of the surrounding media is added. For instance, in case of aspirin, when combined with sodium bicarbonate, it transforms from a weak acid to a water-soluble salt that dissolves quickly in an alkaline solution. This procedure is referred to as 'dissolution in a reactive media.' In the reactive solvent around the solid particle, the solid drug dissolves quickly. However, the drug may precipitate out of solution with very small particle sizes as the dissolved drug molecules diffuse outward into the bulk solvent. These small particles have a huge surface area collectively, dispersing and redissolving easily for faster absorption when they come into contact with the mucosal surface.

When drug like tetracycline is combined with any calcium containing excipient, it leads to the formation of insoluble complex resulting into slow dissolution and poor absorption. Excipients are added to the formulation to achieve the desired rate of drug release as required in CRDDS. For instance, excipients that make a drug more aqueous soluble, typically increase the drug absorption and dissolution. Excipients may prolong the drug residence time in the digestive system, increasing the overall amount of drug absorbed. To improve drug diffusion over the intestinal wall, excipients may function as carriers. Many excipients, on the other hand, may delay disintegration of the formulation and hence reduce drug absorption (Indurkhya et al., 2018).

Route of Drug Administration

Oral

It is the most common and preferred route of drug administration as it can be self-administered, convenient, cheap, have high patient compliance, and is non-invasive. Bioavailability is less than the parenteral route since the drug needs to cross a number of biological barriers before its entry into the blood. Its release can be modified to produce immediate, sustained, prolonged, delayed action by the use of various polymers and varying disintegrants concentration. Oral route displays delayed onset of action as compared to the parenteral route, lower C_{max} as well as higher T_{max}. Drugs should have gastric pH stability, enzymatic stability and produce no gastric irritation for administration through oral route. These limitations can be overcome by enteric coating (Bhati and Raja; 2012).

Topical

This route of drug administration refers to the application of the drug to the skin's surface or the mucous membranes of the eye, ear, nose, mouth, vagina, etc. with the goal of limiting the drug's therapeutical effects on the drug's absorption through the skin's surface or into the mucous membrane's layers. Creams, liniments, ointments, gels, lotions, sprays, powders, aerosols, and drops are the types of topical formulations. A high local concentration of a drug is delivered by the topical mode of administration without altering the overall circulation. However, systemic circulation/absorption is highly frequent and can have a negative sequence of events. This systemic absorption

is occasionally used for its medicinal benefits. First-pass metabolism, presytemic elimination, or GI incompatibility of a drug could be avoided by this route. Also, a drug with a short half-life and narrow therapeutic index is well suited to administer through this route (Shargel et al., 2012).

Parenterals

The intravenous route is the most common parenteral route. Intramuscular and subcutaneous are preferred route for CRDDS because the action is to be prolonged for 24 hours to 12 months. A small amount of drug is administered. Factors important are solubility of the drug in surrounding tissue, molecular weight, partition coefficient and pKa of the drug. This route offers the advantage of bypassing the first-pass metabolism. Drugs that show very low absorption when given through the oral route are well suited for parenteral administration. The active form of the drug directly reaches the bloodstream without any interference from the GI environment (Shargel et al., 2012).

Transdermal Patch

In this route of administration, the drug is delivered into the systemic circulation through the skin. In a few cases (such as oestrogen replacement therapy), transdermal administration can deliver the drug over a prolonged period of many hours or days without causing any gastrointestinal discomfort or first-pass effects. Many transdermal products work similarly to zero-order infusion processes in that they continuously supply drugs to the body, henceforth maintaining the plateau level of the drug. The permeation of drugs through the skin is the rate-limiting step in transdermal drug delivery (Shargel et al., 2012).

Formulation Factors Affecting Drug Dissolution

Since bioavailability is majorly affected by solubility in aqueous media, and BCS Class II and IV drugs have poor solubility and consequently poor dissolution rate, many formulation strategies are employed to combat this limitation like the formation of an inclusion complex. Furthermore, excipients such as super-disintegrants, wetting agents, polymers, and many more are utilized to improve the dissolution profile of the finished dosage form.

The complexation of poorly soluble API with complexing agents modifies their dissolution profile in various oral dosage forms. Cyclodextrins are most commonly used as complexing agent, as they as comparatively safe and well tolerated. In a study, an inclusion compound was formed between Carbamazepine and hydroxypropyl-β-cyclodextrin (HP-β-CD) which improved the drug's solubility by 95 folds. pH adjusting excipients creates an acidic or alkaline micro-environment after dissolving in gastric fluid due to the provision of H^+ or OH^- ions, facilitating dissolution and absorption of drugs. Citric acid, tartaric acid, and carbonic acid are a few examples. *In vivo* dissolution and absorption of paracetamol were enhanced by the inclusion of $NaHCO_3$ in tablets as indicated by higher C_{max} and lower T_{max}. Surfactant when added in formulation improves the wettability of API and consequently enhances its dissolution in physiological fluid, like SLS when added in 5*%w/v* concentration enhanced dissolution of celecoxib by three folds.

In addition to these, using soluble fillers like lactose, sugars, and sugar containing excipients such as mannitol, glucose, and sucrose ester, or formulating amorphous solid

dispersion improves the rate and extent of *in vivo* dissolution, thereupon enhancing the bioavailability.

In Vitro In Vivo Correlation (IVIVC)

IVIVC establishes a qualitative and/or quantitative relationship between the *in vitro* release profile of dosage form, like dissolution rate and extent, and *in vivo* response like plasma drug concentration. The plot of *in vivo* fraction absorbed and *in vitro* fraction dissolved demonstrate correlation, that too Level A correlation if the plot is linear with a slope of 1 (Emami, 2006).

IVIVC is divided into four levels based on the type of correlation established. *Level A* correlation is point-to-point correlation as discussed above, it is the highest level of correlation, *Level B* correlation compares the mean *in vitro* dissolution time (MDT) of formulation with mean *in vivo* residence time (MRT). *Level C* correlation relates to single time point parameters, example- t50% v/s AUC/T_{max}, and the fourth is Multiple Level C correlation, which establishes a relationship between one or multiple pharmacokinetic parameters and the extent of drug dissolution at multiple time points (Lu et al., 2011).

IVIVC is an important tool in predicting the *in vivo* performance of a drug product from its dissolution profile. Thus, it is desirable to develop an *in vitro* dissolution test which can discriminate products if there is variation in the physical properties of API, drug product composition, manufacturing process, etc. Such tests are called discriminatory dissolution tests (Qureshi, 2006).

The establishment of IVIVC is important in the optimization of the formulation and manufacturing process, support biowaivers, alternative for *in vivo* bioavailability studies, and in quality control of manufactured lot and scale-up post-approval changes (SUPAC) (Emami, 2006).

Biopharmaceutical Drug Classification (BCS) System

BCS System categorizes drugs into four classes based on properties of solubility and permeability. BCS guides the determination of the condition wherein IVIVC of the drug product can be established, as both solubility and permeability properties affect the absorption profile of the product **(Table 1.2)**. For Class III and IV compounds, IVIVC is unlikely however; it may be possible in certain instances for Class III drugs, depending on intestinal transit and relative rate of dissolution. For Class II drugs, IVIVC is most

TABLE 1.2: BCS classification with IVIVC expectation

Class	*Solubility*	*Permeability*	*Absorption rate control step*	*IVIVC expectation*
I	High	High	Gastric emptying	When dissolution rate is lesser than gastric emptying rate, correlation is expected. Otherwise limited or no IVIVC correlation
II	Low	High	Dissolution	If similarity between *in vitro* and in *vivo* dissolution rate proven, IVIVC is expected unless dose is very high
III	High	Low	Permeability	Limited or no correlation expected
IV	Low	Low	Case by case	Limited or no correlation expected

appropriately established as dissolution is the only rate-limiting factor. Class I drugs are highly soluble and permeable, but when designed as a modified release product, release profile controls the rate of absorption, *Level A* IVIVC is mostly obtained (Emami, 2006; Lu et al., 2011; Dressman and Christos, 2000).

Absorption versus Dissolution Rate

Formulation initially dissolves and releases its content in the GItract, following oral administration, and then only absorbed into the bloodstream to illicit biological response. So, the absorption rate is dependent on and affected by the dissolution rate. In the case where dissolution is the rate-limiting step, means the rate of absorption of the drug is much faster than its dissolution, absorption is totally dependent on the rate of drug dissolution, i.e., faster the rate of dissolution, faster will be the appearance of the drug in the systemic circulation (Dunne et al., 1999; Levy, 1961). In a study with a different formulation of salicylamide, a linear correlation was demonstrated between the rate of absorption and dissolution for all types of formulation (Bates, 1969). Many times absorption peak time is used as an alternative to the rate of absorption, as the latter is usually difficult to determine. So, the absorption peak time can be correlated with dissolution data to give IVIVC.

Percent of Drug Dissolved versus Percent of Drug Absorbed

The percentage of drug dissolved and percent of drug absorbed may be directly proportional when the drug is absorbed rapidly after dissolution. However, when absorption is a rate-limiting step, as in BCS Class III compounds, the amount and rate of drug absorbed reduces and become independent of the dissolution rate. In such a case, the establishment of *Level A* correlation is unlikely, but *Level C* Correlation can be demonstrated (Stavchansky, 2008).

Maximum Plasma Concentrations versus Percent of Drug Dissolved in Vitro

When a drug product has a high dissolution rate, a large percentage of the drug is available at the absorption site for absorption, thereby a higher maximum plasma drug concentration may be observed. But, with a drug product that provides a slow release of the compound, resultant plasma concentration will decrease. For such instances, research to improve the dissolution profile or to maximize the availability of the drug at the site of absorption is done. In conclusion, a drug product, which shows a higher percentage of drug release may achieve higher C_{max} and in a relatively shorter time period (T_{max}). For example, in *in vitro* dissolution and *in vivo* bioavailability testing of different brands of ciprofloxacin, maximum plasma concentration was achieved with the formulations, which were having more than 80% release in 20 minutes (Fahmy and Eman, 2014).

Serum Drug Concentration versus Percent of Drug Dissolved

It is similar to the relationship established between maximum plasma concentration and percent drug dissolved. With a highly bioavailable drug product, the serum drug concentration will rise with the increase in *in vitro* dissolution. IVIVC conducted for a different lot of tolbutamide tablet showed similar serum drug concentration vs time and percent drug dissolved vs time profile, with a correlation coefficient around 0.9 (Simmon, 2016).

PHARMACOKINETICS CONSIDERATIONS FOR NOVEL AND CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

The term 'pharmacokinetics' is coined from the Greek word 'pharmakon' and 'kineticos', which means 'drug' and 'kinetics', respectively. Hence, pharmacokinetics can be defined as the movement of drug into, through, and out of the body. It encompasses the process of absorption, distribution, metabolism, and excretion (ADME) of the drug. These pharmacokinetic parameters are derived by the estimation of drug concentration in the blood/plasma/serum. This information is used to estimate the time of onset, duration, and intensity of the effect of drug. This usually depends upon the rate and extent of drug's uptake from its absorption site, the rate, and extent of the drug's distribution to various tissues as well as the site of action and rate of elimination of the drug from the body.

Pharmacokinetics helps in the measurement of the exact values of an independent variable i.e. concentration of the drug that defines the dependent variable i.e. the pharmacological response. This refers to the fact that the concentration of drug available should be enough at the target site to evoke a response but should not produce any toxic effect (Terry, 2019; Turfus et al., 2017). In a nutshell, a complete understanding of all these processes enables the design of a drug formulation in such a way that it provides maximum benefits with minimum risk. It also facilitates dose adjustment as per the requirement of the individual patient's physiology (Grogan 2022). The goals of CRDDS are to minimise fluctuations in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner and to maintain therapeutically effective plasma drug concentration levels for a longer period of time. The target features for any temporal CRDDS are the rate of drug administration, the length of delivery, and the dosage interval. The time of drug delivery (t_{del}), which is used to design CRDDS, is typically assumed to be shorter than the dosage interval (Sood and Panchagnula, 2003).

Absorption

In the pharmacokinetics theory, absorption is paramount since it comprises the transfer of an unmetabolized drug from its site of administration to the systemic circulation of the human body **(Fig. 1.1)**. The process of absorption is dependent upon the active drug

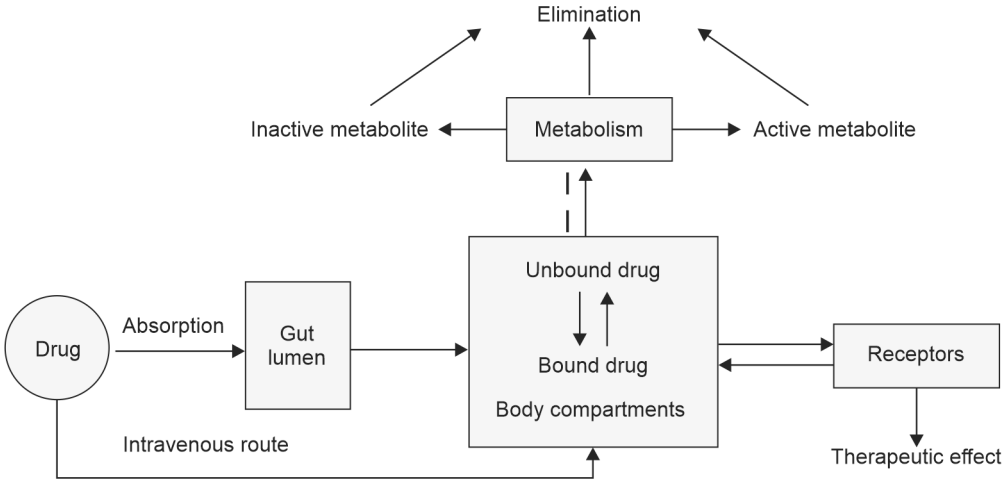

Fig. 1.1: Illustration of pharmacokinetic process inside human body

TABLE 1.3: Examples of drugs acting as inducer, inhibitor and substrate for CYP450 isoenzyme family

Isoenzyme	*CYP1A2*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP2E1*	*CYP3A4 and CYP3A5*
Inducer	Amiodarone, cimetidine, ciprofloxacin, fluvoxamine	Amiodarone, fluconazole, fluoxetine, metronidazole, ritonavir, trimethoprim/sulfamethoxazole	Fluvoxamin, isoniazid, ritonavir	Amiodarone, cimetidine, diphenhydramine, fluoxetine, paroxetine, quinidine, ritonavir, terbinafine	–	Clarithromycin, diltiazem, erythromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, ritonavir, telithromycin, verapamil
Inhibitor	Carbamazepine, phenobarbital, rifampin, tobacco	Carbamazepine, phenobarbital, phenytoin, rifampin	Carbamazepine, phenytoin, rifampin	-	Ethanol, isoniazid, tobacco	Carbamazepine, *hypericum perforatum*, phenobarbital, phenytoin, rifampin
Substrate	Caffeine, clozapine, theophylline	Carvedilol, celecoxib, glipizide, ibuprofen, irbesartan, losartan	Omeprazole, phenobarbital, phenytoin	Amitriptyline, carvedilol, codeine, donepezil, haloperidol, metoprolol, paroxetine, risperidone, tramadol	Acetaminophen, theophylline, verapamil	Alprazolam, amlodipine, atorvastatin, cyclosporine, diazepam, estradiol, simvastatin, sildenafil, verapamil, zolpidem

the remainder (l-EH) to escape into the systemic circulation. The liver then expels this leftover from the bloodstream at a rate known as the hepatic clearance rate (ClH. equal to QHEH), where QH is the liver's blood flow. So, if F fraction of the drug is absorbed and undergoes presystemic elimination, then after oral administration the area under concentration/time curve (AUC_0) for dose D_0 is expressed as:

$$AUC_0 = FD_0(1\text{-}E_H)/Q_HE_H \qquad \text{(Eq. 1.4)}$$

The further details have been mentioned in hepatic clearance section later.

Drugs with variable bioavailability due to first-pass metabolism will be challenging to formulate into CRDDS, the issue of drug loss will be dose-dependent, and if the drug is slowly released over an extended period of time, the bioavailability will be significantly reduced. An extensive first-pass metabolism of a drug negatively impacts the minimum effective concentration for the therapeutic action.

In the case of intestinal presystemic elimination, it is a well-known fact that the drug is metabolized by gut flora and the intestinal wall but its precise estimation is lacking. Drugs that are administered by oral IV or inhalation route can undergo pulmonary presystemic elimination. Intrinsic clearance, hepatic extraction, route of administration, and patient's diseased condition are some major factors affecting the presystemic elimination of drugs. When the drug comes in contact with the vast surface of the endothelial cells after its passage through the pulmonary vascular bed its metabolic transformation occurs (Routledge and David, 1979).

Different examples of drugs undergoing first-pass metabolism/presystemic elimination have been mentioned in **Table 1.4**.

TABLE 1.4: Examples of some drugs undergoing presystemic elimination/first pass metabolism

S.No	*Drug*	*Type of elimination*	*Metabolite*	*Comments*	*References*
1.	Propranolol	Hepatic	4-hydroxy-propranolol	High hepatic extraction leading to presystemi-celimination and low bioavailability	Routledge and Shand, 1979
2.	Lidocaine	Hepatic	Monoethylgly-cinexylidide (MEGX) and glycinexylidide (GX)	Undergoes extensive first-pass hepatic meta-bolism hence only administered paren-terally	Shanton, 2006
3.	Papaverine	Hepatic	4'-, 6- and 7-desmethyl papaverine, O-demethylated papaverine	Rapidly metabolized in man, with formation of different demethy-lated metabolites and excreted mainly by kindney	Rosazza et al., 1977 Belpaire et al., 1978
4.	Morphine	Hepatic	Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)	-	Poulain et al., 1988

Contd.

TABLE 1.4: Examples of some drugs undergoing presystemic elimination/first pass metabolism *(Contd.)*

S.No	*Drug*	*Type of elimination*	*Metabolite*	*Comments*	*References*
5.	Imipramine	Hepatic	N-desmethylimipramine (desipramine), 2-hydroxyimipramine, and 10-hydroxyimipramine	The difference in clinical response of imipramine is majorly affected by the difference in its metabolism	Brosen et al., 1999
6.	Metoprolol	Hepatic	α-hydroxymetoprolol	The amount of metabolite of metoprolol majorly depends upon the patients who are poor hydroxylators and extensive hydroxylators	Lennard et al., 1982
7.	Alprenolol	Hepatic	4-hydroxyalprenolol and eleven other metabolites	Shows dose dependent presystemic elimination	Hoffmann et al., 1978
8.	Chlorpromazine	Intestinal	Monoglucuronide of N-desdimethyl chlorpromazine, 2-Methoxypromaine	Compound undergoes demethylation, sulphoxidation, hydroxylation and conjugation with glucuronic acid and sulphate in the body.	Beckett et al., 1963
9.	Isoproterenol	Hepatic and Intestinal	3-O-methyl isoproterenol and sulfate conjugate	Isoproterenol is immediately active upon infusion. Its half-life is 2.5 to 5 minutes. Conjugation in hepatic and pulmonary tissues is the major method of metabolism. Excretion occurs via urine in the form of sulfate conjugates	Szymanski and Davinder, 2022
10.	Salicylamide	Hepatic	Salicylamide glucuronide, salicylamide sulfate, and gentisamide glucuronide	Glucuronidation, sulfation, and hydroxylation are the mechanism involved in metabolism	Song et al., 1974
11.	Sulfasalazine	Intestinal	m 5-aminosalicylic acid and sulfapyridine	The active metabolites treats ulcerative colitis and also prevents its relapse	Peppercorn, 1984

Elimination and Excretion

Excretion is defined as "the process whereby drugs and their metabolites moves form internal to external environment". The kidneys filter the majority of substances, which are then expelled from the body through the urine or faeces. Filtration, secretion, and

safety. Contrarily, bioavailability variations may result in significant therapeutic nonequivalence for drugs with a very narrow therapeutic index.

In current times where most of the new chemical entity is poorly water-soluble the problem of poor bioavailability is inevitable (Mueller, 2009). Low bioavailability is frequently caused when there is not enough time for the GI system to absorb the substance. Time at the absorption site may not be enough if the drug is difficult to dissolve or cannot pass through the epithelial membrane (for instance, highly ionized and polar drug molecule). In these circumstances, bioavailability is frequently both low and very variable. Orally administered drugs must have to pass through the most frequent sites of first-pass metabolism, before reaching the liver, which are the intestinal wall and the portal circulation. As a result, many drugs might be metabolized before they attain the desired plasma concentrations. Most commonly, oral dose formulations of slowly absorbed, poorly water-soluble drugs have limited bioavailability. Poor bioavailability could be due to chemical processes that hinder the process of absorption. They consist of complex formation, such as that between tetracycline and polyvalent metal ions, hydrolysis by stomach acid or digestive enzymes, such as the sulfoconjugation of isoproterenol, conjugation in the intestinal wall, adsorption to other drugs, such as digoxin to cholestyramine, and metabolism by luminal microflora.

Bioavailability can be assessed by measuring the area under the plasma concentration-time curve, bioavailability is often evaluated. AUC is the determinant of a drug's bioavailability that is the most accurate **(Fig. 1.2)**. The total amount of drug that enters systemic circulation unmodified is directly inversely related to AUC. If the curves for a drug product's plasma concentration are essentially superimposable, then the extent and rate of absorption may be deemed to be bioequivalent.

The degree of drug absorption causes an increase in plasma drug concentration; the peak plasma concentration is attained when the rate of drug absorption and elimination are equal. Given that drug clearance starts as soon as it reaches the bloodstream, bioavailability calculations based on the peak plasma concentration might be deceptive. The most popular general indication of absorption rate is peak time, which is when the maximum plasma drug concentration is attained; the later the peak time, the slower the absorption.

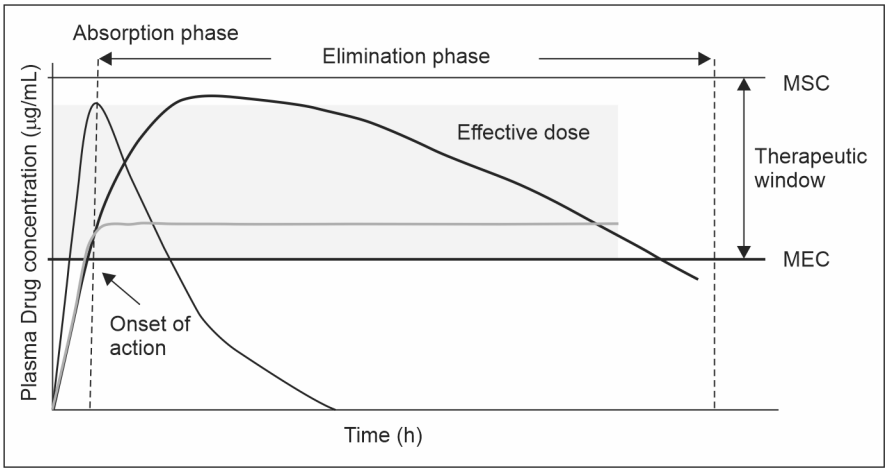

Fig. 1.2: Typical curve of plasma drug concentration versus time for immediate release, controlled release and zero-order release drug delivery system

steady state during an infusion. A drug acquires a given steady-state concentration after 4 to 5 half-lives when administered regularly or in a consistent amount (such as an infusion), and there is no further accumulation in the body with additional doses. This is the situation because the drug's infusion rate and clearance rate will have reached equilibrium, maintaining a constant net drug concentration in the body. The dosage, dosing interval, and clearance all affect this steady-state concentration's value (Hallare and Valerie, 2020). If the rate of absorption and the rate of excretion are equal, a drug is a suitable option for CRDDS. Higher $t_{1/2}$ drugs are already extended systems and do not require the formation of a CRDDS. Drugs having $t_{1/2}$s that are less than or equal to 24 hours make good candidate for CRDDS. If the drug's half-life of elimination ($t_{1/2}$) is less than two hours, a greater dose of the drug must be included in the dosage form.

Elimination half-life curves, like the one in **Fig. 1.3**, that show the amount of a drug in the body over time with time on the independent axis and drug plasma concentration on the dependent axis often serve as a visual representation of half-life elimination. In these graphs, the integral area under the curve (AUC) represents the total drug exposure over time (AUC). If a drug does really follow first-order kinetics, then the integral rate rule of first-order processes states that the elimination curve should exhibit a logarithmic decay (Equation 8). One can derive the half-life equation, which is frequently tested and utilized in clinical practice, by solving the differential equation 1.23 (Borowy and John, 2018).

$$t_{1/2} = \frac{0.693}{k} \qquad \text{(Eq. 1.22)}$$

$$\text{t-half} = 0.693 * V_d / CL \qquad \text{(Eq. 1.23)}$$

where V_d is the volume of distribution and CL is the clearance

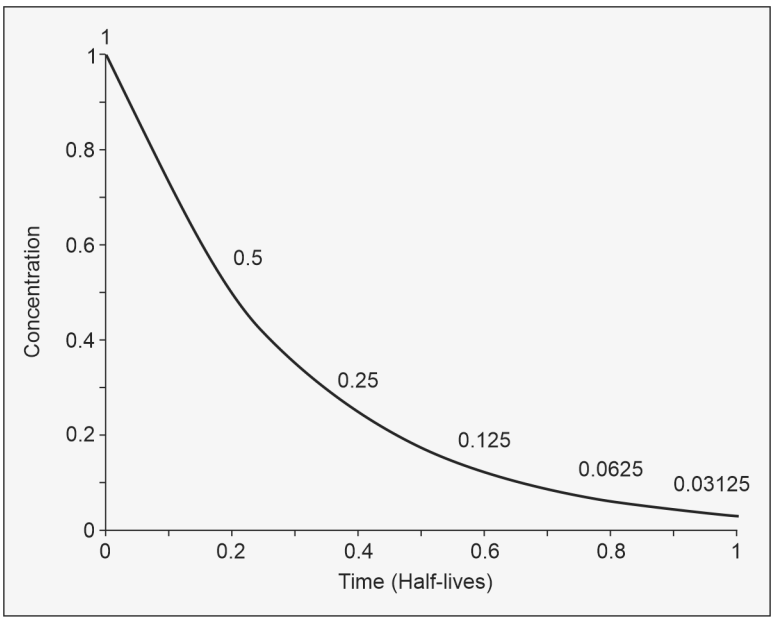

Fig. 1.3: Half-life elimination curve

Fincher, Julian H. "Particle size of drugs and its relationship to absorption and activity." J. Pharma. Sci. 57, no. 11 (1968): 1825–1835.

Giacomini, K.M., Huang, S.M., Tweedie, D.J., Benet, L.Z., Brouwer, K.L., Chu, X., Dahlin, A., Evers, R., Fischer, V., Hillgren, K.M. and Hoffmaster, K.A., International Transporter Consortium 2010. Membrane transporters in drug development. Nat. Rev. Drug Discov, 9, pp.215–236.

Golightly, Larry K., Susan S. Smolinske, Michael L. Bennett, Earl W. Sutherland, and Barry H. Rumack. "Pharmaceutical excipients." Med Toxicol Adverse Drug Exp. 3, no. 2 (1988): 128–165.

Grogan S, Preuss CV. Pharmacokinetics. [Updated 2022 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557744/

Hallare J, Gerriets V. Half Life. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2022. PMID: 32119385.

Hendriksen, Barry A., Manuel V. Sanchez Felix, and Michael B. Bolger. "The composite solubility versus pH profile and its role in intestinal absorption prediction." AAPS PharmSci 5, no. 1 (2003): 35–49.

Herman, Timothy F., and Cynthia Santos. "First pass effect." (2019).

Hoffmann, Kurt-Jürgen, Anders Arfwidsson, Karl Olof Borg, and Inger Skånberg. "Study of the metabolic pathways of alprenolol in man and the dog using stable isotopes." Biol. Mass Spectrom 5, no. 11 (1978): 634–640.

Horde GW, Gupta V. Drug Clearance. [Updated 2022 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557758/

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-note-guidance investigation-bioavailability-bioequivalence_en.pdf

Indurkhya, Arpna, Mahendra Patel, Piyoosh Sharma, Sara Nidal Abed, AbeerShnoudeh, Rahul Maheshwari, Pran Kishore Deb, and Rakesh K. Tekade. "Influence of drug properties and routes of drug administration on the design of controlled release system." In Dosage form design considerations, pp. 179–223. Academic Press, 2018.

Jain, Shashank, Niketkumar Patel, and Senshang Lin. "Solubility and dissolution enhancement strategies: current understanding and recent trends." Drug Dev. Ind. Pharm. 41, no. 6 (2015): 875–887.

Jennifer Le. 'pharmacology/pharmacokinetics/drug-bioavailability." 2022 (https://www.msdmanuals.com/enin/professional/clinical)

Jinno, Jun-ichi, Naokimada, Masateru Miyake, Keigo Yamada, Tadashi Mukai, Masaaki Odomi, Hajime Toguchi, Gary G. Liversidge, KazutakaHigaki, and Toshikiro Kimura. "Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs." J Control Release 111, no. 1–2 (2006): 56–64.

Kamaly, Nazila, BasitYameen, Jun Wu, and Omid C. Farokhzad. "Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release." Chem.Rev. 116, no. 4 (2016): 2602–2663

Krämer, Stefanie D. "Absorption prediction from physicochemical parameters." Pharm. sci. technol. today 2, no. 9 (1999): 373–380.

Ku, M. S. "Salt and polymorph selection strategy based on the biopharmaceutical classification system for early pharmaceutical development." Am Pharm Rev 13, no. 1 (2010): 22–30.

Lennard, Martin S., Joseph H. Silas, Stephen Freestone, Lawrence E. Ramsay, Geoffrey T. Tucker, and Hubert F. Woods. "Oxidation phenotype—a major determinant of metoprolol metabolism and response." N Engl J Med 307, no. 25 (1982): 1558–1560.

Levy, Gerhard. "Comparison of dissolution and absorption rates of different commercial aspirin tablets." J. Pharma. Sci. 50, no. 5 (1961): 388–392.

Li, Shoufeng, SuiMing Wong, Sundeep Sethia, Hassan Almoazen, Yatindra M. Joshi, and Abu Serajuddin. "Investigation of solubility and dissolution of a free base and two different salt forms as a function of pH." Pharm Res 22, no. 4 (2005): 628–635.

Liu, Dandan, Hao Pan, Fengwei He, Xiaoyu Wang, Jinyu Li, Xinggang Yang, and Weisan Pan. "Effect of particle size on oral absorption of carvedilol nanosuspensions: in vitro and in vivo evaluation." Int J Nanomedicine 10 (2015): 6425.

Liu, Xiangli, Bernard Testa, and Alfred Fahr. "Lipophilicity and its relationship with passive drug permeation." Pharm Res 28, no. 5 (2011): 962–977.

Loftsson, Thorsteinn. Drug stability for pharmaceutical scientists. Academic Press, 2014.

Lu, Ying, Sungwon Kim, and Kinam Park. "In vitro–in vivo correlation: Perspectives on model development." International Journal of Pharm. 418, no. 1 (2011): 142–148.

Mallick, Subrata, SatyanarayanPattnaik, Kalpana Swain, and Pintu K. De. "Current perspectives of solubilization: potential for improved bioavailability." Drug Dev. Ind. Pharm.33, no. 8 (2007): 865–873.

Mansoor A, Mahabadi N. Volume of Distribution. [Updated 2022 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545280/

Martinez, Marilyn N., and Gordon L. Amidon. "A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals." J. Clin. Pharmacol 42, no. 6 (2002): 620–643.

Mueller, Christa E. "Prodrug approaches for enhancing the bioavailability of drugs with low solubility." Chem. Biodivers.6, no. 11 (2009): 2071–2083.

Onetto AJ, Sharif S. Drug Distribution. [Updated 2022 Jun 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567736/

Peppercorn, Mark A. "Sulfasalazine: pharmacology, clinical use, toxicity, and related new drug development." Ann. Intern. Med. 101, no. 3 (1984): 377–386.

Poulain, P., P. J. Hoskin, G. WOAO Hanks, O. A-OMAR, V. A. Walker, A. Johnston, P. Turner, and G. W. Aherne. "Relative bioavailability of controlled release morphine tablets (MST continus) in cancer patients." BJA: Br J Anaesth61, no. 5 (1988): 569–574.

Quintanar-Guerrero, David, Eric Allémann, Hatem Fessi, and Erie Doelker. "Applications of the ion-pair concept to hydrophilic substances with special emphasis on peptides." Pharm Res 14, no. 2 (1997): 119–127.

Qureshi, Saeed A. "Developing discriminatory drug dissolution tests and profiles: Some thoughts for consideration on the concept and its interpretation." Dissolution Technol 13, no. 4 (2006): 18–23.

Rosazza, John P., Marianne Kammer, Leisa Youel, Robert V. Smith, Paul W. Erhardt, Duyen H. Truong, and Steven W. Leslie. "Microbial models of mammalian metabolism O-demethylations of papaverine." Xenobiotica 7, no. 3 (1977): 133–143.

Routledge, P. A., and D. G. Shand. "Clinical pharmacokinetics of propranolol." Clin. Pharmacokinet. 4, no. 2 (1979): 73–90.

Routledge, Philip A., and David G. Shand. "Presystemic drug elimination." Annu. Rev. Pharmacol. Toxicol. 19, no. 1 (1979): 447–468.

Saifee, M., N. Inamda, D. Dhamecha, and A. Rathi. "Drug polymorphism: a review." Int. J. Health Res. 2, no. 4 (2009): 291–306.

Sandri, Giuseppina, M. Cristina Bonferoni, Franca Ferrari, Silvia Rossi, and Carla M. Caramella. "The role of particle size in drug release and absorption." In Particulate Products, pp. 323–341. Springer, Cham, 2014.

Sandri, Giuseppina, M. Cristina Bonferoni, Franca Ferrari, Silvia Rossi, and Carla M. Caramella. "The role of particle size in drug release and absorption." In Particulate Products, pp. 323–341. Springer, Cham, 2014.

Scheife, Richard T. "Protein binding: what does it mean?." Dicp 23, no. 7–8 (1989): S27-S31.

Sen Gupta, Anirban. "Role of particle size, shape, and stiffness in design of intravascular drug delivery systems: insights from computations, experiments, and nature." Wires NanomedNanobi 8, no. 2 (2016): 255–270.

Serajuddin, Abu TM. "Salt formation to improve drug solubility." Adv. Drug Deliv. Rev. 59, no. 7 (2007): 603–616.

Shahrin, Naila. "Solubility and dissolution of drug product: A review." International Journal of Pharm. Life Science. 2, no. 1 (2013): 33–41.

Shahrin, Naila. "Solubility and dissolution of drug product: a review." International Journal of Pharm. Life Science. 2, no. 1 (2013): 33–41.

Shanmukhan, Nikhitha K., Arun Radhakrishnan, Vinoth Maniarasan, Gowthamarajan Kuppusamy, and Samuel Gideon. "Bioformulative concepts on intracellular organ specific bioavailability." Ther.Deliv. 9, no. 10 (2018): 775–796.

Shargel, L., B. A. Yu, and S. Wu-Pong. "Biopharmaceutic considerations in drug product design and in vitro drug product performance." Applied Biopharmaceutics and Pharmacokinetics. 6th ed. New York: McGraw-Hill (2012): 361–89.

Silva, Daniela Amaral, Gregory K. Webster, Nadia Bou-Chacra, and RaimarLöbenberg. "The significance of disintegration testing in pharmaceutical development." Dissolution Technol 25, no. 3 (2018): 30–8.

Simmons, Donald L. Peristaltic Dissolution Assembly as a Bioequivalence Surrogate: A Review. (2016): 1–27.

Smith, D. A., and L. Cucurull-Sanchez. "The adaptive in combo strategy." (2007): 957–969.

Song, Chull S., Herbert L. Bonkowsky, and Donald P. Tschudy. "Salicylamide metabolism in acute intermittent porphyria." Clin. Pharm. Therap. 15, no. 4 (1974): 431–435.

Sood, Anurag, and Ramesh Panchagnula. "Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index." Int. J. Pharm. 261, no. 1–2 (2003): 27–41.

Stanton, M. S. "Class I antiarrhythmic drugs: Quinidine, procainamide, disopyramide, lidocaine, mexiletine, tocainide, phenytoin, moricizine, flecainide, and propafenon." Card electrophysiol: from cell to bedside (2006): 890–903.

Stavchansky, Salomon. "Scientific perspectives on extending the provision for waivers of in vivo bioavailability and bioequivalence studies for drug products containing high solubility-low permeability drugs (BCS-Class 3)." The AAPS journal 10, no. 2 (2008): 300–305.

Szymanski MW, Singh DP. Isoproterenol. [Updated 2022 Sep 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526042/

Taniguchi, Chika, Yohei Kawabata, Koichi Wada, Shizuo Yamada, and Satomi Onoue. "Microenvironmental pH-modification to improve dissolution behavior and oral absorption for drugs with pH-dependent solubility." Expert Opin. Drug Discov 11, no. 4 (2014): 505–516.

Terry P. Kenakin, Chapter 9 - Pharmacokinetics, Editor(s): Terry P. Kenakin, A Pharmacology Primer (Fifth Edition), Academic Press, 2019, Pages 245–293, ISBN 9780128139578

Turfus, S., R. Delgoda, D. Picking, and B. J. Gurley. "Pharmacokinetics pharmacognosy." Boston: Academic (2017).

Wadhwa RR, Cascella M. Steady State Concentration. [Updated 2022 Mar 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553132/

Wanat, Karolina. "Biological barriers, and the influence of protein binding on the passage of drugs across them." Mol. Biol. Rep. 47, no. 4 (2020): 3221–3231.

Waring, Michael J. "Lipophilicity in drug discovery." Expert Opin. Drug Discov 5, no. 3 (2010): 235–248.

Wolff, K. (2010). First-Order Elimination Kinetics. In: Stolerman, I.P. (eds) Encyclopedia of Psychopharmacology. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978–3-540–68706-1_1522

Xiao, Jianbo, and Petra Hogger. "Editorial (Thematic issue: advances in the pharmacokinetics of natural bioactive polyphenols)." Curr. Drug Metab. 15, no. 1 (2014): 1–2.