Chapter III

Drug Delivery and Pharmacokinetics
3. Drug Delivery and Pharmacokinetics

3.1 Drug Delivery

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. It could also refer to the administration of drugs at controlled rate (slow, quick, or sustained), to a targeted site, and by innovative methods. The method by which a drug is delivered can have a significant impact on its efficacy. Some drug products give maximum therapeutic benefit only at an optimal concentration range. At concentrations above the optimal range, the drug would produce toxic effects and produce no therapeutic benefit whatsoever, below it. Also, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared...
with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

Medications can be taken in a variety of ways—by mouth, by inhalation, by absorption through the skin, or by intravenous injection. Each method has advantages and disadvantages, and not all methods can be used for every medication. Improving current delivery methods or designing new ones can enhance the use of existing medications. Microneedle arrays are one example of a new method to deliver medications through the skin\textsuperscript{63–65}. In these arrays, dozens of microscopic needles, each far thinner than a strand of hair, can be coated or filled with a medicine. The needles are so small that, although they penetrate the skin, they don’t reach nerves in the skin, thus delivering medications painlessly.

3.1.1 Classification

Routes of administration are usually classified by application location (or exposition). The route or course the active substance takes from application location to the location where it has its target effect is usually rather a matter of pharmacokinetics (concerning the processes of uptake, distribution, and elimination of drugs). Nevertheless, some routes, especially the transdermal or transmucosal routes, are commonly referred to routes of administration. The locations of the target effect of active substances are usually rather a matter of pharmacodynamics (concerning e.g. the physiological effects of drugs). Furthermore, there is also a classification of routes of administration that basically distinguishes whether the effect is local (in "topical" administration) or systemic (in "enteral" or "parenteral" administration).

The options are limited by the available forms of any given drug. Still, there are advantages and disadvantages to consider with any route of administration.
Oral

The oral route is the most convenient as it is the most economical and easiest mode of dosaging. However, with drugs that cause irritation to the GIT and other side effects, the complications associated increase.

Topical

Topically administered drugs are those applied for local action and systemic effects. They include those at or on the surface of the skin, those that exert their actions on the stratum corneum, and those that modulate the function of the epidermis and/or the dermis. Some examples include creams, ointments, gels, suspensions, pastes, foams, sprays, lotions, and aerosols.

Sublingual

This is the route of administration by which the pharmaceutical products are delivered by diffusion through tissues under the tongue into the blood. Typical examples include barbiturates, cardiovascular drugs, opioids, analgesics, steroids, drugs with poor gastrointestinal bioavailability, enzymes, vitamins and minerals.

Inhalation

Inhaled medications are generally absorbed quickly, and act both locally and systemically. Proper technique with inhaler devices is necessary to achieve the correct dose. Some medications can have an unpleasant taste or irritate the mouth.

Drugs administered by inhalation through the mouth are to be atomized to smaller droplet sizes to enable them to pass through the windpipe (trachea) and into the lungs. Smaller the droplet sizes deeper the drug product can reach the lungs and greater will be the amount of drug absorbed. From the lungs, they get absorbed into the bloodstream.

Injection

The term injection encompasses intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration. Injections act rapidly, with onset of action in 15–30 seconds for IV, 10–20 minutes for IM, and 15–30 minutes for SC. They also have essentially 100% bioavailability, and can be used for drugs that are poorly absorbed or ineffective when given orally. Some medications, such
as certain antipsychotics, can be administered as long-acting intramuscular injections. Ongoing IV infusions can be used to deliver continuous medication or fluids.

Disadvantages of injections include potential pain or discomfort for the patient, and the requirement of trained staff using aseptic techniques for administration. However, in some cases patients are taught to self-inject, such as SC injection of insulin in patients with insulin-dependent diabetes mellitus. As the drug is delivered to the site of action extremely rapidly with IV injection, there is a risk of overdose if the dose has been calculated incorrectly, and there is an increased risk of side effects if the drug is administered too rapidly.
3.1.2 Delivery Vehicles

Drug carrier systems like liquid crystal and vesicle dispersions, micellar solutions, and nanoparticulate dispersions consisting of particles ranging 10–400 nm diameter hold a great promise as novel drug delivery systems. The goal of such novel systems is to obtain optimized drug loading and release characteristics, durable shelf-life and lesser toxicity.

3.1.2.1 Micelles

Micelles are designed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions and are of great importance for novel drug delivery applications. The drugs can be trapped in the core of block copolymer in micelles and transported at concentrations surpassing their inherent aqueous solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream. A final feature that makes amphiphilic block copolymers attractive for drug delivery applications is the fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with crosslinkable groups can increase the stability of the corresponding micelles and improve their temporal control. Substitution of block copolymer micelles with specific ligands is a very promising strategy to a broader range of sites of activity with a much higher selectivity.

3.1.2.2 Liposomes

Liposomes are a form of vesicles that consist either of many, few or just one phospholipid bilayers. The polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer according to their affinity towards the phospholipids. Participation of nonionic surfactants instead of phospholipids in the bilayer formation results in niosomes. Channel proteins can be incorporated without loss of their activity within the hydrophobic domain of vesicle membranes, acting as a size-selective filter, only allowing passive diffusion of small solutes such as ions, nutrients and antibiotics. Thus, drugs that are encapsulated in a nanocage-functionalized with
channel proteins are effectively protected from premature degradation by proteolytic enzymes\textsuperscript{76–78}. The drug molecule, however, is able to diffuse through the channel, driven by the concentration difference between the interior and the exterior of the nanocage.

3.1.2.3 Dendrimers

Dendrimers are nanometer-sized, highly branched and monodisperse macromolecules with symmetrical architecture. They consist of a central core, branching units and terminal functional groups. The core together with the internal units, determine the environment of the nanocavities and consequently their solubilizing properties, whereas the external groups the solubility and chemical behaviour of these polymers. Targeting effectiveness is affected by attaching targeting ligands at the external surface of dendrimers, while their stability and protection from the Mononuclear Phagocyte System (MPS) is being achieved by functionalization of the dendrimers with polyethylene glycol chains (PEG)\textsuperscript{66,79}.

3.1.2.4 Nanoparticles

Nanoparticles (including nanospheres\textsuperscript{45,80,81} and nanocapsules\textsuperscript{51,61} of size 10-200 nm) are solid state amorphous or crystalline particles that can encapsulate a drugs for controlled release as well as for provide protection against chemical and enzymatic degradation. Nanocapsules are vesicular drug delivery systems wherein the drug particles are restrained inside a cavity that is surrounded by a distinctive polymer membrane. Nanospheres are carriers wherein the drug is physically and uniformly dispersed throughout the polymeric matrix. Nanoparticles can be prepared from both biodegradable polymers as well as synthetic non-bio-degradable polymers. In recent years, the utility of biodegradable polymeric nanoparticles have attracted substantial attention as prospective drug delivery strategies due to their applications in the controlled release of drugs, in targeting particular organs / tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes.

3.1.2.5 Nanosponges

“Nanosponges” have emerged promising carriers for treating cancer\textsuperscript{82,83}. It comprises of a scaffold of specialized minute polyester particles that are smeared with disease-targeting composites containing an anticancer drug. Once the nanosponges reach the intended site, they
securely and gradually undergo degradation, thus releasing the medication at the tumor site at a steady, controlled rate. Preliminary research has also been carried out to show that the nanosponges can be used to treat glaucoma, the fourth leading cause of blindness.\textsuperscript{84–86} Since these systems restrict the discharge of drugs throughout the entire body, the nanosponge and related drug carrier systems may make it possible to revive the usage of drugs that were formerly considered unsafe for disease management.

![Figure 3-2: Nanotechnology based carriers used for drug delivery. Source: Public domain](image)

3.1.3 Cargo

Perhaps the most obvious route to improving disease treatment would be to focus on the medications themselves. But there are also other treatment options. Drug delivery researchers are also exploring the use of genes, proteins, and stem cells as treatments.

Taking cues from the body’s natural process for preventing the immune reaction, the researchers developed microscopic, biodegradable particles that can selectively shut down immune cells associated with the autoimmune disorder multiple sclerosis (MS). Bound with pieces of the protein myelin, the insulating material covering nerve cells that is destroyed in MS, the microparticles were effective at preventing the start of MS in mice and at stopping disease progression when injected after the first sign of illness. The microparticle therapy may also be
useful in treating other immune-related conditions, including allergies, or to suppress organ rejection in transplant patients.

3.1.4 Targeting Strategies

Working backwards on a problem can sometimes reveal a solution. In drug delivery research, this means starting with a delivery method that has a known target, which may be whole organs (heart, lung, brain), tissue types (muscle, nerve), disease-specific structures (tumor cells), or structures inside of cells.

Made from modified viruses, viral nanoparticles take advantage of the natural ways that viruses have developed to slip past immune defenses and enter cells. This means they do not need to be modified as much as other types of nanoparticles to behave in desired ways, and their actions within the human body are well understood. Plant-based viral nanoparticles are also biodegradable, harmless to humans, easy to use, and cheap to produce. Further research aims to develop viral nanoparticles that can deliver chemotherapy drugs directly to tumors. Such an advance would reduce the severe side effects usually associated with cancer treatment.
3.2 Pharmacokinetics

Pharmacokinetics, is often simply defined as, what the body does to a drug. It refers to the transport of drug into the body, through the body and out of the body. Pharmacodynamics on the other hand is what a drug does to the body. It deals with receptor binding, post-receptor effects, and the various chemical interactions. Pharmacokinetic properties of a drug are determined by the onset, duration, and intensity of a drug’s effect and depend on aspects like mode of administration and the dosage of the drug\textsuperscript{87,88}. Generally, both pharmacokinetics and pharmacodynamics of a drug are studied in conjunction to understand the drug's final pharmacological effect on the body.

Though a number of models have been developed to simplify and study the various processes that occur during the drug-body interactions, the multi-compartment model (the ADME scheme), gives the best approximation to reality.

- **Absorption** - the process of a substance entering the blood circulation.
- **Distribution** - the dispersion or dissemination of substances throughout the fluids and tissues of the body.
- **Metabolization** (or biotransformation, or inactivation) – the recognition by the organism that a foreign substance is present and the irreversible transformation of parent compounds into daughter metabolites.
- **Excretion** - the removal of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

It also is sometimes referred to as LADME\textsuperscript{89} to include liberation of the drug from the formulation or ADMET\textsuperscript{90} to include toxicity profile of the drug.

Often the latter two phases namely, metabolism and excretion, are grouped together as ‘elimination’. The study of these distinct phases involves the use and manipulation of basic concepts in order to understand the process dynamics. In order to fully comprehend the kinetics of a drug it is necessary to have detailed knowledge of a number of factors such as: the properties of the substances that act as excipients, the characteristics of the appropriate biological membranes and the way that substances can cross them, or the characteristics of the enzyme reactions that inactivate the drug.
Since major work in this thesis is related to the oral dosage forms for improving the dissolution characteristics, the discussions are focused on and limited to the drug absorption of orally delivered drugs.

3.2.1 Absorption

The process of movement of drug from the site of administration to systemic circulation is called as absorption. It is the process by which orally delivered drug molecules cross biological membranes associated with the GI tract. It, however, is also relevant for drugs delivered via other modes of administration such as subcutaneous, intra muscular and transdermal routes of administration of drugs. Moreover, the pharmacokinetic profile of a drug can be easily and significantly altered by regulating the factors affecting the absorption.

Any drug product must be absorbed before any of its medicinal effects can have an effect. Drug absorption is a function of several factors such as drug’s physicochemical properties, the way it has been formulated, route of administration and so on. Unless delivered intravenously, a drug has to overcome and cross quite a few semipermeable cell membranes and barriers before it finally reaches the systemic circulation. Cell membranes are biological bimolecular lipid matrix barriers that selectively inhibit passage of drug molecules. They determine membrane permeability characteristics\textsuperscript{91,92}. Drugs cross these cell membranes by several mechanisms such as passive diffusion, facilitated passive diffusion, active transport, or pinocytosis. Sometimes various globular proteins embedded in the matrix function as receptors and help transport molecules across the membrane\textsuperscript{93,94}.

3.2.1.1 Physical factors influencing absorption

- **Blood flow to the absorption site:**
  Blood flow to the intestine is much greater than the flow to the stomach; thus, absorption from the intestine is favored over that from the stomach.

- **Total surface area available for absorption:**
Because the intestine has a surface rich in microvilli, it has a surface area about 1000-fold that of the stomach; thus, absorption of the drug across the intestine is more efficient.

- **Contact time at the absorption surface:**
  If a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

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**Figure-3-3: Sequence of events in the absorption of orally administered drugs.**

There are four probable sources of incomplete absorption after oral administration of a solid drug product:

- The drug is not released from its formulation over appropriate time duration into the solution to the relevant sites in the GI tract from where it can be well absorbed.
- The drug gets decomposed in the GI tract or forms a complex that is not absorbable.
- The drug is not transported efficiently across the gut wall in the apical to basal direction.
• The drug is metabolized or eliminated on its way to the systemic circulation.

Moreover, the GI tract is a very dynamic system in terms of its physiological and morphological features. Thus the drug characteristics such as the release rate, the decomposition, complexation must be analyzed keeping in mind the transport of the drug across in the GIT and across the gut wall\textsuperscript{95}. For a drug to be sufficiently absorbed, the release of the drug as well as its subsequent uptake must happen within the time taken for the drug dosage form to traverse the GIT especially where its absorption is maximum while the process of decomposition/complexation and elimination must be slowed down and minimized.

3.2.2 Physiological conditions of GIT

The GIT serves as a good barrier to prevent the entry of toxic materials & pathogens. However, specialized mechanisms exist which allow the particle transport. Peyers patches (PP) exist all along the intestine (maximum in Ileum)\textsuperscript{96,97}. These are composed of lymphoid tissue and a specialized epithelium called M cells interspersed between the normal epithelial cells\textsuperscript{98,99}. M cells lack fully developed microvilli (unlike neighboring absorptive cells). Mucus layer is lesser on M cells. Particles are transported via passive diffusion or active transport (carrier mediated). Particles are transported via passive diffusion or active transport (carrier mediated). Diffusion can be either transcellular or paracellular via aqueous channel. The transcellular uptake of particles across M cells is influenced by the size, surface charge and surface characteristics of the nanoparticles\textsuperscript{100}. Particles diffuse through the mucus, get in contact with the cell surface and then finally vesicular transport (endocytosis) from mucosal to serosal side occurs. Depending on the size of the particles, they are transported by the lymph to the blood or to any other organ. Paracellular transport could also occur between the cells for smaller (nano) particles\textsuperscript{101,102}.

Physiological factors of the GIT that affect absorption include the transit time of drug dosage forms through the GIT, environmental factors such as the pH, enzymes and presence/absence of food, disease situations within the GIT, the condition of the mucus and unstirred water layer, the GI membrane and pre-systemic metabolism.

In order to gain an insight into the numerous factors that can potentially influence the rate and extent of drug absorption into the systemic circulation, a schematic illustration of the steps
involved in the release and absorption of a drug from a tablet dosage form is presented in Figure. It can be seen from this that the rate and extent of appearance of intact drug in the systemic circulation depend on a succession of kinetic processes.

Figure 3-4: Schematic illustration of the steps involved in the release and absorption of a drug from a tablet dosage form. Source: Public domain

The slowest step in this sequence (rate-limiting step) would control the overall rate and extent of entrance of intact drug in the systemic circulation. The rate-limiting step varies from drug to drug. For a drug which has a very poor aqueous solubility, the rate at which it dissolves in the gastrointestinal fluids is often the slowest step and the bioavailability of that drug is said to be dissolution-rate limited.

Other potential rate-limiting steps include the rate of drug release from the dosage form (this can be by design, in the case of controlled-release dosage forms), the rate at which the stomach empties the drug into the small intestine, the rate at which the drug is metabolized by enzymes in the intestinal mucosal cells during its passage through them into the mesenteric blood vessels, and the rate of metabolism of drug during its initial passage through the liver (the ‘first-pass’ effect).
Food-drug interactions can also alter the pharmacokinetic and pharmacodynamic profile of various drugs that may have clinical implications. Absorption and metabolism are the phases where food has most effect. Mechanisms related to food effects on drug absorption have been described under 5 categories: those causing decreased, delayed, increased or accelerated absorption, and those in which food has no significant effect\textsuperscript{103,104}. Among the major variables that interface between differential effects of food and postprandial bioavailability are: (i) the physicochemical characteristics and enantiomorphic composition of the drug; (ii) timing of meals in relation to time of drug administration; (iii) size and composition of meals (especially fat, protein and fibre); and (iv) dose size\textsuperscript{105,106}. However, the influence of food is mainly an issue of the design of the drug formulation. In addition, the mechanism of ‘food effect’ may involve physiological as well as sensory responses to food, such as changes in gastrointestinal milieu and gastric emptying rate, reflex action, and may also involve the site and route (either portal or lymphatic) of drug absorption.

3.2.3 Nanoparticles for Improved Absorption of poorly soluble drugs

For oral drug delivery, the drug particles must dissolve to be absorbed. Though there have been some reports that uptake of nanoparticles can be facilitated via various cellular/paracellular processes\textsuperscript{107}, enhanced absorption primarily necessitates improving the bioavailability of the poorly water-soluble compounds. Nanosizing maximizes the amount of soluble drug that is free to be absorbed. This is especially true for poorly water-soluble compounds absorbed at a defined region of the gastrointestinal tract. A large percentage of compounds are absorbed maximally at the duodenal–jejunal area. If dissolution is not complete when the dosage form transits this area, bioavailability will be seriously compromised. Similarly, if bioavailability depends on the nutritional state of the subject or is not dose proportional, nanoparticle formulations have been shown to reduce or eliminate such effects.
Nanoparticle formulations basically consist of the drug, an external phase (which is typically water and a minimal amount of stabilizer), and a reagent that has a proven history of safe use for the intended application. Buffering and/or isotonicity agents can be added, provided they are compatible with the formulation and donot disrupt the colloidal stability of the nanoparticulate formulation. In essence, the drug-particle formulation approach provides an opportunity to have safer, less toxic parenteral medications that lend themselves to opportunities for dose escalation, enhanced efficacy, and improved patient tolerability.

The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programs are poorly water-soluble.\(^{1}\)
Such drugs often have an erratic absorption profile and highly variable bioavailability because their performance is dissolution-rate limited and is affected by the fed/fasted state of the patient.

Figure 3-6: The diagram demonstrates one of the primary issues associated with poorly water-soluble molecules whose bioavailability is dissolution-rate limited. On the left, large drug particles cannot adequately dissolve, which results in the inability to be absorbed. On the right, nanometer drug particles are rapidly dissolved during transit through the gut, thus maximizing absorption and improving bioavailability.

In essence, the drug-particle formulation approach provides an opportunity to have safer, less toxic parenteral medications that lend themselves to opportunities for dose escalation, enhanced efficacy, and improved patient tolerability. A few examples demonstrating the benefits of using a nanoparticle technology such as NanoCrystal Technology for parenteral products in clinical studies have been published for intravenous and pulmonary applications. In all cases, the
formulations have proven to be well tolerated and provide alternate formulation approaches for poorly water-soluble therapeutics, thus broadening their applications and use.

Figure 3-7: A few of the primary benefits observed when a poorly water-soluble compound is formulated using a nanoparticle approach.

The advantages of using nanoformulations for overcoming absorption related problems are highlighted in Figure 3-8. (a) The bioavailability of a poorly water-soluble model compound formulated as a nanoparticle dispersion (red) or as a conventional crude suspension (yellow). (b) The bar graphs show the comparison in the fed/fasted variation in bioavailability of a model compound when formulated as nanoparticle dispersion (red) or as a crude suspension (yellow). Many poorly water-soluble molecules whose bioavailability is dissolution rate limited are not dose
proportional. (c) A dose-escalation study is shown demonstrating dose proportionality for a nanoparticle formulation of a poorly water-soluble compound.

One final point that should be addressed is the potential alteration in biodistributional properties that can potentially result when a compound is dosed using a nanoparticulate platform. It is well established that various physical properties of a particulate carrier can affect tissue distribution\textsuperscript{111,112}. The tissue distribution following intravenous injection of nanoparticulate carriers that involve encasement or encapsulation technology such as liposomes and various polymeric carriers have been extensively studied\textsuperscript{52,81}. Size, surface, and shape are important if the intention is to target or avoid rapid uptake of the particulates by the mononuclear phagocytic system (MPS) of the lung, liver, spleen, and bone marrow.

For drug nanoparticles that do not involve encapsulation technology, tissue distribution is also dictated by the solubility of the compound. If a compound is soluble in the blood pool, the drug nanoparticle, on dosing, will exhibit a pharmacokinetic and tissue-distribution profile very similar to the compound dosed as a solution. Alternatively, if the compound is practically insoluble in the blood pool, when dosed, drug nanoparticles will behave very similarly to the other nanoparticulate platforms described above; that is, size and coating can be used to target or avoid the MPS system. This ability to use a particulate carrier to control tissue distribution of a compound can be beneficially used to direct high concentrations of drug to diseased sites while limiting exposure to healthy tissue.

The activity of a compound depends on its ability to dissolve and interact with the relevant biological target, either through dissolution and absorption or dissolution and receptor interaction. The poor bioavailability of poorly water-soluble molecules that are not permeation-rate limited can be attributed to dissolution-rate kinetics. The dissolution rate is directly proportional to the surface area of the drug, according to the Noyes-Whitney model for dissolution kinetics. Drug particles reduced in size from 10 microns to 100-nm particles generate a 100-fold increase in surface-area-to-volume ratio.
3.3 References


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