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Introductory Chapter: Drug Delivery Concepts

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1. Introduction

Drug delivery systems (DDSs) are pharmaceutical formulations or devices that help in achieving targeted delivery and/or controlled release (CR) of therapeutic agents in our body [1]. Following administration, the DDSs liberate the active ingredients, and subsequently, the bioactive molecules are transported across various biological barriers to reach the site of action. The scientists have contributed substantially to understand the role of different physiological barriers in efficient transport of drugs in the circulatory system and drug movement through cells and tissues. In addition, their significant contribution to the development of a number of new modes of drug delivery has entered clinical practice. Despite a significant advancement in the process of new drug design and discovery, many drugs have unacceptable side effects due to interaction of the drug with parts of the body that are not the target for the drug. Sometimes, side effects occur depending on the medication, the mode of delivery, and response from our body. The buildup of high blood plasma drug concentration due to accumulation of drug from repeated administration of conventional DDS may lead to untoward side effects. Hence, the attempts must be made to afford better patient compliance effect from the reduction in the number and frequency of doses needed to maintain the desired therapeutic responses. These side effects can vary greatly from person to person in type and severity. The method by which the drug is delivered can have a significant impact on its efficacy.

It is necessary to develop suitable DDS for all drugs to allow their effective and safe application to the patient. Indeed, DDSs control the drug release rate and drug absorption and ultimately the therapeutic effects along with side effects of the drug. Ideal DDSs ensure that the active drug is available at the site of action according to the need of patient for an intended duration. The drug concentration at the appropriate site should remain in the therapeutic
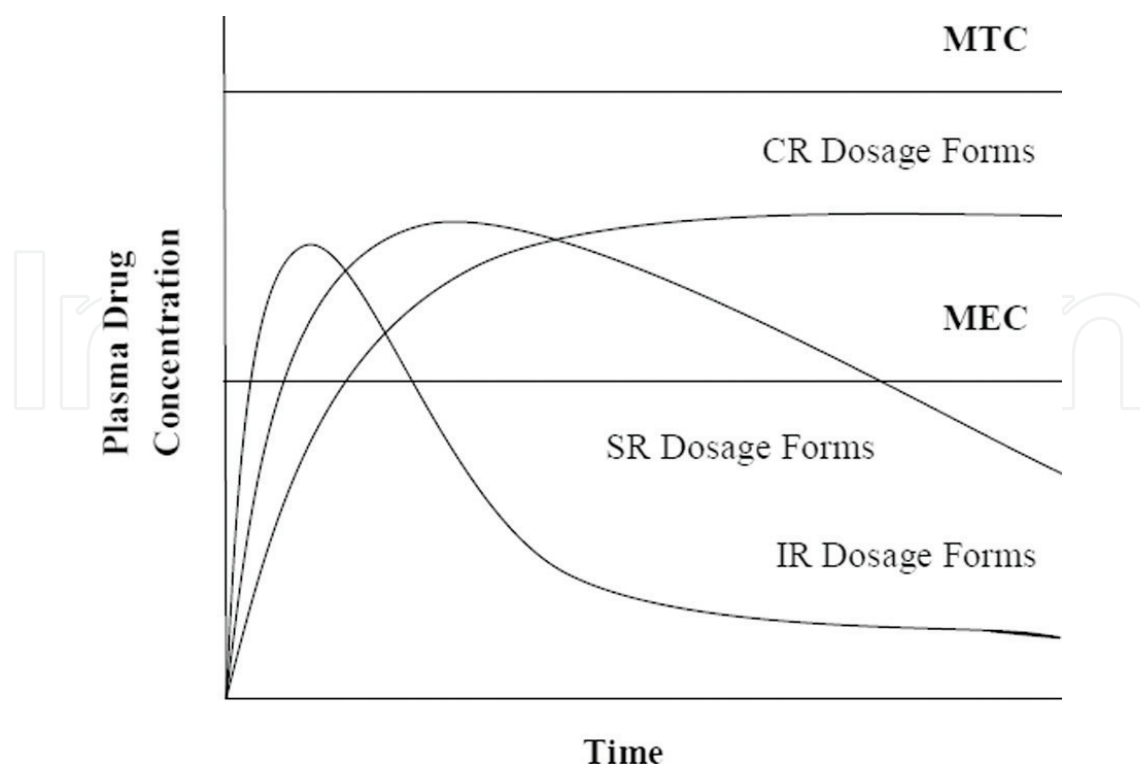
Figure 1. The drug plasma levels after single oral administration of a drug from (a) IR dosage form, (b) SR dosage form, and (c) CR dosage form.

window, that is, between minimal effective concentration (MEC) and minimal toxic concentration (MTC). This concept is illustrated in **Figure 1**.

The maintenance of drug concentration in therapeutic range depends on the frequency of dosing, the drug clearance rates, the route of administration, and the DDS employed. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. DDS can be classified according to their physical state, site/route of administration, and the rate of drug release. The dosage form may be gaseous (e.g., anesthetics), liquid (e.g., solutions, emulsions, and suspensions), semisolid (e.g., creams, ointments, and gels), and solid dosage (e.g., tablets and capsules) [2]. Drugs can be administered directly into the body through injection or infusion termed parenteral drug delivery. Depending on the site of administration, one can differentiate among intravenous, intramuscular, subcutaneous, intradermal, and intraperitoneal administration. Mostly semisolid dosage forms including creams, ointments, and gels are applied onto the skin to enter into the body. However, the liquid dosage forms, such as emulsions, or solid dosage forms, such as transdermal patches, can also be used. Dosage forms can be classified into immediate release (IR) and modified release (MR). IR dosage forms allow the drug to dissolve in the gastrointestinal contents, without delaying or prolonging the dissolution or absorption of the drug. In MR dosage forms, the time course and/or location of drug release is chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. MR dosage forms include both delayed and extended release drug products.

Delayed release dosage forms release the active ingredient at a time other than immediately after administration, for example, enteric-coated dosage forms or colon-specific dosage forms. These systems delay the release of drug until the dosage form reaches the small intestine. In this way, they can protect the drug from degradation in the low-pH environment of the stomach or protect the stomach from irritation by the drug. The dosage form is coated with polymer that dissolves and releases the drug at higher pH during its travel from low-pH environment of the stomach to the high-pH environment of the small intestine. Once this occurs, the release is again immediate, and the resulting plasma concentration versus time curve is similar to the one for IR dosage forms. Extended release products (sustained release (SR) and controlled release systems) are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to the drug presented as a conventional dosage form. IR dosage forms are designed to achieve quicker onset of drug action than that achieved by delayed or extended release dosage forms, which are often desirable to increase the stability, safety, and efficacy of the drug, to improve the therapeutic outcome of the drug treatment, and/or to increase patient compliance and convenience of administration.

The extended release DDS can be of either sustained release (SR) or controlled release (CR) dosage forms. The polymer-based matrix or reservoir sustained release systems maintain the rate of drug release over a longer period and reduce the frequency of dosing. Conversely, CR DDSs are designed to predict constant plasma drug concentrations regardless of the biological environment of the application site. Therefore, CR systems actually control the drug concentration in the body, whereas SR systems just regulate the release of the drug from the dosage form [3, 4]. Further, SR systems are basically restricted to oral formulations, while CR systems can be administered through various routes, including transdermal, oral, and vaginal administration.

Ideally, the release rate from the dosage form should be the rate-determining step for drug absorption and in fact for the drug concentration in the plasma and target site. The resulting plasma concentration versus time curves become increasingly flatter from IR to extended release dosage forms, indicating the prolonged maintenance of drug in the therapeutic range after a single administration of the dosage form. Controlled DDSs have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms [5]. Controlled drug release and subsequent biodegradation are important for developing successful formulations. The release mechanisms involve desorption of surface-bound/ adsorbed drugs; diffusion through the carrier matrix or polymer membrane surrounding drug core; matrix erosion; combination of erosion/diffusion process; and responsiveness to stimuli such as light, changes in pH, or temperature.

The formulation scientist must optimize the bioavailability of the drug. To achieve this goal, the delivery systems should allow the drug to reach the systemic circulation, more importantly to the target site in the body to avoid side effects by preventing the exposure of drug to the nontarget sites. In addition, the drug must be physically and chemically compatible with the formulation excipients in the dosage forms and stable microbiologically. The delivery systems should be designed in such a way that it can improve the patient compliance. One can design an oral dosage form instead of parenteral formulations for the drug, which can

allow self-administration of the dosage forms. Moreover, the pharmaceutical quality of the delivery systems must be ensured in accordance with the regulatory specifications to facilitate reproducible drug release from the system and minimize the influence of the body such as food effects on drug release. It is also necessary to investigate the feasibility of the developed DDS to be scaled up from the laboratory to the production scale.

However, controlled release systems do not exclusively deliver the drug to the target organ. For this reason, the target-specific drug delivery systems must be designed in order to control biodistribution of the drug. Consequently, various novel concepts have been emerged to meet the specific needs of an ideal drug delivery system. This chapter introduces a brief description of targeted drug delivery mechanism along with some of the novel-targeted drug delivery options.

2. Targeted drug delivery

Very few drugs bind selectively to the desired therapeutic target, and hence, some targeting approaches are required to destine the drug in desired tissue or organ to reduce efficacy and dose-related toxicity. The concept of targeted drugs is not new, but dates back to 1960 when Paul Ehrlich first postulated the concept of "magic bullet," and this continues to be a challenge to implement in the clinic. The challenges include the selection of proper target for a particular disease, drug for effective treatment and stable, biodegradable drug carriers while avoiding the immunogenic and nonspecific interactions that efficiently clear foreign material from the body. Moreover, the preparation of the delivery system should be easy or reasonably simple, reproductive, and cost-effective. Nanoparticles (NPs) are potentially useful as carriers of active drugs and, when coupled with targeting ligands, may fulfill many attributes of a "magic bullet." Furthermore, the NPs offer several potential advantages including increased efficacy and therapeutic index, improved pharmacokinetic effect, reproducible sizes with opportunity for surface functionalization, ability to entrap both hydrophilic and lipophilic drug, increasing stability of drug from enzymatic degradation, thereby delivering entrapped drug intact to various tissue and cells for site-specific and targeted delivery and thus decreasing drug toxicity. The size and other characteristics can be manipulated depending on the drug and intended use of the product [6]. The drug targeting strategies must meet two basic requirements to achieve effective drug delivery. The drugs should reach the desired sites after administration, with minimal loss of the dose and activity in blood circulation. Second, the drugs should act only on target cells without harmful effects to healthy tissue [7]. Two strategies have been adopted for drug targeting: *passive targeting* and *active targeting*.

2.1. Passive targeting

Passive targeting exploits natural conditions of the target organ or tissue to direct the drug to the target site. For example, passive targeting takes advantage of the unique pathophysiological characteristics of tumor vessels, that is, leaky vasculature with 100–800 nm pores enabling nanodrugs to accumulate in tumor tissues. Typically, tumor vessels are highly disorganized

and dilated with a high number of pores, resulting in enlarged gap junctions between endothelial cells and compromised lymphatic drainage. The leaky vascularization, coupled with poor lymphatic drainage, serves to enhance the permeation and retention of NPs within the tumor region. This is often called enhanced permeability and retention (EPR) effect [8]. The drug-loaded NPs are preferentially accumulated in tumor tissue than normal cells, solely due to their small particle size rather than binding. The NPs cannot readily cross the blood capillaries of normal tissues because they are held up with tight junctions. Therefore, passive targeting approach can assist in depositing a higher amount of drug in solid tumors than that of free drug.

In addition to the EPR effect, the passive targeting is supported by microenvironment surrounding tumor tissue that is different from that of healthy cells. The fast-growing tumor cells require more oxygen and nutrients to maintain high metabolic rate. Consequently, glycolysis is stimulated to acquire more energy and creates an acidic environment [9]. This advantage can be exploited to target chemotherapeutic agents to the tumor cells. The pH-sensitive NPs have been prepared that remain stable at physiological pH 7.4 but degrade at the acidic pH of the tumor and liberate the drug molecules. In case of cancer treatment, the size and surface properties of drug delivery NPs must be controlled specifically to avoid uptake by the reticuloendothelial system (RES) to maximize circulation times and targeting ability [10].

2.2. Active targeting

One way to overcome the limitations of passive targeting is to attach ligands such as antibodies, peptides, vitamins, aptamers, or small molecules by a variety of conjugation chemistries to the surface of the nanocarriers that only bind to specific receptors on the cell surface [11]. For high specificity, however, the receptors need to be highly expressed on tumor cells rather than on normal cells. The targeting conjugates are internalized by receptor-mediated endocytosis mechanism. The targeting ligands bind with the receptors first, followed by endosome formation with the enclosure of the ligand-receptor complex by plasma membrane. The endosome is then transferred to specific organelles, and drugs are released by acidic pH or enzymes.

3. Novel delivery modalities

To prevent chemical degradation, harmful side effects, and improve drug bioavailability and accumulation in the desired site, various drug delivery and drug targeting systems are currently under development. The delivery carriers can be made slowly degradable, stimuli-responsive (e.g., pH, ionic strength, temperature, ultrasound, light, electricity, enzymes), and even targeted (e.g., by conjugating them with specific ligands). Over last two decades, nanotechnology has shown potential benefits in improving drug delivery and targeting properties and therefore opens up new markets for pharmaceutical and drug delivery companies. The drug delivery systems are also designed to overcome some physical barriers, such as the blood-brain barrier (BBB) for better location and effectiveness of the drug at the target site. Due to their small size, the NPs can pass through certain biological barriers.

Polymeric NPs are colloidal particles with a size range of 10–1000 nm, which are fabricated using biodegradable synthetic polymers, such as poly (lactide-*co*-glycolide), polyacrylates, and polycaprolactones; nonbiodegradable synthetic polymers, such as poly (methyl methacrylate), polyacrylamide, poly (vinyl alcohol), and poly (ethylene glycol); or natural polymers, such as albumin, gelatin, alginate, gellan gum, and chitosan [12]. Sometimes, blends or graft copolymers of natural and synthetic polymers are also used. In recent years, biodegradable polymeric NPs have attracted considerable attention in the fabrication of potential drug delivery devices due to easy removal of degraded fragments from the body via normal metabolic pathways.

Various methods, such as solvent evaporation, spontaneous emulsification, solvent diffusion, salting out/emulsification-diffusion, and polymerization, have been used to prepare the NPs [13]. Depending upon the method of preparation of NPs, the drug is confined to a cavity surrounded by a polymer membrane (nanocapsules) or dispersed physically and uniformly in the polymer matrix (nanospheres). The drug is loaded via hydrophobic interactions between drugs and nanocarriers. The drug can also be conjugated to polymeric carriers via covalent chemistry.

An important feature of targeted particle delivery system is the ability to simultaneously carry a high amount of drug while displaying ligands on the surface of particles. The overall binding strength of NPs to target is a function of both the affinity of the ligand-target interaction and the number of targeting ligands present on the particle surface [14].

The drug-loaded particles are internalized into cells in determining their biological activity. The particles of as large as 500 nm size can be internalized by nonphagocytic cells via energy-dependent process. The particles with <200 nm diameter are internalized via clathrin-coated pits, but larger ones are taken up by cells via caveolae membrane invaginations [15]. However, the internalization of particles can be mediated independent of both clathrin and caveolae pathways. To facilitate efficient internalization, NPs have been targeted against internalizing receptors, and an increased therapeutic activity has been observed in some tumor models [16, 17].

Targeting ligands include any molecule that recognizes and binds to target antigen or receptors overexpressed or selectively expressed by particular cells or tissue components. The antibodies or their fragments, peptides, glycoproteins, vitamins, or carbohydrates are the common class of ligands. The NPs are made long circulating by making their surface hydrophilic after coupling or coating poly(ethylene glycol) (PEG). Functionality could also be introduced by incorporating PEG with functional end groups for coupling to target ligands.

There has been a considerable progress in the field of gene delivery using polymeric NPs. For gene delivery, the plasmid DNA is introduced into the target cells, and the genetic information is ultimately translated into the corresponding protein [18]. To achieve this, an efficient vector that possesses high transfection efficiency, biodegradability, targeting ability, DNA protecting ability, stimuli sensitivity, and low cytotoxicity for delivering a target gene to specific tissues or cells must be selected to cure both the genetic and acquired diseases of human [19]. Despite more gene transfection efficiency, viral vectors may pose a significant risk to patients, while nonviral carriers are inherently safer than viral carriers [20]. Furthermore,

the nonviral carriers are expected to be less immunogenic with a possible versatile surface modification [21]. The nonviral vectors are usually made of lipids or polymers with/without using other inorganic materials. The NPs can protect genes against nuclease degradation and improve their stability [22]. Furthermore, they can be used for targeted delivery purpose. Because the biopolymers are non-toxic, biodegradable, and biocompatible, the biopolymer-based non-viral vectors are also being tested for safe and efficient gene delivery.

The liposomes are the most clinically established nanosystems for drug delivery. They are self-assembled spherical vesicles of bilayer structures of phospholipids and cholesterol surrounding an aqueous core, and their size can be controlled as small as 50–100 nm. The vesicles are biocompatible and biodegradable and confer the ability to entrap both hydrophilic and hydrophobic drugs. The variation in composition of lipid membrane and surface chemistry, the liposome properties, such as size, surface charge, and functionality can be easily manipulated. The incorporation of polyethylene glycol (PEG) prevents interactions with plasma proteins, retards recognition by the RES [23], and thus enhances the liposome circulation lifetime, that is, stealth liposomes. Liposomes can also be conjugated with active-targeting ligands, such as antibodies or folate for target-specific drug delivery. Their efficacy has been demonstrated in reducing systemic effects and toxicity, as well as in attenuating drug clearance [24]. Despite potential advantages, the liposomes as targeted drug delivery carriers are associated with some major drawbacks like poor control over drug release rate, leakage of drug into the blood, low encapsulation efficiency, industrial scale-up, and poor storage stability [25, 26].

Recently, extensive work and experiments with solid lipids resulted in the invention of lipid-based solid particles in the submicron range (10–1000 nm). These NPs are made up of bio-compatible and biodegradable lipids with potential application in drug delivery. They possess a solid lipid core matrix that can solubilize lipophilic molecules for enhancing bioavailability. The physiologically similar lipid core of triglycerides or fatty acids or waxes is stabilized by surfactants (emulsifiers). All classes of emulsifiers (with respect to charge and molecular weight) can be used to stabilize the lipid dispersion. It has been found that an emulsifier combination may prevent particle agglomeration more efficiently [27]. The lipid NPs combine the advantages of lipid emulsion and polymeric NPs while overcoming the temporal and *in vivo* stability issues that trouble the conventional and nanoscale delivery approaches [28]. A variety of materials can be used to engineer solid NPs for targeting tissues by either passive or active targeting.

Lipid-polymer hybrid NPs are core-shell structures comprising polymer cores and lipid shells, which exhibit complementary characteristics of both polymeric NPs and liposomes, particularly in terms of their physical stability, biocompatibility, and *in vivo* cellular delivery efficacy [29]. In core-shell-type lipid-polymer hybrid NPs, a biodegradable polymeric core is surrounded by a shell composed of phospholipid layers. The hybrid architecture can provide advantages such as controllable particle size, surface functionality, high loading of multiple drugs, tunable drug release profile, and good serum stability [30].

Several drugs do not have adequate physiochemical characteristics such as high lipid solubility, low molecular size, and positive charge, to traverse blood-brain barrier and deliver drug into the brain [31]. Therefore, the delivery of drugs to central nervous system (CNS) is a challenge

for treating neurological disorders. The drugs may be administered directly into the CNS or administered systematically for targeted action in the CNS. The osmotic and chemical opening of the blood-brain barrier as well as the transport/carrier systems constitutes some of the widely reported strategies to promote the permeation of blood-brain barrier (BBB) and delivery of drugs in brain. In conjunction with the net delivery of drug, the access to the intended target site within the CNS is also important. To serve this purpose, the drugs may be conjugated with various nanostructures such as liposomes and NPs and a suitable route of administration can be sought. It has been postulated that nanoscale drug carriers possess a great potential for improving the delivery of drugs through nasal routes to deliver drugs to the brain. Among other mucosal sites, nasal delivery is especially attractive for brain-targeted drug delivery, as the nasal epithelium is characterized by its relatively high permeability, vuscularized mucosa, and low enzymatic activity. If a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached and drug transport into the brain and/or cerebrospinal fluid (CSF) via the olfactory receptor neurons may occur [32].

Transdermal systems in the form of patches deliver the drugs across the skin barrier for systemic effects at a predetermined and controlled rate. Due to concentration gradient between the transdermal patch and blood, the drug will continue diffusing into the blood for prolonged period of time and maintain constant drug concentration in the blood flow. Transdermal drug delivery avoids problems such as gastrointestinal irritation, metabolism, pH-dependent variation in delivery rate, and interference with gastric emptying due to presence of food. However, slow penetration rates, lack of dosage flexibility and/or precision, and a restriction to relatively low dosage drugs are the major limitations. The stratum corneum of the skin forms a formidable barrier against uptake, and thus transdermal delivery is difficult to achieve. The substances having molecular weight greater than 500 Da [33] and hydrophilic characteristics encounter the difficulty in absorption through skin. Penetration enhancers often have to be added to the delivery system to improve delivery into or through the skin. Recently, it has been demonstrated that atmospheric-pressure argon microplasma irradiation (AAMI) can improve skin permeability of drugs without the need of injection needles and skin damages [34]. AAMI can be a promising alternative to promote drug delivery through the skin and simultaneously minimize the pain from other manipulations related to skin penetration enhancement. However, the feasibility of atmospheric microplasma irradiation is still under investigation for enhancing percutaneous absorption of drugs.

The delivery of drug to a specific target in the body is comparable to the magic bullet principle applied in nuclear medicine. Nuclear medicine may advance drug development by visualizing biodistribution and site of action [35]. The biodistribution and release kinetics of drug from the novel formulations can be quantified by radiolabeling with γ-emitting radionuclide. Many nuclear medicine departments have participated in the assessment of drug performance and toxicity in contributing data to clinical trials. The application of nuclear medicine techniques to the evaluation of pharmaceutical formulations has been an interesting area of work. Scintigraphy can be used to determine the position of drug release and assess site-specific absorption of orally administered drugs, for example, the evaluation of controlled release formulation designed to release the drug specifically in colon [36]. Hence, the importance of nuclear medicine in drug delivery application has been described in detail in this book.

4. Future considerations

The new delivery methods could enhance the performance of drugs by increasing effectiveness, safety, and patient compliance and ultimately reduce healthcare costs. Nanotechnology could be strategically implemented in developing new drug delivery systems that can expand drug markets. Nanomaterials are poised to take advantage of existing cellular machinery to facilitate the delivery of drugs. However, clinical development of drugs is halted because of poor biopharmaceutical and undesirable pharmacokinetic properties. Novel delivery technologies are being tested for overcoming the barriers toward safe delivery of drugs. An in-depth understanding of novel strategies constitutes the primary focus and subsequent demonstration of easy scale-up of the formulations with favorable pharmacokinetics and toxicity profiles could augment the translation of research findings into practical therapeutics. A collaborative effort among scientists in various disciplines, including medicine, materials science, engineering, physics, and biotechnology could potentiate the translation of novel laboratory innovation into commercially viable medical products.

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