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# 2.5.12

# Drug Delivery Systems

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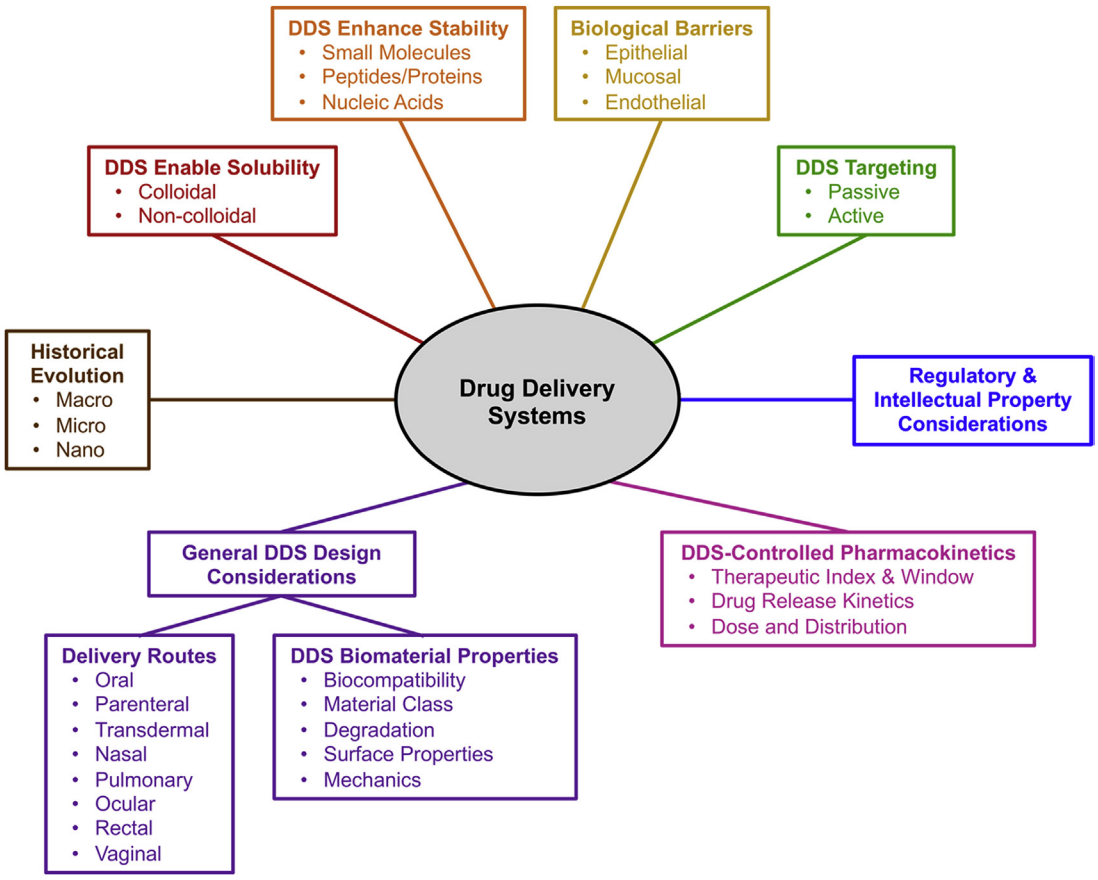
Biomaterials are outstanding platforms to ensure controlled, reproducible drug delivery. Furthermore, biomaterials play a critical role in enhancing or enabling drug efficacy for both traditional small molecule drugs and new classes of drugs, such as nucleic acids and proteins, that suffer from delivery challenges associated with instability and poor tissue localization. This chapter overviews drug delivery challenges as well as subsequent design and use of biomaterial drug delivery systems (DDSs) to overcome these hurdles. Fig. 2.5.12.1 summarizes the key aspects of DDS development from basic research to clinical applications that are discussed in this chapter. Although highly sophisticated, targeted, bioresponsive DDSs have only recently started delivering on ambitious promises, the concepts and approaches being developed are rooted in longstanding historical motivations. Therefore a brief overview of DDS history from its origins to today is first presented to provide a framework for understanding current biomaterial DDS design. For additional information on drug formulation and DDSs, please see these excellent in-depth reviews (Bader et al., 2014; Galaev and Mattiasson, 2010; Hilery et al., 2001; Hillery et al., 2002; Holowka and Bhatia, 2016; Mahato and Narang, 2018; Saltzman, 2001; Sinko, 2017).

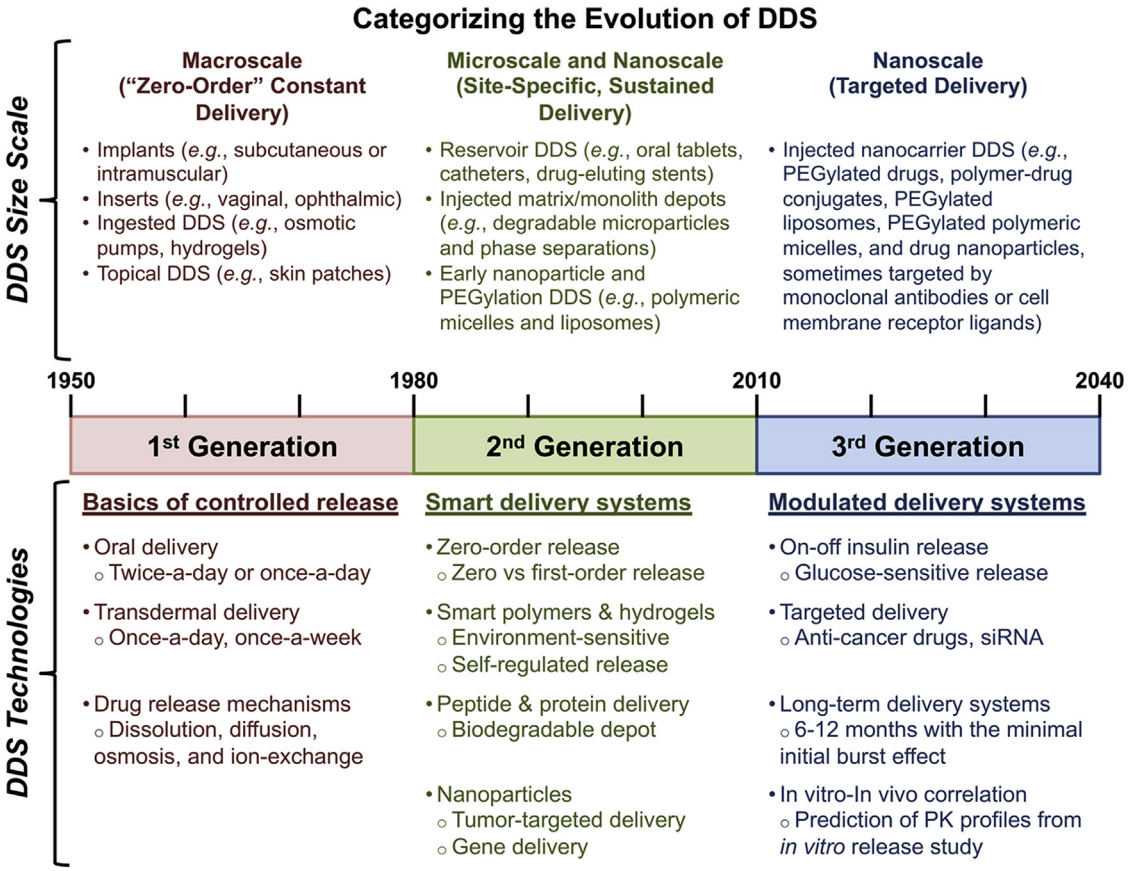
## History of DDS Development

Routine, periodic drug administration to achieve therapeutic efficacy has been used for more than 150 years. In the 1850s, John Snow documented how periodic chloroform inhalation maintained anesthetizing effects throughout surgical procedures (Snow, 1858). In the early 1920s, Frederick Banting, Charles Best, and John Macleod identified that well-controlled, routine administration of insulin was necessary to treat diabetes (Herring, 1924; Banting and Best, 1922). These findings led to an early understanding of the typical "peak and trough" pharmacokinetics (PK) curve of drugs (see the section "DDSs to Improve Drug Pharmacokinetics"), which preceded the great advances in DDS development during the 20th century.

Pharmaceutical formulations capable of prolonging drug activity and reducing dosing frequency entered the market in the early 1950s (Fig. 2.5.12.2). In 1952, Smith Kline & French introduced the first commercial controlled-release formulation product, known as Dexedrine Spansules (Park, 2014). This product consisted of macrospheres coated with a "wax-fat" layer (e.g., a mixture of glyceryl monostearate and bees wax), a formulation now commonly known as a reservoir, of varying thickness to control capsule dissolution and drug release (Blythe, 1956). However, the PK of such products varied greatly from patient to patient. In 1956, Riker Laboratories, Inc. introduced the first Food and Drug Administration (FDA)-approved pulmonary DDS, the pressurized metered dose inhaler, and dramatically advanced the therapeutic aerosol industry (Stein and Thiel, 2017; Anselmo and Mitragotri, 2014). These events marked the beginning of what has been defined as the first




• **Figure 2.5.12.1** Overview drug delivery system (DDS) development. (Adapted from Park, K., 2014. Controlled drug delivery systems: past forward and future back. J. Control. Release 190, 3–8.)




• **Figure 2.5.12.2** Evolution of drug delivery systems (DDS) since 1950. (Adapted from Park, K., 2014. Controlled drug delivery systems: past forward and future back. J. Control. Release 190, 3–8; Yun, Y.H., Lee, B.K., Park, K., 2015. Controlled drug delivery: historical perspective for the next generation. J. Control. Release 219, 2–7). *PK*, Pharmacokinetics.

**TABLE 2.5.12.1 Early Macroscopic Drug Delivery Systems Developed by Alza Corp**

| Product | Material | Purpose | Drug | Year Approved |
|---|---|---|---|---|
| Ocusert | Poly(ethylene-*co*-vinyl acetate) | Antiglaucoma ophthalmic insert | Pilocarpine | 1974 |
| Progestesert | Poly(ethylene-*co*-vinyl acetate) | Contraceptive intrauterine device | Progesterone | 1976 |
| Transderm Scop | Polypropylene | Antimotion sickness skin patch | Scopolamine | 1979 |

generation of drug delivery (i.e., 1950–80) (Fig. 2.5.12.2) (Park, 2014).

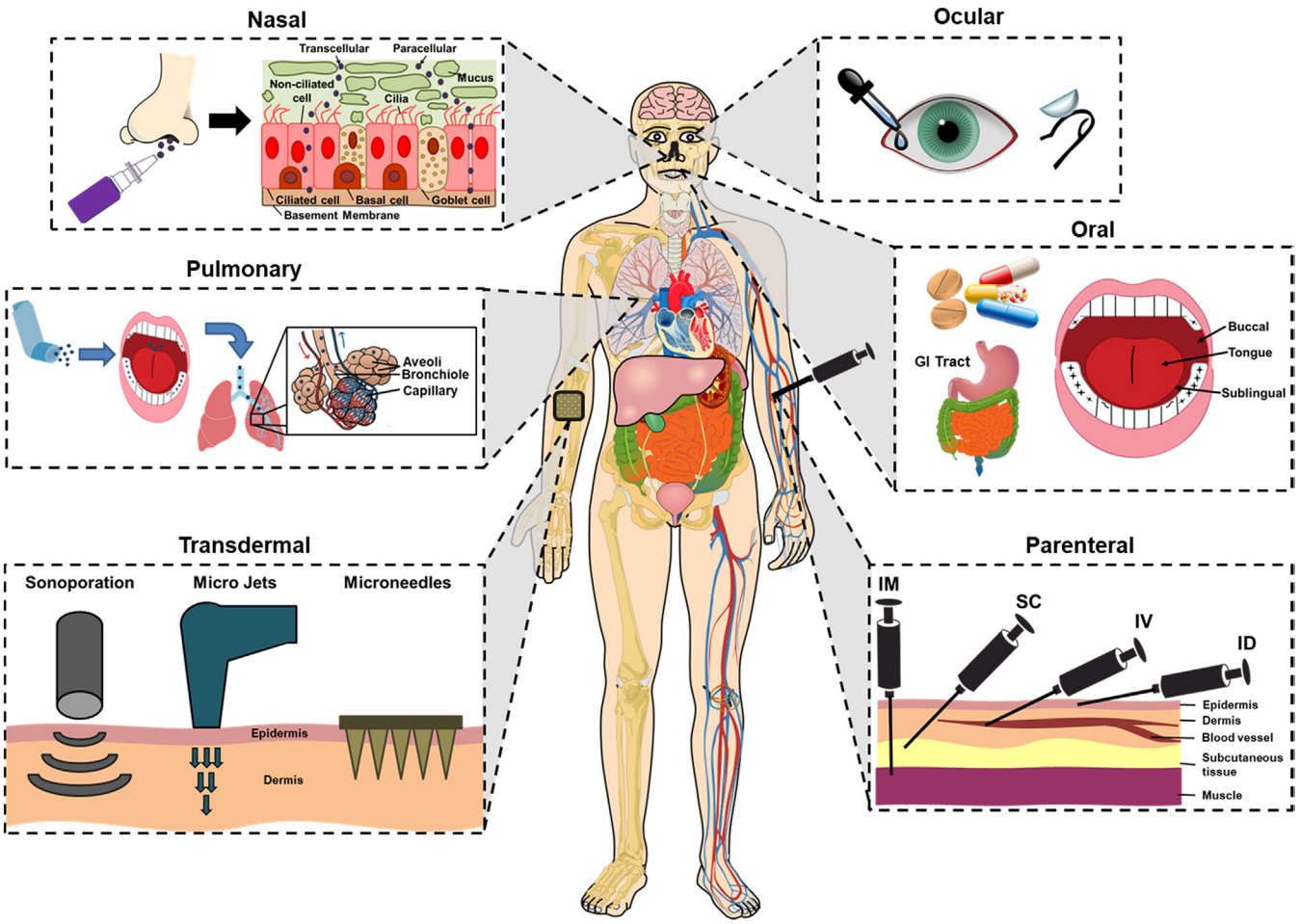
In the mid-1960s, Alejandro Zaffaroni, inspired by his biochemistry and endocrinology training, envisioned DDSs that would release drugs with reproducible and predictable kinetics, independent of the patient (Hoffman, 2008; Urquhart, 2000; Zaffaroni, 1991). Simultaneously, Judah Folkman showed that a capsule made of silicone rubber (later termed "Silastic") filled with drug, e.g., a reservoir, enabled sustained release (Folkman and Long, 1964). This concept led to the first zero-order reservoir DDS (Hoffman, 2008). Zaffaroni founded the first company dedicated to the concept of controlled drug delivery in 1968, Alza Corp., and Folkman was enlisted to head the Scientific Advisory Board (Hoffman, 2008). In 1971, Alza Corp. defined the key components of a DDS as "a drug delivery module comprising the drug, rate controller, and energy source" that were housed in a "platform" (Zaffaroni, 1991). The first controlled DDS products based on this definition were macroscopic designs with reservoirs of constant drug concentration enclosed in rate-controlling membranes made of polymers, such as Silastic or poly(ethylene-*co*-vinyl acetate) (Table 2.5.12.1). These first-generation DDSs employed different release mechanisms, including dissolution-, diffusion-, osmosis-, and ion exchange-based mechanisms, to produce devices that exhibited zero-order release rates to maintain constant drug plasma concentrations (Park, 2014). As such, this period established the basic understanding of DDSs and is characterized by the macroscopic size scale of DDSs developed (Fig. 2.5.12.2) (Park, 2014; Hoffman, 2008).

The second generation of drug delivery (1980–2010) included both micro- (~1980s) and nano- (~1990–2000s) sized DDS as well as "smart" DDS technologies (Fig. 2.5.12.2) (Park, 2014; Hoffman, 2008). The new technologies included depot DDSs using polymer microparticles, hydrogels, or phase-separated formulations (Park, 2014; Binauld and Stenzel, 2013). Many of these DDSs, such as the first FDA-approved matrix/monolithic depot DDS, Zoladex and Lupron introduced in 1989 (Park, 2014; Anselmo and Mitragotri, 2014; Zhang et al., 2013), were based on polyesters, such as poly(lactic acid) and poly(lactic-*co*-glycolic acid) (PLGA) that had been used previously in degradable sutures (Hoffman, 2008; Ulery et al., 2011). These degradable DDSs exhibited first-order release kinetics and were micron-sized particles. Furthermore, "smart" or environmentally triggered chemistries were developed to enable drug delivery in response to an external stimulus, such as pH or temperature (Park, 2014; Binauld and Stenzel, 2013).

During the late 1980s and 1990s, interest and activity rapidly grew in the development of injectable nanocarriers, which are discussed in the section "DDSs to Enhance Stability." This interest stemmed largely from two advances. First, the concept of poly(ethylene glycol) (PEG) conjugation to proteins to increase drug circulation times and decrease immunogenicity was spearheaded by Enzon Pharmaceuticals, Inc. in 1981 (Hoffman, 2016). Second, the discovery of the enhanced permeability and retention (EPR) effect in 1984 (Matsumura and Maeda, 1986; Maeda et al., 1985) provided strong rationale and motivation for the development of nanocarriers that passively target solid tumors, leading to the development of Doxil, a PEGylated lipososmal doxorubicin approved in 1995 (Hoffman, 2008; Barenholz, 2012). Both PEGylation and the EPR effect contributed to the idea of passive targeting discussed further in the section "DDS Targeting." Altogether, these advances aided in the development of site-specific and smart DDSs during the second generation of drug delivery (Fig. 2.5.12.2).

The third generation of drug delivery (i.e., 2010–present) (Fig. 2.5.12.2) has sought to modulate DDSs and understand how they behave in vivo to streamline development for licensure. Active targeting has also become a major focus in the field during this period and is discussed in more detail in the section "DDS Targeting." Global nanoscale DDS research and development has increased steadily since the United States pioneered the use of national funds for such efforts with the announcement of the National Nanotechnology Initiative in 2000 and the passage of the 21st Century Nanotechnology Research and Development Act in 2003 (Bobo et al., 2016; Jia, 2005). For example, the number of FDA investigational new drug approvals for nanoscale DDS products has increased since 2003 despite increasingly stringent FDA regulations and escalating costs for new drug formulation licenses to more than US$2.6 billion per drug (DiMasi et al., 2016). However, translation of actively targeted DDSs into the clinic has been slow and no targeted DDS has been approved to date.

Although many of the early DDS developments were focused on small molecule delivery, another recent focus has been on DDSs for macromolecular drug candidates, including peptides, proteins, and nucleic acids (e.g., DNA and siRNA). Onpattro (e.g., patisiran), which was developed by Alnylam Pharmaceuticals, Inc. as a lipid nanoparticle DDS,




• **Figure 2.5.12.3** Summary of typical drug delivery routes. Additional drug delivery routes include topical, rectal, vaginal, and intrathecal (not shown). *GI*, Gastrointestinal tract; *ID*, intradermal; *IM*, intramuscular; *IV*, intravenous; *SC*, subcutaneous.

became the first FDA-approved RNAi drug in 2018 (Mullard, 2018). Ultimately, the third generation will be defined by the success of these innovative modulated and targeted DDSs in clinical applications (Abdelwahed et al., 2006).

The remainder of this chapter focuses on the biomaterials used in DDSs as well as the design challenges and approaches to overcome these hurdles, including pertinent examples in use and under development. For a more detailed overview of the interesting history of the DDS field from its origins until today, the reader is referred to several review articles (Park, 2014; Hoffman, 2008; Urquhart, 2000; Zaffaroni, 1991; Zhang et al., 2013; Bobo et al., 2016).

## General Considerations in DDS Design

### Routes of Drug Delivery

Common routes of drug delivery for conventional drugs are oral, parenteral, transdermal, nasal, ocular, pulmonary, rectal, vaginal, and intrathecal (Fig. 2.5.12.3). Oral administration has excellent patient compliance and ~90% of current conventional drugs are administered via this route. In fact, tens of billions of pills are annually consumed worldwide for aspirin alone (Anselmo and Mitragotri, 2014). However, oral delivery suffers from challenges associated with the harsh environments of the oral cavity, stomach, and intestines, as well as poor transport across the epithelial mucosal layer of the intestine, which is discussed further in this chapter (see the section "DDS Design to Overcome Biological Barriers"). Moreover, after systemic adsorption, orally delivered drugs are subject to first-pass metabolism by intestinal and liver enzymes, which results in drug degradation upon initial administration, thereby reducing unaltered drug concentration in the blood. Parenteral administration, accounting for more than 10 billion annual drug administrations worldwide (Kermode, 2004), includes intravenous, subcutaneous, and intramuscular injections. The parenteral route ensures that effective drug concentrations are rapidly achieved but suffers from poor patient compliance due to injection site pain (Spain et al., 2016; Rubin et al., 2009; Zambanini et al., 1999; Deacon and Abramowitz, 2006). Transdermal delivery has excellent patient compliance but has traditionally been limited to drugs that are small and lipophilic. Nasal, pulmonary, and vaginal routes are also of interest due to high epithelial surface area, leading to rapid drug efficacy; however, due to challenges associated with delivery across the epithelial mucosa,

these routes are also limited to small, lipophilic compounds. DDS designs seek to enhance drug efficacy and/or enable new routes of administration that avoid adverse side effects, address low patient compliance, or overcome biological barriers as discussed in the section "DDS to Overcome Biological Barriers."

## DDS Biomaterials Design Considerations

As highlighted previously in Chapter 1.1.1, a biomaterial is "a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ or function in the body," with a focus on "treat" for DDSs. All biomaterials, including DDSs, must be biocompatible, that is, perform as designed without adverse effects. Thus DDSs should deliver drugs at the intended concentration, with appropriate kinetics, and to the target tissue. Behavior deviating from this expectation could result in adverse events or even death. Therefore understanding how biomaterials interact with the body is critical for DDS design. DDS biomaterials have the potential to interact with target and off-target tissues, adsorb proteins, and potentiate immune reactions. Biocompatibility is highly dependent upon DDS route of delivery; systemic introduction has significantly different expected interactions than transdermal, oral, or even depot-based delivery systems. Although many biomaterial properties are already highlighted in this textbook (see Section 1.2), this section will focus on the important aspects of biomaterials design with respect to DDS development.

## Biomaterials Used in DDSs

Of the three main classes of biomaterials (metals, ceramics, and polymers), polymers are the most common platform for DDSs. Polymers have many advantages over other classes. Polymers can be fabricated into complex shapes and structures with a wide range of bulk compositions and physical properties. Furthermore, polymers have tunable chemistries, including controllable, responsive properties (e.g., stimuli responsive), yet allow for robust and flexible conjugation or incorporation of various drug classes. Synthetic rather than natural materials are often utilized as they are amenable to formation by controlled processes, which lead to highly reproducible structure–function relationships. The reader is encouraged to review Chapter 1.3.2 for details about synthesis and characterization of polymeric biomaterials (Cabral et al., 2018).

## DDS Biomaterial Properties

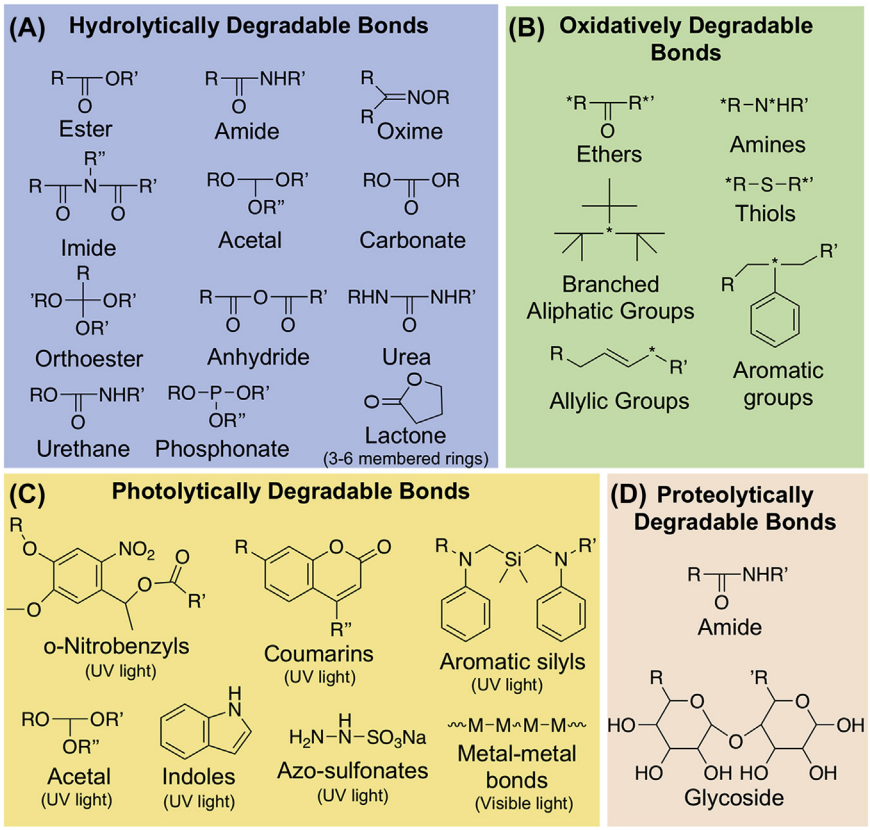
### *Degradation*

DDSs can be designed from both nondegradable and degradable materials to align with the intended application. For implanted DDSs, degradable materials can be used to control drug release, which is discussed in greater detail within the section "DDSs to Improve Drug Pharmacokinetics," and avoid secondary retrieval surgeries and outcomes associated with long-term biomaterial persistence. As discussed in Chapter 1.3.2, degradation can be controlled or uncontrolled (unintended) but falls into one of four classes: hydrolysis, oxidation, photolysis, and proteolysis. Briefly, hydrolytic degradation requires electrophiles susceptible to nucleophilic attack by the hydroxyl oxygen of water. Hydrolytically degradable groups include esters, amides, oximes, urethanes, urea, carbonate, acetal, phosphonate, anhydride, lactones, and imides (Fig. 2.5.12.4A). Oxidation is an inherently uncontrolled degradation mechanism that occurs when free radicals, resulting from inflammatory reactions, abstract hydrogens from branched aliphatic hydrocarbons, phenols, or other aromatic groups, thiols, amines, ethers, and carbon–carbon double bonds, causing polymer chain scission (Fig. 2.5.12.4B). Although photolysis or photodegradation is common for drugs, only recently has it been exploited to controllably degrade/alter biomaterials (Pasparakis et al., 2012; Watanabe and Ohtsuki, 2016). Light-sensitive functional groups include nitrobenzyl derivatives, coumarins, azo sulfonates, metal–metal bonds, indoles, vinyl ketones, and aromatic silyl derivatives (Pasparakis et al., 2012; Watanabe and Ohtsuki, 2016). Chemical structures and requisite wavelength ranges mediating photoreaction of these chemical moieties are shown in Fig. 2.5.12.4C. Finally, proteolysis of natural materials, including carbohydrate, glycoprotein, protein, and proteoglycans, occurs when enzymes attack amides and glycosidic linkages (Fig. 2.5.12.4D).

DDS degradation depends on the relative rates of degradation and diffusion by the reactant (e.g., water, radicals, photons, or enzymes). This rate is a function of biomaterial hydrophilicity, crystallinity, surface area to volume, and pore size, as discussed in Chapter 1.3.2. For example, the highly crystalline anhydride-based polymers that comprise the biodegradable polymer Gliadel undergo surface degradation, while less crystalline PLGA-based polymers typically bulk degrade (Shoichet, 2009). Both nondegradable and degradable materials may succumb to biological responses, such as inflammation, that can cause either unexpected or expedited degradation. If the biological environment deviates significantly due to atypical inflammatory responses (e.g., excessively acidic pH or increased reactive oxygen/nitrogen species generation), degradation, and therefore drug release rates, may be increased (Helle et al., 2002; Heller, 1990; Heller et al., 2000, 2002).

### *Surface Properties*

As with any biomaterial, surface properties are a key design parameter for DDSs. Surface properties are particularly important for systemically delivered DDSs and implantable systems since surface interactions will control cell–material behaviors that affect drug delivery. Surface properties, such as hydrophilicity, roughness/curvature, and surface chemistry, lead to different levels of protein adsorption (as discussed in Chapter 1.2.4). If a permanent implant or depot is used, the repertoire of cells at the implant site can interact directly with the biomaterial or adsorbed proteins, leading to acute and possibly chronic inflammation or a foreign body reaction (FBR) (see Chapter 2.2.2). These reactions may



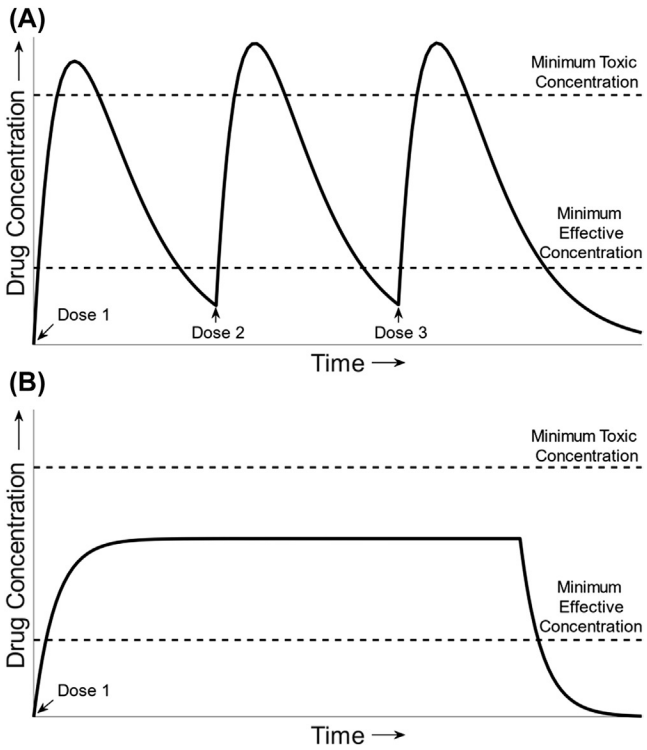

• **Figure 2.5.12.4** (A) Hydrolytically, (B) oxidatively, (C) photolytically, and (D) proteolytically degradable groups found within biomaterials and drugs that are susceptible to controlled or uncontrolled degradation. *Indicates group susceptible to radical attack during oxidation, R, R′, R″ are generic hydrocarbon groups (Mahato and Narang, 2018; Pasparakis et al., 2012; Temenoff and Mikos, 2009). *UV*, Ultraviolet.

compromise controlled drug release. For example, inflammatory responses include reactive oxygen and nitrogen species and enzyme production. These reactants can expedite material degradation or cause uncontrolled degradation, which will lead to dramatic changes in drug release kinetics. Note, uncontrolled degradation of polymers is discussed in depth within Chapter 1.3.2. The FBR is characterized by collagenous capsule formation around foreign materials that is a diffusional hindrance to drug release. This effect can be seen even with inert, unreactive biomaterials commonly used in DDSs, such as poly(tetrafluoroethylene) (Teflon), poly(urethanes), and poly(dimethylsiloxanes) (PDMSs), where capsules of ~100 μm thick have been described (Ratner, 2002). Fibrous encapsulation due to FBR has been credited for inadequate control over steroid release from Norplant, an implantable device formed from PDMS-based Silastic (Ratner, 2002). Furthermore, FBR-related inconsistencies with drug delivery may also underpin the predominance of implantable depot applications within immune privileged tissues, such as the eye, brain, and prostate (e.g., eye: Ocusert, Vitrasert, Restisert, Ozurdex; brain: Gliadel; prostate: Vantas, Viadur).

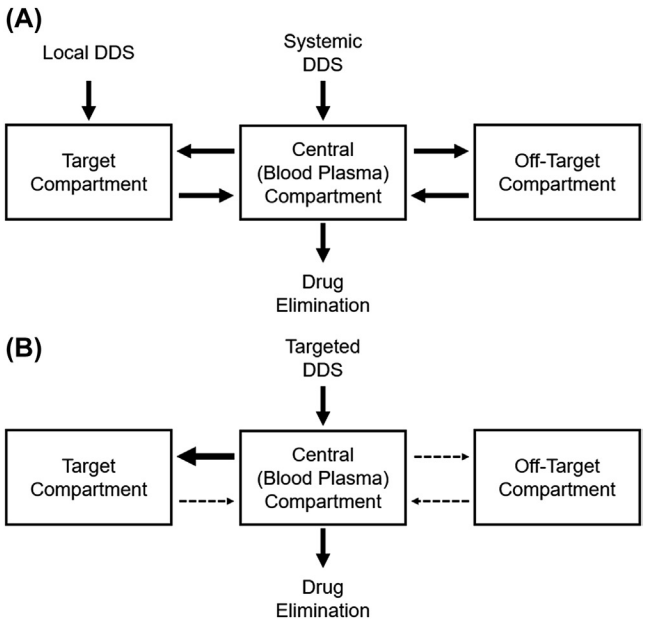
For parenteral DDS, protein adsorption can also occur (Cedervall et al., 2007; Monopoli et al., 2012) and dramatically change naïve biomaterial surface properties, which may impact circulation time and/or biodistribution. Biomaterial geometry, size, charge, and surface chemistry influence the protein–corona composition and adsorbed protein structure, and as many as 300 different proteins have been shown to be bound to nanoparticle surfaces irrespective of material class, charge, or hydrophilicity after 30-s incubations in serum (Tenzer et al., 2013; Huhn et al., 2013; Lundqvist et al., 2008; Fleischer and Payne, 2014; Parveen et al., 2017). Protein adsorption can then result in nonspecific cellular uptake by immune cells in the mononuclear phagocytic system (MPS) residing in the liver, spleen, and lymph nodes (Blanco et al., 2015).

## Mechanics

The mechanical properties of implantable or transdermal DDSs can also impact drug delivery success. The relative crystallinity and elastomeric nature of polymeric systems (see Chapter 1.3.2) can affect resistance to mechanical forces exerted during placement (Temenoff and Mikos, 2009). If the material cracks or breaks during placement or duration of use, the increased surface area can lead to significant alterations in drug release due to a greater surface area-to-volume ratio and decreased biocompatibility due to an amplified FBR (Temenoff and Mikos, 2009). Altered inflammatory and/or FBR reactions can also result from tissue mechanical damage due to mismatched biomaterial depot and tissue properties (Temenoff and Mikos, 2009).




• **Figure 2.5.12.5** Pharmacokinetics (PK) curves of plasma concentration of a drug versus time for two types of delivery systems: (A) typical bolus PK for multiple dosing with oral tablets or injections; (B) zero-order PK for one dose of controlled drug delivery from a specific formulation or device.




• **Figure 2.5.12.6** A basic pharmacokinetics compartment model showing the interactions between blood plasma, target tissues, and off-target tissues. (A) Typical systemic drug delivery delivers to blood plasma either directly (i.e., intravenous injection) or indirectly (i.e., oral pills), which is transported to the target and off-target tissue. Accumulation in other compartments occurs through transport processes that typically follow first-order kinetics. Elimination of most drugs ultimately occurs by excretion by the kidneys, and hence is dependent on drug plasma concentration. Local delivery in the target tissue bypasses compartmental transport into the target but does not affect transport kinetics out of the target compartment and into others. (B) Targeted drug delivery systems (DDSs) alter the transport kinetics by increasing the affinity for the target compartment, which is described in the section "DDS Targeting".

## DDSs to Improve Drug Pharmacokinetics

### Pharmacokinetics

One of the primary motivations for the development of DDSs is to improve the therapeutic window (TW) of drug-based therapies. The TW is the range of drug concentrations that produce therapeutic benefit without causing intolerable harm. This concept is related to the therapeutic index (TI), which is the ratio of the minimum toxic concentration divided by the minimum effective concentration. Drugs with a narrow TI are more difficult to use clinically and correlate with increased complication rates compared with wider TI drugs (Blix et al., 2010). Typically, TI is intrinsic to a drug; however, DDSs can be used to dramatically improve its apparent TW. The effects of DDSs on TI are generally PK and consist of release rate modulation, dosage control, and localization.

The relationship between PK, the TW, and drug delivery is demonstrated in Fig. 2.5.12.5. Administration of a single large dose follows typical first-order PK (e.g., oral delivery) producing a spike in blood plasma drug concentration where the desired therapeutic concentration is achieved only for a short period of the time postadministration. This rise and fall follows the *LADME* sequence. *LADME* stands for *Liberation* of the drug from the formulation, *Absorption* of the drug into the blood, *Distribution* of the drug throughout the body, including action of the drug at various sites—especially at and within cells, *Metabolism* of the drug, usually in the liver, and finally *Elimination* of the drug from the body, usually by excretion through the kidneys in the urine. Elimination rate is typically described in terms of a first-order half-life ($t_{1/2}$), which is the time required for maximal blood plasma drug concentration to decrease by half. Note that in the absence of a drug delivery vehicle or excipients in a formulation, the "L" can be disregarded. Zero-order release maintains constant drug concentration in the blood plasma, ideally within the TW, after an initial equilibration period. The area under the PK curve (AUC) of drug concentration is used to quantify drug exposure. Higher AUC indicates greater drug exposure over time and is a useful comparison for different DDS systems. Additionally, the DDS can be used to localize drug concentrations to specific PK compartments, concentrating drug in target tissues rather than off-target tissues (Fig. 2.5.12.6). DDSs can also improve bioavailability, defined as the proportion of unaltered drug after administration, by reducing drug–serum protein binding and premature enzymatic degradation.

Many DDS strategies improve AUC by reducing elimination rate to increase $t_{1/2}$. Conjugation of drugs, including proteins and small molecules, and DDSs to hydrophilic

PEG ("PEGylation") improve the circulation time by reducing elimination in the kidneys through increased solubility and physical size (Veronese and Pasut, 2005). PEGylation is particularly useful for drugs that are rapidly eliminated and has been shown to enhance therapeutic utility of antibody therapeutics and chemotherapy agents, such as Taxol and doxorubicin (Pasut and Veronese, 2009). Albumin-functionalized conjugates, such as paclitaxel-based Abraxane, have similar circulatory PK effects to PEGylation with benefits that include reduced drug chemistry modification and improved bioavailability (Green et al., 2006). However, albumin conjugates suffer from preferential liver and tumor biodistribution (Kratz, 2008). Nanocarrier systems, such as liposomes, polymeric nanoparticles, and others (see the section "DDSs to Improve Drug Solubility") increase circulation time of drugs as they are too large (>4–6 nm) to pass through the glomeruli of the kidneys (Wilhelm et al., 2016). In cases where drug elimination is similar to or faster than absorption or pharmacodynamic effects, a DDS can be critical for the clinical application of a drug candidate.

## Dosage and Distribution Control

DDSs allow better control of dosage to match the TI. Control can come via feedback (i.e., electrical control via sensors or from physical interactions with the body) or simple rate-limited release to improve convenience or better match the therapeutic concentration of a drug with a narrow TI. As an example, insulin is a hormone with a narrow and rapidly changing therapeutic concentration that is dependent upon food intake and composition, activity level, and blood glucose concentration. A fully integrated glucose sensor coupled with insulin release could act as an artificial pancreas and remove the burden of constant monitoring and calculation of insulin dosages, providing improved quality of life and reduced risk of hypo- or hyperglycemia. Current insulin delivery pumps, such as wearable modules that deliver insulin through a persistent subcutaneous injection site, offer excellent control over blood glucose levels and improve patient compliance, but still require user input despite attempts at automation (Bergenstal et al., 2010). One biomaterial DDS solution under development is the use of phenylboronic acid, a glucose-responsive moiety, as a sensor for insulin release from systemically delivered mesoporous silica nanoparticles (Zhao et al., 2009). DDSs designed for convenience include extended-release oral capsules, transdermal delivery patches, and implanted depots, which are covered in the section "DDSs to Overcome Biological Barriers."

## Controlling Drug Release Kinetics

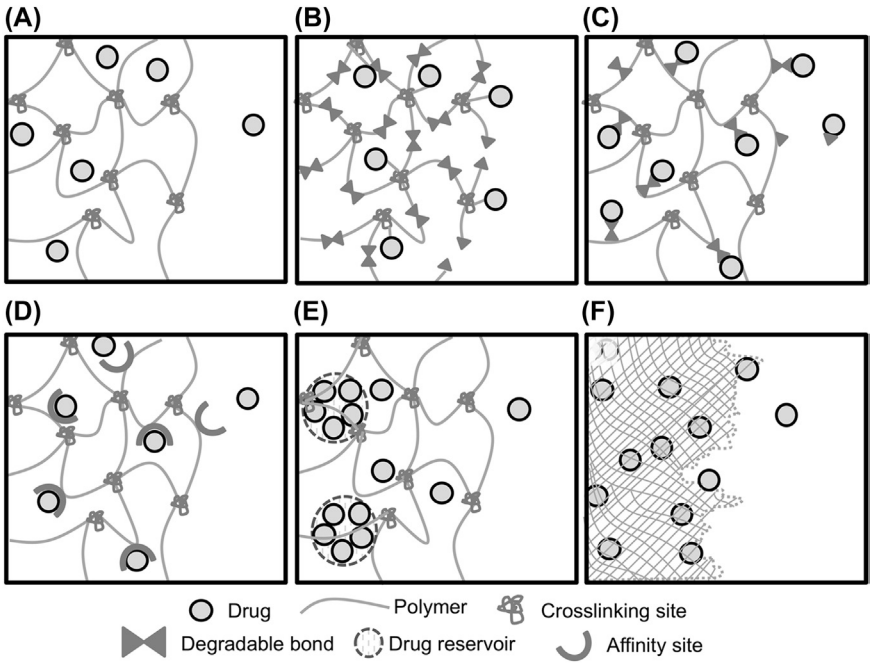
Modifying drug delivery rate can be sufficient to ensure maintenance of the TW. Drug release rate from a DDS can be controlled via several mechanisms, including diffusion, dissolution, affinity, swelling, and ion exchange (Fig. 2.5.12.7). Table 2.5.12.2 lists examples of FDA-approved DDSs that exploit these delivery mechanisms. Diffusion from DDSs is common and driven by concentration gradients. The general categories for these DDSs are matrix or reservoir-type systems. Matrix-based systems, which are also known as monoliths, contain drug uniformly dispersed within the material and are commonly accompanied by an initial "burst" release of drug upon placement due to rapid diffusion of surface-localized drug. If the material is hydrophilic, swelling mediates diffusion-controlled release. If the material is hydrophobic, drug releases after water penetration enables a diffusive path. In addition to "burst" release, diffusive release from matrix devices inherently follows first-order kinetics and requires coupling with degradable DDS materials to modify the release profile. Reservoir systems contain drug within an inner core surrounded by a permeable membrane layer that controls release and can achieve zero-order release with appropriately designed membrane–drug combinations.

Dissolution is liberation of matrix-entrapped drug as a function of matrix degradation or dissolution rate (Fig. 2.5.12.7). The kinetics of drug delivery by dissolution is controlled by DDS properties, including pore size, degradable bonds, and hydrophobicity, rather than drug solubility and mobility, as in diffusion. However, drug release is often dependent upon both drug diffusion and dissolution, as dissolution or degradation alters the DDS pore size, thus liberating greater amounts of drug over time.

Affinity-based systems exploit noncovalent interactions, including electrostatic, van der Waals, hydrophobic, and hydrogen-bonding interactions between drug and DDS to control drug release rate (Fig. 2.5.12.7). Affinity-based DDS release rates are tunable and based on the association constant of drug–ligand interactions, which allow for release of multiple drugs with various kinetics. However, a priori identification of affinity ligands is necessary for affinity-based release. Several ligands have been identified; these include cyclodextrin, heparin, albumin, and various cationic DDSs to release a variety of drugs, including small molecule antibiotics, proteins, and nucleic acids (Bader et al., 2014; Fu et al., 2011; Oss-Ronen and Seliktar, 2011; Rivera-Delgado et al., 2016; Vulic and Shoichet, 2014; Wang and von Recum, 2011).

Charged drug molecules can be loaded into an ion exchange resin to provide control over release rate as a function of the ionic environment. Ion exchange is particularly suitable for enteral delivery routes, as ion exchange resins are typically inert, functionalized poly(styrene) derivatives formed into micron- or millimeter-scale beads that pass through the digestive tract safely (Guo et al., 2009). These resins have found commercial success in many over-the-counter extended release formulations (Table 2.5.12.2).

Swelling of osmotic pumps can control mechanical dispensing systems to achieve variable drug release (Table 2.5.12.2). An osmotic pump is a compartment surrounded by a semipermeable membrane typically composed of cellulose acetate. The membrane controls diffusion of water into the osmogen: a material with high osmotic pressure, such as sugars or salts, embedded into a carrier such as poly(ethylene oxide) or poly(hydroxypropyl methylcellulose). The influx




• **Figure 2.5.12.7** Mechanisms of drug release from drug delivery systems (DDSs). Release of drugs from DDSs can be controlled by a number of mechanisms. (A) Drug is encapsulated within a DDS with mesh/pore size to allow for diffusive release of the encapsulated drug with optional diffusional membrane barrier. (B) Drug is tethered to a DDS that degrades hydrolytically, oxidatively, photolytically, or proteolytically to control release. (C) Drug is tethered to the DDS by a degradable tether, and released upon linker cleavage via hydrolysis, oxidation, photolysis, or proteolysis. (D) Diffusive release of encapsulated drug is controlled by affinity interactions between the DDS and the drug. (E) Diffusive release of encapsulated drug is prolonged by delayed release of the drug from a matrix or reservoir. (F) Drug is encapsulated within a degradable DDS and released by dissolution as the material degrades. Not to scale. (Adapted from Van Hove, A.H., Benoit, D.S., 2015. Depot-based delivery systems for pro-angiogenic peptides: a review. Front. Bioeng. Biotechnol. 3, 102.)

of water to the osmogen increases the pressure inside the container, forcing the drug or drug carrier through microdrilled pores within the membrane. There are many variations of osmotic pumps, from the single-component elementary osmotic pump (Theeuwes, 1975) to multistage, multichamber systems, all of which can range from ingestible pills to implantable devices. Release kinetics can be tuned from zero-order to complex profiles simulating multiple separate doses (Malaterre et al., 2009). More detailed reviews of osmotic pumps can be found within Malaterre et al. (2009) and Herrlich et al. (2012).

## DDSs to Improve Drug Solubility

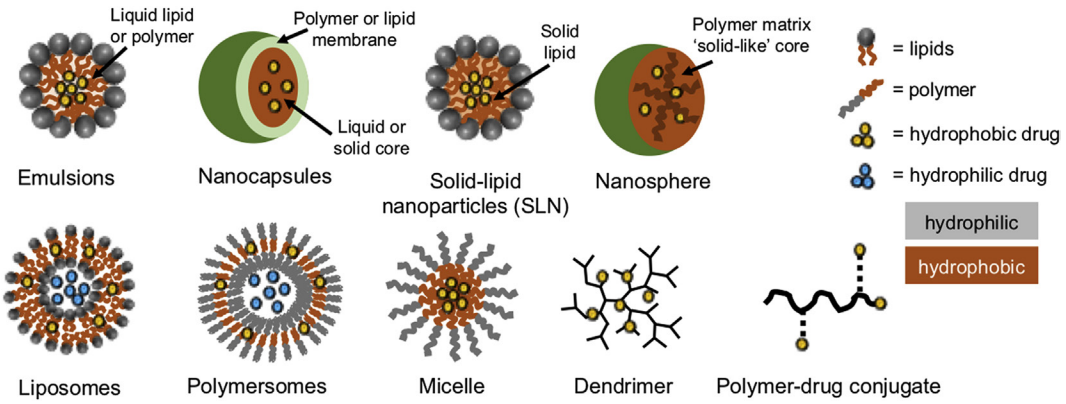
Drug solubility is vital for successful delivery. Dose variations, poor and unknown absorption profiles, low bioavailability, and subpar therapeutic efficacy are limitations associated with systemically delivered, poorly soluble, small molecule drugs. The intrinsic link between solubility and drug efficacy is described by Lipinski's rule of 5, which predicts that compounds with molecular weight <500 Da, H-bond donors ≤5, H-bond acceptors ≤10, and octanol–water partition coefficient (log P) <5 are more likely to succeed clinically due to better absorption and distribution (Choy and Prausnitz, 2011). However, approximately 40% of approved small molecule drugs and 70%–90% of pipeline agents are poorly soluble (<100 μg/mL) (e.g., do not follow Lipinski's rule of 5) (Kalepu and Nekkanti, 2015). Conventional approaches to improve drug solubility include salt formation, pH adjustments, and prodrug formulations. Unfortunately, these conventional strategies are not applicable for all drug candidates. Therefore colloidal and noncolloidal DDSs have been developed to enhance drug solubility. Many of these approaches also have the added benefit of improving drug stability, biodistribution, and cell uptake. However, for simplicity this section will focus only on improved solubility. Drugs can be dissolved, entrapped, encapsulated, chemically bonded, or adsorbed on DDSs and released by diffusion, dissolution, or swelling (Fig. 2.5.12.8). A brief introduction to these DDSs follows and highlights examples of solubility-enhancing DDSs with their routes of delivery, advantages and disadvantages, and the biomaterials employed (Table 2.5.12.3). While this section only focuses on nanoscale DDSs due to space constraints, there are similar approaches to enhance drug solubility using both micro- and macroscale formulations, such as tablets and capsules. For more comprehensive reviews, the interested reader may reference Chapter 1.3.8 and Cabral et al. (2018), Cerpnjak et al. (2013), Callender et al. (2017), Prasad et al. (2018), Date et al. (2010), Narvekar et al. (2014), Stegemann et al. (2007), and Letchford and Burt (2007).

**TABLE 2.5.12.2 Sample of Clinically Approved Drug Delivery Systems (DDSs) With Various Release Mechanisms**

| Clinically Approved DDS | Release Mechanism | Polymer | Degradable Bond | Drug(s) | References |
|---|---|---|---|---|---|
| Gliadel | Dissolution | Bis(*p*-carboxyphenoxy) propane-*co*-sebacic acid | Anhydride | Carmustine, temozolomide | Zhang et al. (2013); Bock et al. (2010); Lawson et al. (2007) |
| Zoladex, Lupron Depot, Sandostatin LAR, Neutropin depot, Trelstar, Eligard, Risperdal Consta, Vivitrol, Somatuline, Ozurdex | Diffusion and Dissolution | Poly(lactic-*co*-glycolic acid) | Ester | Goserelin acetate, Leuprolide acetate, polifeprosan 20/ carmustine, glucose/ octreotide acetate, recombinant human growth hormone, triptorelin pamoate, minocycline, Leuprolide acetate, risperidone, naltrexone lanreotide, dexamethasone | Zhang et al. (2013) |
| Atridox | Diffusion and Dissolution | Poly(lactic acid) | Ester | Doxycycline hyclate | Zhang et al. (2013) |
| Capronor | Diffusion and Dissolution | Poly(caprolactone) | Ester | Levonorgestrel | Ulery et al. (2011) |
| Implanon, Nexplanon, Probuphine, Ocusert, Vitrasert | Diffusion | Ethylene-*co*-vinyl acetate | ND | Etonogestrel, buprenorphine, pilocarpine, ganciclovir | Major et al. (2016); Schneider et al. (2017) |
| Norplant, Jadelle, Mirena, Skyla, Liletta, Kyleena | Diffusion | Silastic | ND | Levonorgestrel | Major et al. (2016) |
| Onpattro | Affinity | Cholesterol and poly(ethylene glycol)-conjugated lipid nanoparticle complex | ND | siRNA | Mullard (2018); Hoy (2018); Morrison (2018) |
| Delsym, Tuzistra XR, Betoptic S | Ion Exchange | Poly(styrene) sulfonate | ND | Dextromethorphan, codeine, chlorpheniramine, betaxolol | Guo et al. (2009); Jani et al. (1994); Yoshida et al. (2013); Raghunathan et al. (1981) |
| Osmosin, Acutrim, Procardia XL, Ritalin SR, Xanax XR | Osmotic pump | Hydroxypropyl methylcellulose, poly(ethylene oxide), Cellulose acetate, other cellulose derivatives | ND | Indomethacin, phenylpropanolamine, nifedipine, methylphenidate, alprazolam | Malaterre et al. (2009); Herrlich et al. (2012); Keraliya et al. (2012) |

*ND*, Nondegradable.

For additional information beyond referenced works, see Van Hove, A.H., Benoit, D.S., 2015. Depot-based delivery systems for pro-angiogenic peptides: a review. Front. Bioeng. Biotechnol. 3, 102; Liechty, W.B., et al., 2010. Polymers for drug delivery systems. Annu. Rev. Chem. Biomol. Eng. 1, 149–173; Mishra, S., De, A., Mozumdar, S., 2014. Synthesis of thermoresponsive polymers for drug delivery. Methods Mol. Biol. 1141, 77–101.




• **Figure 2.5.12.8** Schematic showing different drug delivery system platforms discussed herein.

## Colloidal DDSs

Colloidal DDSs include a variety of nanoscale carriers that improve drug solubility by incorporating drug within a reservoir or matrix. Emulsions are early examples of colloidal DDSs. Because of their long-standing use in a variety of industries, including cosmetics, food, and agriculture, emulsions inevitably evolved into DDSs. Emulsions (Fig. 2.5.12.8) are heterogeneous dispersions of oil and water that improve drug solubility by increasing the surface area of the drug. The idea that increasing drug surface area improves drug solubility subsequently propelled the development of more advanced nanocarriers, including nanospheres, solid-lipid nanoparticles (SLNs), nanocapsules, micelles, polymersomes, and liposomes.

Nanospheres and SLNs are composed of a solid lipid or polymer matrix core that loads a variety of hydrophobic drugs (Fig. 2.5.12.8). Despite being formulated with different materials (i.e., lipids, polymers), drug loading in nanospheres and SLNs is achieved by selecting a core material with excellent drug solubility. Additional information can be found in Table 2.5.12.3.

Nanocapsules, micelles, polymersomes, and liposomes (Fig. 2.5.12.8) can be broadly categorized as reservoir DDSs. Specifically, nanocapsules have hydrophobic liquid or solid cores surrounded by a single layer of polymer or lipid corona, while micelles form a hydrophobic core and hydrophilic corona through the self-assembly of amphiphilic polymers (Fig. 2.5.12.8) (Letchford and Burt, 2007). The core of nanocapsules and micelles may also serve as a reservoir for hydrophobic drugs that can also enhance drug stability. In these carriers, the size of the hydrophobic region and drug–core interactions control loading capacity. A major advantage of nanocapsules and micelles is their stable core, which reduces premature drug loss. Specifically, micelles are thermodynamically stable, and are associated with low critical micelle concentration, allowing for maintenance of loaded material for long periods of time.

Polymersomes (Fig. 2.5.12.8) are amphiphilic copolymers, while liposomes are amphiphilic lipids that self-assemble into bilayered structures (Fig. 2.5.12.8). Polymersome formulations are complex and depend on the weight fraction of the hydrophilic block to ensure uniform distribution (Letchford and Burt, 2007; Discher et al., 2007; Rideau et al., 2018). Both polymersomes and liposomes enable the delivery of various molecules, including small molecule hydrophobic drugs within the bilayer and, in contrast to other carriers, hydrophilic molecules (e.g., nucleic acids or proteins) within the core (Rideau et al., 2018). Similar to the other carriers, polymersome and liposome drug loading are highly dependent on drug interactions with the carrier's bilayer or core. To reduce rapid clearance of liposomes, PEG was introduced as a surface modification on Doxil, the first colloidal DDS approved by the FDA in 1995 (Lian and Ho, 2001). Since then, additional liposomal formulations have adapted PEG surface modifications resulting in various marketed DDSs, as listed in Table 2.5.12.3.

Colloidal DDSs range from core-based carriers to more complex bilayered structures. Regardless of the carrier type, drug loading and drug release kinetics are dictated by the lipid/polymer composition, drug–carrier interactions, and nanoparticle size (Prasad et al., 2018; Allen and Cullis, 2013; Kataoka et al., 2001; Mukherjee et al., 2009).

## Noncolloidal DDSs

Dendrimers are highly branched polymer chains that are stable and easy to modify (Table 2.5.12.3) (Prasad et al., 2018; Marx, 2008; Boas and Heegaard, 2004; Morgan et al., 2006). Dendrimers have evolved over time from simple structures that enable covalent or electrostatic drug loading to more complex hydrophobic-to-hydrophilic structures that enable core encapsulation of hydrophobic drugs (Marx, 2008; Boas and Heegaard, 2004; Duncan and Izzo, 2005; Li et al., 2007). Examples of dendrimers, including the most prominent, poly(amidoamine) (PAMAM) (Duncan and Izzo, 2005; Esfand and Tomalia, 2001), are provided in Table 2.5.12.3, and information about the various biomaterials used for dendrimer formulations can be found in the following references (Buhleier et al., 1978; Hawker and Fréchet, 1990; Turnbull and Stoddart, 2002).

Polymer–drug conjugates (PDCs) are made of three components: the polymer, a linker, and the drug, as shown in Fig. 2.5.12.8. PDCs can achieve high drug loading via covalent linkages and exhibit tunable properties through

**TABLE 2.5.12.3 Summary of Drug Delivery Systems (DDSs) That Address Poor Aqueous Solubility With Associated Advantages, Disadvantages, and Examples**

| DDS Type | Advantages | Disadvantages | Examples | Material | Delivery Routes | References |
|---|---|---|---|---|---|---|
| Emulsions | Liquid formulations facilitate faster absorption, adaptable for hydrophobic and hydrophilic drugs | Toxic excipients, phase separation over time, rapid clearance | TOCOSOL paclitaxel, Norvir, Restasis, cyclosporine A | Soybean, cottonseed, and safflower oils, Tween, Pluronics, etc. | Oral, parenteral, transdermal, ocular | Prasad et al. (2018); Narvekar et al. (2014) |
| Nanocapsules | Chemically stable, biocompatible, and reproducible | Delayed release of active drugs, loading capacity dictated by size of reservoir | SOLUDOTS-PTX | Poloxamer | Parenteral | Kothamasu et al. (2012) |
| Solid-Lipid Nanoparticle (SLN) | Easy scale-up, high lipid content, affordable, biocompatible lipids used | Limited drug loading potential, contains a mixture of colloidal structures, rapid clearance | Ciprofloxacin-loaded SLNs | Triglycerides, fatty acids, steroids, waxes, etc. | Oral, parenteral, topical | Zhang et al. (2013); Mukherjee et al. (2009) |
| Nanosphere | Flexibility in how drug is incorporated, tunable polymer | Rapid clearance, poor reproducibility | Eligard | MePEG-*b*-PLA, PEG-*b*-PDLLA, PEG-PCL, etc. | Parenteral | Ventola (2017) |
| Micelles | Thermodynamically stable, high drug loading, controllable release kinetics | Complex polymer chemistry | Estrasorb, Genexol-PM[a] | PLGA, MePEG-*b*-PDLLA, MePEG-*b*-PCL, MePEG-*b*-PLDA, etc. | Topical, parenteral | Yokoyama (2011) |
| Liposomes, polymersomes | Adaptable for hydrophobic and hydrophilic drugs (both), stable and less permeability (polymersomes) | Immunogenicity, toxicity, and cellular uptake, poor circulation time (liposomes) | Doxil/Caelyx, Marqibo, Onivyde | Phospholipids, PEO-*b*-PBD, etc. | Parenteral | Discher et al. (2007); Lian and Ho (2001); Allen and Cullis (2013) |
| Dendrimer | Enables incorporation of diverse drugs, stable, size is controllable, easy to modify | Low yield, complex synthesis | VIvaGel[b] | PAMAM, PPI | Transdermal, oral, ocular, and pulmonary | Esfand and Tomalia (2001); Larson and Ghandehari (2012) |
| PDC | Selective delivery due to linker chemistry, can tune PK via conjugate molecular weight | Complex design, steric hindrance during drug incorporation | SMANCS, Oncaspar, Plegridy, Krystexxa | PEG, HPMA | Parenteral, topical | Larson Ghandehari (2012) |

*HPMA*, Poly(*N*-(2-hydroxypropyl) methacrylamide); *MePEG*, methoxy(poly(ethylene glycol)); *MePEG-b-PLA*, methoxy(poly(ethylene glycol))-*block*-poly(D,L-lactic acid); *MePEG-b-PLDA,* methoxy(poly(ethylene glycol))-*block*-poly(ld–lactide); *PAMAM*, poly(amidoamine); *PDC*, polymer–drug conjugate; *PEG*, poly(ethylene glycol); *PEG-b-PDLLA*, poly(ethylene glycol)-block-poly(D,L-lactide); *PEG-PCL*, poly(ethylene glycol)-poly(ε-caprolactone); *PEO-b-PBD*, poly(ethylene oxide)-*b*-poly(butadiene); *PLGA*, poly lactic-*co*-glycolic acid; *PPI*, polypropylenimine; *SMANCS*, poly(styrene-*co*-maleic acid)-neocarzinostatin.
[a]Denotes European Medicines Agency approval.
[b]Denotes clinical trials.

linker selection and molecular weight. However, PDCs can also diminish drug efficacy due to steric hindrance of conjugations close to or at drug active sites (Duncan, 2003; Ulbrich and Subr, 2010; Xu et al., 2015). Various biomaterials have been explored to develop PDCs, including PEG and poly(*N*-(2-hydroxypropyl) methacrylamide) (Table 2.5.12.3) (Ulbrich and Subr, 2010; Xu et al., 2015; Larson and Ghandehari, 2012).

## Biomaterial DDSs Can Enhance Drug Stability

For various therapeutic compounds and biomaterial DDSs, instability can be a major hurdle to clinical success. The consequences of unexpected drug or DDS degradation—physically or chemically–are dire. These consequences include loss of potency, formation of toxic by-products, and for DDSs, loss of controlled delivery that may cause drug concentrations outside of the TW (subtherapeutic or toxic). Drug degradation mechanisms are similar to those discussed for DDSs (e.g., hydrolysis, oxidation, photolysis, and proteolysis), which can occur for all drug classes: small molecules, proteins/peptides, or nucleic acids. Use of DDSs has been shown to protect drugs from the various modes of degradation (Silva et al., 2018; Opanasopit et al., 2005), as detailed herein (Chono et al., 2008).

### Small Molecule Drugs

Several small molecule drug candidates perceived to have excellent and selective therapeutic efficacy are unstable due to inclusive degradable groups. For example, esters and lactones are susceptible to hydrolysis and/or proteolysis by enzymes in the gastrointestinal (GI) (oral delivery) and serum proteins, such as albumin, in systemic circulation (Fig. 2.5.12.4) (Silva et al., 2018; Opanasopit et al., 2005; Dube et al., 2011; Di Martino et al., 2017; Ramezanli et al., 2017; Heredia et al., 2016; Montanari et al., 2016). For example, camptothecin and topotecan are potent chemotherapeutic drugs but include lactone rings making them susceptible to hydrolysis (Fig. 2.5.12.4A). Various approaches to protect these drugs include pH-responsive nanospheres of poly(2-hydroxyethyl methacrylate), liposomes, and SLNs (Silva et al., 2018; Iglesias et al., 2018). Another example is vitamin D3, which is a steroid that can undergo oxidation (Fig. 2.5.12.4B) or photolysis-mediated isomerization (Fig. 2.5.12.4C), thus hindering its biological efficacy (Ramezanli et al., 2017). Micelles comprised of PEG, desaminotyrosyl-tyrosine octyl ester, and suberic acid triblock copolymers have been exploited to protect vitamin D3 (Ramezanli et al., 2017).

### Protein/Peptide Drugs

Protein and peptide therapeutics are a growing category of drug entities and have special requirements for stability. Protein therapeutics, such as antibodies and cytokines, as well as peptide therapeutics, can suffer from sequence-specific enzymatic degradation of amide bonds as well as nonspecific enzymatic activity. Additionally, the amino acid functional groups of histidine, tryptophan, methionine, and cysteine are subject to oxidation (Fig. 2.5.12.4B) and tryptophan can photodegrade (Fig. 2.5.12.4C). Various DDSs (i.e., PLGA microspheres, amphiphilic anhydrides, silicone elastomer reservoirs, hydrogel-based systems, and ethylene-*co*-vinyl acetate polymer matrices, etc.) have been explored to protect and controllably delivery proteins/peptides (Van Hove and Benoit, 2015; Patel et al., 2014). Hydrogel-based depot systems are the most commonly used DDSs for protein and peptide delivery with mechanisms of release summarized in Fig. 2.5.12.7.

### Nucleic Acid Drugs

Effective delivery of nucleic acid drugs, including DNA, small RNAs, ribozymes, aptamers, and even CRISPR-Cas9, is of immense interest due to their ability to drug the "undruggable." Through mechanisms subverted from biology, nucleic acid drugs can inhibit, degrade, or alter DNA and/or RNA in ways not possible through traditional low molecular weight drugs or antibodies. However, nucleic acid drugs have significant stability challenges. While some nucleic acid base chemical modifications are protective (Behlke, 2008), generally, nucleic acids are susceptible to degradation by extracellular nucleases and exhibit short half-lives due to renal clearance. For this reason, the majority of nucleic acid-based drugs to undergo clinical trials have only been successfully developed for local delivery (Ozcan et al., 2015), and the development of DDSs to enable systemic delivery for nucleic acid drugs is of high priority (Giang et al., 2014).

Cationic DDSs are predominately used for nucleic acid delivery. Electrostatic interactions of cationic DDSs with anionic nucleic acids protect against enzymatic degradation and achieve nanoparticle formation, which triggers nonspecific intracellular uptake. After nanoparticle DDS uptake, intracellular trafficking through endolysosomes exposes the therapeutic to significant variations in pH (7.4–5) and degradative lysosomal enzymes. This pH gradient provides an environmental stimulus that can be exploited by DDS to escape lysosomal fate. Cationic polymers containing proton-accepting amine groups facilitate endosomal release by osmotic disruption through the "proton sponge" effect (Behr, 1996; Behr, 1997; Boussif et al., 1995; Lynn and Langer, 2000; Pack et al., 2000), which was first proposed by Behr and coworkers (Behr, 1996, 1997). By accepting protons during endosomal acidification, cationic polymers neutralize endosomes and inhibit the typical reduction in pH, resulting in a continued influx of protons and counterions (typically $Cl^-$). This proton influx causes the osmotic pressure inside the vesicle to increase, resulting in greater water influx, swelling, endosomal membrane disruption, and finally the release of the endocytosed cargo. There

are many examples of amine-containing "proton sponge" DDSs, including poly(dimethylaminoethyl methacrylate) (DMAEMA), poly(diethylaminoethyl methacrylate), poly(ethylenenimine), chitosan, poly(lysine), PAMAM, peptides, and cyclodextrin (Ozcan et al., 2015; Xiao et al., 2019; Sun et al., 2018; Smith, 2018; Li et al., 2018; Hong et al., 2018; Zhang and Wagner, 2017; Shi et al., 2017; Palmerston Mendes et al., 2017; Leiro et al., 2017; Ahmed, 2017; Pandey and Sawant, 2016; Miyata, 2016; Ho et al., 2016).

Polymers that are inert under physiological conditions and membrane disruptive at endolysosomal trafficking pH have also been used to prevent nucleic acid drug lysosomal degradation. Mechanistically, protonation of membrane-disruptive polymers causes a hydrophobic transition from an extended, soluble conformation into a compact, membrane interactive globule (Thomas and Tirrell, 1992; Thomas et al., 1994; Borden et al., 1987; Eum et al., 1989; Chen and Thomas, 1979). Membrane-disruptive DDSs include several polymeric and lipid-based formulations, including poly(propylacrylic acid) (PPAA), combinations of PPAA, butyl methacrylate, DMAEMA, and alkylamine-modified poly(styrene-alt-maleic anhydride) (Sun et al., 2018; Zhang and Wagner, 2017; Shi et al., 2017; Miyata, 2016; Buse and El-Aneed, 2010; Jabr-Milane et al., 2008; MacEwan et al., 2010; Sebiakin Iu and Budanova, 2006).

In a landmark achievement in drug delivery, Alnylam Pharmaceuticals' Onpattro (e.g., patisiran) received FDA approval in 2018, making it the first RNAi-based drug brought to market (Mullard, 2018; Hoy, 2018; Morrison, 2018). Developed to treat transthyretin-mediated liver amyloidosis, which is a rare but deadly genetic disease, patisiran is a particle formulation comprised of cholesterol and PEG-conjugated lipids. The lipid moieties contain ionizable amines that complex and protect the siRNA and trigger the proton sponge effect to escape lysosomal degradation upon cell uptake (Whitehead et al., 2014; Jayaraman et al., 2012; Akinc et al., 2008; Wolfrum et al., 2007). In addition to patisiran, numerous other nucleic acid drugs are currently in the developmental pipeline. Of the DDSs employed for systemic delivery of nucleic acids, nearly all are cationic and lipid-based nanocarriers (Ozcan et al., 2015). Continual improvements in rational design of DDSs, especially in controlled synthetic approaches enabling careful structure–function analyses, have the potential to ensure development of highly effective and safe nucleic acid-based therapeutics for clinical applications.

## DDS Design to Overcome Biological Barriers

Many natural barriers exist to prevent free exchange of drugs within tissues and organs. The chemistry and function of these barriers vary among the protective outer epithelial layers, the water- and gas-permeable mucosal membranes, and the tightly interconnected phospholipid membranes of endothelial cells. This section briefly discusses these biological barriers and the ways in which DDSs have been designed to overcome them.

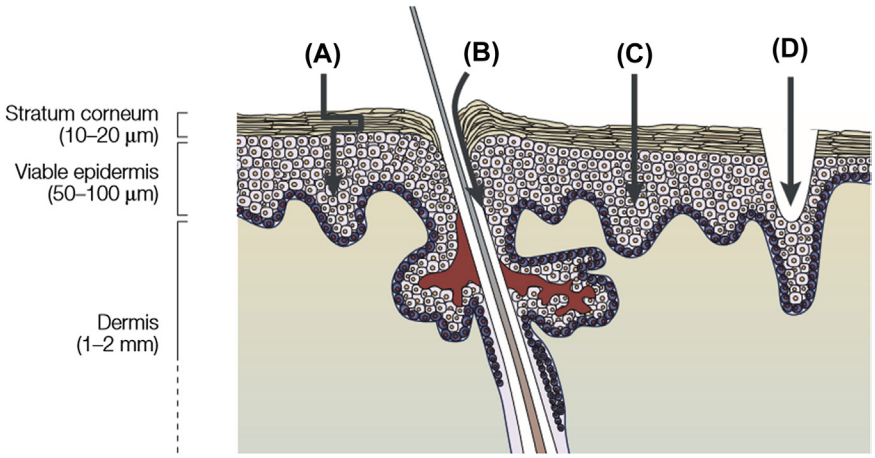
As already introduced in the section "General Considerations for DDS Design—Routes of Drug Delivery," drug delivery routes include oral (e.g., buccal, sublingual, gastric, enteric), parenteral injection (e.g., intradermal, intramuscular, intravenous, and subcutaneous), transdermal, nasal (e.g., insufflation), rectal, vaginal, and intrathecal (Fig. 2.5.12.3) (Vaidhya, 2013; Tiwari et al., 2012; Ensign et al., 2012; Prausnitz, 2004; Naik et al., 2000). The most commonly used methods are parenteral injections due to high drug absorption (i.e., bioavailability) and oral delivery due to patient convenience and compliance. However, all routes have limitations due to known anatomical, physiological, chemical, pharmacological, or psychological barriers. The primary limitations associated with parenteral drug delivery are trypanophobia (i.e., fear of needles) and the requirement of skilled expertise for proper administration. The key limitations of oral drug delivery include poor drug solubility, stability, and bioavailability due to "first-pass metabolism" effects (Ensign et al., 2012). Therefore interest in additional drug delivery routes, most notably transdermal and mucosal approaches, has grown rapidly in recent years. A closer examination of the various drug delivery routes with respect to the epithelial, mucosal, and endothelial barriers is presented next.

### Epithelial Barriers

The epithelium is the outermost of the body's barriers and consists of the epidermis, various mucosal tissues (e.g., pulmonary, corneal, rectal, vaginal, etc.), and the alimentary canal (i.e., GI tract) tissues. These epithelia are the first barriers through which all drugs must pass before reaching target tissues. The primary drug delivery routes used to bypass epithelial barriers are parenteral and transdermal administration, as described next.

#### *Parenteral Administration*

The stratum corneum is the top layer of the epidermis and outermost skin layer that serves as the primary protective barrier to the body due to its unique mechanical and chemical protection (Fig. 2.5.12.9) (Landmann, 1988; Proksch et al., 2008). The stratum corneum consists of dead keratinocytes and intracellular spaces filled with continuous lipid layers (e.g., ceramides, free fatty acids, and cholesterol) measuring approximately 10–15 μm thick (Fig. 2.5.12.9) (Landmann, 1988). Although some small molecule drugs can penetrate the skin, the stratum corneum is impermeable to molecules larger than 500 Da (Bos and Meinardi, 2000), thus limiting drug delivery of higher molecular weight compounds. Mechanical penetration, such as intravenous (IV) injections using hypodermic needles, is a common option for bypassing this barrier and enabling maximal drug delivery to the bloodstream (Fig. 2.5.12.3). Additionally, subcutaneous and intramuscular administrations are the most




• **Figure 2.5.12.9** Schematic representation of a cross-section through human skin and potential routes for drug delivery. The stratum corneum provides nearly all of the barrier functions of the skin by keeping foreign substances out of the body while retaining moisture. Hair interrupts the stratum corneum, but lipid-containing sebum around the hair maintains barrier function. For transdermal DDSs, (A) diffusion, potentially with a chemical enhancer, (B) iontophoresis can enable transport through hair follicles or sweat glands, (C) electroporation can disrupt lipid bilayers, increasing transdermal transport, (D) microneedles puncture skin to enable delivery. (Used with permission from Prausnitz, M.R., Mitragotri, S., Langer, R., 2004. Current status and future potential of transdermal drug delivery. Nat. Rev. Drug Discov. 3 (2), 115–124.)

frequently used parenteral routes after IV (Fig. 2.5.12.3). Drugs delivered intramuscularly are absorbed faster than those delivered subcutaneously due to greater vascularity and volumetric capacity of muscle versus subcutaneous tissue (Guerra and Kitabchi, 1976; Turner et al., 2011). Parenteral administration is useful for any drugs or biologics that are sterile, fast acting, stable in serum, and not inherently suited for oral delivery without advanced DDSs. However, this delivery route is painful, typically requires trained personnel, and may cause difficult-to-control adverse events, including overdose.

### Transdermal DDSs

Besides bypassing the skin through parenteral injection, various transdermal delivery systems provide direct drug administration through the epidermis. Transdermal DDSs are often considered more convenient than parenteral injections and improve patient compliance (Prausnitz and Langer, 2008). Some small molecule drugs can pass through the epidermis and typically follow a "Lipinksi-like" rule set: <500 Da, log P between 2 and 3, and measurable solubility in both oil and water (Wiedersberg and Guy, 2014). For these skin-penetrating drugs, a topical patch or cream can be sufficient for delivery and have gained widespread regulatory approval (Prausnitz and Langer, 2008). However, for drugs with hindered diffusion through the skin, several active delivery systems exist (Prausnitz, 2004; Naik et al., 2000). Active transdermal systems transport the drug across the stratum corneum via mechanical, electrostatic, or chemical means, allowing hydrophilic drugs or larger molecules such as proteins to be delivered. Table 2.5.12.4 provides an overview of these techniques.

Prominent transdermal DDSs include microneedle arrays (Prausnitz, 2004), transdermal jets (Prausnitz and Langer, 2008; McAllister et al., 2014), thermal ablation (Arora et al., 2008), and ultrasonic sonophoresis (Park et al., 2014). These DDSs function by physically transporting drug through the stratum corneum by penetration or electroporation of the lipid layers. Electrostatic techniques include iontophoresis, where charged drug molecules are electrophoretically transported through the stratum corneum, and electroporation, where the stratum corneum (i.e., lipid layers) is disrupted by alternating current. Chemical enhancers improve the transport of drugs across the stratum corneum by acting as a solvent or surfactant to disrupt epidermal cell membranes, increasing drug penetration depths and rates. Enhancers are often used in combination with other active and passive techniques. The reader is directed to reviews of transdermal DDSs for more information (Prausnitz and Langer, 2008; Arora et al., 2008).

### Mucosal DDSs

Mucosal membranes are the other major external barrier tissue found in the body. Mucous membranes are present in the eyes, oral cavity, nasal passages, pulmonary tract, stomach, intestines, urethra, vagina, and anus. These tissues vary in structure and function, but all secrete mucus (Bansil and Turner, 2018). The composition of mucus varies by tissue, but it is an omnipresent hydrogel composed of various mucins expressed by goblet cells in the outer mucosal layers and is well distributed on mucosal *surfaces* due to its shear-thinning properties and constant production (Bansil and Turner, 2018). Mucus dramatically reduces the local diffusion rate of entrapped compounds through a combination of its hydrogel mesh and lipid-binding properties (Bansil and Turner, 2018). However, mucosal barriers can be overcome with careful DDS design.

Important DDS design parameters that affect the ability to cross mucosa include hydrophobicity, electrostatic interactions, van der Waals interactions, size, osmotic solution

**TABLE 2.5.12.4 Summary of Transdermal Drug Delivery Systems (DDS)**

| Delivery Mechanism | Description | Materials | Drugs | References |
|---|---|---|---|---|
| Topical Delivery (passive) | Drug or DDS diffuses through intact skin while a carrier acts as a depot | Vinyl acetate, poly(acrylic acid), poly(vinyl alcohol), Cyclodextrins | Methylphenidate, nicotine, buprenorphine, scopolamine, nitroglycerin | Naik et al. (2000); Prausnitz and Langer (2008) |
| Chemical Enhancers | Solvent disrupts integrity of lipids in stratum corneum, improving drug diffusion | Sodium laurel sulfate, phenyl piperazine, Cell penetrating peptides, Liposomes, Dendrimers | Insulin, testosterone, triamcinolone acetonide | Prausnitz and Langer (2008); Mitragotri (2000); Alkilani et al. (2015) |
| Iontophoresis and electrophoresis | Electrophoretic transport of charged drug molecules or disruption of stratum corneum | Metals (electrodes), poly(vinyl alcohol), poly(vinyl pyrrolidone), poly(acrylic acid) | Lidocaine, fentanyl, acyclovir | Prausnitz and Langer (2008); Ariura et al. (1984) |
| Microneedles | Submillimeter needles penetrate stratum corneum to carry drug through | Silicon, polycarbonate, titanium, poly(lactic acid) | Vaccines, parathyroid hormone, naltrexone | Prausnitz Langer (2008) |
| Thermal Ablation | Heat creates micropores in stratum corneum to allow drug diffusion | Metals | Human growth hormone, interferon α-2b, Insulin | Arora et al. (2008) |
| Transdermal MicroJets | High-velocity jet of liquid or microparticles penetrates stratum corneum by momentum | N/A | Influenza Vaccines (FDA approved) | McAllister et al. (2014) |
| Sonophoresis | Ultrasonic transducer cavitates lipids in stratum corneum along with gel medium | Poly(ethylene glycol), isopropyl trioleate, glycerol trioleate, linoleic acid | Dexamethasone, Insulin, erythropoietin, Heparin | Mitragotri (2000); Prausnitz et al. (2004); Park et al. (2014) |

*FDA*, Food and Drug Administration; *N/A*, not applicable.

conditions, and mucoadhesion (Ensign et al., 2012). These parameters directly affect mucosal contact time, permeability, enzyme inhibition, and uptake rate by specialized mucosal regions, such as Peyer's patches, as described for DDSs in Table 2.5.12.5 (Ensign et al., 2012; Kumar et al., 2016; Rathbone et al., 2015; Aungst, 2000; Shaji and Patole, 2008; Saini and Singh, 2015; Lam et al., 2014). Moreover, mucosal permeation enhancers, similar to transdermal systems, increase mucosa permeability to increase drug diffusion (Ensign et al., 2012; Kumar et al., 2016; Rathbone et al., 2015; Aungst, 2000). Together, increased mucosal contact time, permeability, and enzyme inhibition allow for DDS transport across the mucosal barrier via paracellular (i.e., around cells) or transcellular (i.e., through cells) pathways (Ensign et al., 2012; Kumar et al., 2016; Rathbone et al., 2015).

### *Oral DDSs*

Oral drug delivery is the most common and most convenient delivery route. However, many drugs are difficult to formulate for oral delivery due to low solubility, poor stability, and low absorption within the GI tract (Ensign et al., 2012). As shown in Table 2.5.12.6, variations in epithelial cell type, mucus consistency, surface area, residence time, and pH within the GI tract make oral drug delivery particularly difficult. However, the development of smart DDS that can undergo relatively large and abrupt physical or chemical changes in response to small external changes in environmental conditions has overcome these challenges (Binauld and Stenzel, 2013; Perkins et al., 1999; Liu et al., 2016; Kumar et al., 2017). For example, enteric coatings are polymeric layers that protect drugs against the harsh acidic gastric environment, ensuring drug release in the small intestines. Additionally, DDSs have been designed to be responsive to environmental changes, such as fluctuations in temperature, pH, electric fields, magnetic fields, ultraviolet light exposure, and ionic strength (Binauld and Stenzel, 2013; Schmaljohann, 2006; Gao et al., 2010; Linsley and Wu, 2017; Bear et al., 2016; Mura et al., 2013; Zhao and Moore, 2001; Sood et al., 2016; Hoffman, 2013; Knipe and Peppas, 2014; Koetting et al., 2015), to deliver the right amount of drug to the right place within the GI tract at the right time. Some of these DDSs even release drugs

**TABLE 2.5.12.5 Summary of Mucosal Drug Delivery System (DDS) Design Parameters**

| Mucosal Design Parameter | Description | Drug Delivery Mechanism | Examples | FDA-Approved DDS Examples | References |
|---|---|---|---|---|---|
| Mucosal Contact time | Maintains contact between drug or DDS and mucosal absorption surface for prolonged periods of time | Mucoadhesives, sustained Drug Release | Carrageenan, Chitosan, CMC, CP, Eudragit, HEC, HPC, HPMC, PIB, PIP, POE, pullulan, PVA, PVP, sodium alginate | Actiq (lozenge), NiQuitin (lozenge), Nitroguard (buccal tablet), Onsolis (buccal dissolvable film), Orabase (oral paste), Suboxone (sublingual tablet), Striant (buccal tablet) | Saini and Singh (2015); Lam et al. (2014); Hearnden et al. (2012); Shojaei (1998); Silva et al. (2015) |
| Permeability | The flux of drugs or DDS through the mucosa | Permeability Enhancers | Glyceryl monooleate, lauryl lactate, LCC, PCC, propylene glycol, sodium caprate, sodium caprylate, bile salts (e.g., sodium chenodeoxycholate, sodium glycodeoxycholate, sodium lauryl sulfate, sodium taurocholate, sodium taurodeoxycholate, sodium ursodeoxycholate) | Oral-lyn (oral spray containing bile salts to improve buccal permeability) | Aungst (2000); Shaji and Patole (2008); Hearnden et al. (2012); Shojaei (1998); McCartney et al. (2016) |
| Enzyme Inhibition | Prevents enzyme degradation of drug or DDS | Enzyme Inhibitors | Aprotinin, bestatin, Chitosan, CP, deoxycholic acid, glutathione, Isabgol, soybean trypsin inhibitor, PEG, poly(acrylates), polycarbophil, puromycin, thiomers | Trasylol (IV injection) | Hearnden et al. (2012); Shojaei (1998); Semwal et al. (2014); Karsdal et al. (2015) |

*CMC*, Sodium carboxymethyl cellulose; *CP*, Carbopol 934P; *HEC*, poly(hydroxy ethyl cellulose); *HPC*, poly(hydroxypropyl cellulose); *HPMC*, poly(hydroxypropyl methylcellulose); *HPMC/PVP*, poly(hydroxypropyl methylcellulose)/poly(vinyl pyrrolidone); *IV*, intravenous; *LCC*, lauryl carnitine chloride; *PCC*, palmitoyl carnitine chloride; *PEG*, poly(ethylene glycol); *PIB*, poly(isobutylene); *PIP*, poly(isoprene); *POE*, poly(oxyethylene); *PVA*, poly(vinyl alcohol); *PVP*, poly(vinyl pyrrolidone).

according to circadian rhythms (Jain et al., 2011). However, as previously mentioned, poor drug bioavailability due to "first-pass metabolism" effects within the GI tract or liver markedly limits oral DDS effectiveness (Ensign et al., 2012; Lam et al., 2014). Therefore alternative drug delivery routes capable of reducing or bypassing "first-pass effects" altogether have been widely investigated.

Additional transmucosal drug delivery routes capable of bypassing "first-pass effects" include nasal, sublingual, buccal, ocular, rectal, and vaginal approaches. Sublingual and buccal DDS approaches are two examples that have gained interest recently and have been reviewed elsewhere (see Kumar et al., 2016; Lam et al., 2014; Shojaei, 1998; Silva et al., 2015; Boateng et al., 2015; Mrsny, 2009; Goswami et al., 2008).

## Endothelial Barriers

Once a DDS has crossed the epithelia or mucosa and is absorbed into the bloodstream after administration, a host of new endothelial and cell-associated barriers must be overcome to reach most targets. Endothelial barriers consist of four main components: endothelial cell membranes, tight junctions between cells, the apical surface glycocalyx, and the basement membrane. The endothelial lumen glycocalyx is a thick layer of glycoproteins with embedded proteases. This glycoprotein network inhibits diffusion locally, serving as a barrier for nanoparticles and protein therapeutics (Frey et al., 1996; Aoki et al., 2005). Endothelial cell lipid bilayers prevent free diffusion of most water-soluble compounds over 500 Da due to robust tight junctions, composed of claudins, relegating transport of these molecules to endothelial transcytosis (Lipinski et al., 1997). The basement membrane consists of interconnected laminin and collagen fibers that restrict diffusion of particles greater than 10 nm (Vllasaliu et al., 2014). However, endothelial cell transcytosis can transport nanoparticles up to at least 100 nm in a charge-dependent manner (Bannunah et al., 2014). More detailed reviews of endothelial barriers and their transport mechanisms can be found in Lum et al. (1994), Minshall et al. (2002), and Abbott et al. (2010).

**TABLE 2.5.12.6 Characteristics of Gastrointestinal (GI) Tract Segments**

| GI Tract Segment | Epithelial Cell Type | Mucus Type | Surface Area | Segment Length | Residence Time | pH | Temperature |
|---|---|---|---|---|---|---|---|
| Oral cavity | Stratified squamous | Dilute | 100–220 $cm^2$ | 8–9 cm | Seconds to minutes | 6.2–7.3 | 34–37°C |
| Esophagus | Stratified squamous | Salivary | 200 $cm^2$ | 23–25 cm | 4–8 s | ~7.0 | 36–38°C |
| Stomach | Secretory columnar | Thick, adherent | 3.5 $m^2$ | 0.25 m | 90 min | 1–2 | 36–38°C |
| Duodenum | Simple columnar | Thin, adherent | 1.9 $m^2$ | 0.35 m | 30–40 min | 4–5.5 | 36–38°C |
| Jejunum | Simple columnar | Thin, adherent | 184 $m^2$ | 2.8 m | 1.5–2 h | 5.5–7.0 | 36–38°C |
| Ileum | Simple columnar | Thin, adherent | 276 $m^2$ | 4.2 m | 5–7 h | 7.0–7.5 | 36–38°C |
| Colon and rectum | Columnar dominated | Thick, Increasing | 1.3 $m^2$ | 1.5 m | 1–60 h (35–38 h avg) | 7.0–7.5 | 34–37°C |

## Biomaterial DDSs for Drug Targeting

Tissue targeting of DDSs can ameliorate many side effects, including off-target tissue toxicity, by increasing the width of the TW. Tissue targeting is especially critical for delivery of cytotoxic cancer treatments; the chemotherapeutic drug doxorubicin is dose limited due to off-target cardiotoxicity (Barenholz, 2012). Nanoscale DDSs can be used to passively target tissues based on the carrier physicochemical properties or modified with active targeting ligands to enhance tissue accumulation (Fig. 2.5.12.10). Recent advances in both passive and active targeting are shown in Table 2.5.12.7 and additional information can be found in Chapter 1.3.8.

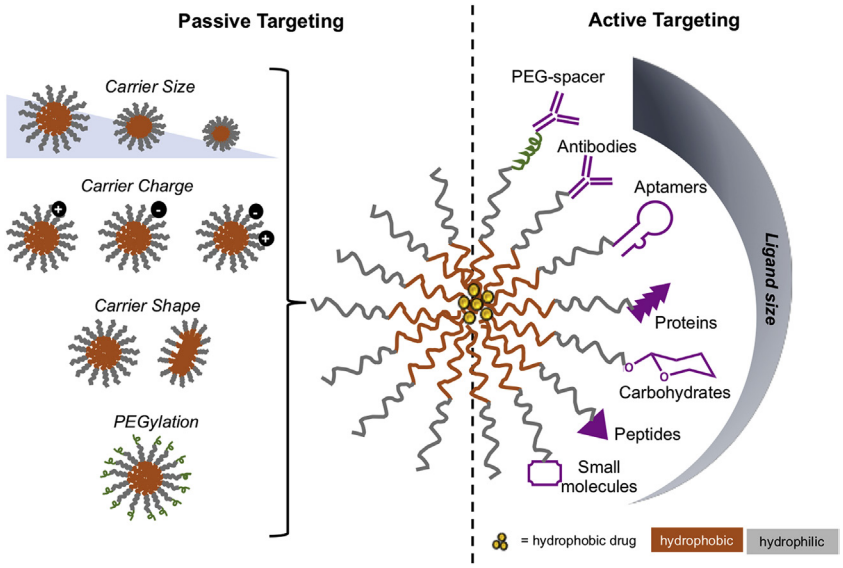
### Passive Targeting

Passive targeting describes tissue accumulation of DDSs based on physicochemical properties and target tissue physiology (Fig. 2.5.12.10). In the 1980s, Maeda et al. observed preferential tumor accumulation of poly(styrene-*co*-maleic acid)-neocarzinostatin drug–polymer conjugates and coined the process as the enhanced permeability and retention (EPR) effect (Matsumura and Maeda, 1986; Maeda et al., 1985). The EPR effect describes the phenomena in which leaky vasculature of the tumor environment is coupled with poor lymphatic drainage, resulting in increased extravasation of macromolecular and nanoparticles into the interstitial space (Accardo and Morelli, 2015). EPR has been subsequently described as a consequence of tissue inflammation, including injury and infection. Passive targeting has evolved since the discovery of EPR, and the evolution has highlighted the importance of DDS physicochemical properties, including size, surface charge, shape, modulus, hydrophobicity, and PEGylation to achieve preferential targeting, as depicted in Fig. 2.5.12.10 (Blanco et al., 2015; Duncan, 2003; Chen et al., 2015; Perry et al., 2011; Merkel et al., 2011; Christian et al., 2009; Cai et al., 2007; Decuzzi et al., 2010; Kolhar et al., 2013; Barua et al., 2013; Banerjee et al., 2016; Beletskii et al., 2014).

A unique advantage of passive targeting is that it requires little to no DDS modification and therefore is relatively simple, which leads directly to lower costs and easier translation (Muro, 2012). Passive targeting is a straightforward approach to achieve tissue-specific accumulation; however, it relies upon EPR. Unfortunately, the EPR effect applies predominantly to inflamed tissues and is not guaranteed to widen the TW to sufficiently limit off-target toxicity for all drugs. In addition to the EPR effect, when a DDS is injected systemically, it undergoes interactions with plasma proteins and subsequent immune cell recognition and uptake within the liver, spleen, and lymph nodes, the MPS (Lucas et al., 2017; Petschauer et al., 2015). MPS can be taken advantage of for passive targeting by altering DDS size, shape, surface modification, surface charge, and particle dose to dramatically impact their distribution (Lucas et al., 2017). For more information regarding the effect of other physiochemical properties of carriers on passive targeting, please refer to the following publications (Blanco et al., 2015; Chen et al., 2015; Perry et al., 2011; Decuzzi et al., 2010; Muro, 2012).

### Active Targeting

The concept of the "magic bullet" (e.g., target-specific drug delivery) was first proposed by Paul Ehrlich (Strebhardt and Ullrich, 2008; Ehrlich, 1900). Although still not a reality due to the body's inherent ability to recognize and clear foreign substances, active targeting has been attempted for a variety of DDSs, targets, and drugs to enhance tissue-specific accumulation (Hoffman, 2008). Active targeting involves direct coupling or adsorption of targeting groups to a DDS leading to greater drug accumulation versus off-target tissues (Fig. 2.5.12.10). The target can be on an organ/tissue, cellular, subcellular, or molecular level, thus requiring appropriate selectivity of the ligand. This section will




• **Figure 2.5.12.10** Schematic representation of passive and active targeting of drug delivery systems. Passive targeting relies on the physicochemical properties of the carrier, including size, charge, and shape. Additionally, surface modification with poly(ethylene glycol) (PEG) has been shown to enhance circulation time and improve targeting. Active targeting is shown displaying the different ligands and associated range in sizes.

briefly discuss the different types of targeting ligands, and the delivery systems that have been explored to further the quest for the "magic bullet."

## Antibodies

Antibodies are promising targeting groups due to specificity toward their respective antigen. Antibodies that are directly conjugated to small molecule drugs are termed antibody–drug conjugates (ADCs). Although ADCs enjoy therapeutic success, they will not be further discussed here as they are outside the scope of biomaterial DDSs. Antibodies are excellent targeting groups due to high target affinity and specificity and myriad functional groups that allow simple and robust DDS conjugation. However, conjugation can lead to impaired antibody affinity due to uncontrolled conjugation in close proximity to antigen binding sites. Additionally, the large molecular weight of antibodies may also dramatically change DDS characteristics. To circumvent some of these challenges, antibody fragments (Fab and Fv or scFv) have been explored. Antibodies and antibody fragments have been conjugated to liposomes (Huang et al., 1980; Heath et al., 1980), polymeric carriers (Kabanov et al., 1989; Song et al., 2010; Seymour et al., 1991; Omelyanenko et al., 1996; Merdan et al., 2003; Song et al., 2005), and PDCs (Ulbrich and Subr, 2010; Xu et al., 2015; Kopecek and Kopeckova, 2010; Minko, 2010). Additional information of antibody-targeted DDSs can be found in Table 2.5.12.7 and in the following reviews (Xu et al., 2015; Bertrand et al., 2014; Friedman et al., 2013; Allen, 2002).

## Proteins

Proteins, such as naturally occurring transferrin or synthetic proteins (e.g., ankyrin), can also be used as targeting moieties. Although typically smaller than antibodies, these proteins still may result in alterations in DDS characteristics and result in poorly controlled functional group conjugations. Currently, there are various transferrin targeted liposomes being developed and undergoing clinical trials, as highlighted in Table 2.5.12.7 and in the following reviews (Bertrand et al., 2014; Friedman et al., 2013; Allen, 2002).

## Peptides

Peptides have excellent potential for targeted DDSs due to their small size, high stability, limited immunogenicity, and ease of conjugation. The development of phage display techniques has enabled identification of various peptide sequences with high specificity and affinity to cellular and microenvironmental targets. The most widely used targeting peptide is arginylglycylaspartic acid (RGD), which binds to integrins upregulated in tumor cells and endothelial cells during tumorigenesis. RGD and other peptides have since been conjugated to liposomes (Accardo and Morelli, 2015; Nishiya and Sloan, 1996; Schiffelers et al., 2002; Garg et al., 2009), polymeric carriers (Hart et al., 1995; Erbacher et al., 1999; Suk et al., 2006; Nasongkla et al., 2004), and PDC (Newman et al., 2018). Additional information of peptide-targeted DDSs can be found in Table 2.5.12.7 and in various reviews (Accardo and Morelli, 2015; Bertrand et al., 2014; Friedman et al., 2013).

## Aptamers

Aptamers are single-stranded oligonucleotides developed with selective enrichment processes to have high affinity for protein targets (Bertrand et al., 2014; Liang et al., 2015; Catuogno et al., 2016). Prostate-specific membrane antigen (PSMA)-targeted aptamers for docetaxel have decreased tumor growth and increased survival (Farokhzad et al., 2006). Despite the potential of aptamer ligands, their

**TABLE 2.5.12.7 Various Examples of Targeting Ligands**

| Ligand | Advantages | Disadvantages | Ligands | Targets | Carriers | References |
|---|---|---|---|---|---|---|
| Antibody | Highly specific and selective | Immunogenic, large size hinders conjugations and contributes to NP size increase, sensitive to environmental changes | Anti-CD44, trastuzumab, anti-HER2 Ab, anti-EGFR Ab#, ScFv-EGFR, etc. | CD44, HER2#, EGFR | Liposomes#, polymer NPs, PDC | Xu et al. (2015); Heath et al. (1980); Song et al. (2010); Merdan et al. (2003); Song et al. (2005); Friedman et al. (2013); Allen (2002); Park et al. (2002); Guo et al. (2018) |
| Aptamer | Easy to synthesize, high affinity and specificity, nonimmunogenic | Easily degraded by enzymes, conjugation stability is challenging, increases size of carriers, expensive to produce | Anti-PSMA aptamer (A9/A10), anti-HER2 aptamer (A6), CH6, etc. | PSMA, HER2, osteoblasts | Polymer NPs, Liposomes, PDC | Bertrand et al. (2014); Friedman et al. (2013); Liang et al. (2015); Catuogno et al. (2016); Powell et al. (2017); Jiang et al. (2015); Cheng et al. (2007) |
| Protein | High affinity | Immunogenic, conjugations are complicated due to presence of multiple functional sites | Transferrin#, affibodies, ankyrin repeat proteins, gp120, etc. | Transferrin-receptor#, EpCAM, HER2, EGFR, DC-SIGN | Liposomes#, polymer NPs, PDC | (Xu et al. (2015); Bertrand et al. (2014); Friedman et al. (2013); Allen (2002) |
| Carbohydrate | Biocompatible, can be easily derivatized | Requires multiple carbohydrate entities to achieve strong binding | Galactose, Mannose, Lactose, HA, Chitosan, etc. | Lectin, CD44 | Liposomes, polymer NPs, polymer–drug conjugates | Xu et al. (2015); Bertrand et al. (2014); Friedman et al. (2013); Allen (2002) |
| Peptide | Small size, improved stability, facile synthesis and conjugation | Can elicit activity on substrate and alter the fate of the NP | RGD, Tet-1, E-selectin binding peptide, CLL1, TBP, etc. | Integrins, E-selectin, TRAP, CLL1 receptor | Liposomes, polymer NPs, PDC | Xu et al. (2015); Accardo and Morelli (2015); Friedman et al. (2013); Allen (2002); Newman et al. (2018); Wang et al. (2017) |
| Small Molecule | Small size, inexpensive to produce, improved stability | Identifying new affinity ligands, subpar specificity and affinity | Folic acid, tetracycline, BP, ACUPA#, etc. | Folate receptor, hydroxyapatite, PSMA# | Polymer NPs#, Liposomes, PDC | Xu et al. (2015); Bertrand et al. (2014); Friedman et al. (2013); Allen (2002); Hrkach et al. (2012); Farrell et al. (2018); Wang et al. (2015) |

# Indicates targeting ligands in clinical trials. Additional examples of active-targeted carriers in clinical trials can be found in Bertrand et al. (2014).
*ACUPA*, *S*,*S*-2-(3-(5-Amino-1-carboxypentyl)-ureido)-pentanedioic acid; *BP*, bisphosphonates; *CLL1*, C-type lectin domain; *DC-SIGN*, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin; *EGFR*, epidermal growth factor receptor; *HA*, hyaluronic acid; *HER2*, human epidermal growth factor receptor 2; *NP*, nanoparticle; *PSMA*, prostate-specific membrane antigen; *TBP*, TRAP-binding peptide; *TRAP*, tartrate-resistant acid phosphate.

susceptibility to enzymatic degradation is a major limitation and may ultimately hinder the clinical utility of aptamer targeting. Additional information of aptamer-targeted DDSs can be found in Table 2.5.12.7 and in the following reviews (Xu et al., 2015; Bertrand et al., 2014; Friedman et al., 2013).

### *Carbohydrates*

Carbohydrate-targeting groups, including galactose, mannose, fucose, and lactose, enable specific binding to lectin-expressing cells. Consequently, lectin-binding liposomes (Chono et al., 2008; Sato et al., 2007; Gregoriadis Neerunjun, 1975; Mauk et al., 1980; Garcon et al., 1988; Ying et al., 2010), polymeric carriers (Sutton et al., 2007), and PDCs have been explored to target a variety of drugs (Xu et al., 2015; Duncan et al., 1983; Seymour et al., 1987; Negre et al., 1992; Kim et al., 2006; Nahar and Jain, 2009). More detailed examples of carbohydrate-targeted DDSs can be found in Table 2.5.12.7.

### *Small Molecules*

Small molecule ligands are associated with benefits, including small size, low cost, and ligand stability. The best-studied small molecule ligand is folic acid due to its nanomolar affinity toward folate receptors (FRs), which are highly expressed in ~40% of cancers (Guo and Lee, 1999; Lee and Low, 1995; van Steenis et al., 2003). Folic acid-targeting carriers have become so successful that they are being explored to screen and identify FR-positive patients prior to treatment. Unfortunately, one of the challenges associated with folate-targeted carriers is expression of FRs within healthy noncancerous tissues, leading to off-target tissue accumulation. Another active targeting carrier, BIND-014, uses a small molecule ligand *S*,*S*-2-(3-(5-amino-1-carboxypentyl)-ureido)-pentanedioic acid to specifically target PSMA and deliver docetaxel, resulting in progression of this DDS to Phase 2 clinical trials (Hrkach et al., 2012). Small molecule ligands have been conjugated to liposomes (Lee and Low, 1995; Wang et al., 1995; Yang et al., 2009; Sarti et al., 1996; Liao et al., 1998; Eavarone et al., 2000), polymeric carriers (Guo and Lee, 1999; van Steenis et al., 2003; Mislick et al., 1995; Yoo and Park, 2004; Flanagan et al., 1989; Wightman et al., 1999; Huang et al., 2007; Vinogradov et al., 1999), and PDCs. While this section highlights just a few small molecule-targeted systems, keep in mind that additional small molecule ligands exist, such as bisphosphonates and tetracyclines, which can target bone tissue (Farrell et al., 2018; Wang et al., 2015). Additional information on these approaches is listed in Table 2.5.12.7 and in various reviews (Bertrand et al., 2014; Friedman et al., 2013).

Maintaining ligand specificity, affinity, and multivalency to enhance binding potential is critical for successful active targeting. For example, DDSs acquire a protein corona almost immediately upon introduction systemically, which can limit active targeting group availability and affinity (Cedervall et al., 2007; Monopoli et al., 2012; Tenzer et al., 2013; Lundqvist et al., 2008). Attachment of spacer arms of various lengths has been explored to reduce both steric hindrances imposed by ligand conjugation as well as the protein corona (Fig. 2.5.12.10).

## Regulatory and Intellectual Property Considerations for DDSs

Pharmaceutical companies routinely pursue DDSs not only to enhance therapeutic efficacy but also to maximize drug financial returns by patenting controlled-release formulations and extending market exclusivity. DDSs are combination products—those that combine drugs, biologics, and/or biomaterials using physical, chemical, or some other means to produce a biomedical device (Anderson et al., 2017; Couto et al., 2012). One of the earliest examples of a combination product was the metered-dose inhaler developed in the mid-1950s by Riker Laboratories, as described in the section "History of DDS Development" (Stein and Thiel, 2017; Anselmo and Mitragotri, 2014; Couto et al., 2012). Although combination products of drugs and devices have existed for more than 60 years, only in the last 15 years have regulatory authorities worldwide provided specific guidance for this product category (Table 2.5.12.8). Due to the increase in number and sophistication of combination products over the last few decades, the United States Congress enacted the Medical Device User Fee and Modernization Act in October 2002. Soon afterward, the FDA established the Office of Combination Products to address combination drug and device products entering the marketplace (Couto et al., 2012). Likewise, other regulatory agencies around the world also began considering or implementing similar changes. However, for simplicity this section focuses solely on the guidance offered by the FDA. The Office of Combination Products determines the product's primary mode of action (PMOA), designates the product's primary function, and then assigns it to the appropriate FDA center for regulatory evaluation (Couto et al., 2012).

### Regulation

Ever since the FDA took these actions to provide guidance documents and offer a single point of contact for regulation of combination products, a general pattern in the process from discovery to development to market entry has been observed (Fig. 2.5.12.11). During product development, sponsors (typically companies) develop combination products. This design and development stage is based on the principle of Quality by Design (QbD). The FDA defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (Q8(R2) Pharmaceutical Development,

**TABLE 2.5.12.8 Summary of Global Regulatory Guidance Documents for Combination Products**

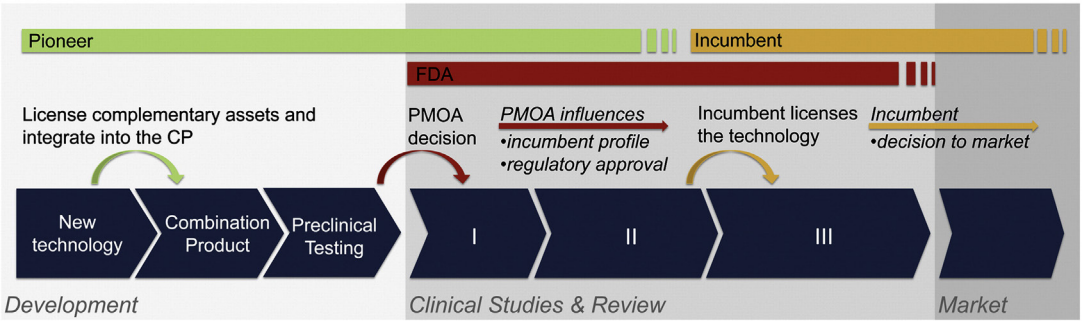
| Country/Region | Regulatory Agency | Combination Products Regulatory Guidance |
|---|---|---|
| United States of America | Food and Drug Administration | 21 CFR Parts 3 and 4 |
| Australia | Therapeutic Goods Administration | Australian Regulatory Guidelines for Medical Devices<br>Australian Register of Therapeutic Goods |
| Brazil | Agência Nacional de Vigilância Sanitária | Medical Devices BRAZIL Demarest e Almedia Advogados: Lex Mundi Publication. 2011 |
| Canada | Health Canada | Food and Drug Regulations<br>Medical Device Regulations<br>Natural Health Products Regulations<br>"Classification of Products at the (Medical) DeviceDrug Interface" |
| European Union | European Medicines Agency | Medicinal Products: Directive 2001/83<br>Medical Devices: Regulation 2017/745 |
| Japan | Pharmaceuticals and Medical Devices Agency | "Handling of Approval Application for Combination Products" dated October 24, 2014<br>Pharmaceutical and Food Safety Bureau (PFSB) Notification No. 1024-(2) of the Evaluation and Licensing Division;<br>PFSB Notification No. 1024-(1) of the Director of Medical Devices Evaluation, Evaluation and Licensing Division;<br>PFSB Notification No. 1024-(9) of the Safety Division; PFSB Notification No. 1024-(15) of the Compliance and Narcotics Division |

2017). More generally, QbD is a development approach where product Critical Quality Attributes are defined through a risk assessment and then development teams work backward to address these key items in the product design (Singh et al., 2010). Sponsor development teams must consider and include design controls (described in 21 CFR 820.30 and ISO 13485) when combining a drug or biologic with a specific delivery device (Anderson et al., 2017). Design controls are a system of checks and balances intended to make systematic assessment of the product design with a focus on the end user as a key part of development (21 CFR 820.30) (C.f.D.a.R. Health, 1997; Kinsel, 2012). This requirement has historically been associated with medical device development but was established for combination products as part of a 2013 revision to FDA guidance (21 CFR Part 4) on Current Good Manufacturing Practices (Anderson et al., 2017). The development stage concludes with rigorous preclinical testing that provides essential data to justify moving into clinical trials.

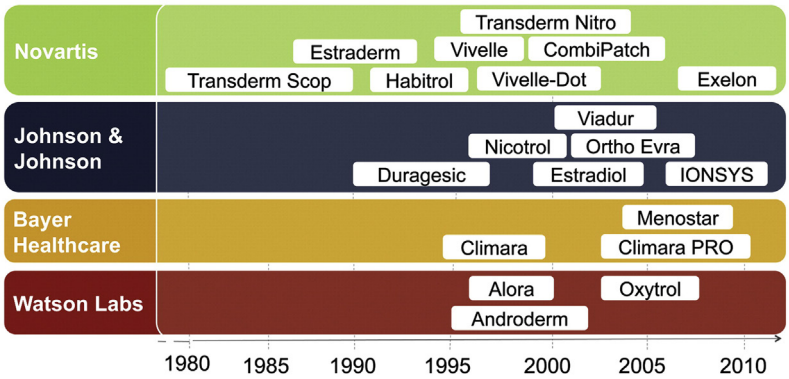
The PMOA assessment is affected by integration of the complementary technologies, execution of QbD during development, and completion of preclinical testing. Regulators use the PMOA to determine which agency center of excellence should support the regulatory approval process. Once the PMOA is defined, the regulatory approval pathway (e.g., drug, biologic, or medical device) becomes clear, and established companies in a specific market, termed incumbents, lead the clinical trials, commercialization, and marketing processes for the combination product (Fig. 2.5.12.11) (Couto et al., 2012). For example, Alza Corp. integrated transdermal patch technology into a product, assisted with the initial regulatory assessment, and modeled a corporate structure for commercialization and marketing that others later followed (Fig. 2.5.12.12) (Couto et al., 2012). Ultimately, if the combination product is successful in clinical trials, the company will execute a market launch to reach patients and maintain ongoing commercial manufacturing, marketing, and annual regulatory filing efforts for the duration of the product's lifetime.

## Intellectual Property

It is not uncommon for the drug development process to require more than 15–20 years of research and development work, including preclinical animal studies and human clinical trials. Thus it is reasonable for pharmaceutical companies to maximize drug financial returns by extending the patent lifetime of the product, thereby postponing the inevitable introduction of generics. One means of doing this is to patent a combination product, such as a new controlled-release formulation with the same drug. However, the commercial feasibility of such a strategy is predicated on a demonstration that the controlled-release formulation is indeed superior in safety and efficacy to the single bolus dose formulation (or a previous controlled-release formulation). Moreover, the cost of the controlled-release formulation must be low enough to ensure a reasonable market penetration. Based on FDA guidance documents, the 505(b)(2) approval pathway allows companies to make small changes to a currently approved drug and still maintain market exclusivity for up to 7 years. This mechanism is less expensive, has a faster approval process, minimizes risk, and maintains market exclusivity. This strategy has led to annual DDS product revenues exceeding $100 billion as




• **Figure 2.5.12.11** Schematic summarizing the dynamics of the development and approval process for drug–device combination products from the corporate, technology, and regulatory perspectives. (Used with permission from Couto, D.S., et al., 2012. Lessons from innovation in drug-device combination products. Adv. Drug Deliv. Rev. 64 (1), 69–77.)




• **Figure 2.5.12.12** Timeline showing Food and Drug Administration approval dates of transdermal patches developed and marketed by companies that followed Alza Corp.'s initial patch commercialization model. (Used with permission from Couto, D.S., et al., 2012. Lessons from innovation in drug-device combination products. Adv. Drug Deliv. Rev. 64 (1), 69–77.)

of 2014 (Anselmo and Mitragotri, 2014). This approach is an excellent example of life-cycle management for DDSs as the product approaches its patent expiry. Often, companies initiate future-generation products even before regulators have approved the previous version(s) of a drug. For more information regarding the combination product regulatory process, life-cycle management, and other related intellectual property considerations, the reader is referred to Chapters 3.5 and 3.6, as well as several review articles (Anderson et al., 2017; Couto et al., 2012; Zylberberg and Matosevic, 2016; Davar and Ghosh, 2010).

## Final Remarks

Over the past 60 years, DDS materials and designs have progressed from external devices and simple off-the-shelf macroscopic polymeric materials to microscopic, degradable, drug-loaded microparticles and ultimately to complex, rationally designed nanocarriers. The DDS field has grown to a multibillion dollar industry over this timeframe. While DDSs have dramatically improved convenience and clinical usefulness of many drugs and enabled new therapeutics, such as siRNA, to become clinically viable, some of the most challenging problems of drug delivery have yet to be fully addressed. As the next generation of DDSs undergoes clinical trials utilizing less invasive DDSs with tissue-specific delivery and more efficient drug dosing, the trend in overcoming the remaining challenges will continue to be driven by innovations in biomaterials development and integration.

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