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Topic: Advanced (Drug) Delivery Systems

Abstract

Drug delivery seeks to improve the safety and efficacy of modern therapeutics. Increasingly, healthcare economics is also involved, seeking to find the best possible technology value (price-to-performance) for any given drug delivery strategy. Value is defined by offering significantly improved therapeutic outcomes over existing drug treatments at lower cost. Competition is acute.

Drug delivery focuses on innovating formulation, the process by which different chemical substances, including the active drug, are combined to produce a final medicinal product. Formulations can be as diverse as liquids, solids, solutions, heterogeneous dispersions, or inhaled vapors. They are employed to efficiently and reliably deliver an increasingly complex set of small and large molecule therapeutic agents to targets. Producing drug stability, both in storage and after exposure to the human body, is an important aspect of drug formulation. This stability is particularly important for biologic drugs (peptides, proteins), and hydrolytically sensitive drugs. Formulation can be directed at the molecular level where chemical conjugation is used to link delivery components together into molecular constructs capable of drug delivery. Beyond conjugation or molecular formulation, particles, aggregates of particles or macroscopic forms, such as liquid boluses, capsules or tablets are most common: oral drug delivery still represents nearly 60% of modern drug formulations marketed today.

Drug delivery targeting, either passively or actively, is used to attempt to get more drug to the desired site and less to off-target sites that might produce toxicity. Active targeting refers to the use of a disease-specific targeting ligand (e.g., lectin, antibody, peptide or affinity tag) to provide tissue-site recognition and binding. Passive targeting refers to non-molecular-affinity approaches to encourage drug accumulation preferentially at a therapeutic site. These might include simple partitioning into selective tissues, hydraulic sequestration, physical accumulation, avoidance of clearance and excretion, and other mechanisms.

Over 70% of new drug candidates in testing are water-insoluble: modern drug discovery processes now select molecular architectures that don't dissolve in bodily fluids. The "new drug" pipeline is full of new molecules with bioavailability, stability, targeted delivery, controlled release, and manufacturability challenges. Drug delivery technologies can help solve these increasing, costly challenges that are required to get them into clinical testing. Many physical and chemical drug formulating approaches are simply directed at getting drugs to dissolve in body fluids at levels sufficient to produce therapy.

Novel drug delivery technologies that improve drug efficacy and safety by controlling the time, rate, and place of drug release in the body; reduce off-site toxicity issues, improve patient compliance; extend patent protection; and provide competitive differentiation for pharmaceuticals are all compelling features of a drug delivery system (DDS).

All drugs have adverse side effects. A Paracelsus approach is still appropriate: "all things are toxic; the toxicity lies in the dose". Toxicity is estimated to be responsible for the pre-clinical attrition of nearly 30% of new drug candidates and remains a major contributor to the high cost of drug development ($billions/candidate). Importantly, this problem often is not recognized until late in clinical trials or post-marketing, and is therefore highly costly. Most often, liver and kidney adverse effects are problems. Causes of drug toxicity include mechanism-based (on-target) toxicity, immune hypersensitivity, off-target toxicity, production of toxic drug metabolites, and bioactivation/covalent modification of host peptides/proteins. Drug delivery seeks to limit toxicity by altering the effective dose, or altering the drug's exposure to the sensitive organ responsible for toxicity. This is approached by changing the route of drug administration (i.e., changing intravenous dosing to transdermal dosing), or changing the drug potency through improved targeting to reduce dosing, or changing drug circulating times (pharmacokinetic/pharmacodynamic profiles) using formulating strategies. Controlling drug exposure to off-target sites

amounts to controlling the drug's "biodistribution" (i.e., where it goes in the body) using passive or active targeting, or site-specific delivery (i.e., local or topical delivery). Nanoparticle formulations injected intravenously are well-known to accumulate (over 95% of injected dose whether targeted or not) in the liver, lungs, spleen, kidney and bone marrow. Controlling nanoparticle biodistributions and circulating times is critical to controlling both their therapeutic and toxic potentials.

Particulate drug formulations (microparticles and nanoparticles) exhibit high specific surface areas (i.e., 100-400 m^2/g). This surface is typically insoluble; that is, both solid particle and surfactant particles present "interfaces" to physiological components. Synthetic surfaces and interfaces presented to physiology are intrinsically reactive: formulation surfaces interact non-specifically with proteins, cells, and enzymes. The intrinsically high surface areas associated with bolus particle injections produce ubiquitous acute reactions in the body. These are usually associated with adverse interactions with the host immune system cells (leukocytes), and host proteins and enzymes in the coagulation and complement cascades. Many different cell types use phagocytosis to actively ingest particles to different degrees (e.g., endothelial cells, epithelial cells, myofibroblasts), but dedicated phagocytes (macrophages, M cells, Kupfer cells, dendritic cells) take up particles at much higher frequency. Toxicity can be associated with unintentional targeting of these cell types (i.e., in the liver, spleen, lung). Intravenous particle injection also targets two blood protein cascades: non-specific protein adsorption to these particles creates surface-adsorbed protein coronas that target these particles for bodily elimination, and protein activation responses that produce blood and complement activation. Blood activation occurs through particle adsorption of circulating blood proteins responsible for hemostasis. Several zymogens (pro-enzymes) in the intrinsic and extrinsic blood coagulation cascades are activated to enzymatic protease action by simple surface adsorption. Once started, these cascades produce serial enzyme activation and amplification converging on the serine protease, Factor X. Subsequent protein activation steps produce thrombin that cleaves blood protein fibrinogen to fibrin, yielding a blood clot or thrombus. Many, if not all, particles administered to blood exhibit corona formation, some pro-coagulant activity and thrombogenic potential from this interfacial activation. Cationic dendrimers are well-known to produce extreme coagulation activation depending on cationic charge density (coagulopathy). A second cascade involves other blood proteins yielding complement activation. The complement system comprises part of the host endogenous immune system that enhances (or complements) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promoting inflammation and attacking the pathogen's cell membrane as a result. Unfortunately, particles activate complement non-specifically through the alternative pathway via spontaneous hydrolysis of the protein, C3, triggering a complex cascade of pro-inflammatory activation steps. Complement proteins often have cell receptors to potentiate their action once produced. Complement activation activates leukocytes and chemotaxis, opsonization, bacterial lysis, T-cell sensitization to antigen-presenting cells, and even pro-coagulant activity. Excessive and uncontrolled complement activation has many detrimental and sometimes fatal consequences. Particles enhance these risks. Many commercial-grade drug nanoparticles are known to activate coagulation and/or complement.

Patient adherence to their specific therapeutic regimen -- taking their medication the intended way -- is increasingly a focus for drug delivery. This is called patient compliance. In the United States alone, more than 50% of prescribed medications are taken incorrectly or not at all, and incorrect use of medications has been linked to up to 125,000 deaths/year. More than $200 billion (approximately 8% of the US healthcare expenditures in 2013) could potentially be saved each year by increasing patient adherence. Drug delivery systems that eliminate patient errors or automatically enforce proper medication dosing and administration are increasingly important.