A comprehensive overview of drug delivery systems: Mechanisms, innovations, and future directions

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Abstract---**Background:** Drug delivery systems (DDS) are critical in enhancing the efficacy and safety of therapeutic agents by controlling their release rate, timing, and location. This comprehensive review covers various DDS mechanisms, innovations, and future directions. **Aim:** The aim of this article is to provide an in-depth overview of the different drug delivery routes, mechanisms, and technologies. It highlights advancements and future prospects in DDS to improve patient outcomes and treatment efficacy. **Methods:** The review synthesizes information from recent advancements and innovations in DDS. It evaluates various drug delivery routes including oral, parenteral, transdermal, transmucosal, pulmonary, and localized methods, as well as emerging technologies such as nanotechnology and advanced drug carriers. **Results:** Key findings indicate significant progress in DDS technologies. Oral drug delivery continues to face challenges such as variable absorption and first-pass metabolism, while parenteral methods offer rapid onset but suffer from patient discomfort. Transdermal and transmucosal systems show promise for improving drug efficacy and patient compliance. Pulmonary drug delivery has advanced with the development of new formulations and devices, and localized delivery methods are improving targeted treatment for cancer and cardiovascular diseases. Innovations such as nanotechnology and engineered bacteria are emerging as transformative solutions for more effective drug delivery. **Conclusion:** The field of drug delivery systems is evolving rapidly with advancements in technology and methodology. Future research

should focus on overcoming existing limitations, such as poor bioavailability and patient compliance issues, and exploring new delivery systems like nanotechnology and gene therapy. The continued development of DDS will likely lead to more effective and personalized therapeutic approaches, enhancing treatment outcomes and patient quality of life.

Introduction

A drug delivery system (DDS) is conceptualized as a formulation or device designed to facilitate the introduction of a therapeutic agent into the body, enhancing its efficacy and safety by regulating the release rate, timing, and location of the drug. This process encompasses the administration of the therapeutic product, the release of active components from the product, and their subsequent transport across biological membranes to the target site. The term "therapeutic agent" also extends to entities like gene therapy, which induces in vivo synthesis of the active therapeutic component. Gene therapy aligns with the broad definition of a DDS, though it may necessitate novel delivery methods for gene vectors. Nonetheless, gene therapy is subject to distinct regulatory controls. A drug delivery system acts as an intermediary between the patient and the therapeutic agent. It can be either a drug formulation intended for therapeutic use, or a device designed to administer the drug. This distinction between drug and device is crucial, as it determines regulatory oversight by drug control agencies. If a device is used for purposes other than drug delivery, such as therapeutic effects through physical means, or if a drug is incorporated into a device to mitigate complications, it is regulated as a device. The classification between drugs and devices is diverse, and the categorization is determined on an individual basis.

Drug Delivery Routes

Medications can be introduced into the human body through various anatomical routes, either for systemic effects or targeted delivery to specific organs and conditions. The selection of the administration route depends on factors such as the disease, desired effect, and available product. Drugs may be delivered directly to the affected organ or administered systemically with targeting to the diseased organ. This classification includes various systemic drug delivery methods by anatomical routes.

Oral Drug Delivery

Historically, the oral route has been the predominant method for administering both conventional and novel drugs, primarily due to its ease of use and widespread patient acceptance. However, this method has several significant limitations: Oral drugs intended for systemic effects often exhibit variable

absorption rates and unpredictable serum concentrations. This variability has led to the development of sustained-release and controlled-release formulations. The acidic environment and pervasive digestive enzymes within the gastrointestinal tract can degrade some drugs before they reach the site of systemic absorption, particularly affecting ingested proteins. Consequently, this route poses challenges for administering biotechnology products. Macromolecules and polar substances frequently struggle to cross the epithelial cells of the small intestine to enter the bloodstream, limiting their use to localized effects within the gastrointestinal tract. Drugs may become insoluble at the low pH levels found in the digestive tract. Since only soluble forms of drugs can be absorbed into the bloodstream, this transition to an insoluble state can significantly reduce bioavailability. Some drugs undergo hepatic inactivation during first-pass metabolism, such as the inactivation of glyceryl trinitrate by hepatic monooxygenase enzymes. Certain drugs can irritate the mucosal lining of the gastrointestinal tract, although this issue can be partially mitigated through coating. Despite these challenges, the oral route remains the most preferred method for drug delivery, with ongoing advancements aimed at improving the efficacy of oral formulations.

Parenteral Drug Delivery

Parenteral drug delivery refers to the introduction of substances into the body via routes other than the gastrointestinal tract, encompassing subcutaneous, intramuscular, intravenous, and intra-arterial injections. Injections targeted at specific organs for localized drug delivery will be discussed in various therapeutic contexts. Parenteral administration is a well-established method in medical practice and is the most common invasive drug delivery approach. Many critical drugs are available exclusively in parenteral form. Conventional syringes, which may be glass or plastic (disposable), can be equipped with autodestruct mechanisms or retractable needles. The benefits of parenteral administration include:
- Rapid onset of action.
- Predictable and near-complete bioavailability.
- Avoidance of gastrointestinal complications associated with oral drug delivery.
- Reliable drug administration in patients who are severely ill or unconscious.

However, parenteral delivery has notable drawbacks:
- Pain and discomfort are associated with injections, which can affect patient compliance.
- Limitations in administering protein products, particularly those requiring sustained release.

Types of Parenteral Injections:
- **Subcutaneous Injections:** These involve administering drugs into the subcutaneous fatty tissue using a hypodermic needle. This method is suitable for self-administration, as seen with insulin for diabetes management. Factors influencing subcutaneous drug delivery include:
  - Molecular size: Larger molecules diffuse more slowly than smaller ones.

o Viscosity: Higher viscosity can hinder drug diffusion.
o Anatomical characteristics: Vascularity and the amount of fatty tissue at the injection site affect absorption rates.

Subcutaneous injections generally have a slower absorption rate and onset of action compared to intramuscular or intravenous injections. The rate of absorption may be improved with the enzyme hyaluronidase. Disadvantages include:

o Difficulty in controlling absorption rates.
o Potential for local irritation and pain at the injection site.
o Necessity to frequently rotate injection sites to avoid tissue damage from unabsorbed drug.

Self-administration systems for subcutaneous injections include conventional syringes, pre-filled syringes, auto injectors, pen pumps, and needle-less injectors. This route remains reliable for peptides and macromolecules.

- **Intramuscular Injections:** Administered deep into skeletal muscles such as the deltoids or gluteal muscles, intramuscular injections offer a faster onset of action compared to subcutaneous injections but are slower than intravenous injections. Absorption is diffusion-controlled and is influenced by the physiological characteristics of the muscle and the properties of the injected solution. Disadvantages include:
  o Pain at the injection site.
  o Limitations on the volume that can be injected based on muscle mass.
  o Potential degradation of peptides at the injection site.
  o Risks of peripheral nerve injury, hematoma, abscess formation, and inadvertent blood vessel puncture.

Intramuscularly administered drugs typically form a depot in muscle tissue from which they are gradually absorbed, with peak concentrations generally occurring within 1 to 2 hours. Factors affecting the rate of drug release from the depot include depot compactness, drug concentration and particle size, solvent nature, product form, flow characteristics, and injection volume.

- **Intravenous Administration:** This method involves injecting an aqueous solution directly into a vein or continuous infusion via a catheter. It is the sole method available for some drugs and is preferred in emergencies due to its rapid onset. Advantages include minimal drug loss, lower required doses, and controlled infusion rates. Particle distribution in intravenous solutions can target specific organs based on particle size, which is useful for organ-specific drug delivery. Disadvantages include:
  o Possible immune reactions to proteins and peptides.
  o Risks of venous trauma, thrombophlebitis, and infections.
  o Potential for extravasation causing tissue irritation and necrosis.
  o Risk of air embolism.

Recent advancements include modifying drug kinetics and metabolic profiles through the use of nanovesicles, such as liposomes, for intravenous administration.

Intra-arterial Drug Delivery

Intra-arterial drug delivery is not commonly used for systemic therapeutic administration. It is primarily employed for regional chemotherapy targeting specific organs and limbs. This technique involves injecting drugs directly into the arteries or perfusing them through catheters placed in arterial vessels. Intra-arterial chemotherapy is notably utilized for treating malignant tumors in the brain.

Transdermal Drug Delivery

Transdermal drug delivery involves administering medications through the skin as an alternative to oral, intravenous, subcutaneous, and transmucosal routes. A comprehensive overview of the technologies and commercial aspects of this approach is available in dedicated reports [1].
Key categories of transdermal drug delivery include:

- **Local Application Formulations:** Such as transdermal gels.
- **Penetration Enhancers:** Substances that facilitate drug absorption through the skin.
- **Drug Carriers:** Including liposomes and nanoparticles.
- **Transdermal Patches:** Adhesive patches that deliver drugs over time.
- **Nanoparticle-based Transdermal Delivery:** Utilizes nanoparticles for enhanced drug delivery.
- **Transdermal Electrotransport:** Uses electrical currents to enhance drug penetration.
- **Physical Modalities:** Methods like needle-free injections that facilitate drug transport through the skin.

Innovative techniques such as hydrogel-forming microneedle arrays combined with electrophoresis have been developed for controlled transdermal delivery of biomacromolecules, expanding the range of drugs that can be administered via this route [2]. Advances in nanotechnology also play a significant role in enhancing transdermal drug delivery, as detailed in Chapter 2 [3].

Transmucosal Drug Delivery

Drugs can be administered through mucous membranes lining various internal passages and orifices of the body. General principles apply across mucous membranes, while specific details are addressed according to anatomical locations such as buccal, nasal, and rectal areas. Drug permeation across mucous membranes occurs via diffusion. At equilibrium, the rate of substance movement through the tissue remains constant, with permeability coefficients unaffected by solution concentration or direction of nonelectrolyte transfer. Similar to skin absorption, the primary pathways for permeation are intercellular rather than intracellular. The use of surfactants, such as sodium lauryl sulfate, and penetration enhancers like oleic acid in propylene glycol can improve drug

diffusion through mucosal surfaces. Advantages of transmucosal drug delivery include:

- Avoidance of injections.
- Enhanced therapeutic efficiency.
- Potential for peptide administration.
- Rapid absorption compared to oral routes.
- Bypassing first-pass hepatic metabolism.
- Greater patient acceptance and lower costs compared to injectable options.

Mucoadhesive controlled-release devices can enhance the effectiveness of transmucosal drug delivery by maintaining drug concentrations within therapeutic ranges, reducing dilution in body fluids, and enabling targeted delivery. Acrylic-based hydrogels are commonly used as mucoadhesive systems, offering flexibility and reduced tissue damage. The adhesive properties of these hydrogels can be improved by incorporating long, flexible poly(ethylene glycol) chains.

Buccal and Sublingual Routes:

Buccal drug absorption depends on factors such as lipid solubility, salivary pH, and the drug's partition coefficient. An ideal vehicle is one where the drug has minimal solubility, facilitating quick systemic absorption due to the rich mucosal network. Buccal administration allows for:

- Rapid systemic absorption and onset of effect.
- Option to remove the tablet if adverse effects occur.
- Avoidance of first-pass hepatic metabolism.
- Prolonged residence time in the buccal cavity for sustained-release formulations.
- Use in patients with swallowing difficulties.

Limitations include the need to keep the tablet in place, potential for rapid dissolution due to excessive salivary flow, and issues with taste affecting patient compliance. These challenges can be mitigated by using patches or sprays.

Nasal Drug Delivery

Nasal drug delivery has been utilized for both topical and systemic effects for many years. Topical applications address conditions such as nasal congestion, rhinitis, and sinusitis, using medications like corticosteroids and antihistamines. The nasal route is advantageous for systemic drug delivery, particularly to circumvent first-pass metabolism and gastrointestinal degradation associated with oral administration. It can also provide direct access to the brain. The nasal cavity is covered by different types of epithelium: squamous and transitional in the anterior third, olfactory epithelium in the upper region, and a ciliated, pseudostratified columnar epithelium in the remaining portion. Cilia in the nasal cavity play a crucial role in mucus propulsion, and drugs can impact ciliary function. Safety assessments for nasal drugs include evaluating their effects on ciliary movement and mucus properties.

Intranasal Drug Delivery:

This route is suitable for drugs ineffective when taken orally, those used chronically, or those requiring rapid systemic absorption. The rate of drug diffusion through the nasal mucosa is influenced by factors such as molecular weight and ability to form hydrogen bonds. For drugs with molecular weights under 300, absorption is less affected by physicochemical properties and occurs via aqueous channels in the membrane. Factors affecting nasal drug absorption include:

- Nasal secretion rate: Higher secretion reduces drug bioavailability.
- Ciliary movement: Faster movement decreases drug absorption.
- Nasal vascularity: Increased blood flow enhances absorption.
- Nasal metabolism: Enzymatic activity in the nasal cavity affects peptide drugs.

A major limitation of nasal delivery is rapid mucociliary clearance, which can lower bioavailability. In situ nasal gelling systems have been explored to provide sustained drug delivery via the nasal route [4].

Enhancement of Nasal Drug Delivery
Enhancing nasal drug delivery involves strategies to increase drug absorption, reduce metabolism, and prolong the drug's residence time in the nasal cavity. Here are the main strategies:

- **Prodrugs and Chemical Modifications:** These involve modifying the drug molecule to improve its absorption through the nasal mucosa.
- **Physical Methods:** Techniques such as using nasal absorptive enhancers can increase permeability.
- **Special Excipient Effects:** Certain excipients in nasal preparations can enhance drug transport through the nasal mucosa.

Characteristics of Absorption Enhancers:
- Pharmacologically inert.
- Nonirritating, non-toxic, and non-allergenic.
- Reversible effects on the nasal mucosa.
- Compatible with the drug.
- Adequate residence time in the nasal cavity.
- No offensive odor or taste.
- Cost-effective and readily available.

Example of an Absorption Enhancer:
- **Chitosan:** A naturally occurring polysaccharide from crustacean shells, acts as a bioadhesive. It prolongs formulation retention on the nasal mucosa and promotes absorption through paracellular transport. Chitosan technology has shown improved bioavailability and rapid onset compared to oral or subcutaneous administration.

Advantages of Nasal Drug Delivery
- **High Permeability:** Compared to the epidermis and gastrointestinal mucosa.

- **Highly Vascularized:** The subepithelial tissue facilitates rapid drug absorption.
- **Rapid Onset:** Typically within half an hour.
- **Avoidance of First-Pass Metabolism:** Bypasses the liver.
- **Avoidance of Gastric Issues:** Useful for patients with conditions affecting the gastrointestinal tract.
- **Ease of Administration:** Familiar to patients through nasal drops or sprays.
- **Higher Bioavailability:** Compared to gastrointestinal or pulmonary routes.
- **Suitable for Peptides:** Effective for peptide drugs.

Disadvantages of Nasal Drug Delivery
- **Disease Conditions:** Nasal diseases can impair drug absorption.
- **Limited Dose:** Restricted by the small absorption area.
- **Limited Time:** Short time available for drug absorption.
- **Effect of Common Cold:** May expel medication from a blocked or watery nose.
- **Not Suitable for All Drugs:** Polar drugs and some macromolecules have poor absorption due to membrane permeability, rapid clearance, or enzymatic degradation.

Current Developments: Researchers are exploring alternative methods, including phospholipids and surfactants as absorption enhancers, and drug delivery systems like liposomes, cyclodextrins, and nanoparticles to improve nasal drug delivery.

Nasal Drug Delivery to the CNS
Nasal drug delivery can target the central nervous system (CNS) by bypassing the blood-brain barrier (BBB) through the olfactory epithelium. The olfactory nerve provides a direct route to the CNS, making it a valuable approach for drugs intended to act directly on the brain.

Gastric Drug Delivery
Orally administered drugs often face challenges in the stomach due to gastric acid and other conditions affecting drug stability and absorption. For example, biological therapies like proteins and peptides can be rapidly degraded in the stomach. **Innovative Approach:** The ingestible self-orienting millimeter-scale applicator (SOMA) has been designed to deliver drugs directly through the gastric mucosa. This device autonomously positions itself in the stomach, delivering insulin with plasma levels comparable to subcutaneous administration. Further validation in large animal models and clinical trials is needed for peptide delivery [5][6].

Colorectal Drug Delivery
Drug delivery to the rectum has a long history, but patients often prefer other routes. Despite this, the colon is suitable for drugs aimed at the large intestine or systemic effects due to its prolonged retention time. Key requirements include:

- **Delivery Form:** Slow release or targeted forms via oral ingestion, enema, or rectal suppository.
- **Overcoming Barriers:** Must pass through the colonic mucus and survive bacterial metabolism.

Factors Influencing Drug Delivery to the Colorectal Area
- **Blood Flow:** Rate of blood flow affects drug absorption.
- **Dietary Components:** Complex carbohydrates can trap molecules.
- **Lipid Solubility:** Lipid-soluble drugs are absorbed more readily.
- **Gastric Emptying and Transit Time:** Affects drug residence time.
- **Motility Patterns:** Determine drug transit and absorption rates.

Advantages of Rectal Drug Administration
- **Large Dosage:** Relatively large amounts can be administered.
- **Bypassing Destructive Environments:** Effective for drugs destroyed by gastric acid or enzymes.
- **Safety and Convenience:** Particularly useful for infants and the elderly, and for emergencies.
- **Independent of Food Intake:** Absorption is not affected by food or gastric emptying.
- **Lower Degradation:** Less degradation compared to the upper gastrointestinal tract.
- **Bypasses the Liver:** For drugs absorbed from the lower rectum.

Disadvantages of Rectal Drug Administration
- **Limited Absorption of Certain Drugs:** Hydrophilic drugs and some peptides may require enhancers.
- **Potential Irritation:** Can cause rectal irritation, proctitis, or bleeding.
- **Alternative Routes:** Oral administration can achieve similar therapeutic goals with fewer complications for drugs not suited for rectal delivery. Despite these challenges, rectal drug delivery remains a valuable option for certain therapeutic needs, offering specific advantages in terms of drug stability and targeted treatment.

Pulmonary Drug Delivery
The use of the pulmonary route for systemic drug delivery has gained attention due to the lung's potential for delivering peptides and the feasibility of gene therapy, such as for cystic fibrosis. Understanding how macromolecules are absorbed through the lungs is crucial for optimizing this delivery method.

Mechanisms of Macromolecule Absorption by the Lungs
The lungs offer a large surface area for drug absorption due to the extensive alveolar epithelium. Key points include:
- **Surface Area and Structure:** The alveoli provide a vast surface area (approximately 100 square meters) with a dense capillary network, which facilitates drug absorption.
- **Barriers to Absorption:**
  - **Surfactant Layer:** Can trap large molecules.

- o **Surface Lining Fluid:** Contains components that can affect drug absorption.
- o **Epithelial Cell Layer:** Thin but a significant barrier for macromolecules.
- o **Extracellular Space and Basement Membrane:** Additional barriers.
- o **Vascular Endothelium:** More permeable to macromolecules than the epithelial layer.

Absorption Mechanisms:
1. **Transcytosis:** Passage through cells, often receptor-mediated, but not significant for macromolecules >40 kDa.
2. **Paracellular Absorption:** Occurs through junctional complexes between cells; more relevant for molecules <40 kDa.
3. **Drug Transporter Proteins:** Involved in the absorption of specific drugs like β2-agonists.

Pharmacokinetics of Inhaled Therapeutics for Systemic Delivery
Accurate pharmacokinetic modeling for inhaled drugs is complex. Methods include:
- **In Vivo Models:** Small rodents are commonly used for assessing pharmacokinetics through controlled dosing.
- **In Vitro Models:** Lung epithelial cell lines help study drug transport kinetics.
- **Ex Vivo Models:** Isolated perfused lungs provide detailed kinetic descriptors for lung absorption and clearance.

Each model has its advantages and limitations, requiring careful selection based on research needs and developmental stages.

Advantages of Pulmonary Drug Delivery
- **Large Absorption Surface Area:** Extensive alveolar surface area enhances drug absorption.
- **Proximity to Blood Flow:** Efficient systemic absorption due to close blood vessel proximity.
- **Avoidance of First-Pass Metabolism:** Bypasses the liver, leading to potentially higher bioavailability.
- **Reduced Dosage:** Smaller doses may be required compared to oral routes for equivalent effects.

Disadvantages of Pulmonary Drug Delivery
- **Aerodynamic Filter:** The lungs have a filtering mechanism that can hinder drug deposition.
- **Mucociliary Clearance:** Mucus lining clears particles from the airways.
- **Variable Deposition:** Only 10–40% of inhaled drug particles typically reach the lungs with conventional devices.

Techniques of Systemic Drug Delivery via the Lungs
Several techniques are being developed or refined:

- **Dry Powders:** Contain higher percentages of active drug compared to liquids, allowing for more efficient dosing and reduced risk of microbial growth.
- **Inhalers:** Deliver liquid formulations directly, avoiding the need to convert proteins to powders.
- **Nanoparticulate Formulations:** Improve delivery to the deep lung and bioavailability.
- **Controlled-Release Systems:** Reduce dosing frequency, increase drug half-life, and could lead to new therapeutic products.

Conclusions and Future of Pulmonary Drug Delivery

The pulmonary route is increasingly established for systemic drug delivery, especially for peptides and proteins. Future developments will likely focus on improving dry powder formulations and device design. Potential advancements include:

- **Effervescent Carrier Particles:** Could improve deep lung deposition and drug release.
- **Inhalable Therapeutics:** Development of new treatments for conditions such as influenza, nausea, and vaccinations. Inhalable antibiotics could target lung diseases like tuberculosis.

Cardiovascular Drug Delivery

Drug delivery to the cardiovascular system involves both systemic and localized treatments, leveraging the vascular system's ability to supply blood to all organs. Key methods include:

- **Direct Intramyocardial Injection:** Delivering drugs directly into the heart muscle.
- **Coronary Venous System Delivery:** Administering drugs via the coronary veins.
- **Cardiac Catheter Injection:** Delivering drugs into coronary arteries through catheterization.
- **Intrapericardial Delivery:** Injecting drugs into the pericardial space.
- **Drug-Eluting Stents:** Releasing drugs directly into arterial lumens from implanted stents.

Drug Delivery to the Central Nervous System

Delivering drugs to the CNS is challenging due to the blood-brain barrier (BBB), which restricts drug access to the brain. Most research focuses on controlled release formulations and novel delivery methods, such as:

- **Systemic Administration:** Traditional approach, still prevalent.
- **Alternative Delivery Methods:** Includes various strategies to bypass or penetrate the BBB for effective CNS drug delivery. These methods and ongoing research aim to improve the efficacy and safety of CNS therapeutics.

Drug Delivery Across the BBB

Crossing the blood-brain barrier (BBB) remains a significant challenge for delivering drugs to the central nervous system (CNS). Nanotechnology-based strategies have emerged as potential solutions to this problem. These strategies

utilize nanoparticles to transport drugs across the BBB, enhancing drug delivery efficacy. Additionally, direct methods such as the lumbar intrathecal route can be employed for pain medications to act on the spinal cord without requiring BBB penetration.

Concluding Remarks on Routes of Drug Delivery

Different routes of drug delivery offer various advantages and limitations. Advances in delivery techniques, such as needle-less injections, can improve patient compliance by reducing discomfort. A comparison of these routes highlights the evolving nature of drug delivery systems and their impact on therapeutic outcomes.

Drug Delivery for Cancer

Cancer treatment involves multiple drug delivery strategies depending on the cancer type, desired effect, and available products. Drug delivery systems (DDS) in cancer therapy focus on innovative approaches to improve efficacy and minimize side effects. Key strategies include direct tumor delivery, systemic targeting, and leveraging molecular biology advancements.

Delivery of Antiangiogenic Agents

Angiogenesis, the growth of new blood vessels from existing ones, is crucial for tumor development. Cancer cells stimulate new blood vessel formation by releasing proteins like VEGF and angiopoietin 2, which in turn prompt endothelial cells to support tumor growth. Targeting these angiogenic processes can inhibit tumor growth by disrupting its blood supply.

- **Integrin Receptors:** Tumor endothelial cells express integrins not found in normal blood vessels, making them targets for antiangiogenic therapies. These therapies include drugs conjugated to integrin-targeting ligands or nanoparticulate carriers.
- **Combination Therapy:** Antiangiogenic agents are often used alongside other therapies to prevent tumor resistance and improve treatment efficacy. Combining them with chemotherapeutics or physical agents like hyperthermia can enhance overall therapeutic outcomes.

Bacterial Agents for Delivery of Anticancer Therapies

Bacterial agents offer innovative approaches to cancer treatment by exploiting their ability to target and accumulate in tumors.

- **Engineered Bacteria:** Nonpathogenic bacteria like E. coli and Bifidobacterium breve have been engineered to deliver anticancer agents or emit detectable light. These bacteria preferentially grow within tumors, providing targeted therapy and continuous drug delivery.
- **Oncolytic Bacteria:** Genetically modified bacteria such as Salmonella can deliver high concentrations of anticancer agents to tumors while minimizing systemic exposure. These bacteria exploit the tumor's immune suppression to persist and deliver therapeutic agents.

Monoclonal Antibodies (MAbs)

Monoclonal antibodies are highly specific therapies that target receptors on tumor cells, offering a more precise treatment with reduced systemic toxicity compared to traditional therapies.

- **MAbs Applications:** They block key tumor cell receptors or recruit the immune system to target cancer cells. MAbs can also be conjugated with toxins to deliver potent drugs directly to cancer cells.

Antibody–Drug Conjugates (ADCs)

ADCs combine the specificity of MAbs with the potency of small molecules, improving the selectivity and efficacy of cancer therapies while reducing systemic toxicity.

- **Examples:**
  - **Kadcyla (ado-trastuzumab emtansine or T-DM1):** For HER2-positive metastatic breast cancer, combining trastuzumab with DM1.
  - **Adcetris (brentuximab vedotin):** For Hodgkin lymphoma and systemic anaplastic large cell lymphoma, combining anti-CD30 with monomethyl auristatin.

Antibody–Enzyme Conjugates

These conjugates target tumor-associated sialosides, which tumors use to evade immune detection. By desialylating tumor cells, antibody–enzyme conjugates enhance susceptibility to immune destruction.

Targeted Delivery of Antibodies in Cancer

Targeted cancer therapies involve:
1. **MAbs Targeting:** Binding to cell surface receptors or tumor microenvironment components.
2. **Small-Molecule Inhibitors:** Acting within cancer cells on proteins like kinases, proteasomes, and polymerases.

These methods can be used alone or in combination with conventional therapies to improve treatment efficacy and patient outcomes.

Drug Formulations

Sustained Release (SR)

- **Purpose**: Extends drug action duration, reduces dosing frequency, minimizes plasma level fluctuations, improves utilization, and reduces adverse effects.
- **Challenges**: Increased cost, variable drug levels due to food intake and individual differences, and complexity in defining optimal release forms.
- **Mechanisms**: Chemical modifications or specialized delivery systems, such as coatings that delay drug diffusion.

Controlled Release

- **Purpose**: Regulates drug delivery at a specific rate and duration, independent of the environment.
- **Applications**: Can deliver drugs over days to years and may include site-specific or targeted delivery.

Programming the Release at a Defined Time

- **Methods**: Physical (e.g., swelling or bursting) or chemical (e.g., enzymatic degradation) mechanisms.

- **Examples**: Port system and Chronset system, which use osmotic pressure and semipermeable capsules for controlled release.

Prodrugs
- **Definition**: Inactive drug forms that convert to the active compound in the body.
- **Requirements**: Adequate access to receptors, activation only at the target site, and retention of the active drug at the site.
- **Example**: l-dopa, which converts to dopamine in the brain.

Novel Carriers and Formulations
- **Focus**: Innovations in drug delivery systems, including new formulations and carriers.
- **Examples**: Various technologies and biodegradable implants that improve drug bioavailability.

Antibody-Targeted Systems
- **Mechanism**: Drugs are linked to antibodies or carried in vesicles like liposomes for targeted delivery.
- **Advantages**: Reduced drug amounts needed, fewer side effects, and enhanced targeting of tumor antigens.
- **Examples**: Immunoliposomes for anticancer drugs and radiolabeled antibodies for imaging and therapy.

Gene Therapy
- **Definition**: Transfer of genetic material to specific cells to alter disease states.
- **Methods**: Includes bacterial vectors (bactofection) and lipid-based technologies for delivering siRNAs.
- **Scope**: Broad range of technologies for targeted and controlled gene therapy.

Cells as Drug Delivery Vehicles
- **Applications**: Encapsulation of drugs in red blood cells (RBCs) or use of cell-based gene therapy.
- **RBCs**: Provide a biocompatible, long-lasting delivery method, but have limited storage life and potential sequestration in the spleen.

Ideal Properties for Drug Delivery Materials
- **Criteria**: Includes size control, biocompatibility, precise drug delivery, minimal immunogenicity, and ease of synthesis.

Innovations for Oral Drug Delivery
- **Fast-Dissolving Tablets**: Convenient, fast absorption, and improved compliance.
- **Softgel Formulations**: Enhance bioavailability of hydrophobic drugs and offer advantages over tablets in terms of stability and absorption.
- **Drug Release Mechanisms**: Geometric configurations and three-dimensional printing (3DP) for controlled drug release.

Drug Delivery Devices

- **Types**: Include pumps, conduits, microchips, and lab-on-a-chip technologies.
- **Applications**: Controlled-release devices, continuous glucose monitoring, and smart tablets for responsive drug delivery. This comprehensive overview captures the evolution and various technologies involved in enhancing drug delivery, focusing on the development of systems that provide sustained, controlled, or targeted drug release, along with innovative devices and formulations [18-20].

Conclusion

The landscape of drug delivery systems (DDS) has expanded significantly with innovative approaches aimed at addressing the limitations of traditional methods. Oral drug delivery remains widely used due to its convenience, but challenges such as variable absorption and first-pass metabolism continue to drive the development of advanced formulations like sustained-release and controlled-release systems. Parenteral drug delivery, including subcutaneous, intramuscular, and intravenous methods, offers rapid onset and high bioavailability but is often associated with patient discomfort and limitations in protein drug delivery. Transdermal and transmucosal delivery methods have demonstrated substantial potential in enhancing drug efficacy and patient compliance. Innovations such as transdermal patches, penetration enhancers, and novel drug carriers like liposomes and nanoparticles are paving the way for more effective and less invasive treatment options. Pulmonary drug delivery is gaining traction, particularly for peptides and gene therapy, due to the large surface area of the lungs and the ability to bypass first-pass metabolism. Advances in formulation techniques and delivery devices are improving the effectiveness of this route. Localized drug delivery strategies, particularly for cancer and cardiovascular treatments, are showing promise in targeting specific sites with minimal systemic side effects. The use of drug-eluting stents, direct intramyocardial injections, and targeted delivery systems are examples of how precision medicine is being integrated into therapeutic practices. Emerging technologies, such as nanotechnology, engineered bacteria, and advanced drug carriers, are expected to revolutionize drug delivery by improving targeted therapy, bioavailability, and reducing side effects. As research continues, it is crucial to address existing challenges, including bioavailability issues and patient compliance, while exploring new avenues for DDS. The future of drug delivery lies in the convergence of technology and personalized medicine, promising more effective and tailored therapeutic interventions.

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نظرة شاملة على نظم توصيل الأدوية: الآليات، الابتكارات، والتوجهات المستقبلية

الملخص:

الخلفية: نظم توصيل الأدوية (DDS) حيوية في تعزيز فعالية وسلامة العوامل العلاجية من خلال التحكم في معدل إطلاقها، توقيت إطلاقها، وموقعها. تستعرض هذه المراجعة الشاملة مختلف آليات نظم توصيل الأدوية، الابتكارات، والتوجهات المستقبلية.

الهدف: يهدف هذا المقال إلى تقديم نظرة عميقة على طرق توصيل الأدوية المختلفة، الآليات، والتقنيات. يسلط الضوء على التقدمات والتوقعات المستقبلية في نظم توصيل الأدوية لتحسين نتائج المرضى وفعالية العلاج.

الطرق: تقوم المراجعة بتركيب المعلومات من التقدمات والابتكارات الأخيرة في نظم توصيل الأدوية. تقيم طرق توصيل الأدوية المختلفة بما في ذلك الفموية، البارينترالية، عبر الجلد، عبر الأغشية المخاطية، التنفسية، والطرق الموضعية، بالإضافة إلى التقنيات الناشئة مثل النانوتكنولوجيا وحاملات الأدوية المتقدمة.

النتائج: تشير النتائج الرئيسية إلى تقدم كبير في تقنيات نظم توصيل الأدوية. تستمر طرق التوصيل الفموية في مواجهة تحديات مثل امتصاص متغير وميتابوليزم أول مرور، بينما توفر الطرق البارينترالية بداية سريعة لكنها تعاني من عدم الراحة لدى المرضى. تظهر نظم التوصيل عبر الجلد وعبر الأغشية المخاطية وعدًا في تحسين فعالية الأدوية وامتثال المرضى. شهد توصيل الأدوية عبر الرئتين تقدمًا مع تطوير تركيبات وأجهزة جديدة، وتحسنت الطرق الموضعية في تقديم العلاج المستهدف لمرضى السرطان وأمراض القلب والأوعية الدموية. تظهر الابتكارات مثل النانوتكنولوجيا والبكتيريا المهندسة كحلول تحويلية لتوصيل الأدوية بشكل أكثر فعالية.

الاستنتاج: يتطور مجال نظم توصيل الأدوية بسرعة مع التقدم في التكنولوجيا والمنهجية. يجب أن تركز الأبحاث المستقبلية على تجاوز القيود الحالية، مثل انخفاض التوافر البيولوجي ومشكلات امتثال المرضى، واستكشاف نظم توصيل جديدة مثل النانوتكنولوجيا والعلاج الجيني. من المرجح أن يؤدي التطور المستمر في نظم توصيل الأدوية إلى طرق علاجية أكثر فعالية وتخصيصًا، مما يعزز نتائج العلاج وجودة حياة المرضى.

الكلمات المفتاحية: نظم توصيل الأدوية، توصيل الأدوية الفموية، توصيل الأدوية البارينترالية، التوصيل عبر الجلد، التوصيل التنفسي للأدوية، النانوتكنولوجيا، العلاج الجيني، توصيل الأدوية الموضعية