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REVIEW ON: TARGETED DRUG DELIVERY SYSTEM(TDDS)

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Abstract: Targeted drug delivery systems (TDDS) represent a significant advancement in the field of pharmacotherapy, offering precise delivery of therapeutic agents to specific cells, tissues, or organs while minimizing systemic side effects. This review provides a comprehensive overview of the design principles and applications of targeted drug delivery systems. Various targeting strategies, including passive and active targeting approaches, are discussed, with an emphasis on ligand-receptor interactions, antibody-mediated targeting, and stimuli-responsive systems. Furthermore, the role of nanotechnology in TDDS design is examined, highlighting the development of nanoparticles, liposomes, and polymeric micelles as versatile carriers for targeted drug delivery. The review also addresses the challenges and future prospects of TDDS, including issues related to biocompatibility, stability, and clinical translation. Overall, this review underscores the potential of targeted drug delivery systems to revolutionize drug therapy by improving efficacy, reducing toxicity, and enhancing patient outcomes.

Keyelements: passive targeting, active targeting, drug formulation, drug route, drug carries system, control release system, conventional drug delivery, Enhanced Permeability, nanoparticles, liposomes, antibodies, peptides,

1. Introduction:- A targeted drug delivery system is a sophisticated approach designed to deliver therapeutic agents (drugs or biologics) to specific cells, tissues, or organs within the body with precision and selectivity. Unlike traditional drug delivery methods that often result in systemic distribution of the drug throughout the body, targeted drug delivery systems aim to localize the therapeutic effect at the intended site while minimizing exposure to non-target tissues. [2]

In essence, targeted drug delivery systems employ various strategies to enhance the specificity and efficacy of drug delivery, such as: [2]

1. **Passive Targeting:** Exploiting physiological properties of the target tissue, such as increased permeability or prolonged retention, to achieve selective accumulation of the drug. [2]

2. **Active Targeting:** Incorporating targeting ligands (e.g., antibodies, peptides) onto drug carriers to facilitate specific recognition and binding to molecular targets overexpressed on the surface of target cells.

3. **Triggered Release:** Engineering drug carriers to respond to specific stimuli (e.g., pH, enzymes, temperature) present in the target microenvironment, leading to controlled release of the drug at the desired location.[2]

4. **Site-Specific Administration:** Utilizing specialized delivery routes or devices to directly deliver drugs to the desired site of action, bypassing systemic circulation.

Targeted drug delivery refers to the precise and selective delivery of therapeutic agents to specific cells, tissues, or organs within the body. Unlike conventional drug delivery methods, which often result in systemic distribution of the drug, targeted delivery aims to localize the therapeutic effect while minimizing off-target effects. Drug delivery systems refer to the methodologies and technologies employed to transport therapeutic substances to their intended site of action within the body.

The primary purpose is to optimize the pharmacokinetics and pharmacodynamics of drugs, enhancing their therapeutic efficacy while minimizing adverse effects.[[2]

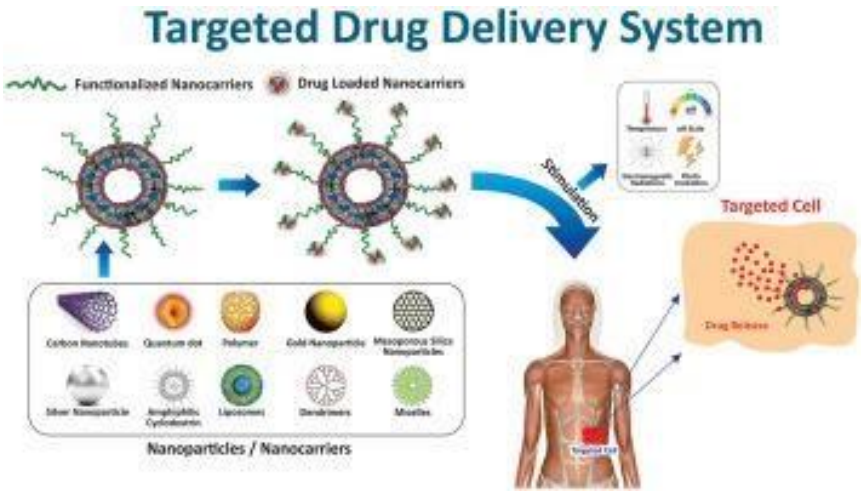

Fig.1.

Components of Drug Delivery Systems:

- **Drug Formulation:** The composition and physical form in which the drug is administered (e.g., tablets, capsules, injections, patches). [5]
- **Delivery Route:** The pathway through which the drug enters the body (e.g., oral, parenteral, transdermal, inhalation).[5]
- **Drug Carrier Systems:** Vehicles or carriers utilized to transport drugs to specific sites within the body (e.g., liposomes, nanoparticles, micelles). [5]
- **Controlled Release Systems:** Techniques to regulate the rate and timing of drug release to maintain therapeutic concentrations over an extended period (e.g., sustained-release formulations, implantable devices).

Components of Drug Delivery Systems:

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Types of Drug Delivery Systems: [23]

- **Conventional Drug Delivery:** Simple formulations and routes of administration without specialized targeting or controlled release mechanisms.

- **Advanced Drug Delivery:** Utilizes specialized carriers, targeting ligands, or controlled release mechanisms to enhance drug delivery specificity and efficacy.

- **Targeted Drug Delivery:** Precision delivery systems designed to target specific cells, tissues, or organs, minimizing off-target effects and maximizing therapeutic outcomes.

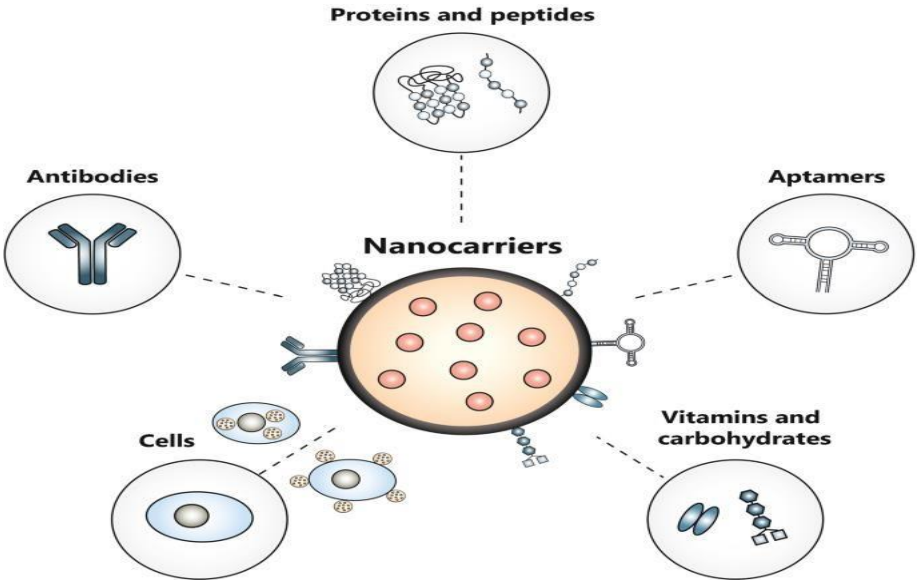


Fig.2

2. Fundamentals of targeted drug delivery:-

1. **Selective Targeting:** Targeted drug delivery systems are designed to selectively deliver drugs to the desired site of action, thereby minimizing exposure to healthy tissues and reducing off-target effects.

2. **Recognition and Binding:** These systems utilize targeting ligands, such as antibodies or peptides, which specifically recognize and bind to molecular targets (e.g., receptors, antigens) overexpressed on the surface of target cells or tissues.

3. **Enhanced Permeability and Retention (EPR) Effect:** Some targeted delivery systems exploit the unique physiological properties of diseased tissues, such as increased permeability of blood vessels and impaired lymphatic drainage, leading to preferential accumulation of drug carriers within the target site.

4. **Controlled Release:** Targeted drug delivery systems often incorporate mechanisms for controlled release of therapeutic agents at the site of action, ensuring sustained and localized drug exposure over time.

Advantages over Conventional Drug Delivery [12,19]

1. **Increased Therapeutic Efficacy:** By delivering drugs directly to the site of action, targeted drug delivery systems enhance therapeutic efficacy by maximizing drug concentration at the desired target while minimizing systemic distribution and dilution.

2. **Reduced Systemic Toxicity:** Targeted delivery minimizes exposure of healthy tissues to the drug, thereby reducing systemic toxicity and adverse effects commonly associated with conventional drug delivery methods.

3. **Enhanced Patient Compliance:** Targeted drug delivery systems can improve patient compliance by reducing the frequency of dosing and minimizing side effects, leading to better treatment outcomes and patient satisfaction.

4. **Potential for Personalized Medicine:** Targeted delivery enables tailored treatments based on individual patient characteristics, such as genetic makeup or disease profile, allowing for more precise and effective therapeutic interventions.

5. **Overcoming Drug Resistance:** Targeted drug delivery systems offer the potential to overcome drug resistance by delivering therapeutic agents directly to drug-resistant cells or by utilizing alternative mechanisms of action.

3. Types of Targeted Drug Delivery Systems:-

1. Passive Targeting

Passive targeting is a strategy in targeted drug delivery systems that takes advantage of the unique physiological characteristics of diseased tissues to achieve selective accumulation of therapeutic agents. Unlike active targeting, which relies on specific molecular interactions, passive targeting exploits properties such as increased permeability of blood vessels and impaired lymphatic drainage in diseased tissues.

Enhanced Permeability and Retention (EPR) Effect

Enhanced Permeability:

In many types of tumors and inflamed tissues, blood vessels exhibit abnormal morphology characterized by large fenestrations or gaps between endothelial cells. This abnormality allows for increased permeability, enabling macromolecules and nanoparticles to extravasate from the bloodstream and accumulate within the tumor or inflamed tissue. [[1]]

Retention:

In addition to increased permeability, tumors and inflamed tissues often have impaired lymphatic drainage, leading to the retention of macromolecules and nanoparticles within the interstitial space. This retention further contributes to the accumulation of therapeutic agents at the target site.

Examples: Liposomes and Nanoparticles **Liposomes:**

Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate hydrophilic or lipophilic drugs within their aqueous or lipid cores, respectively. Due to their nanoscale size and lipid composition, liposomes can exploit the EPR effect to passively accumulate in tumor tissues following intravenous administration. Liposomal formulations of anticancer drugs, such as Doxil® (liposomal doxorubicin), leverage passive targeting to improve drug delivery to tumors while reducing systemic toxicity.

Nanoparticles:

Nanoparticles, including polymeric nanoparticles and lipid nanoparticles, are colloidal particles with sizes typically ranging from 1 to 100 nanometers. Similar to liposomes, nanoparticles can passively accumulate in tumors and inflamed tissues via the EPR effect. They offer versatility in terms of drug loading and surface modification, allowing for tailored delivery of various therapeutic agents. Examples of nanoparticle-based formulations include Abraxane® (albumin-bound paclitaxel nanoparticles) and BIND-014 (polymeric nanoparticles containing docetaxel). [1]

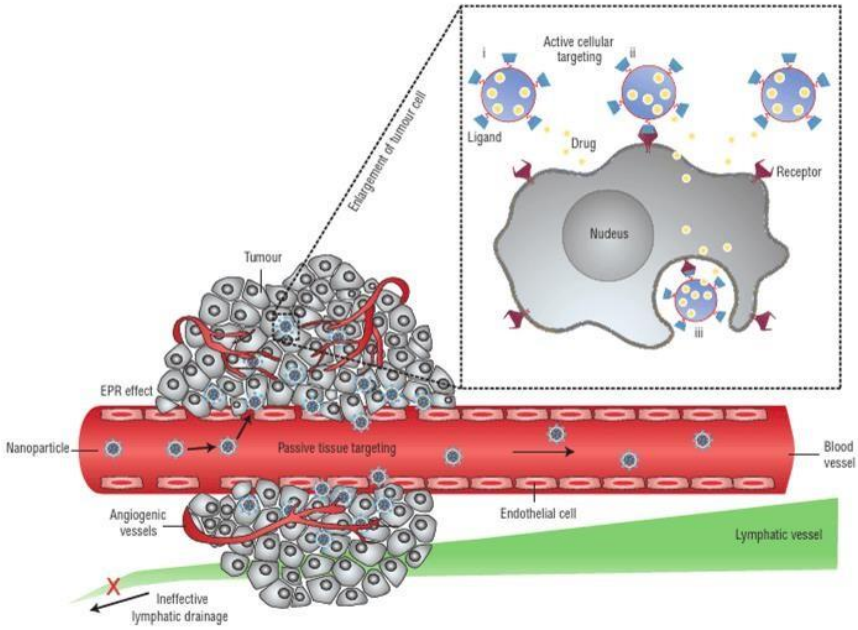


Fig.3.

2. Active Targeting

Active targeting relies on the specific interactions between targeting ligands (e.g., antibodies, peptides, aptamers) conjugated to drug carriers and complementary receptors or antigens expressed on the surface of target cells or tissues. These ligand-receptor interactions facilitate the preferential binding and internalization of the drug carrier into the target cells, thereby enhancing drug delivery specificity and efficacy. [1]

Specificity:

Targeting ligands are selected or engineered to exhibit high affinity and specificity for their corresponding receptors or antigens, ensuring selective binding to the desired target cells while minimizing interactions with non-target cells.

Internalization:

Upon binding to the target receptor, the drug carrier complex is often internalized via receptor-mediated endocytosis, allowing for efficient delivery of the therapeutic payload into the intracellular compartment of the target cells.

Examples: Antibodies and Peptides

Antibodies:

Monoclonal antibodies (mAbs) are highly specific proteins that recognize and bind to unique epitopes present on target antigens. Antibody-drug conjugates (ADCs) combine the targeting specificity of monoclonal antibodies with the cytotoxic properties of chemotherapeutic drugs, enabling selective delivery of potent cytotoxic agents to cancer cells. Examples of FDA-approved ADCs include Adcetris® (brentuximab vedotin) and Kadcyla® (ado-trastuzumab emtansine). [16]

Peptides:

Peptides are short chains of amino acids that can be engineered to exhibit high affinity and specificity for target receptors or cellular markers. Peptide ligands can be conjugated to drug carriers to facilitate targeted drug delivery to specific cell types or tissues. For example, tumor-targeting peptides, such as RGD peptides (arginine-glycine-

aspartic acid), have been utilized to target integrin receptors overexpressed on the surface of cancer cells. Additionally, cell-penetrating peptides (CPPs) can enhance cellular uptake of therapeutic agents by facilitating transport across cell membranes. [16]

4. Key Components of Targeted Drug Delivery Systems:-

1. Carrier Molecules [16]

Carrier molecules serve as vehicles for transporting therapeutic agents to the target site within the body. These carriers can protect the therapeutic payload from degradation, control its release, and enhance its accumulation at the desired location. Common carrier molecules include:

- **Liposomes:** Spherical vesicles composed of lipid bilayers that can encapsulate hydrophilic or lipophilic drugs. Liposomes offer versatility in drug loading and surface modification and can exploit passive targeting mechanisms such as the Enhanced Permeability and Retention (EPR) effect.

- **Polymeric Nanoparticles:** Colloidal particles made of biocompatible polymers that can encapsulate drugs and control their release. Polymeric nanoparticles provide sustained drug release and can be tailored for specific applications through surface modification.
- **Micelles:** Self-assembling structures formed by amphiphilic molecules in aqueous solution. Micelles can solubilize hydrophobic drugs and enhance their stability and bioavailability.

- **Dendrimers:** Highly branched macromolecules with well-defined structures that can encapsulate drugs within their interior void spaces. Dendrimers offer precise control over drug loading and release kinetics.

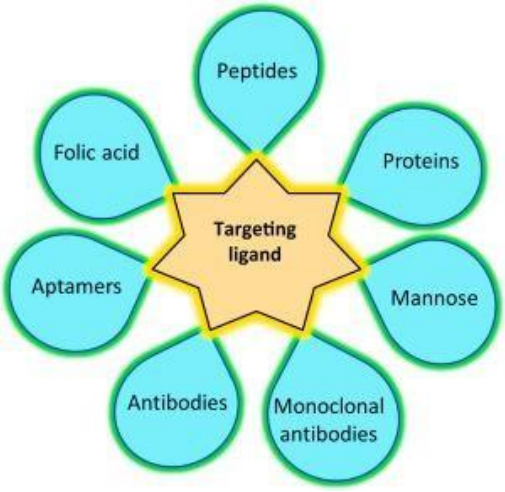
2. Targeting Ligands [15]

Targeting ligands are molecules that specifically recognize and bind to molecular targets (e.g., receptors, antigens) overexpressed on the surface of target cells or tissues. These ligands facilitate the selective delivery of therapeutic agents to the desired site, thereby enhancing drug delivery specificity and efficacy. Common targeting ligands include:

- **Antibodies:** Monoclonal antibodies (mAbs) or antibody fragments that recognize and bind to specific antigens expressed on target cells. Antibodies offer high specificity and affinity for their targets and have been widely used in targeted drug delivery systems, particularly in cancer therapy.

- **Peptides:** Short chains of amino acids that can be engineered to exhibit high affinity and specificity for target receptors or cellular markers. Peptides offer versatility and can be designed to target a wide range of disease-associated molecules.

Aptamers: Short single-stranded nucleic acid molecules (DNA or RNA) that can fold into specific three-dimensional structures and bind to target molecules with high affinity. Aptamers offer advantages such as small size, stability, and ease of synthesis.



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3. Payload (Therapeutic Agents)

The payload refers to the therapeutic agents or drugs that are encapsulated or conjugated to the carrier molecules for delivery to the target site. The choice of payload depends on the specific disease being targeted and may include small-molecule drugs, nucleic acids (e.g., siRNA, mRNA), peptides, proteins, or imaging agents. The payload is designed to exert its therapeutic or diagnostic effect upon reaching the target site, thereby achieving the desired therapeutic outcome.

4.Design and Engineering Considerations:- [1,3,9,20]

Design and engineering considerations are vital in the development of targeted drug delivery systems to ensure their effectiveness, safety, and compatibility with biological systems. Here are the key considerations:

1. Size and Shape of Carriers [[1]]

- **Nanoparticle Size:** The size of carriers, particularly nanoparticles, plays a crucial role in their biodistribution, cellular uptake, and pharmacokinetics. Nanoparticles with sizes ranging from 10 to 200 nanometers are often preferred for drug delivery, as they can passively accumulate in target tissues via the Enhanced Permeability and Retention (EPR) effect.

- **Shape:** The shape of carriers can influence their interaction with biological components and cellular uptake efficiency. Studies have shown that certain shapes, such as spheres, rods, or discs, may exhibit enhanced circulation times, cellular internalization, and tissue penetration compared to others.

2. Surface Modifications [1]

- **Targeting Ligands:** Conjugation of targeting ligands (e.g., antibodies, peptides) to the surface of carriers enables active targeting to specific cells or tissues. Surface modification with targeting ligands enhances the specificity and affinity of carriers for their target receptors, thereby improving drug delivery efficiency.

- **Stealth Coatings:** Coating carriers with hydrophilic polymers (e.g., polyethylene glycol, PEG) can impart stealth properties, reducing recognition and clearance by the immune system and prolonging circulation times in the bloodstream. Stealth coatings enhance the systemic delivery of carriers and minimize immune responses.

3. Stability and Biocompatibility [10]

- **Chemical Stability:** Carriers should maintain their structural integrity and drug-loading capacity under physiological conditions to ensure effective drug delivery. Stability considerations include susceptibility to degradation, aggregation, and premature drug release.

- **Biodegradability:** Biodegradable carriers undergo degradation into non-toxic byproducts over time, facilitating clearance from the body and minimizing long-term accumulation. Biodegradable carriers offer advantages such as reduced toxicity, improved safety, and controlled release of therapeutic agents.

- **Biocompatibility:** Carriers should exhibit compatibility with biological systems and minimal toxicity to host tissues and organs. Biocompatible materials and formulations are essential to prevent adverse reactions, inflammation, or immune responses upon administration.

5. Applications of Targeted Drug Delivery:-

1. Cancer Therapy :[11]

Targeted drug delivery systems play a crucial role in cancer therapy by enhancing the specificity and efficacy of anticancer drugs while minimizing systemic toxicity. Some key applications include:

- **Tumor Targeting:** Targeted delivery systems exploit the overexpression of specific receptors or antigens on cancer cells to selectively deliver cytotoxic agents to tumor tissues, minimizing damage to healthy cells.

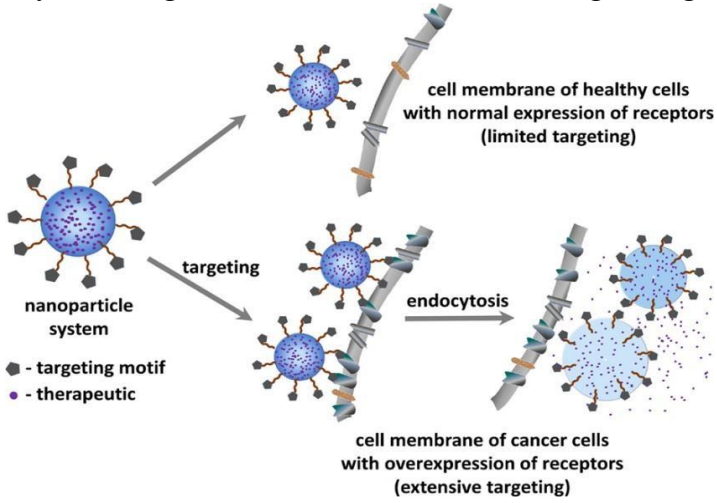

Fig.5.

- **Combination Therapy:** Carrier-based delivery systems enable the co-delivery of multiple drugs with different mechanisms of action, allowing for synergistic effects and overcoming drug resistance in cancer cells.

- **Personalized Medicine:** Targeted drug delivery systems can be tailored to specific molecular signatures of individual tumors, enabling personalized treatment strategies based on the patient's genetic profile or disease characteristics.

2. Treatment of Inflammatory Diseases

Targeted drug delivery systems hold promise for the treatment of inflammatory diseases by delivering antiinflammatory agents directly to the inflamed tissues while minimizing systemic exposure. Key applications include: [19]

- **Localized Drug Delivery:** Carriers can be designed to target inflamed tissues, such as joints in rheumatoid arthritis or the gastrointestinal tract in inflammatory bowel disease, delivering therapeutic agents directly to the site of inflammation. [19]

- **Controlled Release:** Targeted delivery systems enable sustained release of anti-inflammatory drugs, maintaining therapeutic concentrations at the site of action over an extended period and reducing the frequency of dosing. [19]

- **Minimization of Side Effects:** By minimizing systemic exposure to anti-inflammatory drugs, targeted delivery systems can reduce the risk of systemic side effects commonly associated with conventional treatments, such as gastrointestinal disturbances or immunosuppression. [19]

3. Neurological Disorders [4]

Targeted drug delivery systems show promise for the treatment of neurological disorders by improving drug delivery across the blood-brain barrier (BBB) and targeting specific cells or regions within the central nervous system. Key applications include:

- **BBB Penetration:** Nanoparticle-based delivery systems can be engineered to traverse the BBB and deliver therapeutic agents to the brain or spinal cord for the treatment of neurodegenerative diseases, brain tumors, or neuroinflammatory conditions.

- **Targeting Specific Cells:** Targeted delivery systems can selectively target neurons, glial cells, or specific brain regions by incorporating targeting ligands that recognize cell surface receptors or markers associated with neurological disorders.

- **Enhanced Efficacy:** By delivering therapeutic agents directly to the affected brain regions, targeted drug delivery systems can improve drug efficacy while minimizing off-target effects and systemic toxicity.

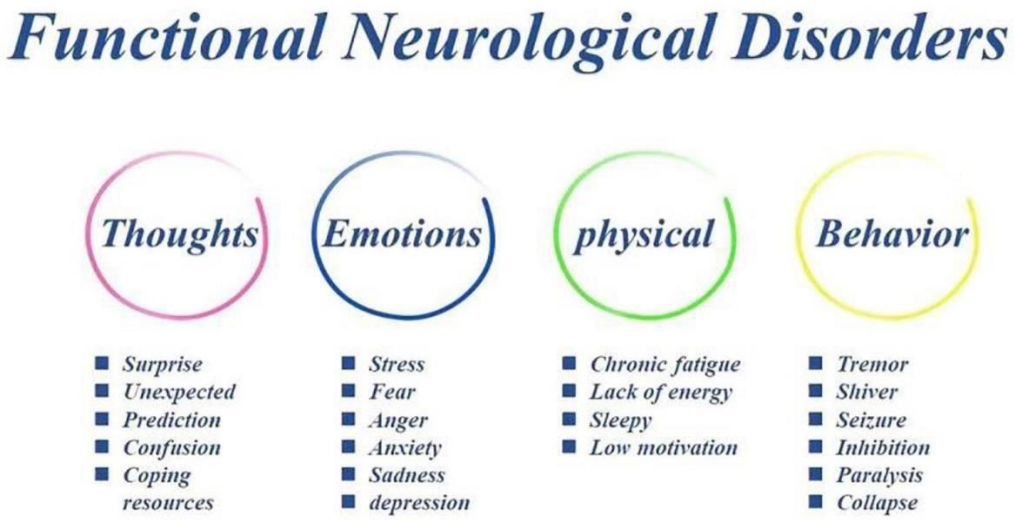

Fig.7

6. Challenges and Future Directions:- [15]

Challenges

1. **Biological Barriers:**
   - **Blood-Brain Barrier (BBB):** The BBB presents a significant challenge for drug delivery to the central nervous system (CNS) due to its selective permeability, limiting the entry of therapeutic agents into the brain. Overcoming the BBB remains a major hurdle for the treatment of neurological disorders. [12]

   - **Tumor Microenvironment:** The complex and dynamic tumor microenvironment presents barriers to effective drug delivery, including dense extracellular matrix, high interstitial pressure, and heterogeneous blood supply. These barriers can hinder the penetration and distribution of therapeutic agents within solid tumors. [6]

2. **Clinical Translation:**
   - **Safety and Efficacy:** Ensuring the safety and efficacy of targeted drug delivery systems in clinical settings is essential for successful translation from preclinical studies to clinical trials. Addressing concerns related to toxicity, immunogenicity, and off-target effects is critical for regulatory approval and patient acceptance.

   - **Scalability and Cost:** Scaling up the production of targeted drug delivery systems for clinical use while maintaining quality control and cost-effectiveness poses challenges. Developing scalable manufacturing processes and addressing economic considerations are essential for widespread clinical adoption.

Future Directions [20]

1. **Emerging Technologies:**
   - **Nanomedicine:** Advances in nanotechnology offer opportunities to engineer nanoscale drug delivery systems with precise control over size, shape, and surface properties. Nanoparticles, liposomes, and dendrimers can be designed for targeted drug delivery, controlled release, and imaging applications.

   - **Gene Therapy:** Targeted drug delivery systems play a crucial role in the delivery of nucleic acidbased therapeutics for gene therapy applications. Lipid nanoparticles, viral vectors, and polymerbased carriers can deliver genes, siRNA, mRNA, or genome-editing tools to specific cells or tissues, offering potential treatments for genetic disorders, cancer, and infectious diseases.

2. **Multifunctional Platforms:**
   - **Theranostic Systems:** Integrating diagnostic and therapeutic functionalities into a single platform enables real-time monitoring of drug delivery and treatment response. Theranostic nanoparticles, equipped with imaging agents and therapeutic payloads, offer opportunities for personalized medicine and precision therapy.

   - **Responsive Systems:** Developing smart drug delivery systems that respond to specific stimuli in the microenvironment, such as pH, enzymes, or external triggers, allows for controlled release and targeted activation of therapeutic agents. Responsive carriers can enhance drug efficacy and minimize off-target effects.

7. Case studies:-

Liposomal Doxorubicin (Doxil®) in Cancer Therapy [14,17,18]

Targeted Drug Delivery System: Liposomes are used to encapsulate doxorubicin, a potent chemotherapeutic agent, and deliver it specifically to tumor tissues.

Clinical Outcomes and Patient Benefits:

- **Enhanced Efficacy:** Liposomal doxorubicin accumulates preferentially in tumor tissues via the Enhanced Permeability and Retention (EPR) effect, leading to higher drug concentrations at the site of action and improved antitumor efficacy. [14]
- **Reduced Toxicity:** By minimizing exposure to healthy tissues, liposomal doxorubicin reduces systemic toxicity and side effects compared to conventional doxorubicin, such as cardiotoxicity and myelosuppression.
- **Improved Patient Tolerance:** Patients receiving liposomal doxorubicin often experience fewer adverse effects, leading to improved treatment adherence and quality of life. [17]

2. Monoclonal Antibody Therapies in Cancer Immunotherapy

Targeted Drug Delivery System: Monoclonal antibodies (mAbs) are engineered to target specific antigens expressed on cancer cells, enabling selective delivery of cytotoxic payloads or immune modulators. [11]

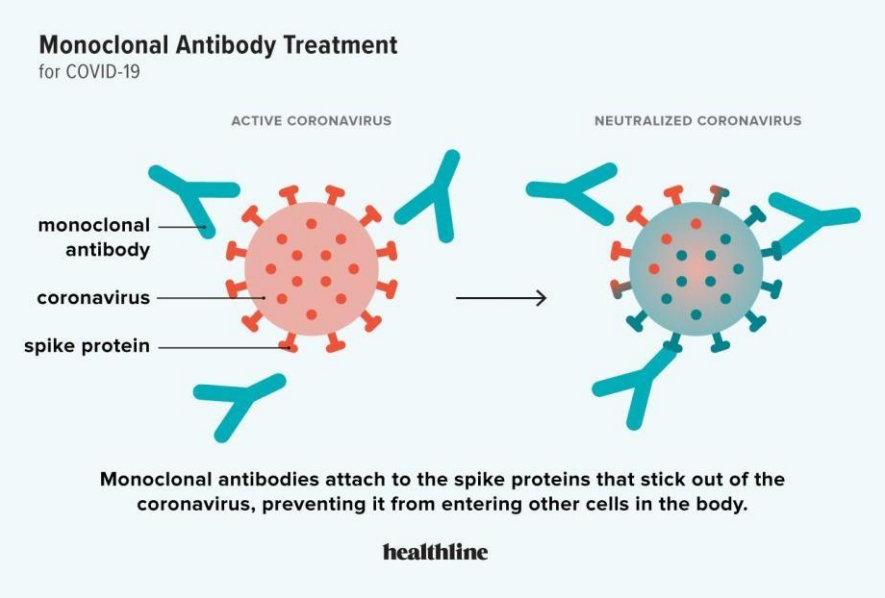

Fig.8

Clinical Outcomes and Patient Benefits:

- **Precision Targeting:** Monoclonal antibodies recognize and bind to cancer-specific antigens, allowing for precise targeting of tumor cells while sparing healthy tissues. [16]
- **Immune Activation:** Some mAbs, such as checkpoint inhibitors (e.g., pembrolizumab, nivolumab), activate the patient's immune system to attack cancer cells, resulting in durable responses and improved survival outcomes. [3]

- **Personalized Therapy:** Monoclonal antibody therapies can be tailored to individual patients based on their tumor's molecular profile, leading to personalized treatment strategies and improved clinical outcomes.[8]

3. Pegfilgrastim (Neulasta®) in Chemotherapy-Induced Neutropenia

Targeted Drug Delivery System: Pegfilgrastim is a pegylated form of granulocyte colony-stimulating factor (G-CSF) that stimulates the production of neutrophils, a type of white blood cell, to prevent chemotherapyinduced neutropenia.

Clinical Outcomes and Patient Benefits:

- **Reduced Risk of Infection:** Pegfilgrastim administration helps maintain neutrophil counts within the normal range during chemotherapy, reducing the risk of febrile neutropenia and serious infections. [22]

- **Minimized Treatment Delays:** By preventing chemotherapy dose reductions or delays due to neutropenia, pegfilgrastim allows patients to receive their full course of treatment on schedule, potentially improving treatment outcomes. [22]

- **Improved Quality of Life:** Patients receiving pegfilgrastim experience fewer chemotherapy-related complications, such as hospitalizations for infections, leading to improved quality of life and treatment tolerability. [21]

Fig.9.

8.Conclusion:-

These case studies highlight the clinical success and patient benefits of targeted drug delivery systems in cancer therapy, immunotherapy, and supportive care. By enhancing drug specificity, reducing systemic toxicity, and improving treatment outcomes, targeted drug delivery systems offer promising solutions for addressing unmet medical needs and improving patient care across a wide range of disease conditions.

Addressing biological barriers, advancing clinical translation, and leveraging emerging technologies are key priorities in the field of targeted drug delivery systems. Overcoming these challenges and exploring future directions will lead to the development of safer, more effective, and personalized therapies for a wide range of diseases, ultimately improving patient outcomes and quality of life.

Targeted drug delivery systems offer promising applications in cancer therapy, treatment of inflammatory diseases, and neurological disorders by enhancing drug delivery specificity, efficacy, and safety. These systems represent a key area of research and development in modern medicine, with the potential to revolutionize treatment strategies and improve patient outcomes across a wide range of disease conditions. [25]

Recap of Key Points:

1. **Definition and Principles:** Targeted drug delivery systems aim to enhance therapeutic efficacy while minimizing systemic side effects by selectively delivering therapeutic agents to the desired site of action.[10]

2. **Components:** Key components of targeted drug delivery systems include carrier molecules (e.g., liposomes, nanoparticles), targeting ligands (e.g., antibodies, peptides), and the therapeutic payload. [10]

3. **Applications:** Targeted drug delivery systems have diverse applications, including cancer therapy, treatment of inflammatory diseases, and neurological disorders, offering improved efficacy, reduced toxicity, and enhanced patient outcomes. [10]

4. **Challenges:** Challenges in targeted drug delivery systems include overcoming biological barriers (e.g., blood-brain barrier), addressing safety and efficacy concerns for clinical translation, and ensuring scalability and cost-effectiveness. [10]

Future Prospects in Targeted Drug Delivery

1. **Emerging Technologies:** Advances in nanomedicine, gene therapy, and other emerging technologies offer opportunities to develop more precise, efficient, and personalized targeted drug delivery systems. [1]

2. **Multifunctional Platforms:** Integration of diagnostic and therapeutic functionalities into single platforms (theranostic systems) and the development of responsive drug delivery systems hold promise for personalized medicine and precision therapy.[1]

3. **Overcoming Biological Barriers:** Continued research efforts are needed to overcome biological barriers such as the blood-brain barrier and the tumor microenvironment, enabling more effective drug delivery to challenging anatomical sites. [1]

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