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A Review on Targeted Drug Delivery

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Abstract:

Delivering drugs to specific sites of action over an extended period improves efficacy and reduces adverse effects. These targeted drug delivery systems are preferred over conventional drug delivery for their higher drug stability, enhanced absorption, and cell-specific action. Different biological processes and events are involved in drug targeting, utilizing various carriers for drug delivery. The strategies for drug targeting differ based on the targeting mechanisms and formulation systems used. Applications in stem cell therapy, gene therapy, 3D printing, and pathogen bio detection represent the latest advances in targeted delivery systems. More formulations have entered the market and clinical trials, while ongoing research and development aim to enhance drug carrier stability, optimize targeting mechanisms, and reduce the complexity and cost of manufacturing these advanced systems.

Keywords: Drug delivery, Drug targeting, drug carriers, cancer.

1. INTRODUCTION

Targeted drug delivery is a type of drug delivery system in which the medicament is selectively targeted or delivered only to the site of action rather than to non-targeted organs, tissues, or cells. The system is based on a method that delivers a specific amount of a therapeutic drug to a particular diseased location within the body over an extended period of time, improving efficacy and reducing adverse effects.

Targeted drug delivery is a type of smart medication delivery system that is extremely effective at delivering drugs to patients. Ideally, targeted drug delivery systems should be biochemically inert (non-toxic), non-immunogenic, physically and chemically stable in vivo and in vitro, with restricted drug distribution to target cells, tissues, or organs and uniform capillary distribution.

There are three main reasons why targeted medication delivery systems are preferred over conventional drug delivery systems. The first is for pharmaceutical reason. When compared to targeted drug delivery systems, conventional medicines have lower solubility and higher drug instability. Conventional medications have low absorption, shorter half-lives, and require a large volume of distribution. These are its pharmacokinetic properties. The third factor is the pharmacodynamics properties of drugs. Conventional drugs have a low specificity and therapeutic index when compared to targeted drug delivery systems.

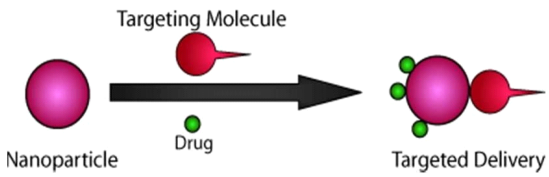

Figure 1: Drug Delivery

Targeted drug delivery is the method of treatment in which the drug is transported to a specific tissue without reaching the remaining part of the body.

In drug targeting, the drug could be delivered to the capillaries at the target spot, to the specific type of cells as in the case of cancer cells and to the specific tissues or organs which recognize the drug carrier.

This typical drug delivery system is accomplished by the drug's absorption across a biological membrane, whereas the targeted technique involves the drug being discharged in an indefinite quantity. The drug delivery system is incredibly integrated, requiring several disciplines, such as chemists, scientists, and engineers, to collaborate and optimize this technology. When developing a targeted system, the system's subsequent standard must take into account the drug's qualities, side effects, the route selected for the drug's delivery, the targeted website, and the illness.

Parenteral drug delivery is intrusive and has short-term consequences. Although oral administration of medications is extremely popular and suitable, it cannot be utilized for certain drugs, such as protein or peptide therapies, due to low oral absorption. These may also deteriorate throughout the Alimentary canal. The limitation of topical creams and ointments is that they only have local effects, not systemic ones. Crucial parameters such as bioavailability, medication absorption, pharmacokinetics, and timing are taken into account for effective drug administration.

To ensure a successful targeted drug delivery system, four key requirements must be met, the drug must be properly loaded into the delivery vehicle, it must be able to evade the body's secretions and reach the desired location, and it must be released at the precise site within the time frame required for its effect. Different sites of interest inside the body need the use of various drug delivery systems, depending on the route to be taken. Drug targeting involves the selective and quantitative accumulation of drugs within an organ or tissue. A comprehensive understanding of the scope of targeting facilitates the selection of the targeting moiety, ligand, or carrier system. Furthermore, targeted delivery enables for a minimal amount of drug to reach non-target organs and tissues, resulting in an effective and safe drug delivery system. In a very broad manner, there are typically three medication targeting levels: first, second, and third, the

molecular level may potentially be allocated as the fourth level. Other classifications for targeting include active and passive targeting, as well as reverse and physical techniques of targeting.

1.1 Ideal property

The targeted drug delivery system must have certain properties which include;

- Must be biochemically inert.
- Non-immunogenic.
- Be physically and chemically stable in both vivo and in vitro environments.
- Provide a therapeutic amount of drug release.
- Ensure minimum drug leaking during transit.
- Carriers should be biodegradable and easily eliminated from the body.
- The product should be non-toxic, compatible with body fluids, and biodegradable.
- Deliver the drug only to the target site.
- Control drug release at a predetermined rate.
- The drug release rate does not impact the pharmacological effect.
- Ensure minimal drug leakage during transit to the target place.
- Use an inert, biodegradable, or easily eliminated carrier.
- Preparation of the drug delivery system should be simple and cost- effective.

1.2 Advantages Targeted drug delivery system

- The drug administration protocol is simplified.
- The drug's toxicity is reduced by targeting a specific location.
- A small dose is sufficient to achieve the desired drug response.
- Avoid the first-pass effect.
- Improved drug absorption at the target site.
- Drug targeting eliminated peak and valley plasma concentrations.
- Extended drug delivery and release.
- Avoid intermittent dosage.
- Improve patient compliance.
- Reduce inter and intra-patient variability.
- Self administration is possible.
- Enhance absorption of drug

1.3 Disadvantages of targeted drug delivery system

- Requires a skill in manufacturing storage, administration.
- Diffusion and redistribution of drug release.
- Rapid clearance of targeted systems.
- Maintaining stability of dosage form is difficult.
- Highly sophisticated technology requires for formulation.

2. Biological Processes And Events Involved In Drug Targeting

2.1 Cellular uptake and processing

Macromolecular assemblies cannot enter by a simple mechanism and must be taken up via a process known as endocytosis. Cellular absorption and processing involves two steps, internalization of the plasma membrane and engulfment of extracellular substances.

Unlike phagocytosis, pinocytosis is a universal phenomenon. Fluid phase pinocytosis capturing molecule is significantly slower than phagocytosis and is directly proportional to the concentration and size.

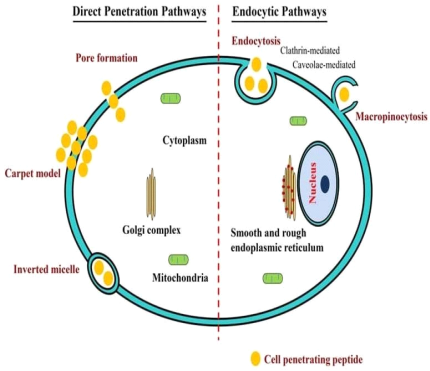

Figure 2: Cellular uptake and processing

2.2 Transport across the epithelial barrier

The oral, buccal, nasal, vaginal, and rectal cavities are lined by one or more layers of epithelial cells. Low molecular mass drugs bypass the epithelial barrier via passive diffusion and selective and non-selective endocytosis. Polar materials diffuse through the tight junctions of epithelial cells. Passive transport is typically higher in injured mucosa, but active transport is dependent on the structural integrity of epithelial cells.

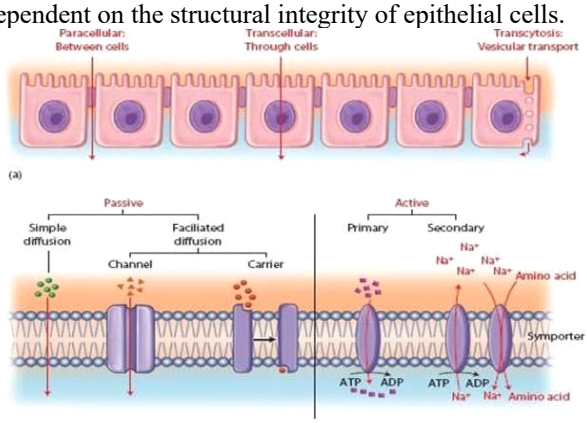

Figure 3: Transport across the epithelial barrier

2.3 Extravasation

Dysfunction of cells located outside the cardiovascular system leads to many diseases therefore a drug to exert its therapeutic effects it must depart from the central circulation this process of trans vascular exchange is called Extravasation which is governed by blood capillary wall.

Factors include extravasation are,

- Pathological and physicochemical factors of the drug.
- Blood and lymph supply structure of the capillary wall.
- Variations in blood capillary structure among organs and tissues.
- Charge macromolecule properties such as shape, size, and HLB.

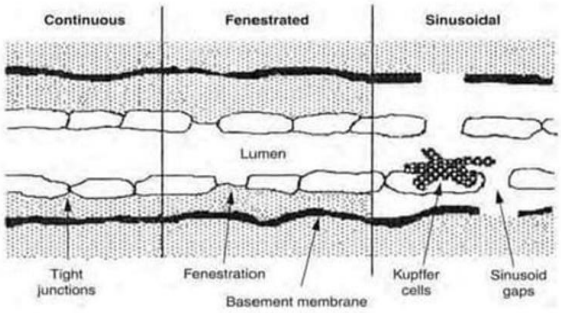

Figure 4: Extravasation

2.4 Lymphatic uptake

Drug molecules can reabsorb into the blood stream promptly after extravasation or enter the lymphatic system and travel to the blood stream via the lymph. Drugs delivered by subcutaneous, intracellular, transdermal, or peritoneal routes can also enter the systemic circulation via the lymphatic system. It is directly proportional to the difference between hydrostatic and osmotic forces.

Factors include lymphatic uptake are,

- Formulation medium and its composition
- Particle size and surface properties
- Particle size and surface characteristics
- Administration route
- Interstitial fluid pH and disease status

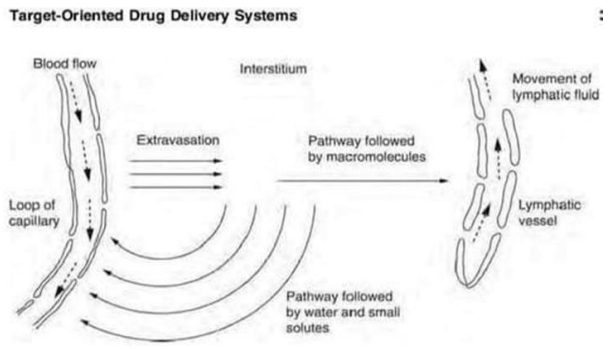

Figure 5: Lymphatic uptake

3. Carriers Used In Drug Targeting

Drug targeting can be attained by using carrier systems. The carriers are systems that are required for transportation of entrapped drug to target sites. The carriers entrap the drug moiety and deliver it into the target site without releasing it into the non-target site. Different types of carriers are used in targeted drug delivery system.

3.1 Nanotubes

Nanotubes are a sort of drug delivery system consisting of a hollow cylindrical tube made of carbon that can be readily filled and sealed with the desired medicament. They are typically utilized to deliver the drug to cancer cells. Carbon nanotubes were used to target tumors in mice. Tumor targeting was achieved using antibody-functionalized, radiolabeled carbon nanotubes.

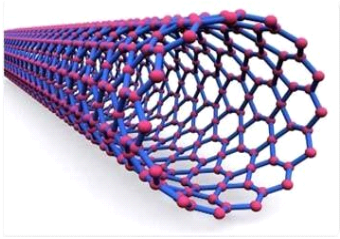

Figure 6: Nanotube

3.2 Nanowires

It is a small-diameter wire made of metal or organic substances. It has a large surface area, which can be modified to allow the nanowire to bind with specific biological molecules once injected into the body. It can be used to diagnose and treat brain illnesses such as seizures, Parkinsonism, and similar conditions. This approach can treat Parkinson's and similar diseases.

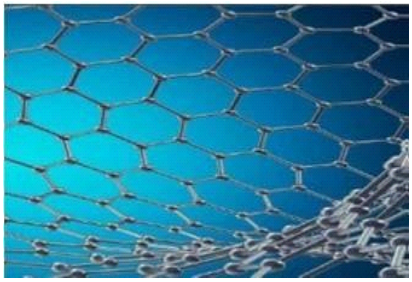

Figure 7: Nanowire

3.3 Nanoshells

Nanoshells are innovative nanoparticle methods that consist of a hollow silica dielectric core surrounded by a gold shell. It can be utilized for both diagnostic and therapeutic purposes. Nanoshells can be coated with antibodies, allowing them to interact with specific targets such as cancer cells.This method is highly effective in targeting the antineoplastic drug. Nanoshells ability are used for cancer imaging and treatments.

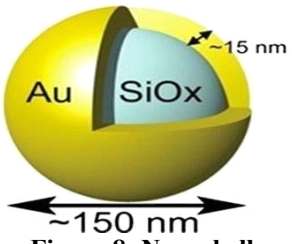

Figure 8: Nanoshell

3.4 Quantum dots

Quantum dots are nanocrystalline semiconductor particles with special optical properties that make them suitable for tumor imaging. This carrier is used effectively for drug targeting in cancer treatment.

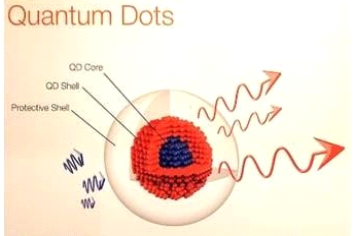

Figure 9: Quantam Dot

3.5 Nanopores

They have incredibly small openings that allow DNA molecules to flow through one at a time. This, allows for highly precise and effective DNA sequencing. This approach has potential applications in genetic engineering and biotechnology.

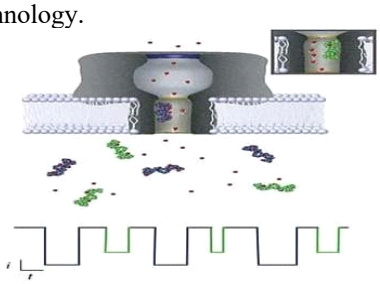

Figure 10: Nanopore

3.6 Gold nanoparticles

Scientists use gold nanoparticles to create an ultrasensitive detection technique for DNA and protein markers associated with the presence of different types of cance, such as breast and prostate cancer. Gold nanoparticles were utilized to diagnose lung cancer.

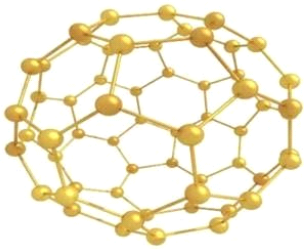

Figure 11: Gold nanoparticle

3.7 Dendrimers

Dendrimers are synthetic nanoparticles with specific diameters. They have a control core surrounded by layers of polymers. The medication can be connected to many places on the surface of dendrimers. They are employed for gene transfection and medical imaging.

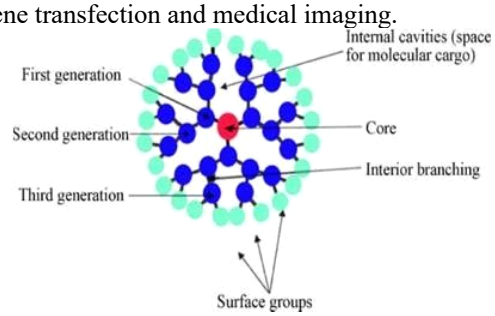

Figure 12: Dendrimer

3.8 Liposomes

Liposomes are small bilayer structure vesicles made from natural phospholipid. They can entrap hydrophilic and lipophilic medicines in aqueous or phospholipid bilayers. The percentage of entrapped drug is determined by the drug's physical and chemical properties, as well as the lipids composition

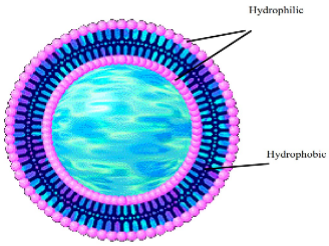

Figure 13: Liposomes

3.9 Niosomes

Niosomes are non-ionic surfactant vesicles that can hold both hydrophilic and lipophilic drugs. Niosomes are more stable than liposomes due to phospholipid's inherent characteristics.It was found that niosomes are effective for targeting antineoplastic drugs, anti- inflammatory, anti- bacterial, anti-fungal and antiviral drugs. Novel niosomal delivery system is used daunorubicin for targeting against acute myeloid leukemia (AML). Piroxicam niosomes are used for analgesic and anti-inflammatory effect at the pain area.

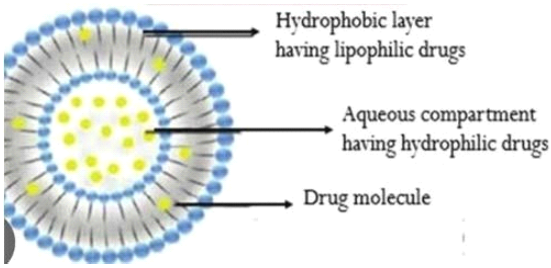

Figure 14: Niosome

3.10 Ufasomes

Ufasomes are a dispersion of unsaturated fatty acid vesicles formed from fatty acid and an ionic surfactant (soap) in the presence of cholesterol. Ufasomes are an excellent drug carrier designed for topical use. The stratum corneum, or outermost layer of the skin, is thought to be the most effective barrier to drug penetration. This problem can be solved by using ufasomes, as they are made up of a lipid membrane that can penetrate the skin. The antifungal activity of oxiconazole was enhanced using ufasomes against Candida albicans.

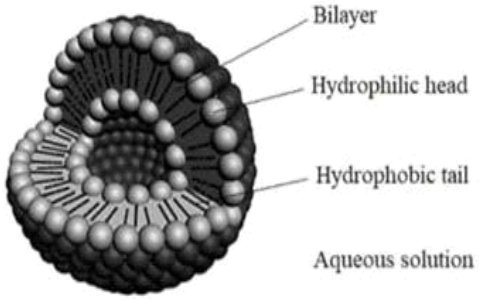

Figure 15: Ufasome

3.11 Pharmacosomes

Pharmacosomes are neutral molecules with both hydrophilic and lipophilic properties, carrying both positive and negative charges. They have an optimum ratio of polyphenol to phospholipids in the form of a complex. The drug is conjucated to the lipoidal complex by electrostatic force or by forming a hydrogen bond. The term pharmacosome is derived from the word Pharmakon, meaning drug and soma, meaning carrier. The conjugation of the drug to the lipoidal complex may be in the form of micelles or hexagonal aggregates.

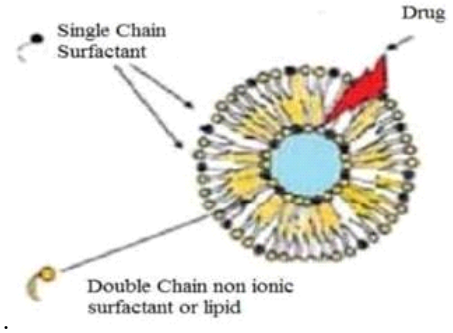

Figure 16: Pharmacosome

3.12 Virosomes

Virosomes are unilamellar vesicles made of phospholipids that are used to carry drugs. The surface of virosomes contains locations to which virus-derived glycoproteins are attached, allowing the virosomes to be recognized and targeted to the target spot within the body. Create a new platform for treating cerebral malignancies with erythro-magneto-HA-virosomes.

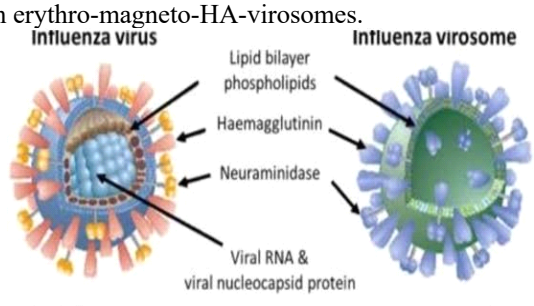

Figure 17: Virosome

3.13 Cubosomes

Cubosomes are nanostructured drug delivery systems prepared from certain lipids. They are described as liquid crystalline nanoparticles having a cubic structure suitable for injection. Azhari et al. used Tween 80 to stabilize phytantriol-based cubosomes for delivering macromolecular therapeutics to the brain.

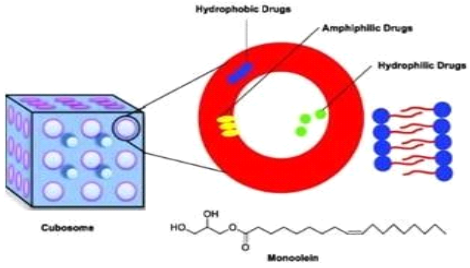

Figure 18: Cubosome

3.14 Nanocrystal

Nanocrystals are the material having a dimension less than 100 nm and present in the form of one crystalline structure.The nanocrystals differ from nanoparticles in that nanoparticles have a dimension of less than 1000 nm. Drug loaded nanocrystals are used in targeting and treatment of cancer.

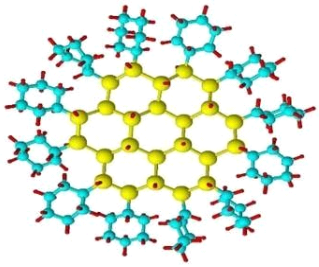

Figure 19: Nanocrystal

3.15 Nanobots

Nanorobotics is a new technology of drug delivery systems. They are a nanoscale machine with a diameter of 10^{-9} m. Self-propelling tailored magneto-nanobots were studies for deep tumor penetration.

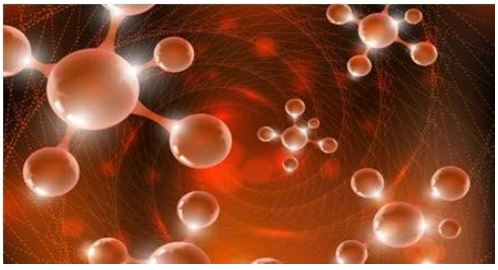

Figure 20: Nanobot

4. Strategies For Drug Targeting

There are several strategies for drug targeting as shown in Figure 21. Drug targeting strategies are used to improve the delivery of drugs to diseased cells and tissues, while reducing side effects in other tissues.

Figure 21: Different strategies for drug targeting.

4.1 Passive targeting

Drug delivery methods that aim to distribute the drugs into the systemic circulation are referred to as passive targeting. Passive targeting is a reaction of the body to the physicochemical features of the medication or the drug delivery system that entraps the drug until it reaches the target spot. Salinomycin passive targeting micelles are used to suppress breast cancer and stem cell cancer.

4.2 Active targeting

In this strategy, the drug targeting is done as a result of the identification of the target group which is attached at the surface of the drug delivery system to the receptors in the target cells. The target group include bioadhesive 0ulphate0 surfactant, antibodies, or albumin protein. The active targeting has three types, First-order targeting (organ targeting), Second-order targeting (cell targeting) and Third-order targeting (intracellular targeting), utilized the folate receptor for active targeting of anticancer drugs.

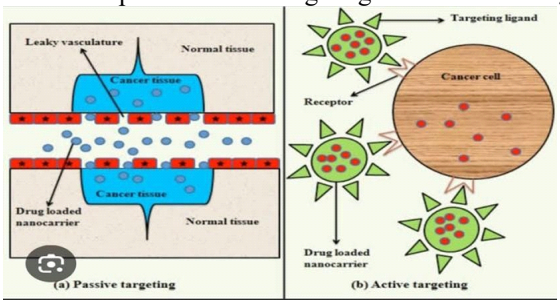

Figure 22: Mechanism of passive targeting and active targeting

4.3 Inverse targeting

The inverse targeting aims to avoid the passive uptake of the drug delivery system by the reticulum-endothelial system (RES). This process can be achieved by suppressing the normal uptake function of RES via injection of a large amount of the blank drug delivery system or large molecules of dextran 0ulphate to make a saturation of RES and suppress the defense mechanism. The inverse targeting is very useful for drug targeting to non-RES organs. Methotrexate drug was used to peritoneal tumors using an inverse targeting technique.

4.4 Ligand mediated targeting

This type of drug targeting depends on the receptor uptake of natural low-density lipoprotein (LDL) particles and synthetic micro-emulsions of LDL particles covered with Apo proteins. Cancers can be treated by using a ligand-mediated targeted approach.

Table 1: Ligands used in drug targeting

Ligands	Target	Tumour target
Folate	Folate receptor	Overexpression of folate Receptor
Transferrin	Transferrin receptor	Overexpression of transferrin Receptor
Galactosamine	Galactosamine receptors on hepatocytes	Hepatoma

4.5 Physical targeting

The goal of the physical targeting technique is to modify the drug delivery systems externally so that they can be directed to a certain location. The application of an electric field, variations in pH, and temperature are examples of physical changes. This approach has great potential for targeting tumors and in gene therapy.

Table 2: Approached in Physical Targeting

Physical Targeting	Formulation System	Mechanism for Drug Delivery
Heat	Liposome	Change in Permeability
Magnetic Modulation	Magnetically Responsive Microspheres Containing Ironoxide	Magnetic Field can retardfluid Flow of particles.
Ultrasound	Polymers	Change in Permeability
Electrical Pulse	Gels	Change in Permeability
Light	Photo responsive Hydro Gels Containing AzoDerivatives	Change in Diffusion Channels, Activated bySpecific Wavelength

4.6 Dual targeting

The dual targeting mechanism involves a drug delivery system in which the carrier has a synergistic effect on the entrapped drug and hence increase the therapeutic effect. For example, a carrier molecule with antiviral activity when loaded with antiviral drug the therapeutic effect in enhanced. Applied dual-targeting for delivery of paclitaxel and curcumin for management of brain tumors.

4.7 Double targeting

The double targeting strategy is a combination of both temporal and spatial, so it is called double targeting. The spatial delivery involves the targeting of the drug to the target site, while the temporal delivery involves the controlling of drug release at the target site. This double targeting mechanism is used for targeting a dendrimer-loaded anticancer drug to the tumor site.

4.8 Drug Delivery to Tumor

For the active drug to reach the disease site, it has to survive crossing through several biological barriers including organs, tissues, cells and intracellular compartments that are not included in the pathological pathways, where it can be inactivated or cause adverse effects. Harming the normal tissue or high doses of chemotherapeutics, which is often not tolerated by patients are major challenges especially in cancer treatment. The aim of drug targeting is to concentrate high amount of drugs within disease site with only a small amount of drug contaminating the normal tissue.

The specifications for targeted drug delivery systems are to provide improved solubility to allow enhanced pharmacokinetics, minimum drug release before reaching targeted site to have better pharmacodynamics profiles, increased drug stability to reduce drug deterioration. Drug

targeting can be achieved by free drug administration, which involves IV injection of low-molecular-weight drug. This administration generally causes rapid clearance from the blood, due to slight amount of drug accumulation in tumor site compared to healthy organs and tissues. Other approaches like passive drug targeting, allows the accumulation of drug in tumors and in tumor cells by means of the Enhanced Permeability and Retention (EPR) effect.

5. TARGETED MEDICAL PRODUCTS: A MARKET REVIEW

Targeted drug delivery systems offers precise delivery of drugs to specific sites in the body, thereby minimizing side effects and enhancing therapeutic efficacy. Listed below are some targeted drug delivery products available in the market: These products illustrate the variety of approaches available in the market for targeted drug delivery, from nanotechnology-based solutions to antibody-drug conjugates and drug-eluting devices.

Table 3: Marketed Targeted Drug Delivery Products

Category	ProductName	Drug/Active Ingredient	Indication	Dosage Form
Antibody-Drug Conjugates (ADCs)	Adcetris	Brentuximab Vedotin	Hodgkin lymphoma, systemic anaplastic large cell lymphoma	50 mg/50 mL (IV infusion)
	Kadcyla	Ado- Trastuzumab Emtansine	HER2-positivebreast cancer	100 mg/4 mL (IV infusion)
Liposomal Drug Delivery Systems	Doxil	Liposomal Doxorubicin	Ovarian cancer, Kaposi's sarcoma, multiple myeloma	20 mg/10 mL (IV infusion)
	Lipodox	Liposomal Doxorubicin	Ovarian cancer, Kaposi's sarcoma,multiple myeloma	20 mg/10 mL (IV infusion)
	Fungisome	Liposomal AmphotericinB	Systemic fungalinfections	50 mg/10 mL (IV infusion)
Monoclonal Antibodies (mAbs)	Herceptin	Trastuzumab	HER2-positive breast cancer,gastric cancer	440 mg/50mL (IV infusion)
	Rituxan	Rituximab	Non-Hodgkin's lymphoma, chronic lymphocyticleukemia	100 mg/10mL (IV infusion)
	Avastin	Bevacizumab	Colorectal cancer	100 mg/4 mL (IV infusion)
	Erbitux	Cetuximab	EGFR-positivemetastatic colorectal cancer	100 mg/50mL (IV infusion)
Polymeric Nanoparticles	Abraxane	Paclitaxel (Albumin-bound)	Breast cancer, non-small cell lung cancer, pancreatic cancer	100 mg/20mL (IV infusion)
Drug-Eluting Stents	Xience	Everolimus-Eluting Stent	Coronary artery disease	Stent (sizevaries)
	Biomatrix	Biolimus A9-Eluting Stent	Coronary artery disease	Stent (size varies)
PEGylated Proteins	Neulastim	Pegfilgrastim	Reducing infectionrisk in chemotherapypatients	6 mg/0.6 mL (SC injection)
	PegGrafeel	Pegfilgrastim	Reducing infectionrisk in chemotherapypatients	6 mg/0.6 mL (SC injection)
Radio immunotherapy	Zevalin	Ibritumomab Tiuxetan	B-cell non-Hodgkin's lymphoma	0.37-0.74MBq/kg (IV infusion)
Microspheres	LupronDepot	LeuprolideAcetate	Prostate cancer, endometriosis,uterine fibroids	7.5 mg, 22.5mg, 30 mg (IM injection)
Generic Biologics/ Bio-similars	Biceltis	Trastuzumab	HER2-positivebreast cancer	440 mg/50mL (IV infusion)
	Reditux	Rituximab	Non-Hodgkin'slymphoma	100 mg/10mL (IV infusion)

6. Application Of Targeted Drug Delivery System

Targeted drug delivery is utilized to treat cardiovascular diseases and diabetes. Regenerative technique is developed to cure various diseases. The development of a number of regenerative techniques in recent year for curing heart disease. Targeted drug delivery are often are used to treat vascular diseases, polygenic disease, but the foremost necessary application of targeted drug delivery is to treat cancer.

Liposomes can be used as drug delivery in the treatment of diseases like tuberculosis. The traditional treatment of TB is skin to chemotherapy which is not that much effective, which may be due to the failure of chemotherapy to make a high enough concentration at the infection site. The liposome delivery system allows for better microphage penetration and better builds a concentration at the infection site

Targeted drug delivery is also used in the stem cell therapy. This therapy helps to regenerate myocardium tissue and return the contractile function of heart by creating a microenvironment before myocardial infarction.

It is also used in 3D printing to investigate how to target cancerous tumor. By printing a plastic 3D shape of tumor, filling it with drug and show therapeutic effect at a targeting location of the drug.

Other promising applications of targeted drug delivery systems are as follows,

- Protein detection
- Bio detection of pathogens.
- Tissue engineering.
- MRI contrast enhancement.
- Drug and gene therapy.
- Probing of DNA structure.
- Drug discovery

7. Conclusion

Targeted Drug Delivery Systems (TDDS) have emerged as a critical innovation in medical science, designed to enhance the therapeutic efficacy of drugs while minimizing their side effects. Unlike conventional drug delivery methods, TDDS focuses on delivering medication directly to the targeted site, such as specific tissues or organs, thereby improving treatment outcomes.

Targeting using various drug carriers, including nanoparticles, liposomes, and monoclonal antibodies, which ensure that the drug is released in a controlled and localized manner. It include benefits of reduced dosage requirements, improved drug stability and solubility, and the avoidance of non-targeted tissues, which significantly reduces potential side effects. TDDS offers the potential for more effective treatments for complex conditions such as cancer, where targeted therapy can directly impact tumor cells while sparing healthy cells.

Future Prospective

While the technology has made significant paces and some formulations have entered clinical trials or the market, continuous research and development are necessary to overcome the remaining challenges. These include ensuring the stability of drug carriers, optimizing the targeting mechanisms, and reducing the complexity and cost of manufacturing these advanced systems. In future it is expected to play an increasingly vital role in precision medicine, offering more effective and safer therapeutic options

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