Targeted Drug Delivery System: An Review

S.P. Sabarigiri[1], Mrs. Malarvizhi[2]
[1, 2] Dept of pharmaceutics
[1, 2] Pallavan pharmacy college.

Abstract- *Drug delivery systems are emerging as one of the most cutting-edge methods in the medical sciences for the detection and treatment of a few fatal diseases. In particular, targeted drug delivery is a technique that delivers a therapeutic substance to a designated sick location of the body over an extended period. It is based on the delivery of the drug molecule to the target site via a carrier or vehicle with site specificity. The drug delivery system is extremely interconnected, so it takes experts from several fields to work together to make it as efficient as possible. This paper aims to summarize the design factors that must be taken into consideration when designing a targeted release system: the drug qualities, the drug side effects, the drug delivery method, the targeted site, and the disease. This review will focus on the development of drug-targeting techniques for clinical application for various therapies.*

Keywords- Targeted drug delivery system, liposomes, Monoclonal antibody, Nanoparticles.

I. INTRODUCTION

Over the past 60 years, controlled medication delivery technologies have improved. Hundreds of controlled-release formulations have been used in clinical trials, and many different delivery devices have been created. But these productive uses have been restricted to a small number of formulations, including oral and transdermal delivery methods.

Poorly soluble drug formulations, protein delivery systems, self-regulated insulin delivery devices, and tailored drug delivery systems are just a few of the many delivery systems that still need to be refined. [1].

A targeted medication delivery system is based on a technique that delivers a specific quantity of a therapeutic substance to a designated sick location of the body over an extended period. This aids in preserving the necessary plasma and tissue drug levels in the body, preventing any drug-induced harm to healthy tissue. The medication delivery system is extremely interconnected, so it takes experts from several fields—including chemists, biologists, and engineers—to work together to make it as efficient as possible. The following design factors must be taken into consideration when designing a targeted release system: the drug qualities, the drug side effects, the drug delivery method, the targeted site, and the disease.

The type of markers or transport carriers, as well as the specific characteristics of target cells, are all taken into consideration when creating products based on this delivery system. vehicles that deliver drugs to certain ligands, receptors, and physically controlled components.

Targeted drug delivery systems should ideally have confined drug distribution to target cells, tissues, or organs and should have uniform capillary distribution. They should also be biochemically inert (non-toxic), non-immunogenic, and physically and chemically stable in vivo and in vitro settings. Drug release should be predictable and under control, and it shouldn't interfere with the way the drug works. It should release the medicine in a therapeutic dosage and experience less drug leakage while in transit [2].

IDEAL PROPERTIES:

- Non-toxic.
- Non-immunogenic.
- Both are stable chemically and physically in vitro and in vivo.
- Dispersion of capillaries uniformly.
- Drug release is controlled and predictable.
- Therapeutic dose of medication released.
- Drug action is unaffected by drug release. [3]

ADVANTAGES:

- keeps away from the stomach area.
- No GI discomfort.
- Increase compliance while lowering healthcare costs.
- keeps first pass effect at an away.
- Usage of medicines having short biological half-lives effectively.
- The therapeutic window is small.
- Non-intrusive and simple to use. [4,6]

DISADVANTAGES:

- No medications that need high blood levels can be given.
- Irritation or sensitization may be brought on by drug formulation.
- A discomfort to wear.
- Possibly not economical.[4,8]

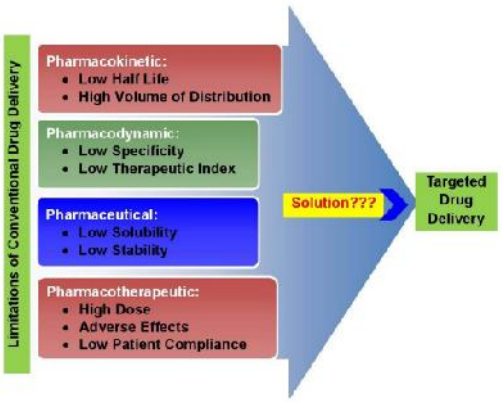

Fig.2

II. TYPES OF TARGETED DRUG DELIVERY SYSTEM: [5]

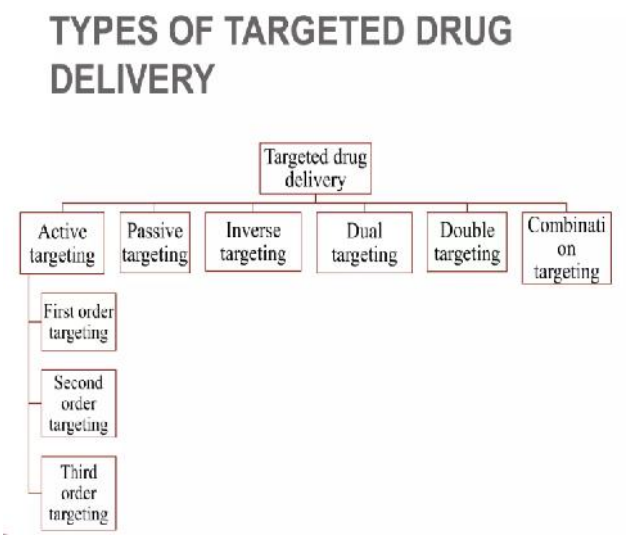

Fig.3

COMPONENTS OF TARGETED DRUG DELIVERY SYSTEM:

Target and drug carriers or indicators make up the majority of a medication delivery system. Target refers to a particular organ, cell, or group of cells that require therapy for a chronic or acute illness. To make this delivery system more site-specific with fewer side effects of drugs and their quantity as well, the route of administration involves drug carriers as an important targeting moiety. After its leakage from its carrier/markers, the drug is then delivered to the specific or targeted site via biological metabolism with its clearance as well as not reaching the non-targeted site. A carrier is a unique molecule or system that is crucial for the efficient delivery of loaded drugs to pre-selected locations. These are designed vectors that carry or deliver the medication to the area of the target cell while keeping the drug within or on them via encapsulation and/or spacer moieties. [6,7,9]

VEHICLE FOR TARGETED DRUG DELIVERY SYSTEM:

Drug delivery vehicles are also referred to as drug vectors which are the most important entities required for the successful transportation of the loaded drug. Drug vectors transport and retain the drug to be delivered within or in the vicinity of the target. They are made capable of performing such specific functions which can be attributed to slight structural modification.[6,8,10]

III. LIPOSOMES

Liposomes are tiny vesicles that are intentionally created and range in size from 20 to 10,000 nm. They are made of phospholipid bilayers around them. Many liposome formulations are quickly taken up by macrophages, and this property can be used to deliver medications specifically to macrophages or to target drugs passively, allowing the drugs gradual release into the bloodstream over time.

For use in non-viral vector-mediated gene therapy, cationic liposomes, and lipoplexes have undergone substantial research.[6,12,13]

IV. MONOCLONAL ANTIBODIES AND THEIR FRAGMENTS

The bulk of techniques based on antibodies' ability to recognize antigens has been created specifically for the treatment of cancer. These tactics primarily target the presence or, more precisely, the expression of tumor cell-expressed antigens.

The combination of a medication and a monoclonal antibody known as an antibody-drug conjugate (ADC) allows for the selective targeting of tumor cell masses or lymphomas[23].

Under physiological circumstances, enzymatic breakage of the linker releases the medication. Mylotarg (emtuzamabozogamicin), a type of antibody-drug conjugate

(ADC) that has been approved by the US Food and Drug Administration (FDA) but voluntarily removed from the US market, is one example. There are now at least 15 antibody conjugates being tested in clinical studies, and another ADC has been filed for approval. [1,2,4,6]

V. APPROACHES AND LEVELS OF DRUG TARGETING:[7,8,9,12]

PASSIVE TARGETING

Passive targeting occurs when biological and pharmacological variables contribute to the drug's accumulation at a particular spot. Usually, cancer's disease pathophysiology or altered tissue features enable passive targeting of medications to accumulate in these organs. especially cancer-related window openingsblood vessels that are created during angiogenesis are larger and have pores that range from 100 to 600 nm, while normal blood vessels have a diameter of about 6 nm.

Additionally, the leaky vasculatures and deficient permeability in the interstitial spaces allow for a larger concentration of nanoparticles. The improved permeation and retention (EPR) effect is the name given to this phenomenon. (17) The body's natural response to the drug-carrier system is another factor in passive targeting. The accumulation of hydrophobic, uncoated nanoparticles plagued by the body's RES is a good explanation for this.

The body's defense immunological system is quickly triggered and releases opsonins whenever any foreign nanoparticle enters the body through an intravenous route.

These opsonins rapidly cover the nanoparticle's surface and direct it toward the liver and spleen, which are RES organs.

Such a passive targeting strategy is frequently successful in directing drugs to the hepatic system. The RES vectors capture many colloidal systems due to passive targeting. Additionally, the RES system's macrophages are essential in the management of illnesses like leishmaniasis, candidiasis, and brucellosis.

ACTIVE TARGETING

Active targeting entails changing the functionality of the medication delivery system or carrier to ensure that the advance reaches its intended website through the carrier's architectural design. There are hardly any opportunities for nonspecific interactions because molecular recognition is so accurate in these situations.

Active targeting refers to a specific ligand-receptor type interaction for the localization of living things that only takes place during blood flow and extravasations. Three completely different levels of targeting are commonly used to categorize this active targeting strategy.

1) 1st order targeting hints at to narrow distribution of the drug carrier systems to the tissue of a planned target website, organ, or tissue, such as compartmentalized targeting in lymphatics, bigger serosa sac, plural cavity, cerebral ventricles, and eyes, joints, and plural cavity.
2) Second-order targeting is the selective administration of medications to particular cell types, such as neoplasm cells, as opposed to the standard cells, for example, the selective administration of pharmaceuticals to Kupffer cells within the liver.
3) Third-order targeting refers to the distribution of a medicine to the targeted cells' animate thing website.

INVERSE TARGETING

The biodistribution movement of the drug carrier system degenerates during inverse targeting. Opsonin causes the RES system to be activated whenever a combination drug delivery system is administered into the body, which is followed by a laborious and rapid biodistribution pattern. An effective strategy to avoid the RES's uptake of mixed particles is inverse targeting. (18) There are certain actionable ways to stay away from RES-rich organs. One method is to pre-inject blank mixture carriers into the RES in larger quantities, or you can employ macromolecules like dextran sulfate. This approach would effectively suppress RES's functions, and as it frequently has the potential to do so in a therapeutic environment, it is rarely recommended. Altering the carrier's scale, surface charge, hydrophilicity, and stiffness is another technique. Switching the carrier's surface deliquescent using a hydrophilic chemical substance is one efficient technique. An effective technique to inverse the targeting of the particles is to coat them with nonionic surfactants like poloxamer 188. Retroviral targeting strategies may employ inverse targeting.

DUAL TARGETING

The dual targeting mechanism uses a medication delivery strategy where the carrier interacts synergistically with the drug that is entrapped to boost its therapeutic impact. For instance, the therapeutic efficacy is increased when an antiviral medication is loaded onto a carrier molecule with antiviral activity. For the treatment of brain tumors, Cui et al.

used dual-targeting to administer the drugs paclitaxel and curcumin.

The term "double targeting" refers to a tactic that combines both temporal and spatial elements. While temporal delivery entails managing drug release at the target site, spatial delivery involves targeting the drug to the target spot. Pitto-Barry et al. used a dual targeting strategy to deliver an anticancer medication laden with dendrimers to the tumor site.

VI. A SIMPLIFIED VERSION OF CURRENT TARGETED DRUG DELIVERY BY NANOPARTICLES.

It is vital to stop placing undue dependence on PEGylated nanoparticles that build up in tumors due to the enhanced permeability and retention (EPR) effect as the area of nanotechnology-based medication delivery has progressed.
It is essential to have a comprehensive grasp of the issues that need to be resolved before developing genuinely focused medication delivery systems. Delivering therapeutic drugs to tumors in the right amounts is necessary for treating cancers. The iv-administered substance will need to permeate tumors, extravasate (i.e., cross vascular walls) into the interstitium, and circulate in the bloodstream. One must comprehend that the target tumor does not receive the majority of the iv-administered medicine, as mentioned.

The actual accumulation of the injected dose varies based on the medication, assay method, and other experimental parameters for the nanoparticle formulation, although it is often less than 5%. Depending on the assay method or the type of nanoparticles, greater results are occasionally seen [8]. It demonstrates three key elements that have an impact on tumor medication delivery as a whole.

Nanoparticles cannot propel themselves, therefore their only means of reaching the target—regardless of location—is through the flow of blood [4]. The likelihood that nanoparticles will hit their target is unaffected by the presence of ligands on the surface of the particles, also known as "active targeting." A sizeable amount of the nanoparticles are absorbed by the reticuloendothelial system (or mononuclear phagocyte system) of the spleen, liver, and lungs during blood circulation [9]. According to popular wisdom, increasing the blood circulation time, such as through PEGylation, would enhance the likelihood of reaching the target [9,10]. It is also believed that PEGylation prevents or reduces absorption by the reticuloendothelial system. Drug delivery nanoparticles are typically larger than 100 nm. The renal clearance of nanoparticles may not be the primary mechanism for the removal of nanoparticles from blood because the threshold size for effective renal clearance is known to be the kinetics of uptake [11] or 70 kDa [12]. The presumptive threshold sizes, however, require additional data to be confirmed. Contrary to popular belief, the medicine is released while in circulation rather than staying inside the nanoparticles and only reaching the target site. Depending on their nature, the nanoparticles may not stay intact in circulation, causing the enclosed medications to be released too soon.

The effect is hypothesized to be responsible for the extravasation of nanoparticles from blood vessels to the interstitium of malignancies. However, the phrase "EPR impact" has been misused by being used indiscriminately as though all iv-administered nanoparticles only reach the tumors. The original Maeda report states that proteins rather than nanoparticles accumulate more readily in malignancies [13]. Even if nanoparticles get to the tumor location, they still need to get through the microenvironment of the tumor, which is known to be very different from that of healthy tissues. Drug penetration is more challenging in tumors than in normal tissues because of the extracellular matrix density and increased interstitial fluid pressure.[2,4,5]

TARGETED MEDICAL PRODUCTS: A MARKET REVIEW

Drug/Marketed Formulation	Strength/Dosage Form	Application
1) Adalimumab	40 mg	Tumor necrosis factor (TNF) blocker
2) HUMIRA	Injection	
3) Cetuximab	100 mg/50 mL	Anticancer targeted therapy
4) ERBITUX	IV Infusion	
5) Daunorubicin	2 mg/mL	HIV-related Kaposi's sarcoma
6) DAUNOXOME	Concentrate for solution for infusion	
7) Cytarabine	50 mg	Intrathecal treatment of lymphomatous meningitis
8) DepoCyt	Intrathecal injection	
9) Paclitaxel	100 mg	Metastatic breast cancer
10) ABRAXANE	Lyophilized powder for injectable suspension	

Fig 4.

VII. CONCLUSION

Delivering a medication molecule to its target site is a challenging undertaking in an organism's intricate cellular

network. Last but not least, targeted drug delivery is emerging as one of the most cutting-edge methods in the medical sciences for the detection and treatment of a few fatal diseases. It is presently at the peak of expansion in terms of clinical and pharmacological research and development, having passed the infancy stage.

Overall, it can be said that the science of site-specific or targeted drug administration has gotten more mature and smart with time and the development of scientific technology thanks to the large database of many investigations. Particularly in the treatment of cancer, the development of drug-targeting techniques for clinical application for various therapies has been identified, examined, and resolved.

Many of these treatments are currently being sold and are in various stages of clinical testing. However, in light of improvements in our understanding of the various processes that result from the administration of medications of interest delivered via carriers or vehicles with site specificity, such techniques should be continually evaluated.

Utilizing the current "bench to bedside" expertise, new solutions under study should undergo periodic examination.

Additionally, in the upcoming years, the understanding of the cellular and molecular mechanisms underlying disease will be made easier by merging knowledge in the drug-targeting sector with technology advancements in molecular biology and molecular medicine.

REFERENCES

[1] Kinam Park et al: Analysis on the current status of targeted drug delivery to tumors J. control release, vol-164 I-2 2012.
[2] Kriti Rani et al: A review on targeted drug delivery: its entire focus on advanced therapeutics and diagnostics Scholars J. of applied medical sciences vol-2 I-1 2014.
[3] Subodh S Satheesh: Targeted drug delivery system-2017.
[4] Amina M. Al. nema: Targeted drug delivery system-2013.
[5] Mahewashsana A. Pathan: Targeted drug delivery system-2019.
[6] Dr. Sonali P.Mahaparale et al: Review on Targeted drug delivery Int. J. of creative research thoughts Vol-8 I-4 2020.
[7] Hoffman AS. The origins and evolution of “controlled” drug delivery systems. J. Control. Release. 2008: 132:153-163. [Pubmed: 18817820]
[8] Ruoslahti E, Bhatia SN, Sailor MJ. Targeting of drugs and nanoparticles to tumors. J. Cell Biol. 2010; 188:759-768. [Pubmed: 20231381]
[9] Jain RK. Transport of molecules in the tumor interstitium: a review. Cancer Res. 1987; 47:3039-3051. [Pubmed: 3555767]
[10] Agnihotri J, Saraf S, Khale A; Targeting: New Potential Carriers for Targetting Drug Delivery System. International Journal of Pharmaceutical Sciences Review and Research, 2011;8(2):120-123.
[11] Gupta M, Sharma V; Targeted drug delivery system: A Review. Research Journal of Chemical Sciences, 2011; 1:134-138.
[12] Vyas SP, Khar RK; Basis of targeted Drug Delivery, CBS Publishers and Distributors Reprint, 2008: 42-46, 74.
[13] Mark SW, Torchilin, Vladimir P; Drug delivery system. Access Science, McGraw Hill Companies, 2011.