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Review on: Targeted Drug Delivery

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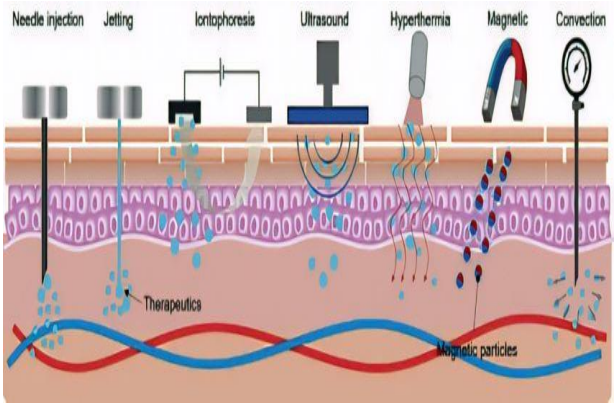
ABSTRACT

Targeted drug delivery, additionally referred to as good drug delivery, could be a methodology of treatment that involves the increase in medicinal drugs in one or few body elements as compared to others. Two strategies are widely used for drug targeting to the specified organ/tissue: passive targeting and active targeting. Drug delivery vehicles transport the drug either at intervals or within the locality of the target. An ideal drug delivery vehicle is meant to cross even stubborn sites like a blood-brain barrier [(1)]. The oral route is attractive to drug Administration because it is associated with patients' acceptability, less stringent protection conditions, and lower cost. [(2)]Recently, nanomedicine has emerged because of the medical application of nanotechnology. Since nanoparticles are very tiny in size, nano drug delivery can allow for the delivery of drugs with poor solubility in water and additionally aid in avoiding the primary pass metabolism of the liver. Nanotechnology-derived drug delivery will cause the drug to stay in blood circulation for a protracted time, thereby resulting in lesser fluctuations in plasma levels and so, token facet effects.[(3)] However, gastrointestinal destruction of labile molecules and low levels of absorption generally render oral delivery of peptides and proteins ineffective. Several strategies have the potential to enhance the efficacy of orally administered drugs. Bioadhesion is an approach for increasing interaction between drugs and the mucosae. Bioadhesive systems can be nonspecific, achieving adhesion via mechanical processes or specific systems that recognize receptors on epithelial cells. Lectins are one group of specific bioadhesives with many suitable properties for targeting cells in the gastrointestinal tract (GIT). This review assesses the potential of lectins in the delivery of drugs and vaccines to the GIT[(4)]. A variety of technologies using physical modes of drug delivery have been developed and investigated to overcome the epithelial cell layer of the GI tract for local and systemic delivery. These technologies include direct injection, jetting, ultrasound, and iontophoresis, which have been largely adapted from transdermal drug delivery. Direct injection of agents using needles through endoscopy has been used clinically for over a century. Jetting, a needleless method of drug delivery where a high-speed stream of fluid medication penetrates tissue, has been evaluated pre-clinically for delivery of agents into the buccal mucosa.[(5)]

Keywords: Targeted drug delivery, targeting ligands, passive/active targeting, Nanotechnology, digestive system, peptides and proteinsineffective bio adhesion, mucous, receptors on epithelial cells.



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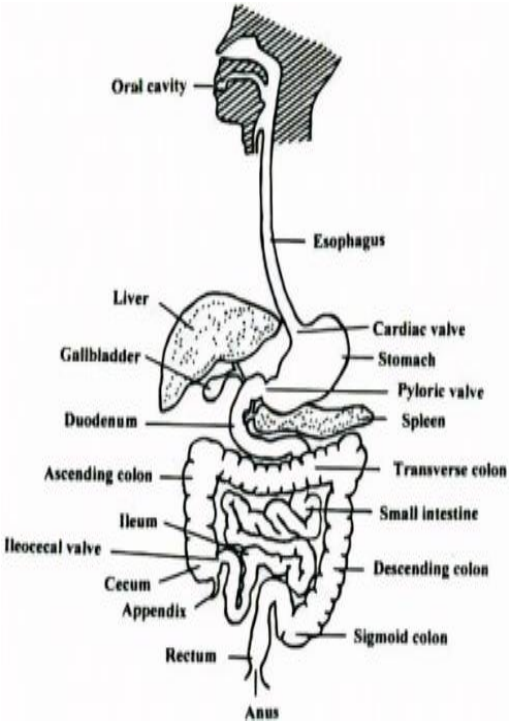
INTRODUCTION

Targeted drug delivery is an effective system that precisely administers medication to patients. Unlike traditional methods, which involve drug absorption through biological membranes, targeted delivery systems release the drug in a controlled and specific manner (6,7). The drug delivery system is highly complex and requires collaboration among chemists, scientists, and engineers to refine the technique. When implementing a targeted release system, it is essential to consider factors such as the drug's properties, potential side effects, the delivery route, the target site, and the specific disease (8).

Products utilizing such a delivery system are being developed with a focus on the specific characteristics of target cells, as well as the nature of markers, transport carriers, or vehicles that deliver the drug to precise receptors and ligands. Ideally, targeted drug delivery systems should be biochemically inert and non-toxic, non-immunogenic, and stable both in vivo and in vitro. They should ensure targeted drug distribution to specific cells, tissues, or organs with uniform capillary distribution. Additionally, these systems should allow for controlled and predictable drug release rates, without affecting the drug's efficacy, while minimizing drug leakage during transit and delivering a therapeutic amount of medication (9,10,11). Conventional dosage forms, including injections, oral formulations (such as solutions and suspensions), tablets, capsules, and topical creams and ointments, each have their own limitations (12). Parenteral drug delivery, while effective for rapid effects, is highly invasive and generally provides only short-term results (13). Although oral administration is widely used and suitable for many medications, it is not effective for certain drugs, such as peptide drugs, due to their poor absorption and potential degradation in the gastrointestinal tract (14). The gastrointestinal tract can degrade some drugs, reducing their effectiveness. Additionally, topical ointments and creams are limited to producing local effects rather than systemic ones (15).

To achieve a successful targeted drug delivery system, four key requirements must be met: retention, evasion, targeting, and release. The drug must be loaded into a suitable delivery vehicle, evade degradation by the body's defenses, remain in circulation long enough to reach the target site and release the drug precisely when needed for optimal effectiveness. Different sites in the body require different delivery methods, depending on the route taken (16,17).

In targeting, drugs accumulate selectively in specific organs or tissues. Understanding the extent of targeting helps in choosing the right carrier or ligand system. Targeted delivery also minimizes drug exposure to non-target tissues, ensuring safety and efficacy. Drug targeting can be categorized into three levels—first, second, and third—with molecular targeting as a possible fourth level. Targeting can also be classified as active, passive, reverse, or physical (18).



Ideal characteristics:[19]

1. It must possess properties that are nontoxic, biodegradable, biocompatible, and stable in both in-vivo and in-vitro environments.

2 . The system must be designed to effectively transport the medication to specific cells, tissues, or organs, ensuring a consistent distribution throughout the capillary network.

3. It is essential that the release of the dug occurs in a controlled and predictable manner over an appropriate duration.

4. It is essential to effectively sustain the drug concentration at the intended site within the therapeutic range for an extended duration.

5. It is essential to ensure minimal drug losses resulting from leakage within the carrier system.

6. The carrier employed must be biodegradable and should be eliminated from the body without causing any toxic interactions.

7. Additionally, the preparation process should be straightforward, reproducible, and cost-effective.

Advantages: [20]

1. The process of giving medication is made easier.

2. The harmful effects of the drug are reduced by focusing on a specific area.

3. A small dose can achieve the intended effect of the drug.

4. It's important to bypass the first-pass effect.

5. There is better absorption of the drug at the targeted location.

6. Targeting the drug led to a steady plasma concentration without peaks and valleys.

Disadvantages :[21]

1. Quick removal of drugs from the body leads to needing to take them more often.

2. The vehicle used in the targeted drug delivery system might trigger an immune reaction.

3. The drug delivery system doesn't stay at the tumor site long enough.

4. Released drugs can spread and move around in the body.

5. Creating, storing, and giving out the targeted drug delivery system needs a lot of specialized knowledge.

6. There could be increased toxicity from challenging drugs building up at the target area.

7. Achieving product stability will be.

Strategies for drug targeting:

1. **Passive targeting**

Passive targeting generally means the methods used to deliver drugs that aim to send the medication directly into the bloodstream [22]. Passive targeting happens when the body reacts to the physical and chemical characteristics of a drug or its delivery system, which keeps the drug contained until it arrives at the intended location[23]. Salinomycin was utilized in passive targeting micelles to help reduce breast cancer and stem cell cancer [24].

2. **Active targeting:**

This approach involves targeting the drug by first identifying the specific group that is connected to the surface of the drug delivery system, allowing it to bind to the receptors on the target cells [40]. The focus is on bioadhesive nonionic surfactants, antibodies, and albumin proteins as the main groups of interest [26]. There are three types of active targeting: First-order targeting, which focuses on organs; Second-order targeting, which is all about targeting specific cells; and Third-order targeting, which deals with targeting inside the cells themselves [27]. Used the folate receptor to specifically target anticancer medications [28].

3. **Inverse targeting:**

The goal of inverse targeting is to prevent the drug delivery system from being taken up by the reticulum-endothelial system (RES)[29,30]. This can be done by injecting a significant amount of a blank drug delivery system or large dextran sulfate molecules to overwhelm the RES and reduce its normal uptake function [25]. Inverse targeting is particularly beneficial for directing drugs to organs that are not part of the RES [31]. For example, Balthasar and Fung applied this strategy to deliver methotrexate specifically to tumors in the peritoneum[32].

4. **Ligand mediated targeting:**

This kind of drug targeting relies on how well receptors take in natural low-density lipoprotein (LDL) particles and synthetic micro-emulsions of LDL particles that are coated with Apo proteins [33]. Veiseh and colleagues used a strategy that involves ligands to specifically target cancer treatment [34].

5. **Physical targeting:**

The physical targeting strategy focuses on making changes to drug delivery systems so they can be directed to specific locations in the body. These changes can involve altering the temperature, adjusting the pH levels, or using an electric field [35]. This approach shows great promise for targeting tumors and genes [36,37]. Weichselbaum and his team utilized physical targeting techniques in their gene therapy research [38].

6. **Dual targeting:**

The dual targeting mechanism is a drug delivery system where the carrier not only transports the drug but also boosts its effectiveness [40]. For instance, if a carrier molecule has antiviral properties and is combined with an antiviral drug, the overall treatment becomes more powerful. Cui and colleagues used this dual-targeting approach to deliver paclitaxel and curcumin for treating brain tumors [38].

7. **Double targeting:**

The double targeting strategy combines both time and location, which is why it's referred to as double targeting [25]. The spatial aspect focuses on directing the drug to a specific area, while the temporal aspect manages when the drug is released at that location[40]. Pitto-Barry and colleagues used this double-targeting approach to deliver a dendrimer-loaded anticancer drug directly to the tumor site [39].

Biological processes

Biological processes involved in drug targeting for the gastrointestinal (GI) tract include:

- Cellular uptake:- The first biological process in drug targeting, this is when molecules are taken up by a cell's plasma membrane. Low molecular mass drugs can pass through the cell wall and plasma membrane by diffusion. Larger molecules, or macromolecules, can't enter cells by simple diffusion and instead are taken up by a process called endocytosis.

- Transport across barriers:- This is a second line of cellular uptake, where molecules must cross the body's epithelial barriers.

- Bioadhesion:- This approach increases the interaction between drugs and the mucosae.

- Enrespo and microbial degradation:-Drugs and dosage forms can be degraded by enzymes and microbes throughout the GI tract.

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- pH variation:- The pH of the GI tract varies along its length, from 7.0 in the oral cavity to 8.0 in the colon. (41)

The Specific Features of GI-targeted Drug Delivery System:

Different drugs target different sites based on the physiological characteristics of some of those sites. Table 1 below highlights some of these features. (42)

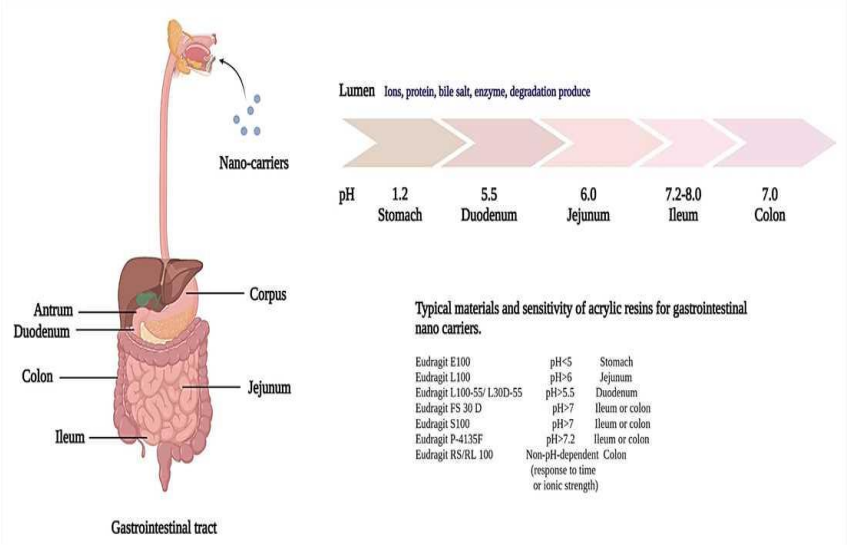

TABLE 1:- Features for GASTRO-INTESTINAL response. (42)

Gastrointestinal parts	Features	Function
Gastric response	Acid resistance(stability), slow response (long duration of action), less irritation to the gastric mucosa not easily cleared by the stomach	Prolong gastric retention time and release drugs continuously to improve local treatment.
Small intestine response	Acid resistance, high bioavailability, and stability, so as not to be destroyed by digestive juices such as stomach acid and bile. Targeted (targeted action on small intestinal tissue)	Intestinal absorption of biodegradable drugs; Absorption of drugs for systemic diseases; Delivery of drugs to the appropriate intestinal absorption site to reduce dose and improve safety
Colon response	Intestinal flora can be used, such as the use of biodegradable materials; targeting and specificity, biocompatibility, and low toxicity (does not affect the intestinal flora)	Sustained release and slow absorption of gastrointestinal degradable drugs; Delivery of local therapeutic drugs to the colon.
Mucous response	Remain in mucus or penetrate mucus, control the slow release of drugs, and target specific factors.	Enhance retention time and the local drug concentration to improve local treatment or systemic absorption. Or reach the epithelial intact and avoid being cleared rapidly to improve local treatment or systemic absorption.

Drug vehicles

A drug carrier, also known as a drug vehicle, is a material used in drug delivery to enhance the drug's selectivity, effectiveness, or safety during administration [43]. These carriers are designed to control how drugs are released into the body, either by gradually releasing the drug over time (typically through diffusion) or by releasing it at the target site in response to certain stimuli like changes in pH, heat, or light. Additionally, drug carriers help improve the drug's bioavailability, especially for drugs that have poor water

solubility or struggle to pass through cell membranes. Various drug carrier systems have been developed, each with its own set of strengths and limitations. Common types include liposomes, polymeric micelles, microspheres, and nanoparticles[44]. The drug can be attached to the carrier in different ways, such as by adsorption, being integrated into the carrier's structure, encapsulation, or covalent bonding. Depending on the type of carrier, multiple attachment methods may be used[45].

Type of vehicles

There are various types of drug delivery systems, including polymeric micelles, liposomes, lipoprotein-based carriers, nanoparticles, and dendrimers. An ideal drug delivery system should be non-toxic, biocompatible, non-immunogenic, biodegradable[46], and able to avoid detection by the body's defense mechanisms.[45]

Peptides

Cell Surface Peptides provide one way to introduce drug delivery into a target cell.[46] This method is accomplished by the peptide binding to a target cell's surface receptors, in a way that bypasses immune defenses that would otherwise compromise a slower delivery, without causing harm to the host. In particular, peptides, such as intercellular adhesion molecule-1, have shown a great deal of binding ability in a target cell. This method has shown a degree of efficacy in treating both autoimmune diseases as well as forms of cancer as a result of this binding affinity.[47] Peptide-mediated delivery is also of promise due to the low cost of creating the peptides as well as the simplicity of their structure.

Liposomes

Liposomes are currently the most common vehicle used for targeted drug delivery[48]. They are non-toxic, non-hemolytic, non-immunogenic, even with repeated injections, and are biocompatible, biodegradable, and can be engineered to evade clearance mechanisms like the reticuloendothelial system (RES), renal clearance, and chemical or enzymatic inactivation, etc [49]. Lipid-based, ligand-coated nanocarriers can encapsulate drugs or contrast agents either in their hydrophobic shell or hydrophilic core, depending on the substance being delivered.[46] However, liposomes face the challenge of rapid uptake and clearance by the RES system and exhibit relatively low stability in vitro. To address this, polyethylene glycol (PEG) can be added to their surface. By increasing PEG concentration by 4-10%, the circulation time in vivo can be extended significantly—from 200 minutes to 1000 minutes.[46] PEGylation of liposomal nanocarriers prolongs their half-life while preserving their passive targeting ability, commonly observed in lipid-based nanocarriers.[50] When used as a drug delivery system, this construct can be designed to become unstable in response to specific triggers, enabling the selective release of the encapsulated therapeutic agent near the target tissue or cells. This system is frequently used in cancer treatment, where the acidic tumor environment—due to an over-reliance on glycolysis—activates drug release.[50].

Additional endogenous triggers, such as reactive oxygen species, glutathione, enzymes, hypoxia, and adenosine-5'-triphosphate (ATP), are also exploited, as these are often abundant in tumor environments. External triggers, including light, low-frequency ultrasound (LFUS), electrical fields, and magnetic fields, are also employed to control drug release. In particular, LFUS has shown high efficacy in controlling the release of drugs like cisplatin and calcein in mice.[51]

Micelles and Dendrimers

Polymeric micelles, another type of drug delivery vehicle, are formed from amphiphilic co-polymers containing both hydrophilic and hydrophobic monomer units[44]. They are useful for carrying drugs with poor solubility, though they offer limited control over size and functional adaptability. However, newer techniques utilizing reactive polymers and hydrophobic additives can produce larger micelles with a range of sizes.[50] Dendrimers, also polymer-based delivery systems, feature a core that branches out at regular intervals, forming compact, dense, spherical nanocarriers.[51]

Biodegradable Particles

Biodegradable particles can target diseased tissue and deliver their payload through controlled-release therapy.[31] Additionally, biodegradable particles equipped with ligands for P-selectin, endothelial selectin (E-selectin), and ICAM-1 have been shown to adhere to inflamed endothelium[52]. Consequently, biodegradable particles hold potential for application in cardiac tissue as well.

Microalgae-based delivery system

Researchers have developed biocompatible microalgae-based microrobots for delivering drugs actively to the lungs and gastrointestinal tract. These microrobots were tested on mice and showed promising results. In the studies, the microalgae motors

were loaded with fluorescent dye or nanoparticles coated with cell membranes and then placed inside a capsule that dissolves in response to changes in pH. In another approach, antibiotic-loaded nanoparticles coated with neutrophil membranes were attached to the microalgae for targeted drug delivery.[53]

Artificial DNA Nanostructures

Advances in DNA nanotechnology have allowed scientists to build artificial nanostructures from DNA and other nucleic acids. These structures don't rely on DNA's role in genetics but instead use it as a building material. There is potential for these DNA-based devices to deliver drugs by responding to specific environmental signals. For example, researchers have created logic circuits using DNA that can release a drug when they detect certain molecules, like specific mRNA[54]. Additionally, a "DNA box" with a controllable lid has been designed. This box can hold a drug and only open to release it when triggered by a particular stimulus. [55]

TARGETED MEDICAL PRODUCTS: A MARKET REVIEW

Physical drug delivery methods targeting the gastrointestinal (GI) tract involve disrupting the epithelial cell layer. Given the GI tract's extensive surface area, it offers a substantial target for drug delivery. These methods aim to: (1) enhance local or systemic drug concentrations beyond what passive routes can achieve, (2) reduce first-pass metabolism, (3) administer macromolecules or sensitive drugs that are difficult to deliver orally or rectally, (4) provide pain-free administration, and (5) enable self-administration. This review examines various physical delivery techniques for the GI tract, including needles, jetting, ultrasound, iontophoresis, and others [56] . Several formulations utilizing targeted cancer therapies are already available on the market. Examples include Myocet (liposomal doxorubicin), Daunoxome (liposomal daunorubicin), Doxil (liposomal doxorubicin), DepoCyt (liposomal cytarabine), and Abraxane (albumin-bound paclitaxel particles). Some notable monoclonal antibodies used in cancer therapy are Rituxan (rituximab) [57].

Lists the products in the market that use passive targeting via the EPR effect, and marketed formulations useful for MPS targeting are listed in Tab;

1. Adalimumab (HUMIRA)

- Formulation: Injection.
- Strength/Dosage Form: 40 mg.
- Application: Tumor necrosis factor (TNF) blocker.

2. Cetuximab (ERBITUX)

- Formulation: IV Infusion.
- Strength/Dosage Form: 100 mg/50 mL.
- Application: Anticancer targeted therapy.

3. Daunorubicin (DAUNOXOME)

- Formulation: Concentrate for solution for infusion.
- Strength/Dosage Form: 2 mg/mL.
- Application: HIV-related Kaposi's sarcoma.

4. Cytarabine (DepoCyt)

- Formulation: Intrathecal injection.
- Strength/Dosage Form: 50 mg.
- Application: Intrathecal treatment of lymphomatous meningitis.

5. Paclitaxel (ABRAXANE)

- Formulation: Lyophilized powder for injectable suspension.

- Strength/Dosage Form: 100 mg.

- Application: Metastatic breast cancer.

CONCULSION:-

Targeted drug delivery systems for the gastrointestinal tract (GIT) have several advantages over conventional drug delivery methods, including:

•Lower side effects

Targeted drug delivery systems can deliver drugs directly to the diseased site, avoiding normal areas of the body.

•Increased therapeutic efficacy

Targeted drug delivery systems can increase the accumulation of drugs at the diseased site.

•Improved oral delivery efficiency

Targeted drug delivery systems can protect therapeutics that are vulnerable to degradation in the upper GIT.

- Some strategies for targeted drug delivery in the GIT include:

Nanocarriers: Nanocarriers can protect drugs until they reach the correct delivery site. They can also be designed to modulate drug release. Gastro-retentive devices: These devices can be used in the stomach to prolong drug retention and achieve sustained drug release. Mucus-penetrating or mucus-interacting systems: These systems can be used in the mucus layer. Biodegradable polymers: These polymers can be used for colon-targeted drug delivery. pH-dependent and microbially triggered systems: These systems can be designed to avoid problems associated with pH or time dependence. [58]

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