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A REVIEW ON ADVANCES IN TARGETED DRUG DELIVERY SYSTEM FOR PRECISION THERAPEUTICS AND DIAGNOSTICS.

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ABSTRACT;

Drug targeting is a new drug delivery strategy that tries to deliver the drug to the target site of action or site of absorption without releasing the drug to any other non-target site.The delivery method is meant to keep the complete medicine without any change till reaching and releasing at the target spot.Targeted drug delivery systems are superior to conventional ones in a number of ways, including increased pharmacological action, fewer side effects, and lower dosage requirements. The primary goal of the targeted drug delivery system is to deliver the therapeutic agent's the pharmacological action only to the sick organs without damaging the healthy ones, particularly when chemotherapeutic medicines are used to treat cancer. Different carriers that preserve and deliver the intact drug to a predetermined organ or tissue can be used to achieve drug targeting. A variety of carriers, including nanotubes and nanowires, quantum dots, nanopores, gold nanoparticles, dendrimers, and transferosomes, can be employed for drug targeting . Passive targeting, inverse targeting, active targeting, ligand-mediated targeting, physical targeting, dual targeting, and double targeting are some of the several pharmacological targeting mechanisms .A helpful delivery method for delivering the therapeutic chemical to a particular location without endangering other organs is medication targeting.

KEY WORDS;
New Drug delivery System,Nanoparticles, Cancer Therapy, inverse targeting.

I .INTRODUCTION:

Overview The biological effects of a drug in a patient depend on the pharmacological qualities of the drug. These effects happen due to the interactions between the drug and the receptors at the site of action of the drug.The efficacy of this drug target interaction has been damaged unless the drug is carried to its site of action at such a concentration and rate that causes the least side effects and maximal therapeutic effects. Targeted medication delivery, is the method of therapy that involves the transportation of the therapeutic substance to specified tissue without contacting the other part of the body. As a result, it exclusively administers the drug to certain parts of the body.The specific type of cells as in the case of cancer cells.[1]

This lowers side effects and increases therapeutic efficacy .In contrast to the traditional drug delivery system, which works by absorbing the drug via the body's semipermeable barrier, it releases the drug in a dose form [2]There are certain drawbacks to traditional dosage forms such injections, oral formulations that include solution and suspension , tablets, capsule and tropical cream, ointment.[3]

Drug administration by parenteral means is quite intrusive and this lowers side effects and increases therapeutic efficacy. In contrast to the traditional drug delivery system, which works by absorbing the drug via the body's semipermeable barrier, it releases the drug in a dose form.

II .PRINCIPLES FOR THE DRUG TARGETING ARE:

1.loading the drug to the target site
avoiding the drug's degradation by bodily fluids
reaching the target site;
and releasing the drug at the designated spot at the scheduled time. [4]

Depending on the route to be taken, different drug delivery mechanisms must be used for different sites of interest within the body. The medication may be administered in drug targeting.

Drug targeting is ideal for medications having low specificity, low therapeutic index, low absorption, short half-life, or an outsized volume of distribution. All such circumstances necessitate formulation of the medications into the specific delivery mechanism. Targeted medication delivery systems limit the unwanted effects by making modifications in the incorrect disposition of the drug and reducing its presence in no targeted locations. At an analogous time, drug targeting also maximizes the therapeutic efficacy of the medicine by preventing its inactivation throughout the travel to the target site.[5]

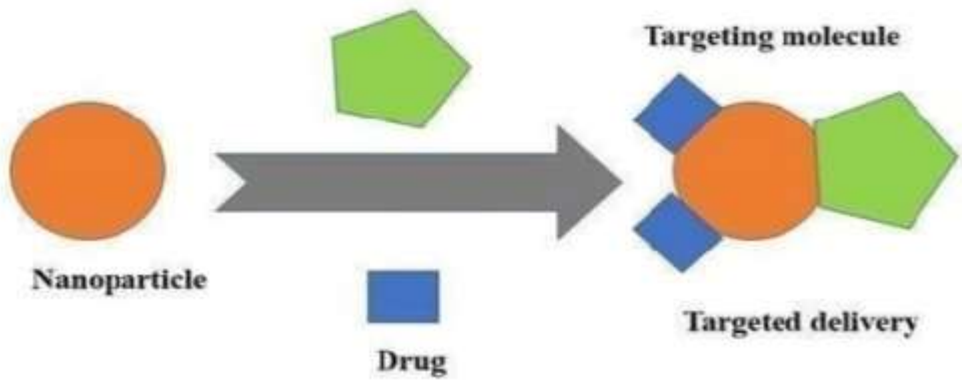

Figure no1 :Targeted Drug Delivery

III .CLASSIFICATION;

Drug targeting has been classified into three types.
A. First order targeting
B . Second order targeting
C. Third order targeting ;implies delivery to specific intracellular compartments in the target cells e.g., Lysosomes.
Basically, there are three approaches for drug targeting
The first approach involves the use of biologically active agents that are both potent and selective to a particular site in the body (Magic bullet approach)[6]
The second approach involves the preparation of a pharmacologically inert form of active drugs that when it reaches the active sites becomes activated by a chemical or every enzymatic reaction (prod rugs approach).[7]
The third approach utilizes a biologically inert macromolecular carrier system that directs a drug to a specific site in the body where it is accumulated and affects its response (carrier approach). [8]

IV .TARGETING DRUG DELIVERY CARRIERS;

1. PASSIVE TARGETING:

Relies on the typical distribution pattern of the drug carrier system When delivered systemically, RES macrophages ea sily eliminate example-
particles that are 5 μm smaller from the blood. This innate defense mechanism of RES gives macrophages the chance to encapsulate tar or conjugate it to the proper carrier system
DD that focusses on systemic circulation is known as passive targeting. This method uses the body's natural reaction to the physicochemical properties of the drug or drug-carrier system to target drugs. This is predicated on the medicine or drugs accumulating in regions that target the place of interest, such tumour tissue.

2.ACTIVE TARGETING:

The reticuloendothelial system's (RES) inherent hydrophobic contacts give the particles this characteristic, allowing the drug-loaded nanoparticle to remain in circulation for a longer amount of time.By using passive diffusion or convection, nanocarriers can transport medications into the tumor mesenchyme or cells through the spaces between tumor capillary pores

3. PHYSICAL TARGETING:

A delivery method that exclusively distributes the medication in a certain setting is referred to as physical targeting. P hysical characteristics include using an external magnetic field or changing the pH or environment.

In contrast to passive targeting (natural buildup through the EPR effect) and chemical targeting (biological markers). By using external magnets for iron-particle medications or ultrasound to release agents in tumors, it helps concentrate medications where they are required, increasing efficacy and lowering adverse effect

[9]

V .TARGETING GIT:

Currently, controlled release drug delivery systems provide for control over the drug's delivery time or place. A more traditional method is to control the drug delivery time course. Drug administration to a particular organ, cell class, or physiological compartment is known as site specific or targeted delivery. Depending on the target site, several site-specific oral controlled release systems have been created, which fall into the following categories:Depending on the target site, a variety of site-specifc:

1. Systems that target the duodenum and stomach
2. Small intestine-specific systems.
3. Lymphatic systems.
4. Colon-specific systems.[10]

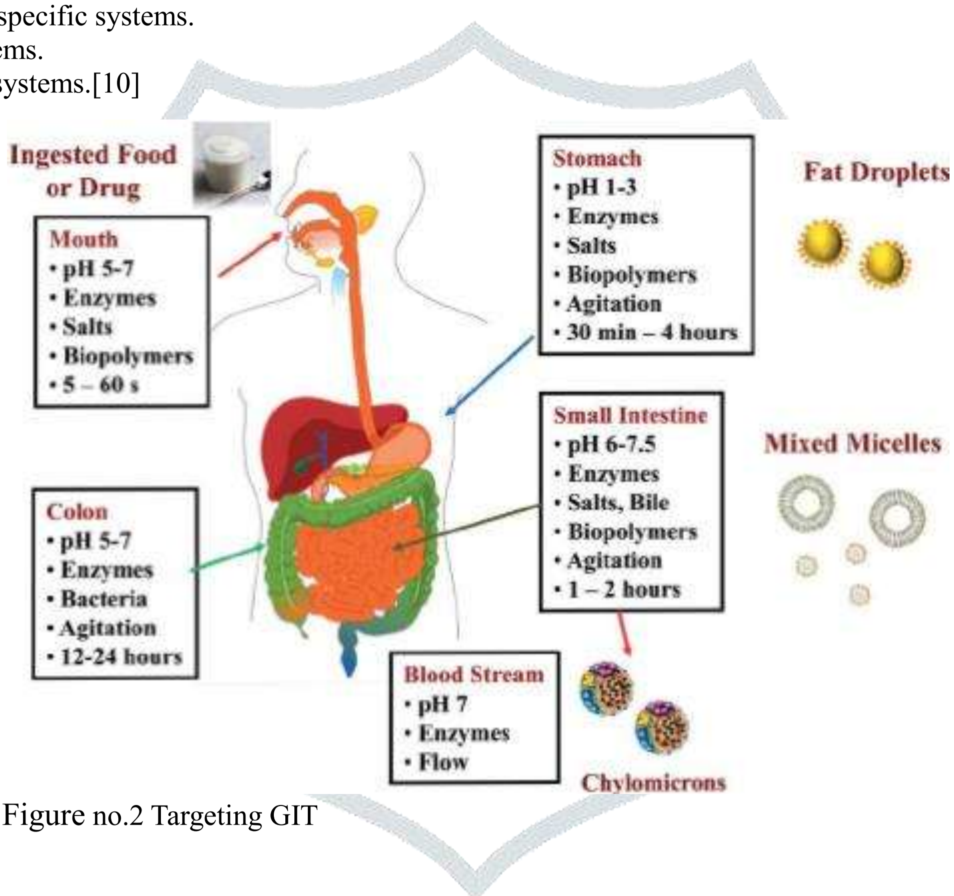

Figure no.2 Targeting GIT

1.The Duodenum or Stomach System;

In order for the active ingredients to reach their ideal absorption location in solution and be prepared for absorption, these systems not only extend the stomach residence time but also extend it across the entire GI tract. These systems are employed in conjunction with:

1. Insoluble medication in intestinal fluid
2. Drugs that work therapeutically in the duodenum and stomach, such as magnesium trisilicate, aluminum hydroxides, and antacids such magnesium oxides, hydroxides, and carbonates.
3. Medications like chlorpheniramine malate that show site-specific absorption from the duodenum.
4. Substances that are largely absorbed from the stomach, such as minerals and some vitamins (VitB, VitC).
5 .Drugs which failed the other conventional sustained release systems have produced satisfactory results with these systems

e.g., Chlordiazepoxide.

2.System Targeted at Small Intestine;

These systems are designed to allow a system to safely pass through the stomach's acidic environment and produce the appropriate intestinal juices. Systems of this kind are utilized with:

1. Drugs, such as enzymes, that stomach acid breaks down.

2. Medications that irritate the stomach lining, such as sodium salicylate.
3. Medications that must operate locally in the colon, such as intestinal antiseptics.[11]

3.Lymphatic systems:

The intestinal lymphatic system is made up of a network of vessels that pass through the small and large intestines and may be involved in the absorption of particles that are given orally and range in size from nanometers to micrometers. The absorption of various nutrients, liquids, and medications is greatly aided by these lymphatics.

The following are the uses of these systems:

1. Preventing the first pass metabolism of the liver
2. Targeted therapy for mesenteric lymphatic disorders and infections.
3. Improved absorption of big, high molecular weight substances like particles and peptides
4. Prevention of the spread of cancer cells.
5. Substances that can be affected by chemicals or enzymes in luminal fluids.
6. Medications that are extremely hydrophilic and ionizable at all pH levels, such as streptomycin.

4.Colon specific systems;

When the stomach is empty, its pH is usually very acidic, around 1–2. After we eat, this acidity reduces because the food acts like a buffer and increases the pH. As the food moves further into the digestive system, the pH gradually becomes less acidic. In the beginning part of the small intestine (the duodenum and jejunum), the pH is around 6.5, and near the end of the small intestine (ileum), it rises to about 7.5.m

However, once the contents enter the colon, the pH starts to drop again. The first part of the colon, called the cecum, usually has a pH of around 6.4, and in many healthy people, the ascending colon can be even more acidic with a pH close to 5.7. As the material continues to travel, the pH changes slightly the transverse colon has a pH of about 6.6, and it slowly returns to a neutral level of around 7.0 in the descending colon.

These natural pH variations throughout the digestive tract are very useful in designing colon-specific drug delivery systems. Scientists take advantage of this by using special pH-sensitive polymers in formulations. These polymers do not dissolve in the acidic stomach environment or in the earlier part of the small intestine. Instead, they stay intact and only begin to dissolve when they reach the colon, where the pH becomes suitable for drug release. This ensures that the drug is protected until it reaches the exact site where it is needed.

Some commonly used pH-dependent polymers for colon targeting include:

1.Eudragit® polymers such as L100 (dissolves above pH 6.0) and S100 (dissolves above pH 7.0)
2.Cellulose acetate phthalate (CAP)
3.Hydroxypropyl methylcellulose phthalate (HPMCP)
4.Polyvinyl acetate phthalate (PVAP)

By using these polymers, the drug can reach the colon safely and release its effect right where it is required, which is especially valuable in the treatment of colon-related diseases like ulcerative colitis, Crohn’s disease, and colorectal cancer[12]

VI .DRUG TARGETING ADVANTAGES:

1.Protocols for administering drugs might be made simpler.
By delivering a medication to its intended place, toxicity is decreased, which lessens detrimental systemic effects.
2.The desired effect can be achieved by administering the drug at a lower dose.
3. Preventing first pass metabolism in the liver.
4.Improvement of target molecules’ absorption, including particles and peptides
5.The dosage is lower than with a traditional drug administration method.
6.There is no plasma concentration peak or trough. Targeting infection cells specifically in comparison to healthy cells. [13]

VII .DISADVANTAGES OF DRUG TARGETING ;

Immune responses to carrier systems given intravenously. Targeted systems are not sufficiently localized into tumor cells.

1 . Drug diffusion and redistribution following release.
2. The formulation calls for extremely advanced technologies.
3 .Needs expertise in administration, storage, and manufacturing.
4.Toxicity symptoms may arise from drug accumulation at the target site.
5.The formulation calls for extremely advanced technologies.
6.The dosage form is difficult to keep stable
7.For instance, resealed erythrocytes must be kept at 4°C.
8 . Drug loading is typically illegal.
For example. Similar to micelles. As a result, it is challenging to forecast or resolve[14]

VIII.PRINCIPLES OF TARGETING DRUG DELIVERY ;

Targeted drug delivery is all about sending a medicine directly to the cells that actually need treatment. Instead of spreading throughout the entire body like most conventional drugs do, targeted systems focus only on the diseased area. This helps improve the drug's effectiveness while reducing unwanted side effects.

To make this possible, scientists first study the special features of the target cells. Many diseased cells, such as cancer cells, have specific receptors on their surface that healthy cells do not have. Drug carriers are then designed to recognize and attach only to those receptors, ensuring that the treatment reaches the right spot.

These drug carriers can be nanoparticles, liposomes, microspheres, monoclonal antibodies, or specially designed polymers. They protect the drug while it travels through the body and release it only when it reaches the target.[15]

The success of a targeted drug delivery system depends on several important factors, including:

How much drug is needed at the target area
The size and shape of the tiny particles carrying the drug
The drug's chemical properties like solubility and molecular weight
The presence of enzymes that may break the drug down
The surface charge and coating of the carriers
The body environment, such as pH and temperature
The type and amount of excipients/polymers used to make the formulation

By modifying the surface of the carriers with ligands or protective coatings, the system can stay in the body longer and better recognize the target cells.
[16]

IX .CARRIERS FOR DRUG TARGETING

1.**LIPOSOMES**:

Originating from the Greek word lipo, which means "fatty" constitution, and soma, which means "structure," Liposome was initially identified by Alec D. Bangham in early 1965. Liposomes have a diameter of 50 nm to several micrometers, making them comparatively small. One or more phospholipid bilayers completely encapsulate the aqueous core of these spherical vesicles. It is remarkable in that it can capture both hydrophilic and lipophilic medications and make site-specific drug delivery to tumor cells easier

Liposomes are basic lipoidal vesicles with a lipid-bilayer structure that are microscopic and nanoscale. Both hydrophilic and lipophilic medicines can be effectively trapped in these bilayers, which are made up of an aqueous core completely encased by a membrane made of lipid molecules. While hydrophilic medications are held in the inner watery core, lipophilic drugs are captured by the bilayer membrane.[17]

2.**NIOSOMES**;

New class of unique vesicular systems is represented by niosomes. They are made up of nonionic surfactants, which are comparatively harmless and biodegradable. They were created as low-cost, stable substitutes for liposomes. Their role has expanded to include various application areas since their early debut to the cosmetics sector. They are currently being vigorously investigated as possible carriers for targeted and prolonged medication delivery. They can be administered by ocular, transdermal, vaginal, and inhalation routes in addition to traditional, oral.

3.**NANOWIRES:**

It possesses a large surface area, so the surface can be treated to allow the nanowire to bind with specific biological molecules when inserted inside the body. It can be used for detecting the causes and treatment of brain diseases, such as seizures, parkinsonism and similar diseases.

4 .**NANOSHELLS**;

New nanoparticle techniques called nanoshells are made out of a silica hollow dielectric core encased in a gold shell. It can be applied therapeutically or for diagnostic purposes. Antibodies can be affixed to the surfaces of nanoshells, enabling them to conjugate specific regions.The antineoplastic medication is effectively targeted by this method.

5.**QUANTNAM DOTS;**

dots are nanocrystalline semiconductor particles with unique optical characteristics that make them useful for tumour imaging. Cancer medications are successfully targeted by this carrier.

6 .**NANOPORES**:

One strand of DNA can travel through them thanks to their minuscule holes. Thus, enable extremely precise and efficient DNA sequencing. Genetic engineering and biotechnology could benefit from this method.[18,19]

X . CONCLUSION;

In an organism's intricate cellular network, delivering a medication molecule to its intended location is a challenging task in and of itself. One of the most promising and cutting-edge methods in the medical sciences for the diagnosis and treatment of a few deadly illnesses is targeted drug delivery. Research and development in the clinical and pharmaceutical domains has advanced past its infancy and is currently reaching its peak. Overall, it can be said that the science of site-specific or targeted distribution of these medications has grown more intelligent and wise with the growth of scientific technology, as seen by the extensive database of various studies. Future therapeutic and diagnostic developments will result from the application of all these tactics and cutting-edge technologies in the clinical setting.

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