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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 drug 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 target. An ideal drug delivery vehicle is meant to cross even stubborn sites like a blood brain barrier. Recently, nano medicine has emerged because 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 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. These include polymer-drug conjugates and nano particulate systems such as liposome's, quantum dots, dendrimers, etc. There are several other approaches as well. These also include the strategies wherein the therapeutic agents are coupled with "targeting ligands" that possess the ability to recognize antigens associated with tumors.

Keywords: Targeted drug delivery, targeting ligands , passive / active targeting , Nanotechnology.

INTRODUCTION

Targeted drug delivery could be a reasonably sensible drug delivery system that is miraculous in delivering the drug to a patient. This typical drug delivery system is completed by the absorption of the drug across a biological membrane, whereas the targeted unharness system is that drug is discharged in a indefinite quantity form [1,2]. The drug delivery system is extremely integrated and needs various disciplines, like chemists, scientist and engineers, to join forces to optimize this technique. once implementing a targeted unleash system, the subsequent standard for the system got to take into account: the drug properties, side effects of the medicine, the route taken for the delivery of the drug, the targeted website, and also the unwellness.(3) Targeted drug delivery system is preferred over conventional drug delivery systems due to following three main reasons. The first being pharmaceutical reason. Conventional drugs have low solubility with more drug instability in comparison to targeted drug delivery systems. Conventional drugs even have poor absorption, shorter half-life and need large volume of distribution. These constitute its pharmacokinetic properties. The third reason constitutes the pharmacodynamic properties of drugs. the traditional drugs have low specificity and low therapeutic index as compared to targeted drug delivery system. Due to these reasons targeted drug delivery system is preferred over conventional drug delivery systems.(4 6)

It differs from the traditional drug delivery system therein , it gets release during a dosage form while the previous functions by the absorption of drug across biological membrane(7) Greogoriadis, in 1981, described the utilization of novel drug delivery for drug targeting as „old drug in new clothes"(8) Conventional dosage forms like injections, oral formulations comprising of solutions and suspensions, tablets, capsules, and topical creams & ointments, carry some disadvantages. Parenteral delivery of medicine is very invasive with ephemeral effects. Oral administration of drug, inspite of being immensely popular and appropriate, can't be used surely drugs, like protein or peptide drugs, due to their poor absorption by the oral route. These could also be degraded within the alimentary canal . Topical creams and ointments have a drawback of being limited to local effects, instead of systemic ones. now a days some important factors also take in consideration like into consideration, several factors like bioavailability, drug absorption processes, pharmacokinetic processes, timing for optimal drug delivery, etc (9)

. There are four principle requirements for a successful targeted drug delivery system: retain, evade, Target and release, i.e., there should be proper loading of the drug into an appropriate

drug delivery vehicle, it must possess a capability to flee the body"s secretions which will degrade it, resulting in an extended duration in circulation and thereby reaching the location of interest and, should release the drug at the precise site within the time that involves effective drug functioning Different sites of interest within the body necessitate the utilization of various drug delivery systems, depending upon the route to be followed.(10,6) In drug targeting, the drugs accumulate within the organ or tissue selectively and quantitatively. A clear understanding of the extent of targeting makes it easy to make a decision the targeting moiety, ligand, or carrier system. Also, targeted delivery allows a minimum amount of drug reaching the nontarget organs and tissues

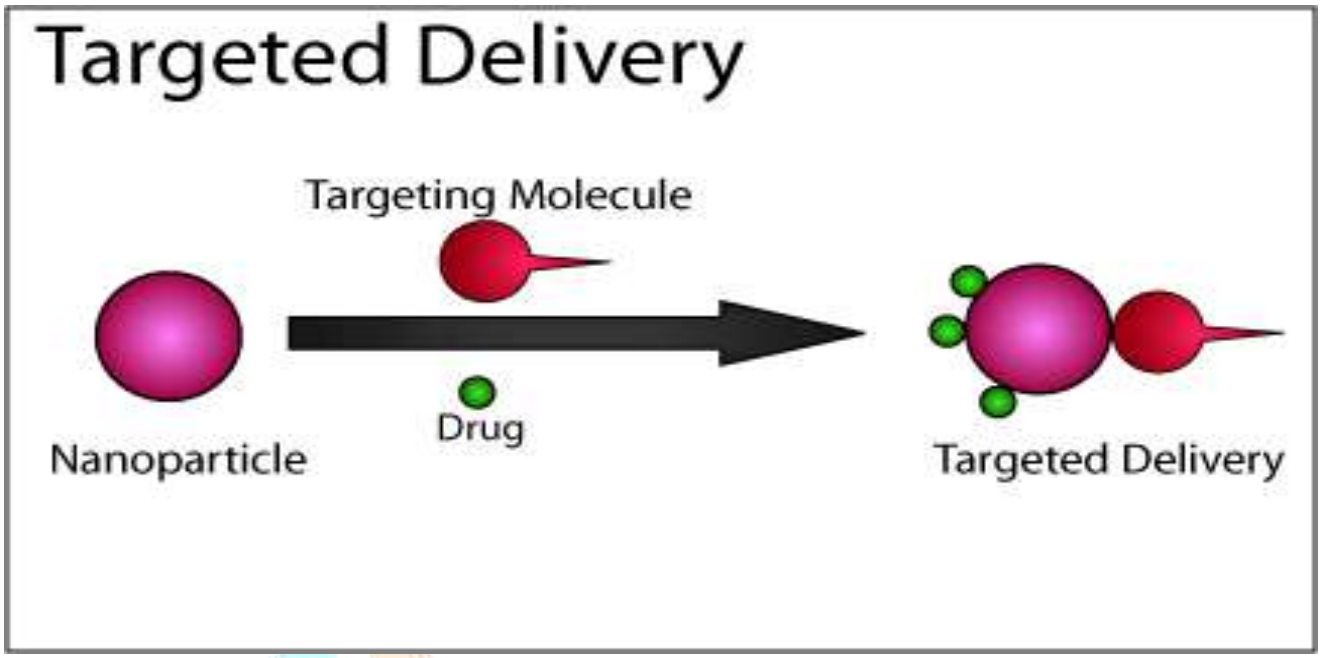
to supply an efficacious and safe drug delivery system. In a very broad manner, there are often three drug targeting levels: first, second, and third; molecular level could also be assigned because the fourth level. There are other way to classify targeting is active and passive targeting, reverse and physical methods used in targeting.(12)

SCHEME AND RATIONALE FOR DRUG TARGETING

Drug targeting is suitable for drugs having low specificity, low therapeutic index, low absorption, short half-life, or an outsized volume of distribution. All such cases necessitate formulation of the drugs into the targeted delivery system.Targeted drug delivery systems minimize the adverse effects by making changes in the inappropriate disposition of the drug and reducing its presence in nontargeted areas. At an equivalent time, drug targeting also maximizes the therapeutic efficacy of the drug by preventing its inactivation during the journey to the target site. Also, there's no degradation of the drug before reaching the location and no touching upon the nontargeted cells thereby total dose is additionally reduced. This is more important in cancer therapy where dose reduction leads to reduced toxicity toward healthy cells. These are some of the factors that must be taken into consideration while designing appropriate targeted delivery system. (13,20)

Characteristics of targeted drug delivery

- Should be biochemically inert.
- Should be non immunogenic.
- Should be physically and chemically stable in vivo and in vitro conditions.
- Should have therapeutic amount of drug release.
- Should have minimal drug leakage during transit.
- Carriers used should be biodegradable or readily eliminated from the body(5)



Applications of targeted drug delivery system

- Targeted drug delivery are often are used to treat several diseases, i .e vascuar diseases , polygenic disease etc .but the foremost necessary application of targeted drug delivery is to treat cancerous tumors . (11)
- 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(14)

Strategies of Drug Targeting

Drug targeting to an area of interest within the body increases the therapeutic effectiveness as well as it reduces the toxicity that may arise otherwise. Two strategies are widely used for drug targeting to the desired organ/tissue.(6)

APPROACHES AND LEVELS OF DRUG TARGETING :-

Passive Targeting

When the biological and pharmacological factors play a task within the accumulation of the drug during a specific site, it's termed as passive targeting. Usually, the disease pathology or changed properties of the tissues in cancer allow gathering of drugs in these organs by passive targeting . Particularly cancer fenestrations developed during angiogenesis are wider with pore sizes in the range of 100_600 nm whereas the normal blood vessels would be only around 6 nm.

Along with this, the interstitial spaces have leaky vasculatures with defective permeability allowing greater accumulation of nanoparticles. This phenomenon is named the improved permeation and retention (EPR) effect .(17) Passive targeting is also due to the response of the body's own natural reaction to the drug_carrier system. This is alright explained by the buildup of hydrophobic, uncoated nanoparticles haunted by the RES of the body.

If any foreign nanosized particle enters in the body by the intravenous route, immediately the body's defense immune system is activated and releases opsonins.

Theses opsonins immediately coat the surface of the nanoparticle and throw the particle to the RES organs, liver, and spleen.Such a passive targeting approach are often well exploited for targeting of medicine to the hepatic system. Many of the colloidal systems are uptaken by the RES vectors thanks to passive targeting. The macrophages of the RES system also play a crucial role in treatments of diseases like leishmaniasis, candidiasis, and brucellosis.(16,20)

Active Targeting

Active targeting involves modification or functionalization of the drug delivery system or carrier so as that the advanced reaches its acceptable website just like the architected carrier. therein cases the molecular recognition is a lot of precise and there square measure hardly any possibilities for nonspecific interactions. Active targeting means that a particular ligand– receptor sort interaction for animate thing localization that happens solely when blood circulation and extravasations. This active targeting approach square measure typically any classified into 3 completely different levels of targeting that square measure 1) 1st order targeting hint to slender distribution of the drug carrier systems to the tissue of a planned target website, organ or tissue e.g. compartmentalized targeting in lymphatics, larger serosa sac , plural cavity, cerebral ventricles and eyes, joints. 2) Second order targeting refers to selective delivery of drugs to specific cell varieties like neoplasm cells and to not the standard cells e.g. selective drug delivery to Kupffer cells among the liver. 3) Third order targeting means that delivery of drug to specifically the animate thing website of targeted cells e.g. receptor

based mostly substance mediate entry of a drug advanced into a cell by endocytosis [15]. Active targeting are often delineated at four levels as shown in fig ;-

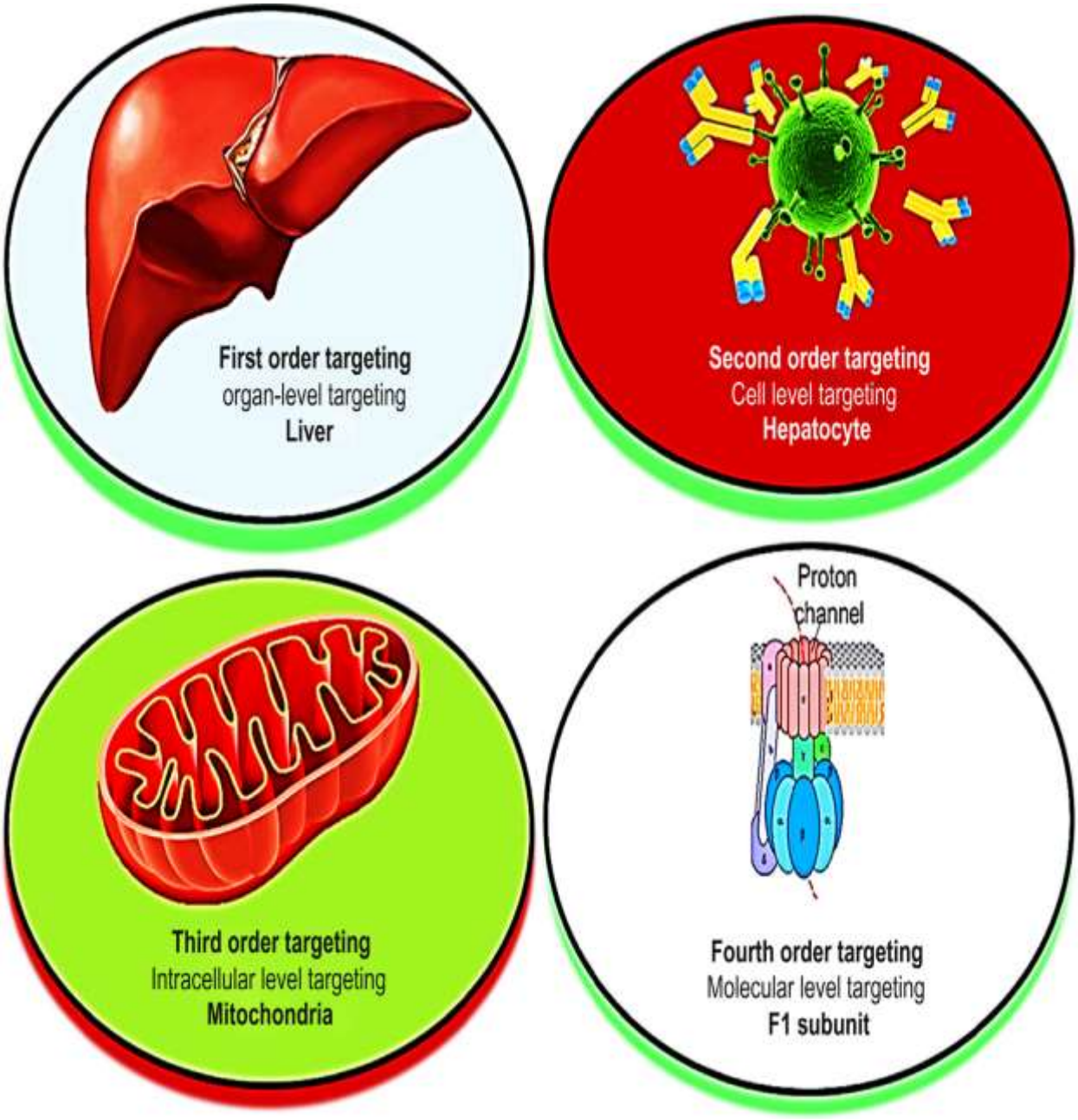


FIGURE 2.4 Levels of drug targeting. Illustration showing different levels of targeting possible in liver.Targeting the liver directly is organ targeting; the liver contains hepatocyte cells, which are involved in cellular targeting. Within the hepatocyte are mitochondria, which are targeted in intracellular or organelle targeting, and finally, the F1 subunit part of mitochondria is involved in molecular-level targeting.

Inverse Targeting

In inverse targeting, there is a degeneration of the biodistribution movement of the drug carrier system. there's activation of the RES system whenever a mixture drug delivery system is injected into the body because of opsonin then there is a laborious and quick biodistribution pattern followed. Inverse targeting could be a plausible commit to bypass the uptake of mixture particles by the RES .(18) There area unit some reportable approaches to avoid the RES-rich organs.a technique is to saturate the RES by pre injection of blank mixture carriers throughout a bigger quantity or use of macromolecules like dextran sulphate .This methodology would truly suppress the functions of RES and is usually not suggested throughout a clinical setting as a result of this is often ready to cause RES Another methodology is to switch the scale, surface charge, hydrophilicity, and rigidity of the carrier. One effective methodology is to switch the surface deliquescent of the carrier by a hydrophilic chemical compound. Coating the particles with nonionic surfactants like poloxamer 188 is an efficient methodology to inverse the targeting of the particles. Inverse targeting may be used for retroviral targeting ways .(19,20)

Drug Delivery to Tumors

Pharmaceutical agents are distributed evenly within the body via regional blood flow regardless of administration route. In order to reach the disease site, the pharmaceutical ingredient has to survive crossing through several biological barriers including other 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. Other aims and specifications of 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 . As mentioned before, drug targeting systems are liposomes, polymers, micelles, nanoparticles, and antibodies. Relatively new anti-cancer chemotherapeutics currently used in clinic present the achievement of the targeting approach (imatinib mesylate (Gleevec®), trastuzumab (Herceptin®), gefitinib (Iressa®), ibritumomab tiuxeta (Zevalin®), gemtuzumabozogamicin (Mylotarg®), and cetuximab (C225, Erbitux®) Drug targeting strategies are also categorized in five different approaches. 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. Second approach, passive drug targeting, allows the accumulation of drug in tumors and in tumor cells by means of the Enhanced Permeability and Retention (EPR) effect. (28)

Characteristics of an ideal drug vehicle

An ideal drug vehicle need to be ready to cross blood brain barriers. It should be recognized by the target cells specifically and selectively . The drug vehicle used need to be non-toxic, non immunogenic and perishable. once recognition, the carrier system need to unharness the drug moiety within the target organs, tissues or cells . The biomodules used as carrier mustn't be omnipresent (existing or being everywhere at identical time). totally different quite drug carrier: drug carrier are going to be Liposome, organism Antibodies and Fragments, changed (Plasma) Proteins, Soluble Polymers, Lipoproteins, Microspheres and Nanoparticles, compound Micelles, Cellular Carriers etc. selection and sort of drug carrier depends mainly on the sort of drug, targeted area to which the drug action is desired and type of disease in which the system is being used. Targeting Moieties includes antibodies, lectins and other proteins, Lipoproteins, Hormones, Charged molecules, Polysaccharides and Low- molecular-weight ligands.(21)

Liposomes

Liposomes are the primary to be explored as drug delivery vehicles. These are vesicles composed of an aqueous core bounded by a hydrophobic lipid bilayer. Solutes in the core, such as drugs, cannot overcome the hydrophobic barrier. However, the bilayer will permit for the absorption of hydrophobic molecules and thus , liposomes are known to be ampiphilic carriers. Liposomes differ in composition, size, number of layers, etc. These can either have one bilayer, known as "unilamellar" or multiple bilayers, termed as "multilamellar". Unilamellar vesicles are further grouped into small unilamellar vesicles (SUVs) and enormous unilamellar vesicles (LUVs) according to their size (Vemuri and Rhodes, 1995). Drugs held and delivered by liposomes have significantly improved pharmacokinetic properties such as the therapeutic index. Also, these have a quick metabolism action, lower toxicity apart from in vitro and in vivo anti-cancerous activity. The encapsulation of drugs by liposomes leads to the prevention of their untimely degradation. Liposomes are often coated with polyethylene glycol, besides other polymers, leading to an increased half-life.These can amplify target-specificity once they're related to ligands or antibodies.Liposomal drugs are among the first nanotechnology products used as therapeutic agents to urge the approval of FDA for the clinical use. DOXIL ® (doxorubicin liposomes) was approved in 1995 as a medicament for Kaposi‟s sarcoma -related AIDS. ligand-conjugated liposomes is responsible for the elevated therapeutic potency of drug. Pervasive preclinical studies further

prominence the importance of targeted liposomes. For example, entire nucleosome, attached to the surface of tumor cells is identified by the antibody 2C5 (mAb 2C5). mAb 2C5- DOXIL liposome conjugation is also use for obtaining enhanced cell targeting. This also results in an improved drug potency. However, it has been found that liposomes are not suitable for sustained release of medicine , which may be a limitation on their part.(22,23,24,25)

Type of Carrier

1) ENDOGENOUS PARTICULATE CARRIERS

Serum albumin resealed erythrocytes and lipoproteins area unit some samples of endogenous carriers. The lipoproteins area unit composed of triglycerides and cholesteryl esters, surrounded by a monolayer of phospholipids. they need the advantage of being endogenous hence they're nonimmunogenic. they're classified into four varieties supported densities: high-density lipoprotein (HDL), lipoprotein (LDL), terribly lipoprotein (VLDL) and chylomicrons.(29)

2) PHARMACEUTICAL CARRIERS

Polymers as carriers allow greater flexibility in both structural and physiochemical properties. Some of the polymeric carriers used in the drug delivery systems include microcapsules, microparticles, nanoparticles, and micelles. Lipids as carriers have liposomes and solid lipid nanoparticles as carriers.(30)

3) CARRIERS WITH TARGETING MOIETIES

Targeting moieties attach to receptors specifically and selectively located on target cells. Carriers having the targeting moieties result in bonding of the moiety with the receptor for a more specific accumulation of therapeutics at the target site as compared with the passive targeting. Some of the targeting moieties are following antibodies, lectins, proteins, lipoproteins hormones, charged molecules of polysaccharides, and low-molecular-weight ligands.(31)

4) CELLULAR CARRIERS

They are the carriers present in the human body that have the inherent property to carry and transport therapeutics from one place to another. Erythrocytes, serum albumin, antibodies, platelets, and leukocytes are some of the cellular carriers.(32)

Components of Drug Targeting

Every drug delivery system consist of a target and the drug carriers or markers required for targeting the site .

Target: - means an organ or a tissue or a cell, which is required the treatment.

Drug Carrier or Marker Drug: - delivery is feasible only by means of a carrier system. Carriers are molecules or the other systems liable for the successful transportation of a drug to the location of interest. Carriers are vectors specifically engineered for the aim of holding a drug inside them. This is possible by means of encapsulation.

Drug delivery Vehicles: - These transport the drug either within or in the vicinity of target. An ideal drug delivery vehicle is meant to cross even stubborn sites like a blood brain barrier. It should be easily recognized by the target cells and therefore the drug-ligand complex hence formed should be stable. These need to be non-toxic, biodegradable as well. The biodegradable nature of drug carrier enables them to be easily cleared away by the body and physiological mechanism, and thus avoids any chance of their accumulation within cells that may lead to cytotoxicity.(7,26)

Smart capsules with GI-tract-location-specific payload release(ajptr)

In the past few years, “smart capsules” that accomplish endoscopy also as biopsy, are developed. Some well-known examples are- PillCam, Enterion capsule, Intel site. However, these devices can't be used for therapeutic purposes during a large population due to the need of tracking the capsule‟s location in real time. Also, there's a requirement for active participation by the patient so as to activate an RF transmitter since the capsule’s location is detected by the optical images conveyed via RF link. This is quite difficult to implement. Another major problem is the power source. Many such devices use on-board batteries, which raises the system expenditure since multiple doses are required just in case of drug delivery. This may also present a threat of danger if the batteries get exposed to body fluids and shorted .Therefore, an alternative to all these approaches has been developed very recently. It comprises of a recharged capacitor, a magnetic reed switch, a spring loaded cap, a nichrome wire and a nylon fuse. The reed switch closes after the capsule is in the vicinity of a permanent magnet that is implanted or worn externally. This discharges the capacitor via the nichrome wire

and the fuse melts, which further leads to opening of the cap and release of drug. There is no need of real-time tracking and therefore, it can be used for the treatment of a number of disorders of the gastrointestinal tract.(27)

(b) Structure of the capsule

It is developed such that the appropriate site for releasing drug is at ileocecal valve, i.e., the juncture of small and large intestine. Thus, diseases concerning the large intestine such as colon cancer, inflammatory bowel disease, Crohn‟s disease, etc. can be well-treated by it (27)

TARGETED MEDICAL PRODUCTS: A MARKET REVIEW

Some of the formulations using targeted therapy for cancer are already available within the market, for instance , Myocet (liposomal doxorubicin) Daunoxome (liposomal daunorubicin). Doxil (liposomal doxorubicin), Depocyt (liposomal cytarabine), and Abraxane (albuminbound paclitaxel particles).Some of the samples of antibodies directed toward cancer therapy include Rituxan (rituximab), Herceptin (trastuzumab), and Campath (alemtuzumab). Table 7.6 lists a number of the marketed formulations that utilize active targeting strategies. Table 7.7 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;

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	

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CONCLUSION

Targeted drug delivery is now developing fast thanks to its potential to deliver drugs at specific sites. This causes injection of a lower amount of dose also as a big decrease in side-effects that were more pronounced earlier due to the inefficacy of any drug delivery system to deliver drugs at the precise site of action. The application of nano technology in drug delivery has particularly enhanced the delivery of medicine . There are numerous nanoparticles that have been approved for clinical use and, although they are still in their development stages, they hold the key2to the future of drug-targeting. Several other approaches have also been developed with similar results. They all outline the brilliant way forward for targeted drug delivery.

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