Review Article

TARGETING : NEW POTENTIAL CARRIERS FOR TARGETTED DRUG DELIVERY SYSTEM

Mrs Jaya Agnihotri*[1], Dr.Shubhini Saraf[2], Dr.Anubha Khale[1]
[1,3]M.E.S. Instititute's , H.K. College Of Pharmacy, Pratikshanagar, Jogeshwari (W) Mumbai 400102, India.
[2]Babu Banarasi Das National Institute of Technology and Management, Faizabad Road, Lucknow, India.
***Corresponding author's E-mail:** arnapadii@yahoo.com

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ABSTRACT

At present 95 percent of all new potential therapeutics have poor pharmacokinetic and biopharmaceutical properties. Hence there is need to develop a suitable drug system that distributes the therapeutically active drug molecule only to site of action, without affecting healthy tissue or organ. Drug delivered can have significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived and concentrations above (or) below the range can be toxic or produce no therapeutic effect. Various drug delivery and drug targeting systems are currently under development. Among drug carrier soluble polymers, microparticles made of insoluble (or) biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, neutrophils, fibroblasts, artificial cells, lipoproteins, liposomes and micelles, immune micelle can be taken into consideration. Nanocarrier have a size range that allows them to be injected without occluding needles and capillaries and are ideal for targeted drug delivery for many disorders like cancer, cardiovascular diseases, brain diseases, many parasitic disorders etc. Among them cellular carriers meet several criterias desirable in clinical applications. The therapeutic index safety profiles and stability of wide variety of therapeutic agents such as small hydrophobic molecules, peptides and oligonucleotides is increased dramatically. Future of targeted drug delivery or clever drug delivery is promising and going to set the new trend in pharmaceutical world.

Keywords: Targeted drug delivery, nanocarrier therapeutic index, cellular carrier, nanoparticles.

INTRODUCTION

For many decades, medication of an acute disease or chronic illness has been accomplished by delivering drugs to patients via various dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories etc. Even today these drug delivery systems are still the primary pharmaceutical products. But these conventional drug delivery systems do not ensure maximum therapeutic responses. To achieve and then to maintain the concentration of drug at the site of action, it is of necessary to take conventional type of delivery system several times a day. This results in a fluctuating drug level, premature biodegradation of the drug, drug toxicity, inability to attain effective drug concentration and patient compliance.

In the year of 1981, Gregoriadis described drug targeting using novel drug delivery system as ´old drug in new clothes'.[1] The concept of designing targeted delivery system has been originated from the Paul Ehrlich, who was a microbiologist, proposed the idea of drug delivery in the form of magic bullet. Selective drug targeting yet remains unachieved. Targeted drug delivery means accumulation of pharmacologically active moiety at desired target in therapeutic concentration at the same restricting its access to normal cellular lining, thus minimizing therapeutic index. In site specific targeted drug delivery, active drug is delivered to very specific pre-selected compartments with maximum activity while reducing the concentration of drug to normal cells. The drug can be targeted to intracellular sites, virus cells, bacteria cell and parasites using different scientific strategies have proven highly effective. The minimum distribution of the parent drug to the non target cells with higher and effective concentration at the targeted site certainly maximize the benefits of targeted drug delivery.

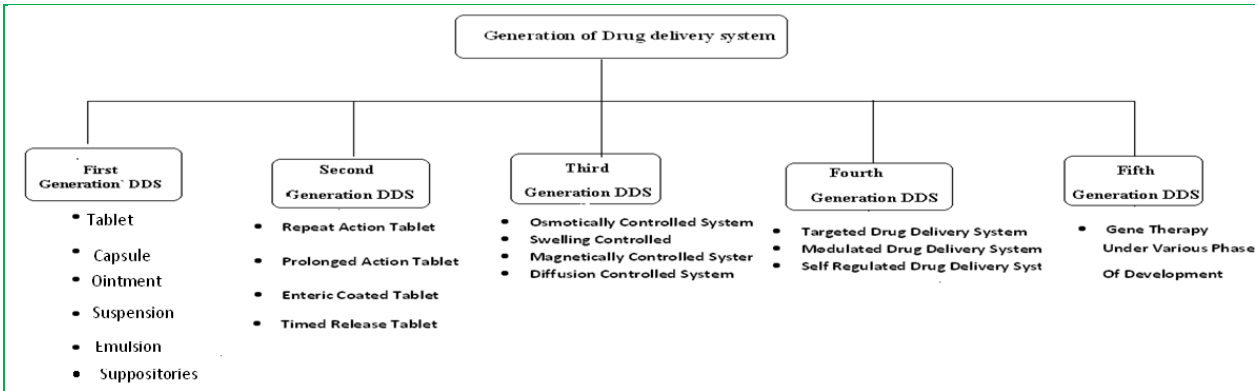


Figure 1: Generations of dosage forms[2]

A Targeted drug delivery system is preferred in the following situations:

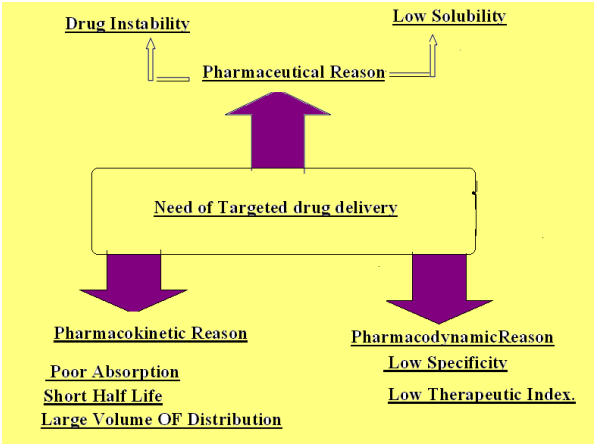


Figure 2: Need of Targeted drug delivery[3]

Properties of ideal Targeted drug delivery

- It should be nontoxic, biocompatible, biodegradable, and physicochemical stable in vivo and invitro.
- Restrict drug distribution to target cells or tissue or organ or should have uniform capillary distribution.
- Controllable and predictable rate of drug release.
- Drug release should not affect the drug distribution.
- Therapeutic amount of drug release.
- Minimal drug leakage during transit
- Carrier used must be biodegradable or readily eliminated from the body without any problem and no carrier should induce modulation of diseased state.
- The preparation of drug delivery system should be easy or reasonably simple, reproductive and cost effective.

COMPONENTS OF TARGETED DRUG DELIVERY[4]

Targets

Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment.

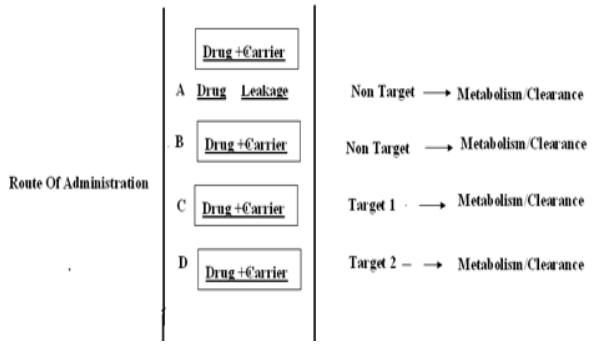


Figure 3: Route of administration vs drug carrier as a targeting moiety

Carrier or markers

Targeted drug delivery can be achieved by using carrier system. Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre selected sites. They are engineered vectors, which retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell.

Table 1: Important Properties Influencing Drug Targeting

Drug	-Concentration, Particulate location and Distribution -Molecular Weight, Physiochemical properties -Drug Carrier Interaction
Carrier	-Type, Amount of Excipients - Surface, Surface Characteristics, size, Density
In Vivo Environment	-P^H, Polarity, Ionic Strength -Surface Tension, Viscosity -Temperature -Enzyme -Electric Field

Development Technique of Formulation System and targeting Strategies

There is a growing need for multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas to control the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs must be taken into consideration. To develop a dosage forms formulation scientist apply knowledge of polymer science, pharmaceutics biopharmaceutics bio-conjugate chemistry, and molecular biology, microbiology.

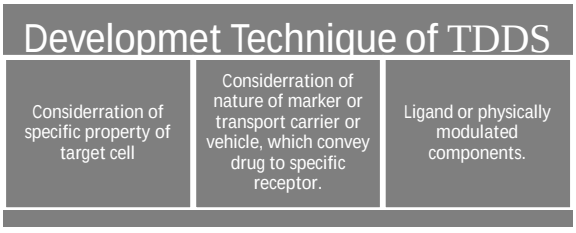
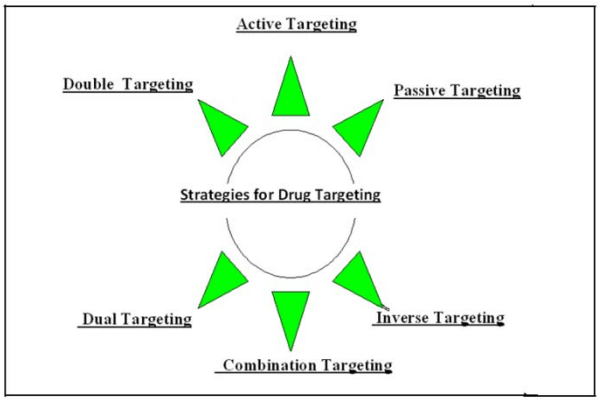


Figure 4: Strategies of drug targeting[5]



A) **Passive Targeting**: Drug delivery systems which are targeted to systemic circulation are characterized as Passive delivery systems. In this technique drug targeting occurs because of the body's natural response to physicochemical characteristics of the drug or drug carrier system. The ability of some colloid to be taken up by the Reticulo Endothelial Systems (RES) especially in liver and spleen made them ideal substrate for passive hepatic targeting of drugs.

B) **Inverse Targeting**: In this type of targeting attempts are made to avoid passive uptake of colloidal carrier by RES and hence the process is referred to as inverse targeting. To achieve inverse targeting, RES normal function is suppressed by preinjecting large amount of blank colloidal carriers or macromolecules like dextran sulphate[6]. This approach leads to saturation of RES and suppression of defense mechanism. This type of targeting is a effective approach to target drug(s) to non-RES organs.

C) **Active targeting**: In this approach carrier system bearing drug reaches to specific site on the basis of modification made on its surface rather than natural uptake by RES. Surface modification technique include coating of surface with either a bioadhesive, nonionic surfactant or specific cell or tissue antibodies (i.e. monoclonal antibodies) or by albumin protein.

First order targeting: It involves distribution of drug carrier system to capillary bed of target site or organ. For example lymphatic's, peritoneal cavity, plural cavity, cerebral ventricles, etc.

Second order targeting: it involves delivery of drug to special cells such as tumor cells or kupffer cells in lives.

Third order targeting: Third order targeting means intracellular localization of carrier bearing drug by the process of endocytosis or via receptor based ligand mediated entry of drug carrier system, where lysosomal degradation of drug complex causes release of drug or gene delivery to nucleolus.

Figure 5: Levels of Active Drug Targeting

Active Targeting can be further classified into ligand mediated & physical targeting.

Ligand mediated targeting:-All the drug carrier system can become functional when they are attached with biologically relevant molecular ligand including antibodies polypeptides oligosaccharides viral proteins and fusogenic residues.[7] These types of engineered carrier selectively make the drug available to the cell or group of cells generally referred as target. In ligand mediated active targeting reaction of a ligand to corresponding receptor enhances the uptake of the entire drug delivery system into the cell. An example of this approach is folate receptor targeting. The folate receptor is 38-KD glycosyl phosphatidylinositol-anchored protein that binds the vitamin folic acid with high affinity (<1nM).Following receptor binding, folate is rapidly internalized by endocytosis, endosomes. It was found that conjugation of folate with radioactive material, small molecule, macromolecule, protein, liposomes does not alter the ability of vitamin to bind the receptor and therefore uptake of such conjugates through receptor mediated endocytosis is enhanced[8].With exception of kidney and placenta, normal tissue expresses low level of folate receptor. In contrast, this receptor is over expressed in many malignant tissues including tumor of ovary, brain kidney, breast, myeloid cells and lung. Moreover, the density of folate receptor on cellular membrane appears to increase as the stage/severity of the cancer worsens.

Physical Targeting:-In this type of targeting some characteristics of environment changes like pH, temperature, light intensity, electric field, ionic strength small and even specific stimuli like glucose concentration are used to localize the drug carrier to predetermined site. This approach was found exceptional for tumor targeting as well as cytosolic delivery of entrapped drug or genetic material.

Table 2: Physically Targeted Drug Delivery System[9]

Physical Targeting	Formulation System	Mechanism For Drug Delivery
Heat	Liposome	Change in Permeability
Magnetic Modulation	Magnetically Responsive Microspheres Containing Iron oxide	Magnetic Field can retard fluid Flow of particles.
Ultrasound	Polymers	Change in Permeability
Electrical Pulse	Gels	Change in Permeability
Light	Photo responsive Hydro gels Containing azo-Derivatives	Change in Diffusion Channels, Activated by Specific Wavelength

D) Dual Targeting: In this targeting approach carrier molecule itself have their own therapeutic activity and thus increase the therapeutic effect of drug. For example, a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed[10].

E) Double Targeting: When temporal and spatial methodologies are combined to target a carrier system, then targeting may be called double targeting. Spatial placement relates to targeting drugs to specific organs,

tissues, cells or even subcellular compartment .whereas temporal delivery refers to controlling the rate of drug delivery to target site.

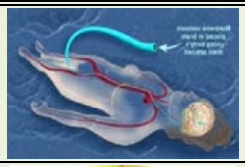
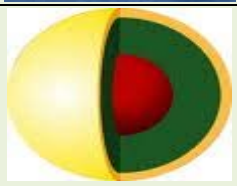
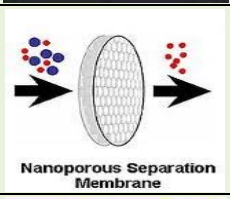
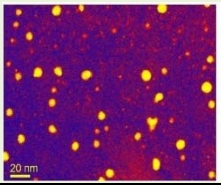
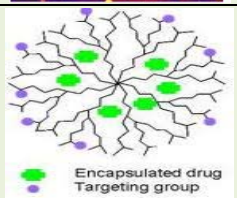
ADVANCED CARRIER FOR TARGETING DRUGS

Microspheres and Microcapsules: Lim and Moss (1981)[11] defined microcapsulation as a process in which solids, liquids or gases are enveloped in a membrane that may be impermeable or semiperrneable. Microsphere or Microparticle differ from the reservoir system known as microcapsules in that they consist of a solid matrix throughout which the drug is distributed. Spenlhaues et.al., (1986)[12] reported on the incorporation of cisplatin. a potent anticancer agent into poly (d.l lactide) microsphere by a process known as solvent evaporation.

Targeting of microspheres is based on the fact the capillary of human body are in microns, so one can easily target the capillary of lungs blood liver etc. by use of microspheres.

Nanoparticles: Rolland et. al., (1989)[13] designed a site specific drug delivery system consisting of polymethacrylic nanoparticles. Gipps et. al., (1986)[14] labeled polyhexylcyanoacrylate nanoparticles with carbon-14 and injected them into mice to ascertain the distribution of particle in the body using liquid scintillation counting.

Table 3: Nanoparticles and their Applications

S. no	Nano carrier	Description	Image Structures	Application
1	Nano Tubes	They are hollow cylinder made of carbon, atoms which can be filled and sealed for potential drug delivery.		Cellular scale needle for attaching drug molecule to cancer cells. As an electrode in thermo cells.
2	Nano wires	the nanowire pinpoint damage from injury and stroke, localize the cause of seizures, and detect the presence of tumors and other brain abnormalities		Technique has potential as a treatment for Parkinson's and similar diseases.
3	Nanoshells	Nanoshells are hollow silica spheres covered with gold. Scientists can attach antibodies to their surfaces, enabling the shells to target certain shells such as cancer cells		Technique has potential for targeting cancerous drug.
4	Quantum dots	Quantum dots are miniscule semiconductor particles that can serve as sign posts of certain types of cells or molecules in the body.		Technique has potential for targeting cancerous drug.
5	Nano pores	Engineered into particles, they are holes that are so tiny that DNA molecules can pass through them one strand at a time, allowing for highly precise and efficient DNA sequencing.		Potential in genetic engineering and bio technology.
6	Gold Nano Particle	Scientist uses gold nanoparticle to develop ultrasensitive detection system for DNA and protein markers associated with many forms of cancer, including breast prostrate cancer.		In cancer Treatment and Genetic engineering
7	Dendrimers	Dendrimers precisely defined, synthetic nanoparticles that are approximately 510 nm in diameter. They are made up of layers of polymer surrounding a control core. The dendrimers surface contains many different sites to which drugs may be attach.		In gene transfection, medical imaging

Liposomes: Liposomes are simple microscopic vesicles in which an aqueous volume is entirely composed by membrane of lipid molecule various amphiphelic molecules have been used to form liposomes. The drug molecules can either be encapsulated in aqueous space or intercalated into the lipid bilayers The extent of location of drug will depend upon its physico-chemical characteristics and composition of lipids (Gregoriadis, 1976)[15].

Niosomes: Niosomes are nonionic surfactant vesicles which can entrap both hydrophilic and lipophilic drugs either in aqueous phase or in vesicular membrane made up of lipid materials It is reported to attain better stability than liposome's. It may prove very useful for targeting the drugs for treating cancer, parasitic, viral and other microbial disease more effectively (Udupa and Pillai, 1992)[16].

Ufasomes: These are bilayer structures formed by using single chain unsaturated fatty acids. **Pharmacosomes**: The term pharmacosome comprises of two main parts - Pharmacon (active principle) and some carriers (Goymann and Hamann, 1991)[17] Vaizogle and Speiser (1986)[18] postulated that amphipathic drug can self assemble to form vesicle and these vesicles are termed as pharmacosomes. Drug covalently bound to lipid may exist in a colloidal dispersion as ultrafine, micelles or hexagonal aggregates which are known as pharmacosomes.

Virosomes: Virosomes are immuno modulating liposomes consisting of surface glycoprotein of influenza virus (immune stimulating reconstituted influenza virosome) muramyl dipeptide etc. Virosomes must be target oriented and their fusogenic characteristics could be exploited in genome grafting and cellular micro injection (Nerome et. al.. 1990)[19].

Proteosomes: It is the term that has been used to describe certain preparation of other membrane protein of meningococci. Proteosome proteins are highly hydrophobic & their hydrophobic protein-protein interaction causes them to form multimolecular membrane vesicles.

Cubosomes: Cubosomes are liquid crystalline phase forming small cubic particles suitable for injection.

Neutrophils: Neutrophils are an attractive carrier system for the transport of diagnostic or therapeutic agents to areas of acute inflammation. They are present in large numbers, can be highly purified to contain carrier proteins within their granules and are designed to accumulate in large number at area of pathology.

Lymphocytes: The concept of lymphocytes as a source of transferring of macromolecules particularly DNA is more defined function of these cells in immune process. Hence it is accepted that lymphocytes acts as a source of macromolecule particularly DNA for other cells.

Fibroblasts: Fibroblasts are used as a source of lysosomal enzymes. The ability of skin fibroblasts to provide continuous source of lysosomal enzymes in-*vitro* was established by Dean et al (1975)[20]. Fibroblasts are advantageous in replacement therapy because no surgery is needed for the recipient. Normal fibroblasts *in-vitro* produce all the enzymes necessary to correct each type of mucopolysaccharides and this obviates the need to isolate and purify or to encapsulate each enzyme.

Artificial cells: Artificial cells envelopes smaller spherical ultrathin membrane systems which contain different enzyme systems. This is useful for sequential type of action in multi enzyme systems and intracellular compartmentalization. Cross-linked protein artificial cells are prepared by using interfacial polymerization of protein. Artificial cells can be used for any type of material which need be microencapsulated by interfacial polymerization technique. For example, microencapsulation of insulin into polylactic acid membrane artificial cells. This is also proved to have great potential as a carrier for vaccines, antibodies, hormones, drugs and biologically active materials.

Resealed erythrocytes: Carrier erythrocytes have many attributes of ideal carrier. Since the patients own erythrocytes may be used, these are no danger of adverse effects from foreign net negative charge due largely to hydroxyl group of sialic acid. The phospholipid content of the membrane is about 50% of the total lipid content. The RBCs membrane mainly encloses cytoplasm and hemoglobin. Some of the hemoglobin is lost and other cellular constituents are retained, the cells on resealing lose some of the properties of normal erythrocyte and termed as resealed erythrocytes. A wide variety of biologically active substances (500-600,000 daltons in size) can be entrapped in erythrocytes. Generally the molecule should be polar or hydrophilic. The term "ghost" refers to almost any preparation of erythrocytes that have been hemolyzed. This hemolysis can be produced by exposure to a hypotonic medium, ultrasounds, heat on low temperature. Ghost preparations are referred to as either resealed (pink) or white ghosts. Conventionally hemoglobin containing preparations are referred to as resealed or pink ghosts while hemoglobin free preparations are referred to as white ghosts. Ideally, white ghost technique should completely remove all intracellular material but no membrane material.

Nanoerythrosomes: Nanoerythrosomes are derivative of erythrocyte ghosts regarded as a new model of drug carrier[21]. Nanoerythrosomes are vesicles prepared by extrusion, sonication or electric breakdown of red blood cell ghosts, the average diameter of these vesicles are 0.1 to 0.2 nm. These spheroid vesicles are known as nanoerythosomes and appear to be stable and to keep both the cytotoxic and antineoplastic activity of daunorubicin against mice leukemia $P338D_4$ cells[22].

Prodrug (s): Prodrugs have also been called latentiated drugs, bioreversible derivatives and congeners. Usually prodrug implies a covalent link between a drug and

chemical moiety, although some times this term is used to characterize some salt of active drug. These approaches are not only very useful in decreasing side effects but also increase/decrease solubility as required, lipophilicity, mask taste and enhance bioavailability. Prodrug technology is generally considered as a useful technique in improving corneal permeability of ophthalmic drug. A more advanced version of prodrug is chemical delivery system (CDS) in which drug is transformed into an inactive derivative which involve a cascade of enzymatic reaction for activation. Chemical drug delivery systems are utilized for sustained drug delivery systems well as site specific targeted drug delivery system .These chemically modulated system can be designed to target specific enzyme or carrier by considering enzyme substrate specificity or carrier substrate specificity in order to overcome various undesirable drug property. In chemical delivery system for eye. Currently the drugs used for ophthalmologic therapy have not been optimized for eye but are basically systemic drugs as β adrenergic agonists or antagonists which are having profound effect when enters into systemic circulation thereby many systemic side effect can be precipitated after topical dosing of drugs in the eye when β blocker such as betaxolol or timolol are used for glaucoma treatment, peripheral bronchial β adrenoreceptor blockade can be precipitated ,which may cause respiratory distress and even death therefore selective drug delivery to eye can conceal many of these unwanted effect.

Monoclonal antibodies (MABs): Research in immunology and cell biology has resulted in the commercialization of naturally produced active drug substances for therapy. Until recently many of these active drug substances were only produced *in-vivo* in the body. Many naturally produced substances are complex molecules and have potential to form drug conjugates which can be selectively taken up by target cells and digested by lysosomal enzymes. MABs are highly specific and recognize only are antigenic determinant or receptor site. MABs coupled with an active drug hold great promises for site specific delivery of biological substances, particularly in cancer chemotherapy. MABs are used together with radioactive markers to locate and visualize the extent of tumors. In kidney transplant, a T -cells MAB against *CD"* a protein of cytotoxic that causes rejection reaction is very useful in suppressing rejection and allowing the transplant to function. This conjugate is reported as OKT3.[23]

CONCLUSION

It is very difficult for a drug molecule to reach its destination (site of action) in the complex cellular network of an organism. Nanotech targeted delivery of drug is becoming one of the brightest stars in the medical sciences. As the name suggests, it assists the drug molecule to reach preferably to the desired site. The inherent advantage of this technique has been reduction in the dose and the side effect of drug. In physical approaches, by virtue of their size smaller than that of blood capillaries, intravenously administered drug carrier get accumulated in liver, spleen and blood capillaries. Orally delivered microparticles are taken up by the peyers patches. This leads to induction of immune response against the antigen released from the microparticles. Also the antigen is protected from the loss of activity in the GI tract. A major limitation is the effective uptake of these particles from the GI tract, which is even less than 1%. A combination of biological approaches enhances their uptake. The biological approach is more specific but it also has some limitations which may be overcome soon, keeping in mind the giant leaps taken by research scientists in the recent past. Nanotechnology in medicine is definitely here to stay.

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