AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Targeted Drug Delivery: A Review

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ABSTRACT

Targeted drug delivery, also known as smart drug delivery, is a method of treatment that involves the increase in medicament in one or few body parts in comparison to others. Two strategies are widely used for drug targeting to the desired organ/tissue: passive targeting and active targeting. Drug delivery vehicles transport the drug either within or in the vicinity of target. An ideal drug delivery vehicle is supposed to cross even stubborn sites such as a blood brain barrier. Recently, nano medicine has emerged as the medical application of nanotechnology. Since nanoparticles are very small in size, nano drug delivery can allow for the delivery of drugs with poor solubility in water and also aid in avoiding the first pass metabolism of liver. Nanotechnology derived drug delivery can cause the drug to remain in blood circulation for a long time, thereby leading to lesser fluctuations in plasma levels and therefore, minimal side effects. These include polymer-drug conjugates and nano particulate systems such as liposomes, 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, Nanoparticles, Therapeutic, Conjugates, Cancer, Release.

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Received 25 November 2015, Accepted 05 December 2015

Please cite this article as: Mishra N *et al*., Targeted Drug Delivery: A Review. American Journal of PharmTech Research 2016.

INTRODUCTION

The biological effects of a drug in a patient depend upon the pharmacological properties of the drug. These effects arise due to the interaction between the drug and receptors at the site of action of the drug. However, the efficacy of this drug-target interaction stands undermined unless the drug is delivered to its site of action at such a concentration and rate that causes the minimum side-effects and maximum therapeutic effects[6]. Targeted drug delivery aims to achieve the same. Targeted drug delivery, also known as smart drug delivery, is a method of treatment that involves the increase in medicament in one or few body parts in comparison to others. Therefore, it delivers the medication only to areas of interest within the body. This offers an improved efficacy of treatment and also reduces side effects [1].

It differs from the conventional drug delivery system in that, it gets release in a dosage form while the former functions by the absorption of drug across biological membrane [2]. Greogoriadis, in 1981, described the use of novel drug delivery for drug targeting as 'old drug in new clothes' [3].

Conventional dosage forms such as injections, oral formulations comprising of solutions and suspensions, tablets, capsules, and topical creams & ointments, possess certain innate disadvantages. Parenteral delivery of drugs is highly invasive with ephemeral effects. Oral administration of drug, inspite of being immensely popular and appropriate, cannot be used for certain drugs, such as protein or peptide drugs, owing to their poor absorption by the oral route. These may be degraded in the gastrointestinal tract. Topical creams and ointments have a drawback of being limited to local effects, rather than systemic ones. Currently drug delivery technology has become refined and it takes into consideration, several factors such as bioavailability, drug absorption processes, pharmacokinetic processes, timing for optimal drug delivery, etc [6].

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 an ability to escape the body's secretions that may degrade it, leading to a long residence time in circulation and thereby reaching the site of interest and, should release the drug at the specific site within the time that calls for effective drug functioning [5]. Different sites of interest within the body necessitate the use of different drug delivery systems, depending upon the route to be followed [5].

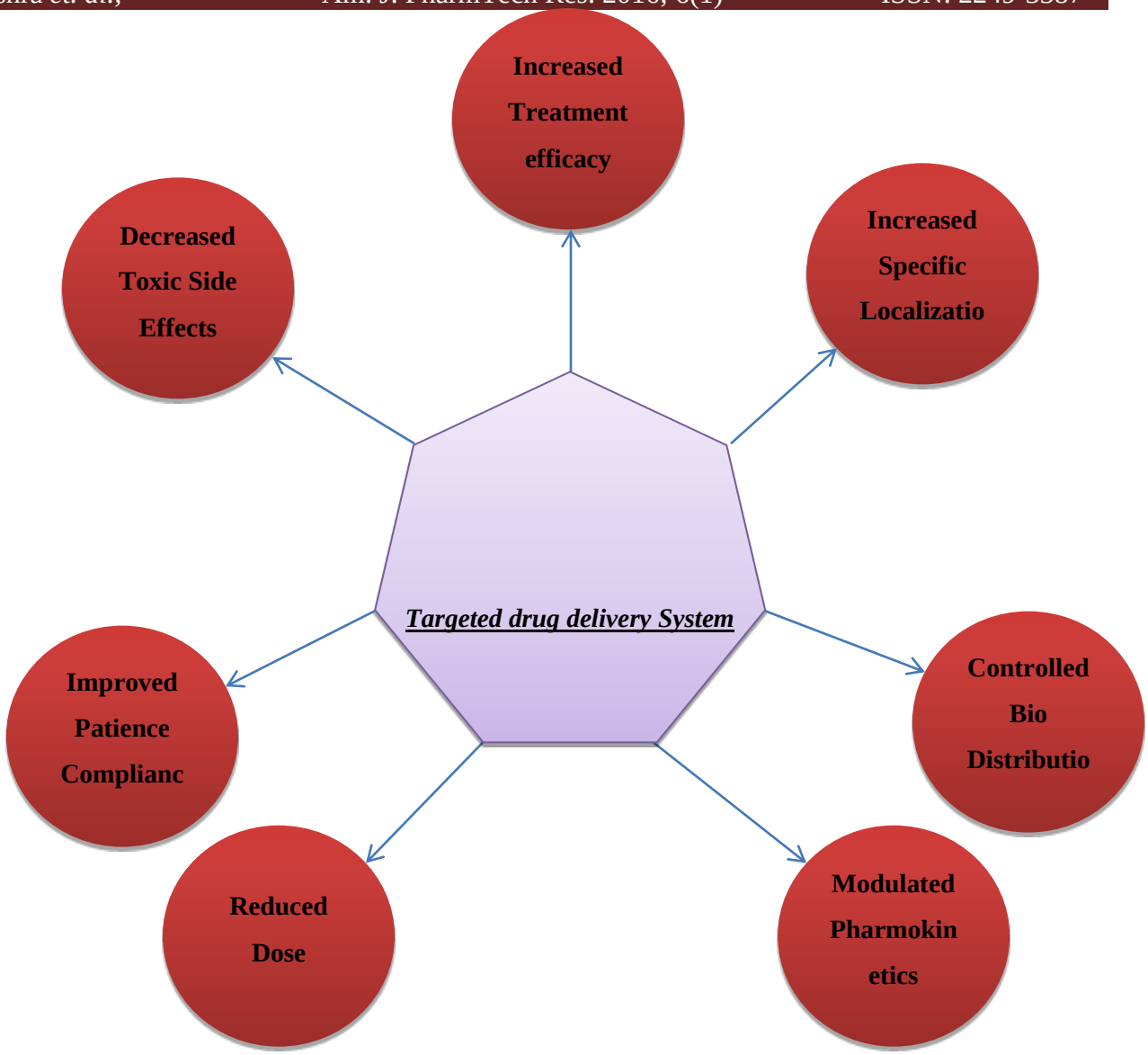

Figure 1: Advantages of a targeted drug delivery system [12].

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 [2].

Passive targeting

This is based on the accumulation of drug at areas around the site of interest, such as in case of tumor tissues. This is called Enhanced Permeability Retention (EPR) effect. Such a types of targeting occurs with almost all types of drug delivery carriers. Passive targeting is actually a misnomer because it cannot really be described as a form of selective targeting.

Although the EPR effect applies for nanoparticle administered, the majority (>95%) of these nanoparticles tend to accumulate in organs other than those of interest such as liver, lungs and

spleen. Thus, it is the distribution of drug by blood circulation. Examples include the use of anti-malarial drugs being targeted for the treatment of microbial infections such as leishmaniasis, candidiasis and brucellosis [2, 5].

Active targeting

Through the use of ligand-receptor interactions, active targeting describes the drug targeting interactions. However, interactions between a ligand and a receptor are possible only when the two are in close propinquity, (i.e. less than about 0.5mm) [5]. The currently available drug delivery systems are able to reach the target by the virtue of blood circulation and extravasation. Therefore, we can conclude that active receptor targeting actually means ligand-receptor interaction but that takes place only after blood circulation and extravasation [5]. Active targeting can further be divided into three different targeting levels.

First order targeting

This is the distribution of drug to capillary beds of target sites- organ or tissue, for example, in case of lymphatic tissue, peritoneal cavity, pleural cavity, cerebral ventricles, eyes, joints, etc [2, 3].

Second order targeting

This is the targeting of drugs to specific sites such as the tumor cells, for example, to kupffer cells in liver [2].

Third order targeting

It is the type of drug targeting wherein the drug is intracellularly localized at the target site via endocytosis or through receptor-based ligand mediated entry [3].

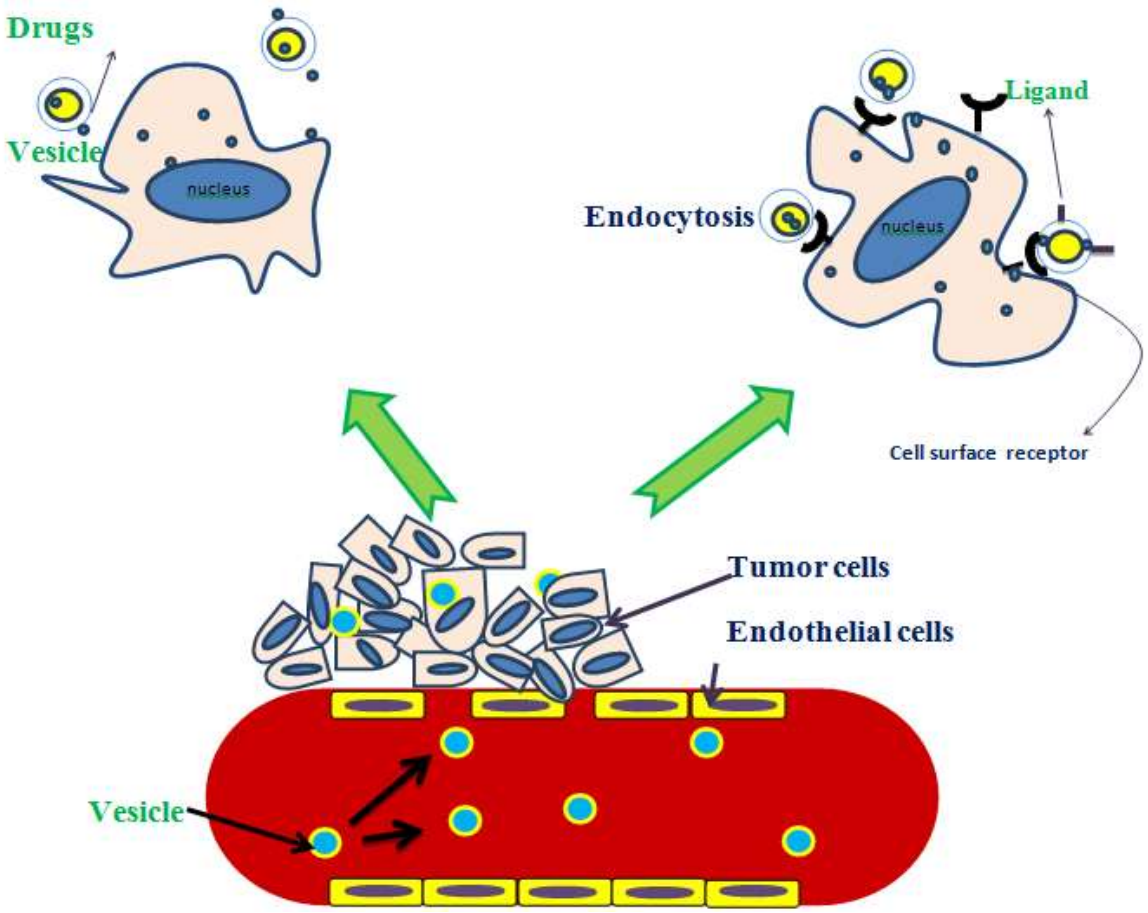

Figure 2: Active Vs Passive targeting

Components of Drug Targeting

Any drug delivery system comprises of a target and the drug carriers or markers required for it.

Target

Target means an organ or a tissue or a cell, which is in need of treatment.

Drug Carrier or Marker

Drug delivery is possible only by means of a carrier system. Carriers are molecules or any other systems responsible for the successful transportation of a drug to the site of interest. Carriers are vectors specifically engineered for the purpose of holding a drug inside them. This is possible by means of encapsulation [2, 3.]

Drug delivery Vehicles

These transport the drug either within or in the vicinity of target. An ideal drug delivery vehicle is supposed to cross even stubborn sites such as a blood brain barrier. It should be easily recognized by the target cells and 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 [2, 9.]

Nanotechnology-based delivery systems

Nanomaterials were initially studied for their properties and then they came into use in different applications. However, the recent observations have been diverted towards the field of drug delivery. This came into being due to complications involved in the use of large-sized materials for drug delivery, such as poor solubility, poor bioavailability, therapeutic inefficacy, side effects and need for targeted delivery of drugs. Recently, nanomedicine has emerged as the medical application of nanotechnology. Therefore, drug delivery at nanoscale has become possible due to the development and fabrication of nanostructures. These nanostructures are assumed to possess the potential of protecting drugs from their disintegration by the various enzymes of the gastrointestinal tract. Since nanoparticles are very small in size, nanodrug delivery can allow for the delivery of drugs with poor solubility in water and also aid in avoiding the first pass metabolism of liver. Nanotechnology derived drug delivery can cause the drug to remain in blood circulation for a long time, thereby leading to lesser fluctuations in plasma levels and therefore, minimal side effects. These particles or structures can easily penetrate tissues and are readily taken up by cells. This allows for effective targeted delivery. The uptake of nano-sized particles is reported to be about 15-250 times higher in comparison to microparticles[8].

Polymer-drug conjugates

Polymer-therapeutics is a field that has progressed a lot over the last decade. Polymer-drug conjugates, arising from polymer therapeutics, comprise of water soluble polymer being conjugated to a drug chemically with the help of a biodegradable coupler. Helmut Ringsdorf, in 1975, first provided a model for pharmacologically active polymers. He gave the idea that polymer drug-conjugates can be used for the delivery of small hydrophobic molecules. Owing to their colloidal nature, these conjugates are stable to sustain in the circulation for extended periods of time. The major difference between these conjugates and drug delivery vehicles with the drug entrapped by physical means in them (e.g. liposomes), is that the polymer-drug conjugates are conjugated chemically and this makes them new chemical entities (NCE). A multitude of drug-conjugates, employing linear polymers, have been manufactured. The most widely explored ones are those made using polyethylene glycol (PEG) and N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers. PEG-protein conjugates are of significant interest, since PEG can provide protection against enzymatic degradation of proteins and also it lowers the absorption by the

reticuloendothelial system. PEGylation of proteins has resulted in the manufacture of various therapeutic products that include many FDA-approved drugs as well, such as- PEG- asparaginase (Oncaspar®), PEG- adenosine deaminase (Adagen®), PEG-interferon α-2a (Pegasys®), PEG-interferon α-2b (PEG-Intron®), PEG-granulocyte colony-stimulating factor (Neulasta®) among others. Oncaspar 1 was introduced in 1994 as an anticancer medicament. It is used for treating acute lymphoblastic leukemia. Another example is of glucagon- like peptide-1. It controls uptake of food as well as release of insulin and is therefore, useful for diabetic patients. However, it is amenable to be degraded by dipeptidyl dipeptidase IV, a blood plasma enzyme. But, its half-life increases upto 40 times, as found by Lee et al., when a single chain of PEG is inserted into it [8, 11].

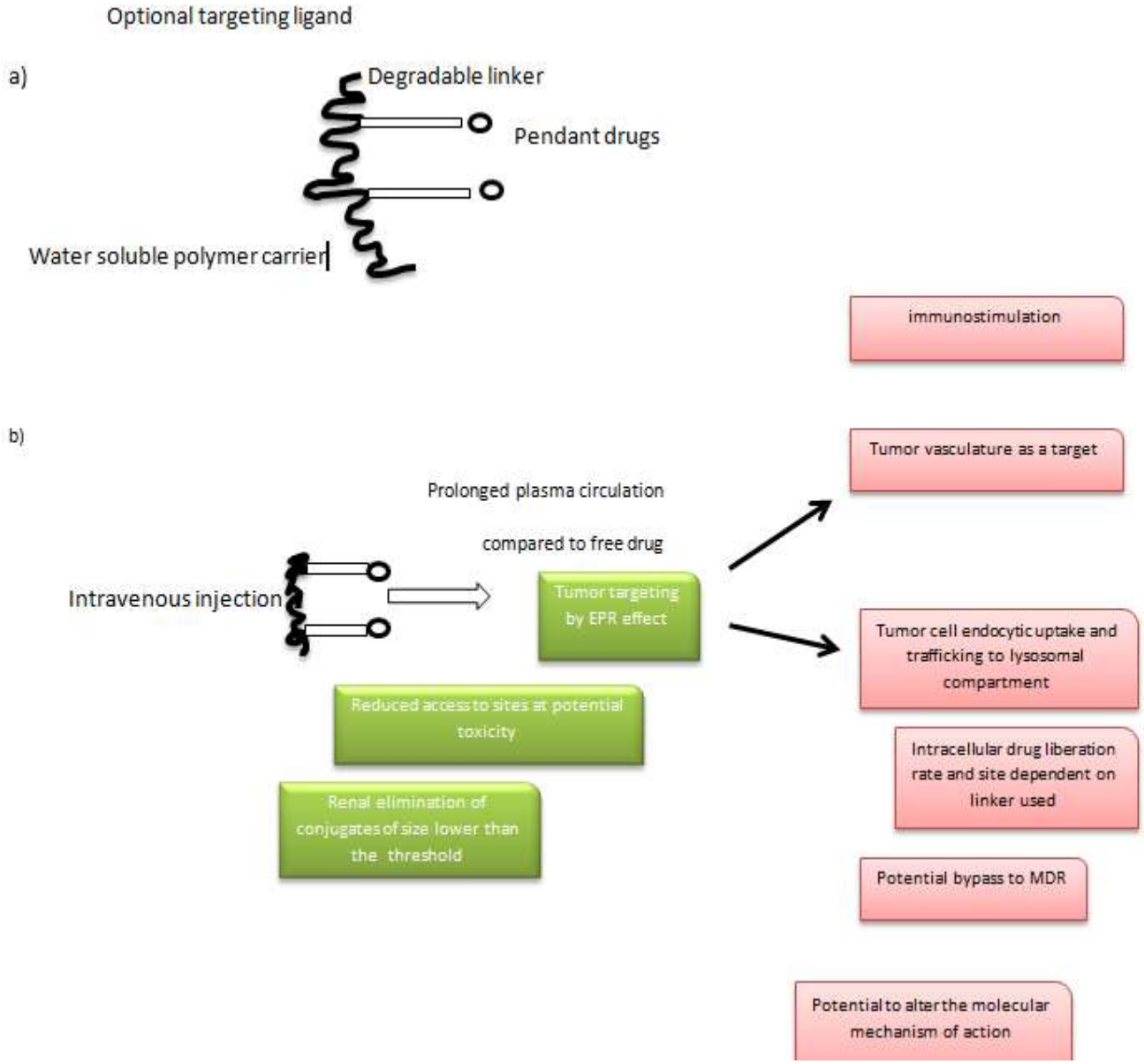

Figure 3: Schematic diagram depicting (a) the structure of polymer-drug conjugates and (b) their mechanism of action [10].

Nanoparticulate drug delivery systems

The National Nanotechnology Initiative (NNI) defines nanoparticles as structures with all three dimensions within the nanoscale (1-100 nm). Nanoparticles can modify or imitate the process occurring in living organisms. Nanoparticle-based targeted drug delivery systems have only recently been reviewed. These can be constructed for drug delivery across a number of biological barriers (Fisher and Ho, 2002; Lockman et al., 2002). It has been investigated that these can even cross the blood brain barrier (BBB) [13, 14].

Liposomes

Liposomes are the first 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 allows for the absorption of hydrophobic molecules and therefore, liposomes are known to be ampiphilic carriers. Liposomes differ in composition, size, number of layers, etc. These can either have a single bilayer, known as "unilamellar" or multiple bilayers, termed as "multilamellar". Unilamellar vesicles are further grouped into small unilamellar vesicles (SUVs) and large 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 can be coated with polyethylene glycol, besides other polymers, resulting in an increased half-life. These can amplify target-specificity once they are associated with ligands or antibodies. Liposomal drugs are among the first nanotechnology products used as therapeutic agents to get the approval of FDA for the clinical use. DOXIL® (doxorubicin liposomes) was approved in 1995 as a medicament for Kaposi's sarcoma -related AIDS. Therapeutic potency of drugs is elevated by their targeted delivery through ligand-conjugated liposomes. Pervasive preclinical studies further emphasize the importance of targeted liposomes. For example, entire nucleosome, attached to the surface of tumor cells is identified by the monoclonal antibody 2C5 (mAb 2C5). Enhanced cell targeting is obtained by the mAb 2C5- DOXIL liposome conjugation. This also results in an improved drug potency. However, it has been found that liposomes are not suitable for sustained release of drugs, which is a limitation on their part [8,13,15,17].

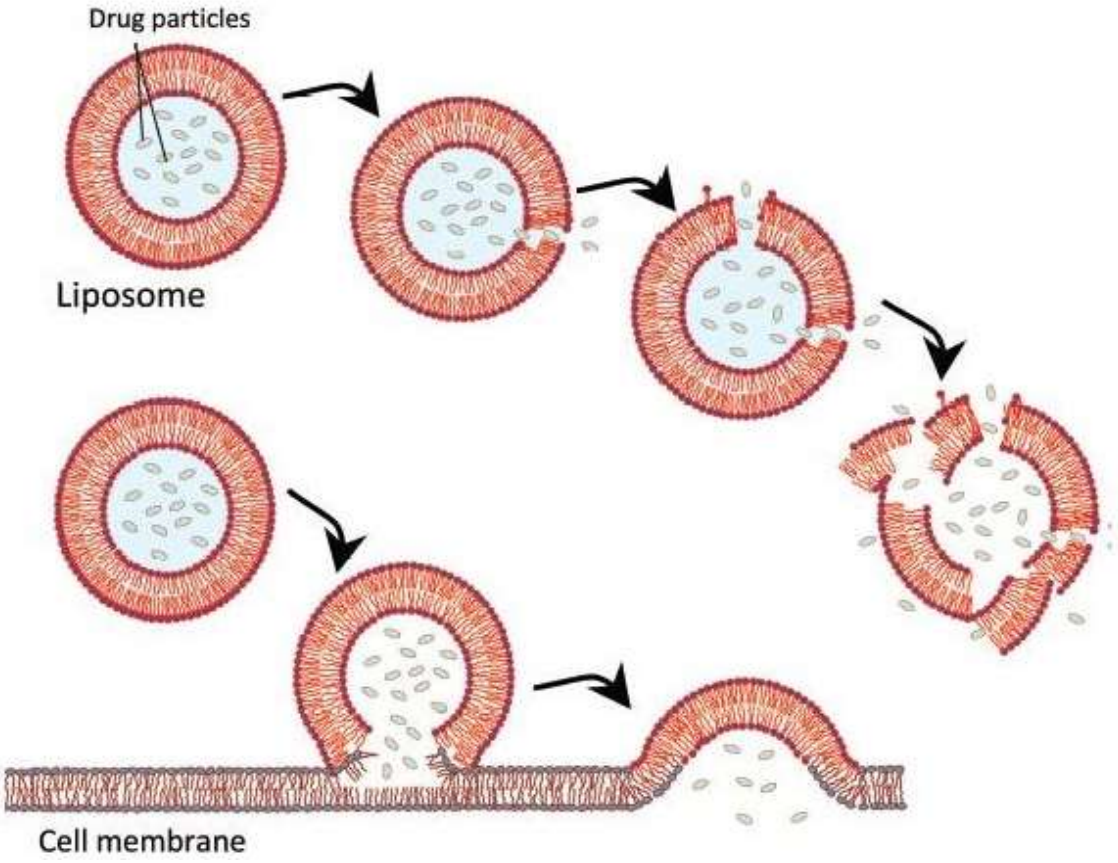

Figure 4: Drug delivery through liposomes [13].

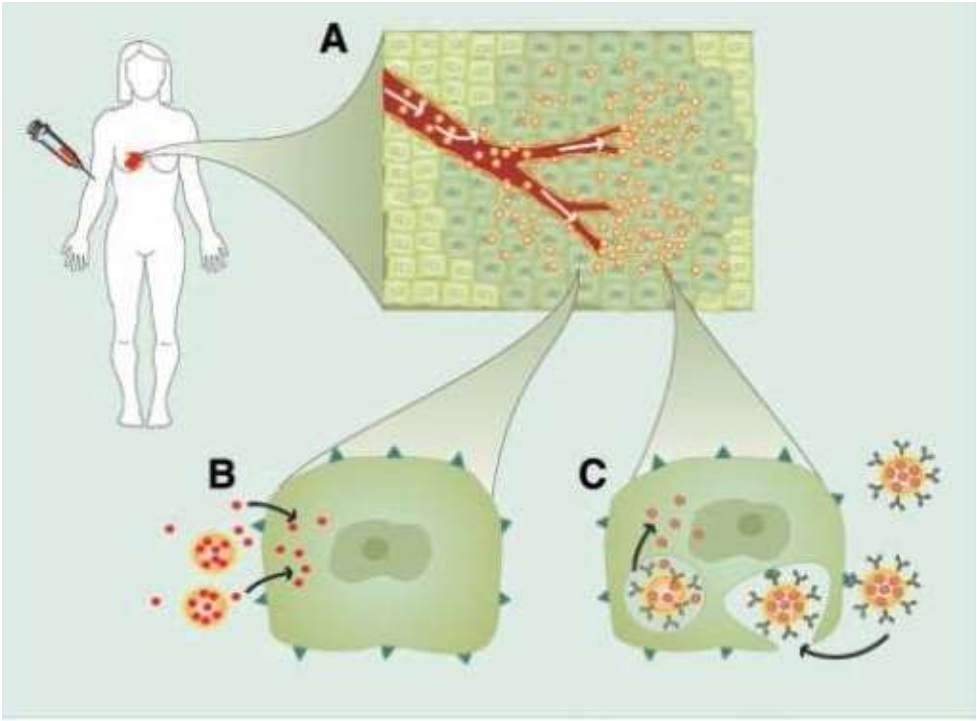

Figure 5: A schematic representation of the accumulation of liposomes, through passive or active targeting, in breast cancer tumors via the EPR effect. (A) Liposomes, containing an

anti-cancer drug, extravasate from blood and accumulate in tumor cells. The dark green cells represent the tumor tissue while the light green portion represents the normal tissue. (B) Liposomes release the anti-cancer drug in the proximity of tumor cells that take them up. (C) Ligand-targeted liposomes bind to cell-surface receptors and finally, the drug reaches its site of action [4].

Lipid-polymer hybrid nanoparticles

Lipid polymer hybrid nanoparticles act as a platform to unite the merits of liposomes and polymer nanoparticles. Several of them have been developed so far. Recently, characterization of polymeric nanoparticles with a lipid coating and comprising a core of PLGA, a shell of PEG and a monolayer of lipid, was done. The core can carry sparsely water soluble drugs, the shell increases circulation half-life and the lipid monolayer at the interface of core and shell serves to boost drug retention and its sustained release from the core. In comparison to polymer-drug conjugate, the lipid-polymer conjugates enable a stable encapsulation of drug, its flexible and sustained release and a longer circulation half-life. A potential drug delivery tool for cancers is a PLGA nanoparticle enveloped by liposome, also known as a "nanocell".

The PLGA-conjugated drug doxorubicin, effective against cancer, is encased in the nanocell. The multilayered shell of lipids aids in combating tumor angiogenesis as it contains combretastatin, an anti angiogenic promoter. Combretastatin disrupts vascular growth in tumors while the controlled release of doxorubicin directly destroys the tumor [17].

Dendrimers

Dendrimers are synthetic, unimolecular, branched nanostructures (approx. 20 nm in size) comprising a core or focal point, multiple branched layers of repeated units and high density function terminal group [15, 17]. The functional group regulates the biocompatibility and physical, chemical properties of dendrimers [13]. The molecular structure of dendrimers makes it possible for them to carry different drugs [17]. The drugs may either be encapsulated in the core via hydrogen bonding, hydrophobic interaction or chemical bonding or these can be adsorbed via covalent bonding on the terminal groups [13, 17].

Bioactive molecules such as DNA can also be carried making use of electrostatic interactions that condense them [17]. Dendrimers are now widely used as drug delivery carriers. Photosensitizers are molecules used in the photodynamic therapy of cancer. They destroy cancerous cell photochemically. The use of dendrimers for delivering photosensitizers was reported by Zhang et al.[16]. Recently, generation 3(G3) PAMAM-implanted porous hollow silica nanoparticles (PHSNPs) have been developed for carrying photosensitizers for photodynamic therapy [18].

Poly(amidoamine) (PAMAM) dendrimes are substantially used for delivering drugs of low molecular weight. Several drugs such as anti-cancer drugs, for example, methotrexate, cisplatin, doxorubicin, 5-FU; anti-inflammatory drugs, for example, ibuprofen, piroxican, indomethacin have been successfully incorporated using PAMAM dendrimers[13]. The potential of these dendrimers can be further intensified by the attachment of targeting ligands to their multivalent surface. An example is of a bifunctional generation 5(G5) PANAM dendrimer conjugated with folic acid and methotrexate drug, it expresses a considerable decrease in tumor size [17]. Other examples include Priostar™ and STARBUST PAMAM dendrimers, developed by the Dendritic Nanotechnologies, Inc. These are used as tools of targeted delivery systems for diagnostic as well as therapeutic purposes [9].

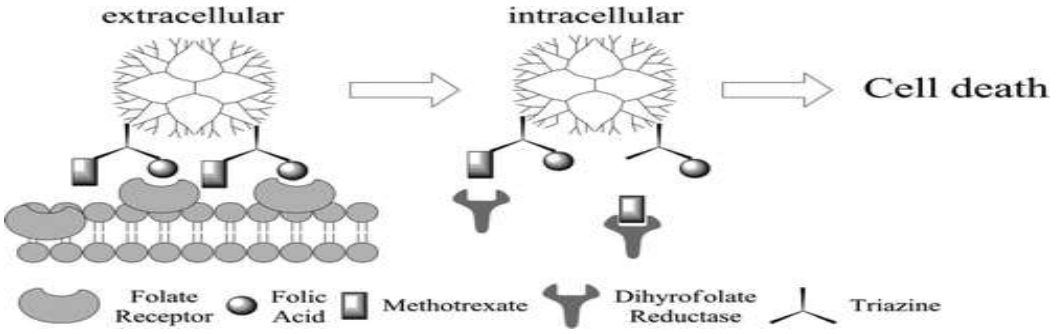

Figure 6: Bifunctional Generation 5 (G5) PAMAM dendrimer conjugated with folic acid and methotrexate drug [19].

Quantum Dots

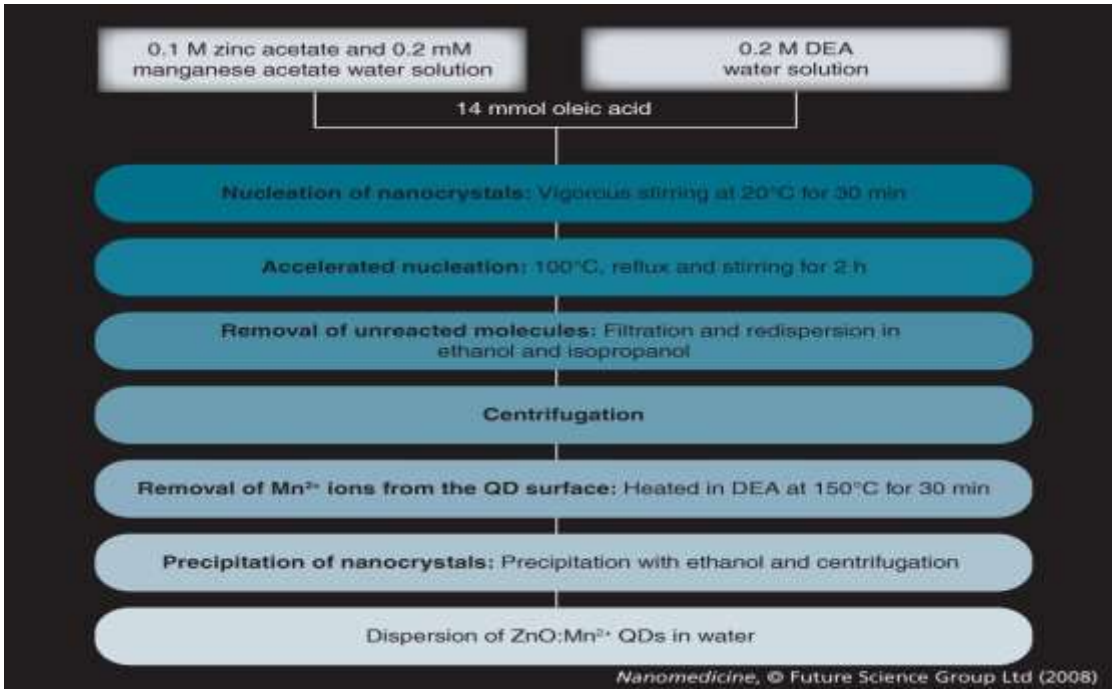

Figure 7: Flowchart depicting the synthesis of ZnO quantum dots doped with Mn [20]

Quantum dots are nanocrystalline semiconductors that range in size from 2 to 10 nm in diameter. Their size increases approximately two-fold after encapsulation by a polymer. These nanocrystals possess distinctive optical properties and are therefore, widely used in the fields of imaging and detection. Hydrophobic drug molecules can be implanted between the core and the layer of polymer cladding [15]. Quantum dots are now found to be efficient enough to carry out targeted drug delivery and imaging of this process concurrently. This is particularly useful in the case of cancer diagnosis and treatment. Quantum dots, made up of ZnO: Mn^{2+}, loaded with drugs and enclosed in chitosan, possess the potential for delivering drugs specifically targeted to tumors and also to report the process of drug delivery at the same time. Apoptosis of tumor cells is expected to improve by the use of ZnO: Mn^{2+} quantum dots [20].

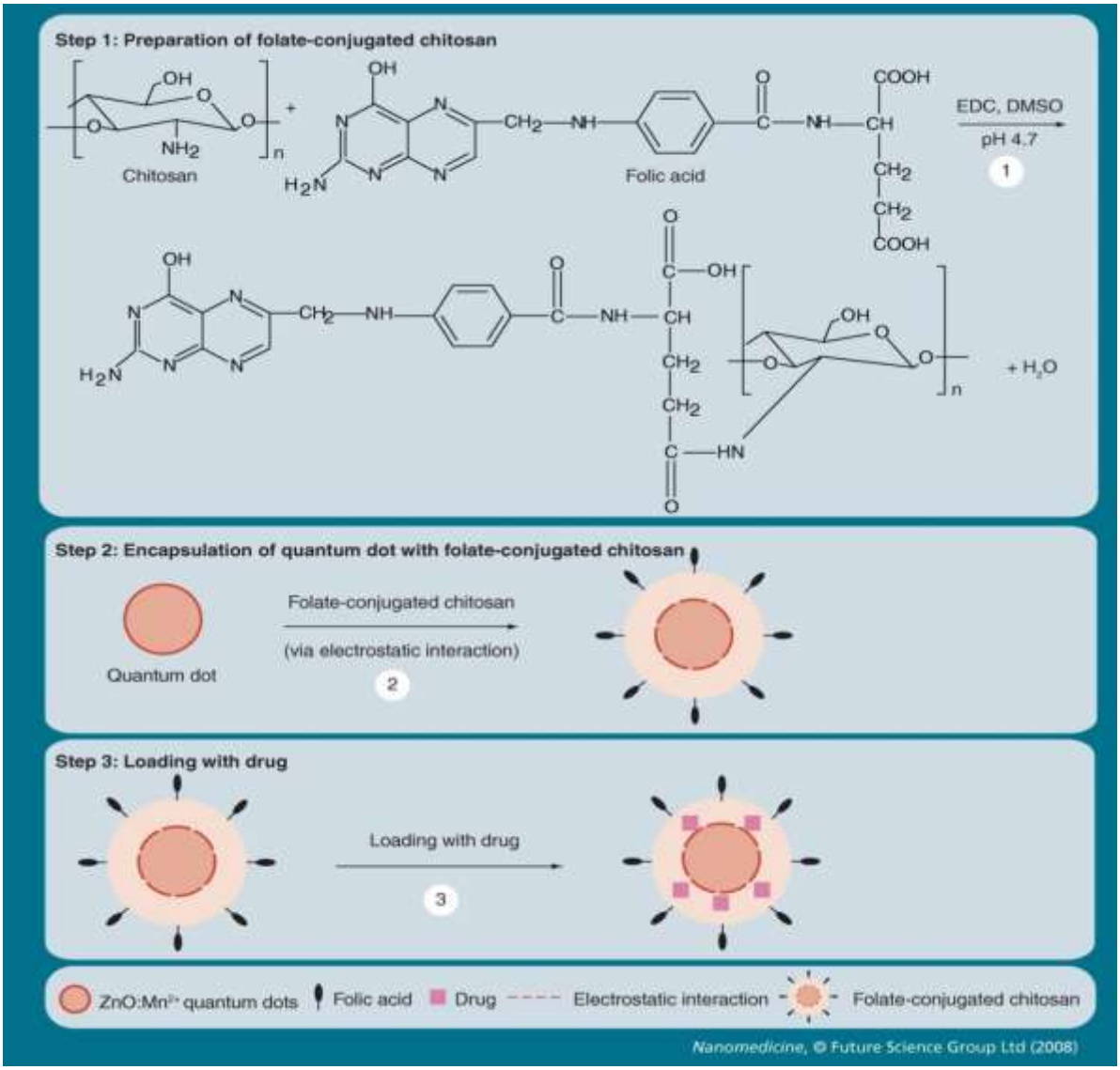

Figure 8: Step-wise representation of the encapsulation of ZnO:Mn^{2+} quantum dots by folate-conjugated chitosan and drug-loading [20].

Hydrogels

Hydrogels are three-dimensional, polymeric cross linked networks capable of imbibing large amounts of water [25, 26]. Hydrogel nanoparticles, known as "nanogels" are fast emerging as a favourable method of nanoparticulate drug delivery systems [25]. Drug loading into the gel matrix is possible due to the highly porous structure. Drug loading and the efficacy of entrapping drug are largely dependent on the drug solubility in the matrix [25]. Rapid release of drug from the polymeric gel matrix takes place owing to the high content of water in hydrogels. This is specifically useful for delivery of hydrophilic drugs. Hydrophobic drugs can also be delivered using hydrogels by the application of certain strategies such as the copolymerisation of hydrogels with hydrophilic monomers or the introduction of cyclodextrins in the structure of hydrogel [26].

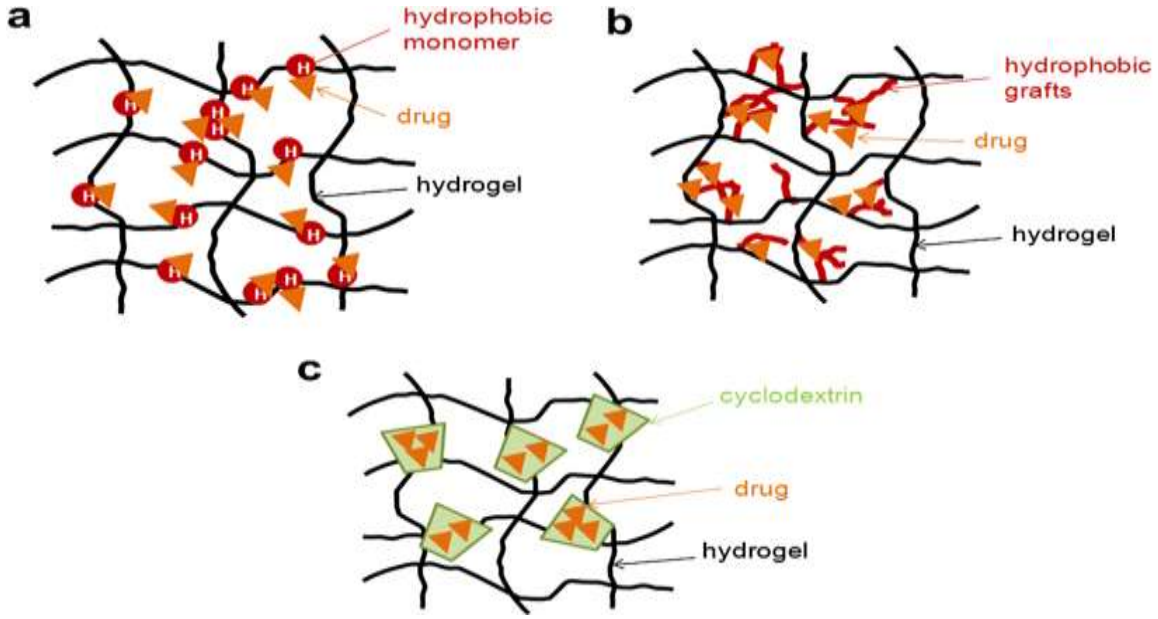

Figure 9: Strategies that are employed for the delivery of hydrophobic drugs through hydrogels (a) random copolymerisation of a hydrophobic monomer; (b) grafting the hydrophobic side-chains; (c) introduction of cyclodextrins [26].

Recently, nanogels loaded with either docetaxel or paclitaxel drugs, targeted to human breast cancer cells, were found to greatly suppress tumor growth in comparison to only abraxane. Therefore, they have a better efficacy to fight breast cancer. Similar results were obtained in case of pancreatic cancer [27].

Nanoparticles wrapped inside human platelet membranes

This is the most recent approach and in its infancy. Nanoparticles in the disguise of human platelets can act as a potential method of treatment, particularly in cases of cardiovascular disorders as well as bacterial infections. Developed at the University Of California, San Diego,

these human platelet-imitating nanoparticles possess the ability for targeted drug delivery, chiefly to sites such as damaged blood vessels and bacteria-infected organs. A demonstration done on infected rats and mice found that these nanoparticles considerably enhance the therapeutic effects of drugs [32].

The nanoparticles are camouflaged with the membranes of human platelets on the outside. This allows them an unhindered circulation in the bloodstream since the immune system recognizes them as their own and therefore, does not attack. Also, the covering of platelet membrane allows binding to the injured blood vessels which accounts for a proper drug targeting. Nanoparticle core, made up of a biodegradable polymer, is encapsulated within the platelet membrane. These nanoparticles are loaded with several drug molecules which make their way out of the core through diffusion and then cross the platelet membrane to reach the target [32.]

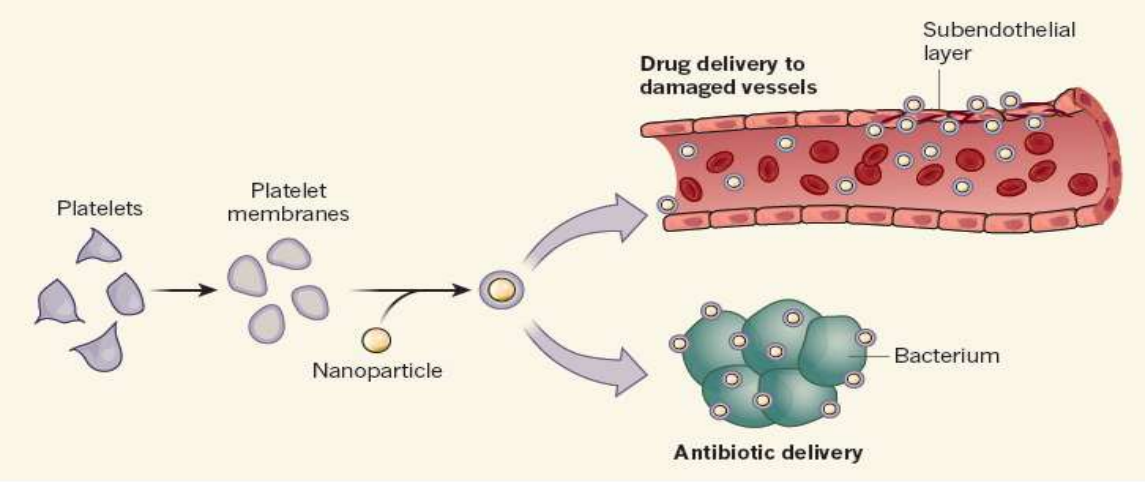

Figure 10: Construction of nanocarriers wrapped inside human platelet membranes [31].

These particles were constructed by the separation of platelets from a blood sample using centrifugation followed by their processing so as to segregate their membranes from the cells. Then, the isolated membranes were broken up into numerous small fragments which were merged to the nanoparticle core surface. The product obtained was a nanoparticle coated by a platelet membrane. These are around 100 nm in size [32].

Since the membranes used are obtained from human blood cells, therefore, these nanoparticles comprise of surface receptors, proteins and antigens that are typically present on a platelet membrane. An experiment was done on the working of these nanoparticles by loading them with docetaxel drug, which blocks the formation of a scar tissue in the lining of injured blood vessels. These were found to heal the vessels by accumulating around the injured sites. Satisfactory results

were also obtained in case of bacterial infections when the platelet-membrane-bound-nanoparticles were loaded with a dose of antibiotics [32].

Nanocapsules

Nanocapsules are miniscule vesicles comprising a solid/ liquid core with a cavity in which the drug is inserted. The cavity is enclosed by polymeric membrane[22,23]. Small interfering RNA or silencing RNA (siRNA), a type of synthetic double-stranded RNA, enveloped in nanocapsule, can be used for targeting estrogen receptor alpha (ER- α), also called NR3A1 [22]. Studies have shown that remarkable reduction in tumor growth (an expression of ER- α in tumor cell) is obtained after these nanocapsules are intravenously injected into estradiol-stimulated human breast adenocarcinoma cell line (MCF-7) xenografts [22, 23]. This has led to the development of a novel method for the treatment of hormone-dependent breast cancers.

Recently, collaboration between the researchers at the Northwestern University, Ilinois and the University of California, Los Angeles (UCLA) has resulted in the development of mechanised silica nanocapsules that release drugs following a pH change [24]. This could be especially useful in the treatment of certain types of cancers.

Other approaches

There are several other approaches for targeted drug delivery apart from the aforementioned ones. These also include the strategies wherein the therapeutic agents are coupled with "targeting ligands" that possess the ability to recognize antigens associated with tumors. Thus, these are specifically useful in cancer treatment.

Niosomes

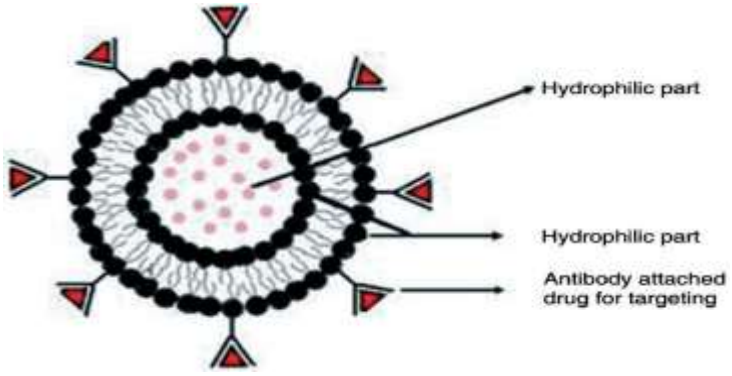

Figure 11: Structure of a niosome [7].

Niosomes are self assembled microscopic vesicles composed of non-ionic surfactants and cholesterol. The non-ionic surfactants belong to the class of alkyl or dialkyl polyglycerol ether and they align themselves in a way so as to form a bilayer. Therefore, their structure is analogous to liposomes which possess a bilayer composed of phospholipids [28, 29]. Niosomes can be used as

replacement for liposomes since the latter are expensive and require special conditions of handling and storage due to the presence of phospholipids which are unstable [28].

Niosomes are classified on the basis of the number of bilayers, size or the method of preparation [30]. The major types are as follows:

(i) Multilamellar vesicles (MLV, ≥ 0.05µ in size)

(ii) Large unilamellar vesicles (LUV, ≥ 0.15µ in size)

(iii) Small unilamellar vesicles (SUV, 0.025-0.05µ in size) [28].

Niosomes are readily taken up by the cells of the reticulo-endothelial systems, thereby making them useful in the case of cancers of liver and spleen [28, 30]. Niosomes can be used to deliver anti-neoplastic drugs as well, which have been known to cause side effects (for e.g., doxorubicin) [28]. These increase the drug's half-life and thus, prolong its stay in blood circulation and reduce the side effects caused by it [30]. Niosomes have been found to exhibit sustained release action and localization of drug [28, 30.]

Smart capsules with GI-tract-location-specific payload release

In the past few years, "smart capsules" that accomplish endoscopy as well as biopsy, have been developed. Some well-known examples are- PillCam, Enterion capsule, Intelisite. However, these devices cannot be used for therapeutic purposes in a large population owing to the requirement of tracking the capsule's location in real time. Also, there is a need for active participation by the patient in order 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 in case of drug delivery. This may also present a threat of danger if the batteries get exposed to body fluids and shorted [33].

Therefore, an alternative to all these approaches has been developed very recently. It comprises of a precharged 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 [33].

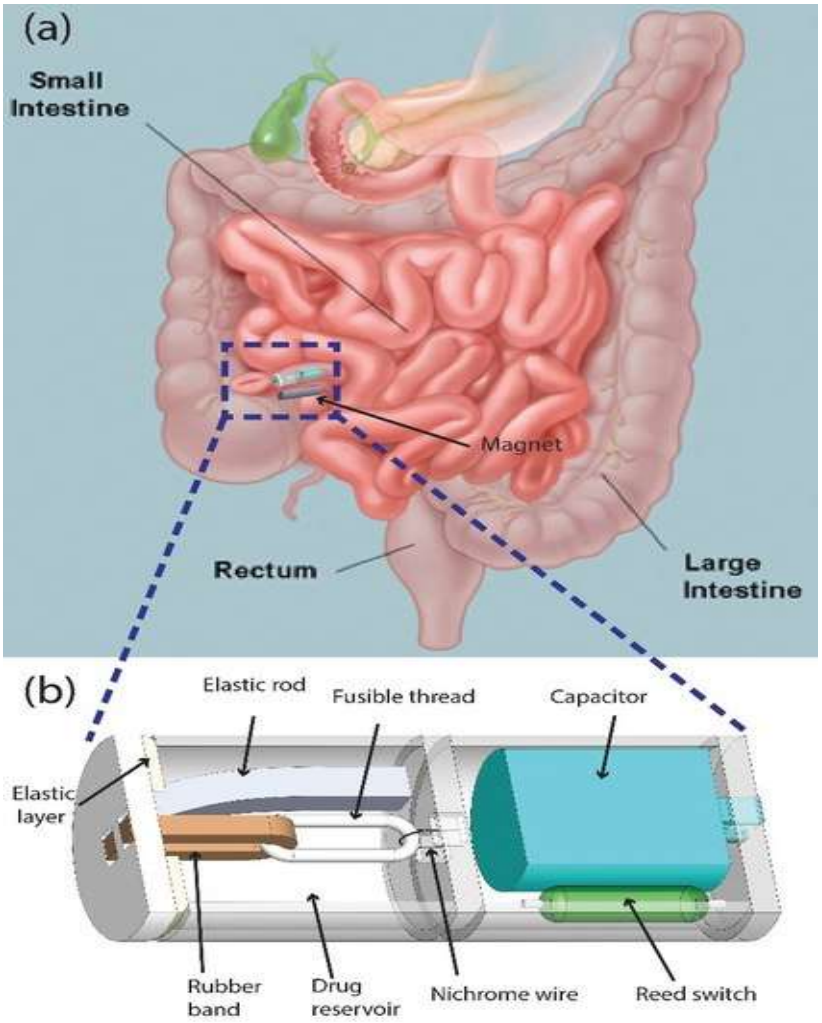

Figure 12: (a) Illustration of the smart capsule with GI-tract-location-specific drug release; (b) Structure of the capsule [33].

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 [33].

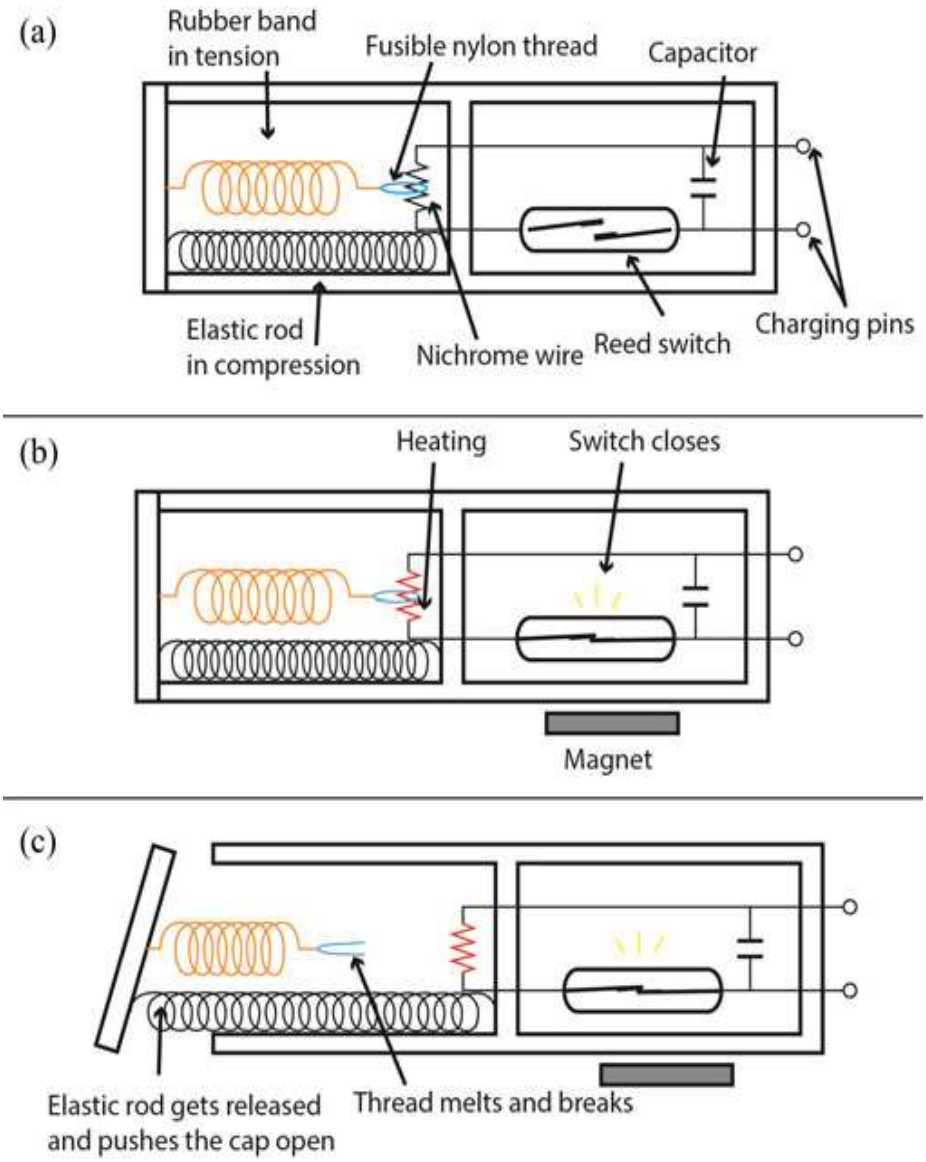

Figure 13: Operation mechanism of the smart capsule [33].

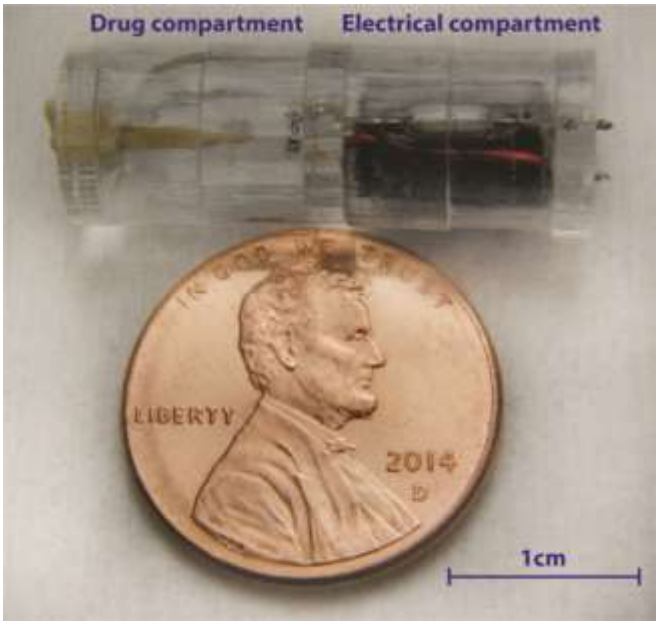

Figure 14: A photograph of the complete smart capsule with an estimate of its size [33].

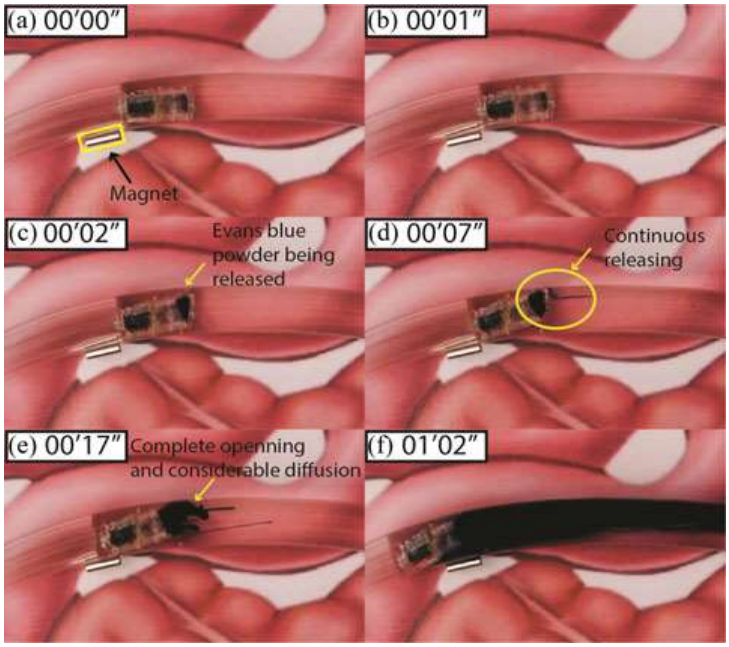

Figure 15: Snap-shots of an in-vitro experiment that clearly show the capsule travelling next to the magnet [33].

Therapeutic monoclonal antibodies

Monoclonal antibodies (mAbs) are molecules produced in the laboratory such that they adhere to distinct defects in cancerous cells. They imitate the natural antibodies in the body [34]. Monoclonal antibodies are engineered by either "hybridoma technology" or "antibody libraries". Monoclonal antibodies that possess a high binding affinity as well as specificity towards any target antigen are generally produced using antibody libraries. For example, antibody libraries with applications in

gene therapy can select mAbs mediating phage-endocytosis by the body cells[35]. Therapeutic monoclonal antibodies (TMAs) have mainly found use as naked antibodies. However, now these are utilized in targeted drug delivery owing to the fact that targeted drug delivery systems can overcome the side-effects caused by conventional chemotherapy of cancer [36]. There are now twelve registered TMAs for cancer therapy out of which five are used for hematological cancers. These antibodies are- Orthoclone OKT3®, Rituximab (Rituxin®/ Mabthera®), Transtuzumab (Herceptin®), Alemtuzumab (Campath®/Mabcampath®) , Ibritomomab tiuxitan (Zevalin®), Tositumomab (Bexxar®), Cetuximab (Erbitux®), Bevacizumab (Avastin®), Panitumumab (Vectibix™), Ofatumumab (Arzerra™), Ipilimumab (Yervoy™), Pertuzumab (Perjeta™). The first TMA for cancer therapy approved by the Food and Drug Administration (FDA) was Orthoclone OKT3®. This was in September 1992. The most recent one is Pertuzumab that was approved in 2012. Since then, mAbs have been gradually implemented in cancer therapy. Presently,[39] TMAs are being marketed after receiving regulatory acceptance. This is a small number as there are over 160 candidates of TMAs for cancer therapy currently being tested by more than 500 clinical trials. Out of these, more than 70 of them are Phase III trials [36]. Rituximab or Rituxin, approved as a treatment method for the patients of Non-Hodgkin's Lymphoma (NHL), was approved in 1997. This chimeric antibody targets CD 20, which is a glycosylated phosphoprotein found on cell-surface. Overexpression of CD 20 is found in different types of leukemias. Rituxin causes certain infusion reactions to occur, which causes the release of cytokines. Presently, Rituxin is engaged in the treatment of different forms of NHL such as Chronic Lymphocytic Leukemia (CLL), Follicular Lymphoma (FL) and Diffuse Large B-cell Lymphoma, along with chemotherapy. Now, its use has become a standard in case of NHL, FL, and CD 20^+ CLL. Other antibodies that target CD 20 are Ibritomomab tiuxitan, Tositumomab, Ofatumumab among others [36].

Another example is Alemtuzumab, a CD 52-targeting, completely-humanized antibody. CD 52 is a cell-surface glycoprotein that is glycosylphosphatifylinositol-anchored and shows expression on both normal and cancerous T and B lymphocytes. It was approved by FDA in 2001 for CLL treatment. It induces apoptosis, apart from lymphopenia of T and B cells and immunosuppression [36.] The mechanisms for the killing of tumor cells by mAbs have been depicted in figure 16. The killing of cells can be an outcome of various mechanisms such as the direct action of mAb, which can further result from either the blockage of receptor or apoptosis induction or drug delivery; the immune-mediated mechanisms such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), etc; mechanisms that affect vasculature of tumor. All the aforementioned procedures have been successfully implemented in clinic [37].

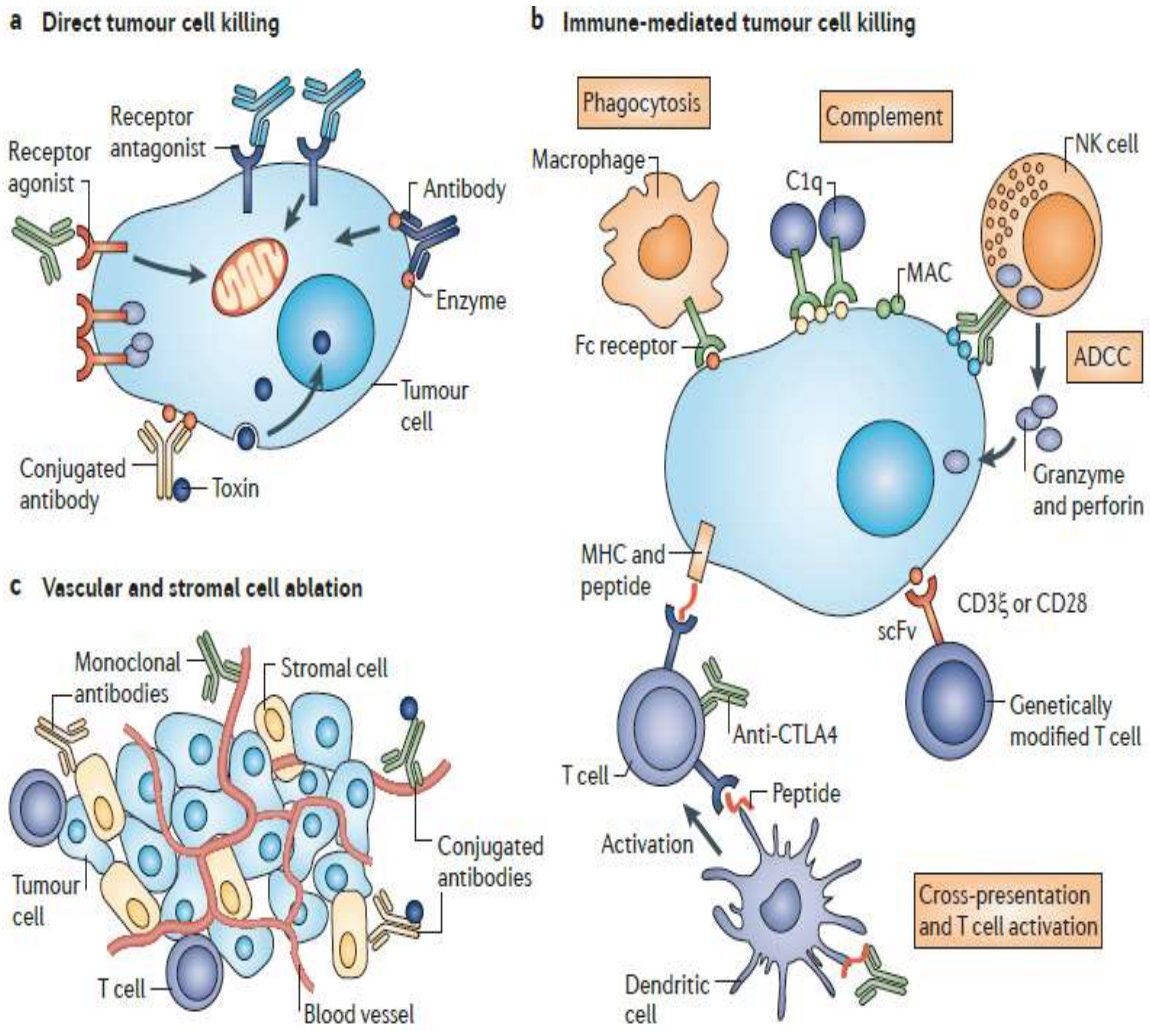

Figure 16: Mechanisms of killing tumor cells by monoclonal antibodies [37]

Most of the successfully-applied antibodies are intact molecules of immunoglobulin G (IgG). Loaded nanoparticles and intact immunoglobulins are the chief antibody constructs that find potential applications in drug delivery. They target A 33 (transmembrane glycoprotein), Epidermal growth factor receptor (EGFR), transferrin, etc. [37.]

CONCLUSION

Targeted drug delivery is now developing fast due to its potential to deliver drugs at specific sites. This causes injection of a lower amount of dose as well as a significant decrease in side-effects that were more pronounced earlier because of the inefficacy of any drug delivery system to deliver drugs at the specific site of action. The application of nanotechnology in drug delivery has particularly enhanced the delivery of drugs. There are numerous nanoparticles that have been approved for clinical use and, although they are still in their development stages, they hold the key

to the future of drug-targeting. Several other approaches have also been developed with similar results. They all outline the bright future of targeted drug delivery.

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