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REVIEW ON TARGETED DRUG DELIVERY CARRIERS USED IN NANOBIOMEDICAL APPLICATIONS

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Running: Targeted Drug Delivery Carriers in Nanobiomedical Applications

ABSTRACT

Targeted drug delivery (TDD) is an advanced and smart method of delivering drugs to the patients in a targeted sequence that increases the concentration of delivered drug only at the targeted body part of interest (organs/tissues/cells). This will in turn enhance efficacy of treatment by reducing side effects and the required dose of the drug. TDD ensures a certain defined minimally required constant amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body thereby avoiding any damage to the healthy tissue *via* the drug. Various drug carriers that are envisaged in advanced delivery systems are soluble polymers, inorganic nanoparticles, magnetic nanoparticles, biodegradable microsphere polymers (synthetic and natural), neutrophils, fibroblasts, artificial cells, lipoproteins, liposomes, micelles and immune micelle. In selecting such a vehicle, important factors to consider are chemical and physical

properties drugs, side effects or cytotoxicity to healthy cells, route to be taken for the delivery of the drug, the targeted site, and the disease. As such, TDD formulations are prepared by considering the specific properties of target cells, nature of markers or transport carriers or vehicles, which convey drug to specific receptors, and ligands and physically modulated components.

Keywords: Targeted drug delivery, nanoscience and nanotechnology, strategies of drug targeting, drug delivery carriers, nanomedicine.

1. INTRODUCTION

1.1 Routes of Drug Administration

In Pharmacology, the term Route of Drug Administration refers to the path by which the drug is taken into the body. It is classified according to the location of drug administration; *i.e.,* oral route and intravenous route, dermal, per rectal, intra-osseous *etc*. Routes are also classified based on the target of action where the target may be local, as in topical treatment, or systemic. In the systemic drug administration, if the drug is delivered through the gastrointestinal (GI) tract it is then called eternal drug administration. But if delivered *via* routes other than GI tract, it is parenteral drug administration [1]. As such, drug administration can be effected through several routes which include oral administration, injection (parenteral administration) into a vein (intravenous route) or muscle (intramuscular route), space around the spinal cord (intrathecal route), or beneath the skin (subcutaneous route). Some drugs are placed under the tongue (sublingual route) or between gums and cheek, while some drugs are inserted in the rectum (rectal route) or vagina (vaginal route), spayed into the nose and absorbed through nasal membranes (nasal route), breathed into lungs, usually through the mouth and nose (nebulization) [2-5]. Some are applied to the skin (cutaneous route) for a local (topical) or body-wide (systemic) effect or delivered through skin by a patch (transdermal route) for a systemic effect [6]. The route chosen may depend on the purpose and each route has its own advantages and disadvantages (Fig. **1**).

Drugs in the form of liquids, capsules, tablets or chewable tablets are usually administered orally because the oral route is the most convenient and minimally invasive [7, 8]. It is the most

common route of administration of drugs which are not susceptible to degradation by gastrointestinal enzymes, gastric acid, and bile. Parenteral administration is preferred, when a drug is unstable in GIT, if higher dosage is required, for improved efficacy, for faster action, to obtain higher blood levels and when the enteral route is not possible: comatose patients, patients on a ventilator, swallowing difficulties, prematurity *etc*. Parenteral administration is done via intravenously, intramuscularly, intrathecally or subcutaneously [9]. In the intravenous route, a cannula in inserted to a vein and a solution containing the drug is administered either as a single dose or by continuous infusion. In the intramuscular route, a long needle is inserted through skin and subcutaneous tissue into a muscle of upper arm, thigh or buttock. In the intrathecal injection, a needle is inserted between two vertebrates in the pine into the epidural space and the drug is injected into the spinal canal with the aid of a small amount of local anesthetic to numb the injection site [10]. In the subcutaneous route, a needle is inserted to fatty tissues underneath skin and the specific drug of interest is injected to the extracellular space and from their absorbed in capillaries or lymphatics for transport *via* blood stream. Subcutaneous route is used for many protein drugs because, for these drugs, oral route cannot be used due to their denaturing in the digestive tract [11]. A few drugs are taken sublingually or buccal route to dissolve and absorb directly to capillaries lying underneath the tongue. These drugs are usually not swallowed and this route is preferred only for a few drugs. Some drugs that are administered in buccal forms include the atypical antipsychotic drug asenaphine, opioid drugs such as buprenorphine, naloxone given as IV, IM, SC, and fentanyl, anti-anginal drug nitrogycerine, antiemetic Prochlorperazine, hormone replacement drug (Androgenic hormone testosterone) testosterone and nicotine gum as patch (transdermal), intranasal *etc*. as a smoking cessation aid and benzodiazepine that is used to treat epileptic seizures. Some orally administered drugs could also be administered per-rectally as suppository. Here, the drug is mixed with a waxy substance that dissolves and liquefies in the rectum. Drugs such as acetaminophen used to treat fever, diazepam for seizures, and laxatives can be administered through the rectal route [12]. In the vaginal route, drugs are administered as a solution, tablet, cream, gel, suppository or ring. Here, the drug is absorbed slowly through the vaginal wall mostly for local effect. Eye disorders are treated through ocular route. Here, the drug is mixed with an inert substance to make a liquid, gel or ointment to enable them to be applied directly to the eyes. These drugs include artificial tears, acetazolamide which is given orally or IV for glaucoma, betaxolol usually given orally,

phenylephrine, tropicamide and they produce local effects [13]. However, some of these drugs may enter the bloodstream and can cause unwanted side effects. Otic route is used to treat ear inflammations and infections. Here, solutions or suspensions of ear drops are applied only to the outer ear canal. If the drug is used for a long time or in excess, drugs may enter the bloodstream casing side effects. Hydrocortisone, ciprofloxacin and benzocaine are some drugs that can be administered by this route.

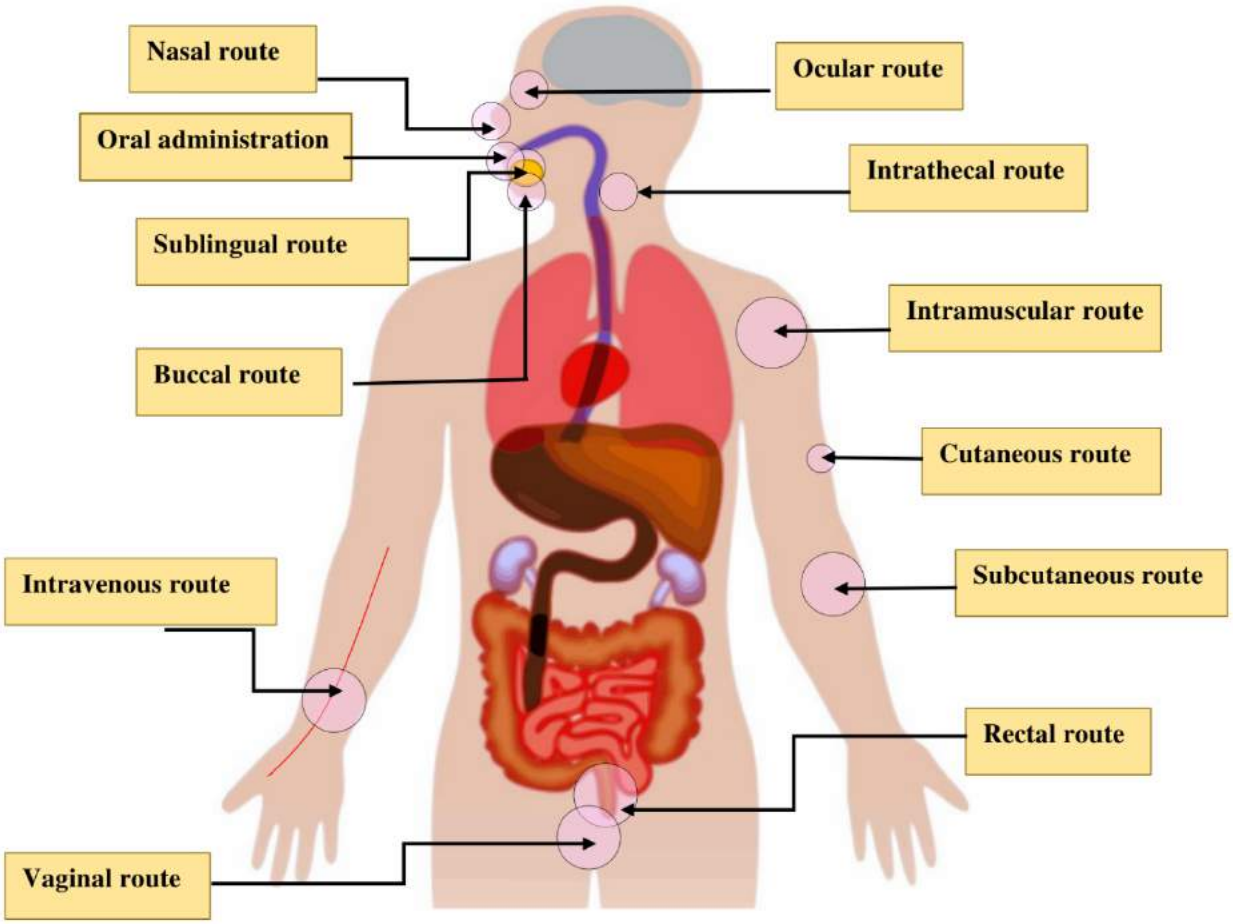


Figure 1: Various routes of drug administration (Human body adapted from https://www.goodfreephotos.com/public-domain-images/anatomy-figure-vector-clipart.png.php. Accessed on 224/07/2018 @ Peradeniya, Sri Lanka.)

Drugs in the form of droplets in air are breathed-in to absorb through the thin mucous membrane lining the nasal passages. This route is preferred when the drug is required to work quickly. Drugs such as calcitonin, sumatriptan and corticosteroids can be administered through nasal route. If the drug is to be inhaled through mouth, the droplet size should be smaller than those used in nasal route for them to pass through trachea into the lungs [14]. Smaller droplets go deeper and they are absorbed into bloodstream inside the lungs. Only a few drugs are administered thus because inhalation should be monitored carefully [15]. Aersolized bronchodilators and steroids used in asthma management in the form of metered-dose inhalers and general anesthetics are administered thus. In the nebulization, ultrasonic or jet nebulizers are used and drugs such as salbutamol and ipratropium are administered through nebulization. If the drug is directly deposited in the lungs, cough, wheezing, shortness of breath are possible side effects. Contamination of the drug in the surrounding air is also likely which may cause undesirable effects to people staying nearby [16].

Transdermal route utilizes a patch on the skin where the drug is mixed with a liquid such as alcohol and adsorbed into the patch [17]. Here, the drug is transported through the skin into the bloodstream without having to inject it to the bloodstream. Drugs that are to be administered slowly and continuously for a long period are preferred to be administered transdermally. Drugs that are quickly eliminated from the body require frequent administration and perhaps transdermal route is best suited for such drugs. Drugs such as nitroglycerin used to treat chest pain, hyoscine used to treat motion sickness, clonidine used to treat hypertension, fentanyl used for pain relief could be administered transdermally [18].

1.2 Limitations of Conventional Drug Administration Routes

When a drug is administered orally, absorption of the drug in this route may begin in the mouth and stomach but most drugs are usually absorbed in the small intestine and travels to liver before

being transported to its target site *via* the Systemic circulation. The drug when present in the intestinal wall and liver may get chemically altered by the metabolism which would reduce the amount of actual drug reaching the target site [19]. As such, a higher dosage is required to compensate for metabolic losses of the drug. Food and other drugs present in the digestive tract may also affect the amount and rate of drug absorption. As such, some drugs are prescribed to be taken in empty stomach before a meal while some others after a meal and some drugs should not be taken with other drugs and some should not be taken in the oral route at all. Some drugs can irritate the digestive tract leading to ulcers. Some drugs are absorbed poorly or erratically in the digestive tract or they can be destroyed by the high acidic conditions or by the action of digestive enzymes present in the stomach. Protein drugs such as recombinant human proteins such as insulin, growth hormones and erythropoietin, and monoclonal antibodies such as Remicade and Rituxan are not administered orally. Vaccines other than oral polio vaccine are not administered orally because these vaccines containing inactivated viruses whose proteins are digested in the stomach. Oral polio vaccine contains live or attenuated virus which is resistant to high acidity prevailing in the stomach [20].

Some drugs, even administered parenteral, can react with components present in blood, sometimes producing toxic products or adducts which may cause cytotoxicity to healthy cells. For example, cisplatin, that is used to treat many cancers such as ovarian carcinoma. Advanced bladder carcinoma and testicular carcinoma are labile in water and require high chloride concentration for its stability. As such, cisplatin is injected in the form of saline solution containing 1% of the active ingredient. The two chloride ligands bound to platinum in diamminnedicholoroplatinum(II) are labile ligands which can be replaced by aqua ligands unless the chloride concentration in the solution is high enough to stabilize the ligands in the complex. When injected in the blood stream they can be replaced by thiol containing proteins particularly low molecular weight thiol proteins forming thiol adducts which are toxic products [21].

1.3 Targeted Drug Delivery

Targeted Drug Delivery (TDD) is a method of drug delivery which is tailor-made to deliver a drug to required specific organ/tissue/cell or receptor. This helps improve bioavailability and efficacy of the drug while reducing cytotoxicity to healthy cells which in turn to result in lower

dosage requirement compared to that is needed in traditional drug administration. Ideally, TDD systems should be biochemically inert (non-toxic), non-immunogenic, physically and chemically stable *in vivo* and *in vitro* conditions. Additionally, they should have restricted drug distribution to target cells or tissues or organs and should have uniform capillary distribution. TDD should have controllable and predictable rate of drug release and drug action should not depend on the release kinetics. It should have therapeutic amount of drug release and minimal drug leakage during transit. Carriers used should be bio-degradable or readily eliminated from the body without any problem. The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective.

Cancers [22], autoimmune diseases, neurological disorders, pulmonary diseases, cardiovascular diseases and most other conditions require effective, safe, specific targeting of drugs to certain receptors or direct delivery into the organ [23] and TDD is expected to serve to these needs. TDD also helps the safer transport of the drug to the required receptor site/organ allowing the drug to be released only at that site/organ. This eliminates possible side reactions of the drug with the components in blood and other cells, sometimes forming toxic products and thereby reducing the required drug concentration.

The drug delivery technology has now become refined. It takes into consideration of several factors such as, bioavailability, drug absorption processes, pharmacokinetic processes and timing for optimal drug delivery [24]. There are four principle requirements for a successful TDD system. These four requirements are: (i) retention, evasion, targeting and release (ii) proper loading of the drug into an appropriate drug delivery vehicle, (iii) ability to escape the body's secretions that may degrade it, and (iv) long residence time in circulation and thereby reaching the site of interest and releasing the drug at the specific site within the time that calls for effective drug functioning. If TDD system fulfills all these four requirements it is an ideal TDD system which will not harm any healthy cell/organ. As such, a TDD system is preferred over conventional drug delivery systems due to several reasons. Conventional drugs have low solubility, have poor absorption, shorter half-life, and require large volume of distribution and more drug instability in comparison to TDD systems. The conventional drugs have low specificity and low therapeutic index which are known as pharmaco-dynamic properties of drugs. TDD system is expected to overcome all these problems [25].

1.4 Strategies of Drug Targeting

Drug targeting to an area of interest within the body essentially helps to increase the therapeutic effectiveness and to reduce the toxicity of the drug. As depicted in Fig. (**2**), there are basically six strategies used for drug targeting to the desired organ/tissue of interest. These six strategies are Passive Targeting, Active Targeting, Inverse Targeting, Physical Targeting, Dual Targeting and Double Targeting.

Figure 2: Different Strategies of Drug Targeting.

1.4.1 Passive targeting

This is based on the accumulation of drug at areas around the site of interest, such as tumor tissues, in higher quantities when compared to healthy body parts [26]. Such an accumulation at an area of interest is called Enhanced Permeability Retention (EPR) effect [27]. Solid tumors have inherent abnormalities of tumor vasculature. Conventional anticancer drugs rely on passive targeting due to the fact that comparatively higher concentration of the drug is accumulated in cancerous cells due to faster and higher blood supply to them. This is due to the stimulation of blood vessel growth by signaling out angiogenic factors. These abnormalities of tumors can be further exploited for passive targeting of anticancer drugs, particularly nanoparticulate anticancer drugs. Nano-sized macromolecular anticancer drugs are relatively large and hence those administered intravenously can escape renal clearance. These large-sized drugs are unable to penetrate through tight endothelial junctions of normal blood vessels and hence their

concentrations build up in the plasma to result in long plasma half-life for these drugs. They are then forced out of blood to concentrate in tumor tissues since the latter have abnormal vascular nature. This result is progressive building up of nanoparticulate drugs in tumors up to several-fold higher concentrations than that in plasma. The build-up is further facilitated since the solid tumors have no efficient lymphatic drainage. Another example for passive targeting is the ability of anti-malarial drugs to be targeted for the treatment of microbial infections such as leishmaniosis, candidiasis and brucellosis [28].

1.4.2 Active Targeting

As described above, some drugs, particularly nanoparticulate drugs have their own passive targeting. Targeting can be enhanced by deliberately introducing ligands having high affinity to receptors either to drugs or by co-encapsulating the drug and required ligands in nanoparticles to result in ligand-receptor interactions in order for drug to find the receptor site more efficiently and effectively. However, interactions between a ligand and a receptor work only when the two are in close proximity of around less than 0.5 nm. As such, active receptor targeting actually occurs only after blood circulation and extravasation of the drug to the cancerous cells. One classic example is the folic acid-folate receptor interactions. Folate receptors (FRα, FRβ and FRγ) are glycoproteins which have cysteine-rich cell-surfaces. These receptors have high affinity to folate and hence they mediate cellular uptake of folate. Folate receptors such as FRα are present in very low levels in ordinary tissues but they are expressed at high levels in many cancers in order to meet the folate demand of rapidly dividing cells under low folate conditions. This is exploited in the administration of anti-FRα antibodies, high-affinity antifolates, folate-based imaging agents and folate-conjugated drugs and toxins [29-37]. As such, folate can be co-encapsulated with the active drug or combination of drugs in porous nanoparticles for active targeting of the formulation to cancer cells.

Active targeting can be sub-divided into three different targeting levels; First Order, Second Order and Third Order Targeting. In the first order targeting, the drug is distributed to capillary beds of general target sites such as organ or tissue. In lymphatic tissues, peritoneal cavity, pleural cavity, cerebral ventricles, eyes and joints are such targeting sites. In the second order targeting, the targeting of drugs is aimed at specific sites such as the tumor cells. One such example is the

targeting of drugs to Kupffer cells in liver [38]. Third order targeting is the next type of drug targeting wherein the drug is intracellularly localized at the target site via endocytosis or through receptor-based ligand mediated interactions.

1.4.3 Inverse Targeting

When the passive uptake of colloidal carrier is avoided by Reticulo Endothelial Systems (RES) the process is called inverse targeting of drugs. In order to achieve this, regular function of the RES is suppressed by pre-injecting a large amount of blank colloidal carriers or macromolecules such as dextran sulphate. This approach facilitates the saturation of RES and suppression of defense mechanism. This type is commonly considered as an effective approach to target drug(s) to non-RES organs of the body [39].

1.4.4 Physical Targeting

Physical targeting utilizes some characteristics of environment conditional changes like pH, temperature of the system, light intensity, magnetic field, electric field or ionic strength and other small and even specific stimuli like glucose concentration or gaseous concentration are used to localize the drug carrier to predetermined site [40]. This approach is the most preferred one in nanoparticulate drug targeting to tumors as well as in cytosolic delivery of entrapped drug or genetic materials. This is because these physical factors can indeed help control release of the drug at the site of the cancer.

1.4.5 Dual Targeting

The specialty in this targeting approach is that the carrier molecule itself has its own therapeutic activity and hence increases the therapeutic effect and the activity of the drug. For instance, a carrier molecule with its own antibacterial or antifungal activity can be loaded with antibacterial

drug or antifungal drug and the net synergistic effect of drug conjugate or the composite can be observed [41]. For example, ZnO nanoparticles have antibacterial activities and when antibacterial drugs are loaded in porous ZnO nanoparticles both the carrier and the drug are effective against the bacteria and hence the corresponding TDD is dual targeting.

1.4.6 Double Targeting

When temporal and spatial methodologies are joined to target a carrier system then it is termed dual targeting. Here, the spatial placement targets drugs to specifically identified organs, tissues, cells or even subcellular compartments and temporal delivery enables controlling the rate of drug delivery to target site of interest [42].

1.5 Targeted Drug Delivery Carriers

Targeted drug delivery requires specific carrier systems. TDD carrier is a special molecule, particle, composite or system, essentially required for effective transportation of loaded or encapsulated drug up to the targeted site. They are purposely engineered vectors capable of retaining the drug inside or onto them either *via* encapsulation and/or *via* bonding with the help of a spacer moiety. These drug-containing carriers should be able to preferentially transport to the vicinity of target cells. Any drug delivery system includes a target and the drug carriers or markers essential for it. Here, the target means an organ or a tissue or a cell or a receptor which is in need of treatment. An ideal drug delivery vehicle should even have the following requirements. They should be capable of crossing even tenacious sites such as a blood-brain barrier, easily recognized by the target cells, and the drug-ligand complex, if formed, should be stable, non-toxic and biodegradable after completion of the task assigned to it. Biodegradable nature of drug carrier is essential so that it can be cleared away by the body through physiological mechanisms, thus avoiding any chance of their accumulation within cells that may lead to cytotoxicity. Nanotechnology-based delivery systems [43] are now studied for their utilization in the field of TDD. Recently, nanomedicine has emerged as a powerful field of applications of nanotechnology in medical sector. Drug delivery at nanoscale has now become possible due to the development and fabrication of various nanostructures [44]. These nanostructures are capable of protecting drugs from their fragmentation by various enzymes

of the gastrointestinal tract and carry the drug right into the target in safest possible manner. 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 [45-47]. Advantages of nanoccarier based TDD over conventional DD include higher surface area to volume ratio, higher and more reactive activity centers, stronger adsorption capacity and other characteristics such as morphological preferences. Nanoparticle-based TDD to specific organs is commonly used by modifying antibodies, aptamers such as oligonucleotide or peptide molecules, folic acid and other biological molecules such as DNA, RNA [48]. These carriers have relatively unique and specific mode of controlling and releasing drugs to the targeted sites. Mode of controlling and releasing drugs of nanocarriers is initially an outbreak release, and finally, leading to a constant release for a long period of time. Hence, nanocarriers for drugs can significantly extend the efficiency of drugs at limited concentration, deliver at lesser intervals with significantly lower doses and considerably reduced side effects with less suffering of patients from various types of diseases.

1.5.1 Liposomes

Liposomes are the first to be discovered as drug delivery vehicles. These are vesicles consisting of an aqueous core bounded by a hydrophobic lipid bilayer as diagrammatically shown in Fig. (**3**).

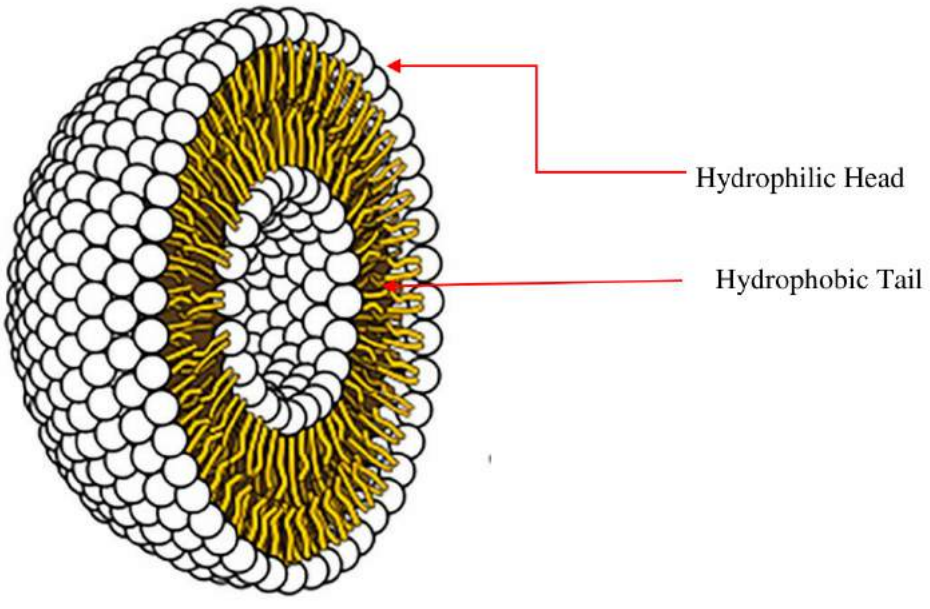


Figure 3: Cross-section through liposome (Adapted from Philcha [Public domain], *via* Wikimedia Commons). Accessed on 04/02/2018 @ Peradeniya, Sri Lanka.

Solutes such as polar drug molecules entrapped inside the core are so tightly entrapped so that they find it difficult to overcome the hydrophobic barrier [49]. The bilayer permits the absorption of hydrophobic molecules so that liposomes can carry both hydrophilic and hydrophobic molecules. Therefore, they are termed amphiphilic carriers. Different liposomes may differ in their biochemical composition, size, and number of layers. They can have a single bilayer or multiple bilayers. Drugs held and delivered by liposomes have significantly enhanced pharmacokinetic properties with high therapeutic index; *i.e*., the ratio between the amounts of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity. Other advantages of liposomes are that they have a fat metabolic action and lower toxicity apart from *in vitro* and *in vivo* anti-cancerous activity. Once drugs are encapsulated in the core of liposomes, the drugs are not in contact with biological fluids containing enzymes, acidity *etc*. Therefore, the drugs are protected from untimely degradation. Additionally, liposomes can be coated with polymers such as poly(ethylene glycol) (PEG) to enable the entrapped drugs to have increased half-life. In order to intensify target-specificity, liposomes can be associated with ligands or antibodies. Such liposomal drugs are already in the clinical use. For example, DOXIL (Doxorubicin.HCl liposome injection) is doxorubicin hydrochloride (Fig. **4**), which is an anthracycline topoisomerase II inhibitor, encapsulated in STEALTH® liposomes (Illustrated in Fig. **5**) for intravenous use which was given the approval in 1995 as a remedy for AIDS-related Kaposi's sarcoma in patients after failing prior systemic chemotherapy or intolerance to such therapy [50, 51]. The STEALTH liposome carriers are composed of cholesterol (3.19 mg/mL), fully hydrogenated soy phosphatidylcholine (HSPC) (9.58 mg/mL) and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2- distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE) (3.19 mg/mL). Each milliliter also contains ammonium sulphate (~ 0.6 mg),

histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control and sucrose to maintain isotonicity. It is important to note that greater than 90% of the drug is encapsulated in the STEALTH liposomes [52].

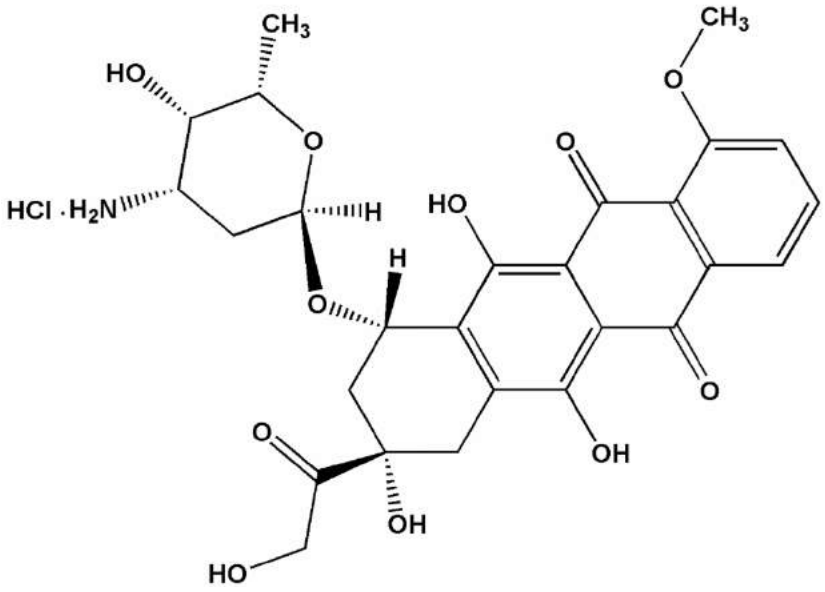


Figure 4: Structure of doxorubicin.HCl [(8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxohexopyranosyl) oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione.hydrochloride.

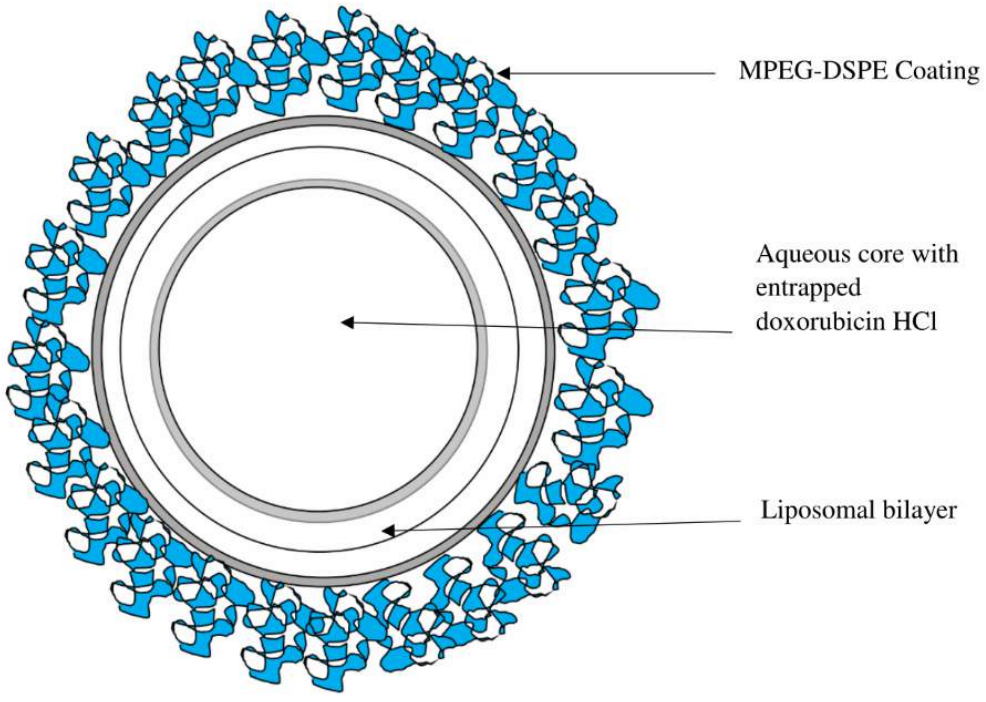


Figure 5: Pictorial representation of STEALTH liposome

DOXIL, in combination with bortezomib, is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy [https://www.rxlist.com/doxil-drug.htm].

Therapeutic potency of drugs is enhanced by their targeted delivery through ligand-conjugated liposomes. Pervasive pre-clinical studies have further proved the importance of targeted liposomes in TDD which can be considered as an improved drug potency. However, it is well known that liposomes are not appropriate for sustained release of drugs, which is a limitation in liposome-based TDD [52].

1.5.2 Dendrimers

Dendrimers (Dendritic polymers) are another type of drug carriers used in TDD. They are synthetic, unimolecular, branched nanostructures (~ 20 nm in size) comprising of a core or focal point and multiple branched layers of repeated units with high density of function terminal groups. The specific characteristics of dendrimers include uniform and controlled size parameters, monodispersity, and modifiable surface group functionalities useful in biomedical applications. The terminal groups can be functionalized with several therapeutic, targeting, and imaging agents in a specific and controllable manner. Dendrimers attain a spherical or globular shape with internal cavities after 3rd and 4th generation of dendrimer series are introduced. These are used to physically encapsulate guest molecules. In Fig. (**6**), chemical structure of polyethylenimine dendrimer belonging to the 4th generation is illustrated [53]. The internal void volume can be used to encapsulate hydrophobic guest molecules and drugs. The resulting drug-encapsulated functionalized dendrimers have important properties such as water solubility and biocompatibility.

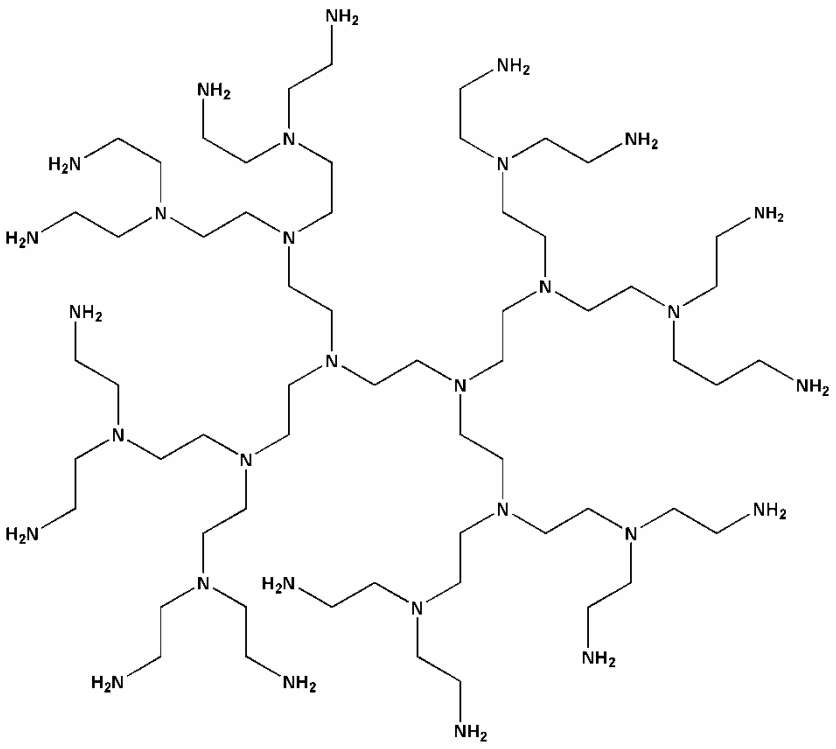
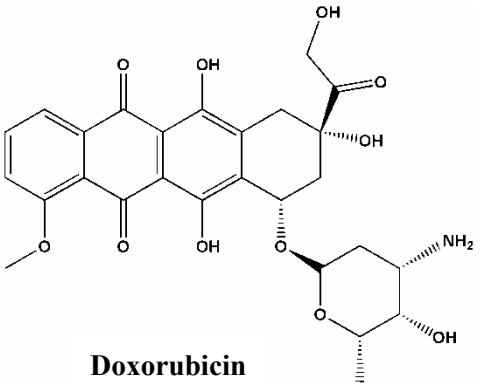


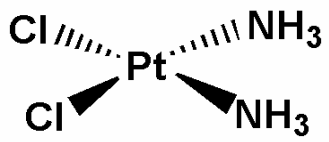
Figure 6: Chemical structure of Polyethylenimine Dendrimer Generation 4 (G4)

Dendrimers can be used as TDD vehicles to carry different drugs. The drugs may either be encapsulated in the core *via* hydrogen bonding, hydrophobic interactions, and chemical bonding or else *via* covalent bonding on the terminal groups. Bioactive molecules such as DNA can be carried using electrostatic interactions. The use of dendrimers for delivering photosensitizers in photodynamic therapy of cancer treatment was reported by Zhang *et al*. Recently, Generation 3 (G3) PAMAM-implanted porous hollow silica nanoparticles (PHSNPs) have been developed for carrying photosensitizers for photodynamic therapy [54]. Poly(amidoamine) (PAMAM) dendrimes are particularly used for delivering low molecular weight anti-cancer drugs, such as, methotrexate, cisplatin, doxorubicin, 5-FU, and anti-inflammatory drugs including ibuprofen, piroxicam, indomethacin (The structural formulae of these drugs are given in Figs. (**7** and **8**)). The potential of these dendrimers can be intensified by attaching targeting ligands to their multivalent surface. As an example, PANAM dendrimer conjugated with folic acid and methotrexate drug was shown to selectively bind and kill KB tumor cells that overexpress folate receptor (FR) *in vitro* and *in vivo* [55]. Surface charge of the dendrimers also have profound effect on drug interactions. For example, positively charged surface of (G4-PAMAM-NH_2) and

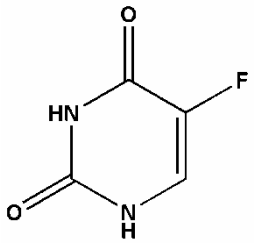
neutral surface (G4 PAMAM-OH), were found to be able to inhibit enzymatic activity of pepsin which has negatively charged surface while negatively charged dendrimer (G3.5 PAMAM-COOH) was not able to inhibit the enzymatic activity of pepsin. This indicates important role played by electrostatic interactions between dendrimers and the proteins [56].



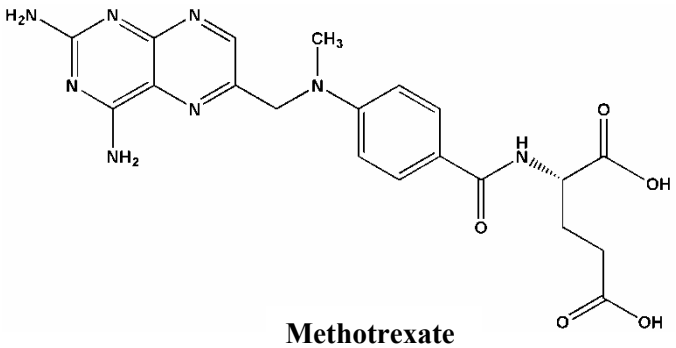
Doxorubicin



Cisplatin

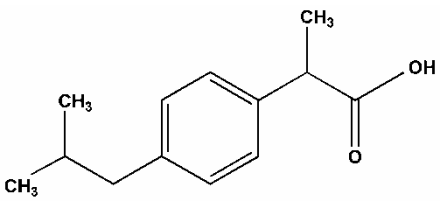


5-Fluorouracil

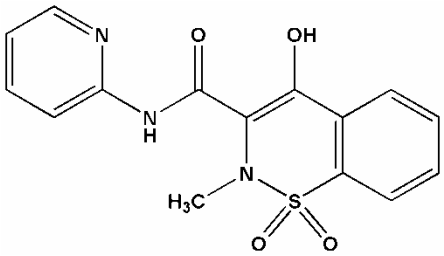


Methotrexate

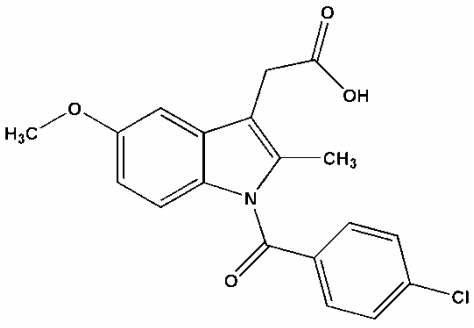
Figure 7: common anticancer drugs



Ibuprofen



Piroxicam



Indomethacin

Figure 8: Common anti-inflammatory drugs

1.5.3 Hydrogels

Hydrogels are three-dimensional structures composed of cross-linked networks of water-soluble polymers. Hydrogels can be made from any water-soluble polymer so that they are associated with wide range of chemical compositions as well as bulk physical properties. Additionally, hydrogels can be readily changed to various physical forms such as microparticles, nanoparticles, coatings and films. As such, hydrogels are commonly used in wide range of applications, including tissue engineering and regenerative medicine, clinical practice [57], experimental medicine, diagnostics, cellular immobilization, separation of biomolecules or cells.

Drug delivery applications of hydrogels are mainly based on their unique physical properties. The affinity of the hydrogels and the density of cross-links in the gel matrix tune their porous structure. The loading capacity of the drug mainly depends on the porosity of the gel matrix. Hydrogels are also generally extremely biocompatible. Biocompatibility is endorsed by the high water content of hydrogels and their physiochemical resemblance. Biodegradability is designed into hydrogels via enzymatic, hydrolytic, or environmental such as pH, temperature, and electric field or magnetic field pathways [58].

Even though there are many advantageous properties, hydrogels also have several restrictions. The low tensile strength of many hydrogels confines their ability to use in load-bearing applications. This can in turn result in the flow away of the hydrogel from a specific targeted site of interest. The quantity and homogeneity of drug loading into hydrogel metrics may be inadequate, especially in the case of hydrophobic drugs. The large pore sizes and high water content of most hydrogels normally result in rapid drug release at the vicinity of the targeted site, over a few hours to a few days. At the same time, some hydrogels are sufficiently deformable to be injectable which is important in surgical implantation.

1.5.4 Lipid-polymer hybrid nanoparticles (LPNs)

To overcome the limitations of polymeric nanoparticles and liposomes in their individual basis, a new generation of delivery vehicles called lipid–polymer hybrid nanoparticles (LPNs) have been

developed. The specificity of LPNs, is that they combine the characteristics of both polymeric nanoparticles and liposomes together to have synergistic effects. They have three components; viz. a polymer core in which the therapeutic drugs are encapsulated, an inner lipid layer inclosing the polymer core, and an outer lipid-PEG layer. The outer lipid-PEG layer acts as a stealth coating that extends *in vivo* circulation time of the LPNs while providing steric stabilization [59]. The inner lipid layer functions as a molecular boundary that reduces leakage of the encapsulated drugs. The inner lipid layer also helps to reduce the polymer degradation rate by limiting inward water diffusion. In other words, it improves for the sustained release kinetics of the drugs.

It is clear therefore that the lipid-polymer hybrid nanoparticles act as a platform to unite the merits of liposomes and polymer nanoparticles. Several of them have been developed by now. Recently, characterization of polymeric nanoparticles with a lipid coating, comprising a core of PLGA, a shell of PEG and a monolayer of lipid, has been carried out [60]. Results are that the core can carry sparingly water soluble drugs, the shell enhances circulation half-life of the drug and the lipid monolayer at the interface of core serves to maintain sustained release of the drug from the core and boost the drug retention. 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 enclosed by liposome, also known as a "Nano cell".

1.5.5 Polymer-drug conjugates

Polymer–drug conjugates (P-DCs) have been developed to replace traditional small molecule therapeutics and offer numerous significant advantages over the traditional methods. These conjugates have been designed to have a covalent bond between a water-soluble polymer and a bioactive molecule [61]. The polymer can safeguard the drug from degradation or chemical reactions with components present in the path. It, therefore, increases drug circulation time, helps control release of drug triggered by differences in pH, temperature, enzyme concentration, or attached ligands for targeting of the desired site of therapeutic need. Further, the polymer-drug conjugates have a specific advantage of increased reduction in the uptake by reticuloendothelial system (RES) or macrophages due to stealth effect of the polymer. In 1975, Ringsdorf was the first to propose a model for pharmacologically active polymers. There, he gave the idea that P-

DCs can be used for the delivery of small hydrophobic molecules, which are otherwise insoluble in aqueous medium, so as to increase the bioavailability of the drug. P-DCs are colloidal nature and stable to sustain in the circulation for prolonged periods of time. One of the major differences between P-DCs and other drug delivery vehicles which utilizing drug entrapment by physical means (*e.g*., liposomes) is that the P-DGs are bonded chemically making them new chemical entities (NCEs). A multitude of drug-conjugates, employing linear polymers, have been recently manufactured. Most widely explored ones are those made using polyethylene glycol (PEG and N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers [62]. PEG-protein conjugates are of significant interest, since PEG can provide protection against enzymatic degradation of proteins and also helps to lower the absorption by the reticuloendothelial system. PEGylating of proteins has resulted in the manufacturing of various therapeutic drug products that include many FDA-approved drugs such as PEG-adenosine deaminase (Adage®), PEG-interferon α-2b (PEG-Intron®) and PEG-interferon α-2a (Pegasus®). These features are important for the development of better cancer chemotherapeutics since they help to overcome limitations such as poor water solubility, short circulation life, non-specific targeting, metabolic instability and dose-dependent toxicity of drugs.

Polymers can be modified by adding functional targeting groups and other moieties to enable them to be used as TDD vehicles. In this scenario, a number of natural and synthetic polymers [63] both bio-degradable and nondegradable, hydrophilic and hydrophobic polymers, with multi-functionalities are currently being explored for TDD. Additionally, polymer composites with lipids and inorganic nanoparticles have also attracted a great deal of attention. These include stimuli- responsive polymers (S-RPs), polymer composites, multifunctional polymers made of co-polymers, and so on [64, 65]. These systems have numerous advantages such as wide range of loading ability of artificial cells, cell mimicking properties of certain polymers, easy functionalization or surface modification and more importantly the ability to have controlled-release kinetics. Due to their low cost, scalable polymeric templates have been recently used to develop artificial cells, such as platelets and biomimetic vesicles [66] for use in TDD.

1.5.6 Magnetic nanoparticles (MNP)

The targeted delivery of anti-tumor agents adsorbed on the surface of MNPs is a favorable alternative to conventional chemotherapeutic methods [67]. MNP can be used to treat cancers in three different ways. Basically, specific antibodies can be conjugated with the MNPs to selectively bind to particular receptors and prevent tumor growth. Targeted MNPs can also be used for hyperthermia for tumor therapy. Drugs can be loaded onto the MNPs for targeted therapy [68]. The drug/carrier complex is then injected into the body either via intravenous or intra-arterial injection. High-gradient, external magnetic fields are used to guide and concentrate the drugs at tumor locations. The magnetic carrier of interest is concentrated at the specific target site *in vivo* manner. Therapeutic agent is then released from the magnetic carrier, either by variations in physiological conditions such as pH, osmolality, or temperature or via enzymatic activity conditions leading to increased uptake of the drugs of interest by the cancerous cells at the target sites [69].

These are micro-and nano-scale magnetic particles loaded or conjugated with drugs that get activated when exposed to an active magnetic field. They release the drug at the specific target site. It is an extremely controllable and effective arrangement of drug targeting. In addition to delivery process, these particles are appropriate for safe image guided drug delivery also.

MNPs avoids RES clearance and provide image guided delivery with magnetic resonance imaging (MRI). It controls releasing of the drug with exceptionally high targeting. Drawbacks of MNPs are gradient loss for deep seated tissues, accumulation of magnetic material at particular targeted site and requirement for specialized manufacturing. Magnetic particles up to 100 nm are generally phagocytosed through liver cells [70].

Iron oxides with core/shell structure are the widely used sources of magnetic materials. Iron oxides have several crystalline polymorphs known as hematite (α- Fe_2O_3), β-Fe_2O_3, maghemite (γ- Fe_2O_3), ε-Fe_2O_3, magnetite (Fe_3O_4), carbonyl iron and amorphous and high pressure forms of iron oxides [71]. Pure metals, such as Fe and Co can also be used as magnetic materials because they have several advantages over iron oxides such as high saturation magnetization, better magnetic properties, and high specific loss of power [72]. However, Fe and Co have worse oxidative stability and higher toxicity than iron oxides. Functionalization of MNPs using amino groups, silica, nanocomposites, and different types of polymers, various surfactant molecules or other organic type compounds is used to achieve better physical and chemical properties [73].

Development of magnetic particle/fluid hyperthermia treatment for cancerous tumors and the controlled and directed transport of pharmaceuticals and therapeutic genes are another promising types of research areas related to targeted delivery of drugs through magnetic MNP.

Organic magnetic carriers are another type of MNP used in the field of delivering drugs. These include magnetoliposomes (ferrofluids entrapped in the liposome core) and polymer magnetic particles. Iron oxide nanoparticles used directly with the drugs are called as inorganic magnetic particles [74]. Incorporation of magnetically responsive or sensitive materials into microspheres or nanospheres makes them susceptible to and applied magnetic field. They can be concentrated at the specifically targeted site by the application of an external magnetic field. Ferriliposomes are other magnetic particles that can be used in combination with MRI for targeted drug delivery and also as theranostics. In order to improve and enhance biocompatibility and safety delivery, currently, various biological magnetic particles, including magnetobiosomes and engineered erythrocytes are being designed. They are considered as highly promising platforms for successful TDD.

1.5.7 Quantum dots (QDs)

Quantum dots are currently found to be significant enough to carry out different industrial applications (Fig. **9**). They can also be used in TDD and concurrent imaging. This is particularly useful in the case of cancer diagnosis and treatment. Quantum dots, made up of zinc oxide doped with Mn^{2+} ($ZnO:Mn^{2+}$), loaded with drugs and enclosed in chitosan, possess a great potential for delivering drugs specifically targeted to tumors. They can report the process of drug delivery at the same time due to their luminescence effects. Apoptosis of tumor cells is expected to improve by the use of $ZnO:Mn^{2+}$ quantum dots. Ideal QD nanomaterials should have the following specific properties [75]. They should not react with the drugs, should have high drug loading capacity and high encapsulation efficiency. There should be an appropriate preparation and purification methods for the QD. QDs that we prepare for targeted drug delivery should have good biocompatibility and should not be toxic to the human body. They should have required mechanical strength and stability and best morphological properties such as appropriate particle size and shape. QDs are 0-D nanomaterials which have unique optical and electrical properties,

due to their quantum-size effects such as quantum confinement effect, dielectric confinement effect, and macroscopic quantum tunneling effect. They have size- and shape-dependent properties and unique surface effects such as surface Plasmon resonance effect. These give rise to many optical properties such as tunable emission, photostability, and brightness, and have a very broad application prospect in biological fluorescent probes and functional materials. Hence, QDs will have diversified biomedical applications [76] in the continued development of life sciences and targeted drug delivery system development (Fig. **9**).

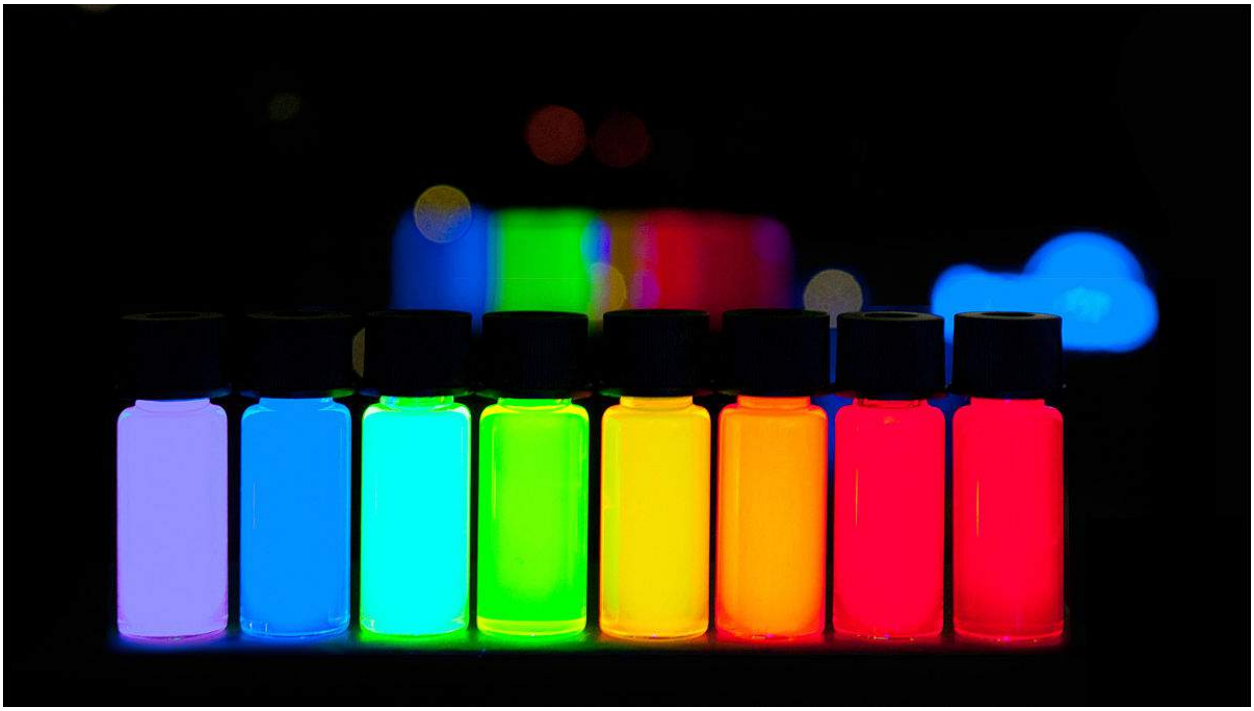


Figure 9: ZnCdSeS alloyed Quantum dots with vivid colours stretching from violet to deep red. (By Antipoff [GFDL (http://www.gnu.org/copyleft/fdl.html) or CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0)], via Wikimedia Commons)

1.5.8 Lipid-based

Liposomes are commonly used for targeting water insoluble drugs, enabling them to be used as targeted delivery systems particularly for such drugs. For example, the biocompatibility and possible diversity with structures and compositions make them suitable for a number of TDD

applications. There are several types of liposomes that are used in the biomedical field. These include conventional liposomes, stimuli-responsive liposomes, stealth liposomes, targeted liposomes, and polymer composite liposomes [77]. Liposome-based drug delivery systems enable passive/active targeting and easy and rapid internalization. They also have low immunogenicity. Another important advantages are high bioavailability and high biocompatibility. But there are some drawbacks as well. Rapid degradation of liposomes in the cell system (uptake by RES (reticuloendothelial system), poor scale-up ability, need for extensive modifications of liposomes for different tasks, are some of those drawbacks [78]. Targeted liposomes and environment- sensitive liposomes are the ones with maximum potential for targeting to cancers and treating neurodegenerative disorders. Several of such prevailing chemotherapeutics have been entrapped in stimuli-responsive liposomes for successful drug targeting.

1.5.9 Inorganic Nanoparticles

Nanostructured materials have exceptional properties and capabilities to make specific interactions with biological systems which can be harnessed predominantly in TDD applications. Several organic nanoparticles have been developed successfully using polymers, liposomes and micelles. But, they have some disadvantages such as low chemical stability, inappropriate drug releasing rates, possibility of microbial contamination, and the effects of the organic solvents used. On the other hand, inorganic nanoparticles are non-toxic, more stable than organic materials, hydrophilic, and biocompatible, and also they have high cellular uptake capacity and non-immunogenic response. Electromagnetic, optical and catalytic properties of metal nanoparticles depend on their shape and size and hence tailor-made material can be made.

Biomedical applications of metal nanoparticles emerged as a result of the development of metal-based nano-conjugates. They were eventually used for drug delivery applications as vehicles for delivering drugs, proteins, peptides, plasmids, nucleic acids for detection, diagnosis and various therapeutic processes. Recently, many industries are developing nanotechnology-based materials for the applications for anticancer drug encapsulation, as prostheses and implants, implanted insulin pumps, and in gene therapeutic applications.

Various inorganic nanoparticles such as calcium phosphates, iron oxide nanoparticles and fullerenes have been synthesized and developed as excellent drug delivery matrices. Carbon nanotubes and nanoparticles and different types of nanoconjugates have been studied as drug delivery carriers. As their size confines to the nanometer range, they can move effortlessly inside the body. Drugs can be either introduced into the nanotube or attached externally or internally on to the particle surface. These nanomaterials include silica, metal nanoparticles, metal hydroxides, carbon and so on. A number of multifunctional, inorganic nanoparticles [79, 80] are being developed for TDD and imaging applications. Carbon-based nanoparticles and gold-based (AuNPs) nanoparticles are very much common in TDD. They have inherent optical properties enabling them in imaging applications. Silica/Alumina/ZnO nanoparticles, quantum dots, metal/oxide/sulfide-based nanoparticles are some such examples. Drawbacks are mainly the issues with regard to toxicity and non-biodegradability leading to accumulation of chemicals in the body. Inorganic nanoparticles [81] with multiple functionalities can be developed which will prompt further research for development of effective cellular delivery systems. Gold-based colloids and nanoshells are currently used in clinical trials for cancer applications.

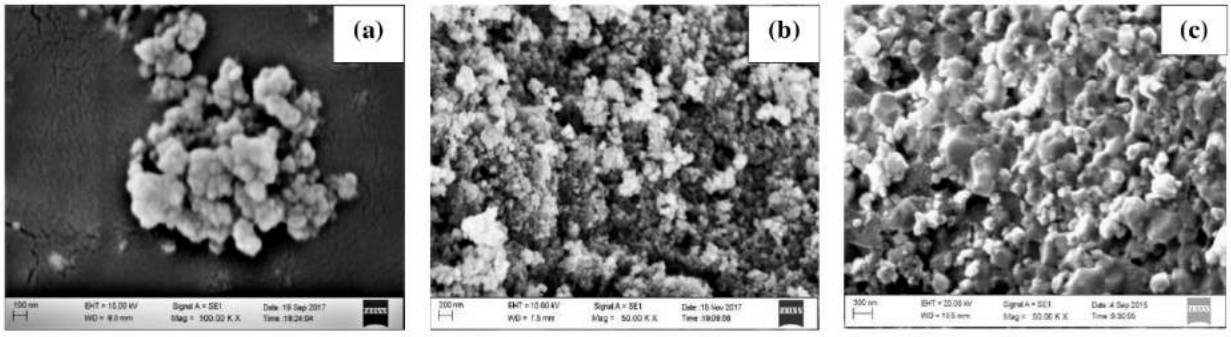


Figure 10: Inorganic nanoparticles for targeted drug delivery (a) Calcium Carbonate NP (b) Zinc Oxide NP (c) Hydroxyapatite NP

Physical research group of university of Peradeniya, Sri Lanka, has developed different types of inorganic nanoparticles for commercially available anticancer drug targeting *via* inorganic nanoparticles. We have been pioneered in synthesizing various inorganic NPs such as $CaCO_3$,

ZnO, TiO_2, MgO, hydroxyapatite and organic NPs such as keratin from bottom-up approach of nanotechnology. They were also developed starting from natural minerals. These nanoparticles were used for encapsulating anticancer drugs such as cisplatin, doxorubicin and Taxol in them. Initially, a template drug, copper bis(8-hydroxyquinoline) was used as anticancer drug and encapsulated in chemically synthesized hollow hydroxyapatite nanocarriers (Fig. **10c**) by varying $NH_4H_2PO_4$:$CaCO_3$ mole ratios. We studied encapsulation efficiency, encapsulation capacity and release kinetics of the drug. The materials prepared were extensively characterized by several independent techniques and the morphological studies were performed by SEM. According to drug loading capacities, drug encapsulation efficiencies and release kinetics, $NH_4H_2PO_4$:$CaCO_3$ mole ratio 2.003:1 is more effective and productive for developing optimized TDD system. By analyzing the results obtained from *in vitro* studies, release of copper bis-(8-hydroxyquinoline) at physiological pH was found to be negligible. However, in acidic medium hydroxyapatite slowly dissolves and releases the drug in a constant manner. So, basically this is a pH-triggered DDS [82]. Encouraged by excellent results obtained, we went on to use actual anticancer drugs such as cisplatin, doxorubicin and Taxol and developed various carriers for them (Fig. **7**). These include porous vaterite nanoparticles, TiO_2 nanoparticles and doped ZnO nanoparticles.

Porous keratin nanoparticles extracted from human hair and ZnO nanoparticles (Fig. **10b**) were developed as nanocarriers for delivering anticancer drug Taxol. Keratin was extracted (2.5%-5.0%) from hair using alkaline hydrolysis followed by re-precipitation using HCl using $NaHSO_3$ as a stabilizer. Morphological structure is spherical and encapsulation of Taxol is confirmed using various characterization techniques.

Cisplatin is a first generation anticancer drug which is very effective in action. It is based on coordination complexes of platinum, and it induces a programmed cancer cell death by attaching to DNA double strands [83]. Porous Calcium carbonate nanoparticles (PCCNP) (Fig. **10a**) were used to encapsulate anticancer drug cisplatin for TDD and slow release application. Vaterite polymorph of calcium carbonate which is basically in spherical morphological structure was well suited for this process and is chemically synthesized using precipitation reaction of $NaHCO_3$ with $Ca(CH_3COO)_2$ in H_2O/EG polar solvent system. PCCNP were characterized using FTIR, SEM, EDAX and XRF to confirm its morphology and the drug encapsulation. Drug releasing was triggered by pH-based mechanism since PCCNPs are pH sensitive. In lower pH values, PCCNP slowly dissolves and releases the anticancer drug cisplatin in to the tumor cells while in

physiological pH conditions and higher pH values the release of the drug is negligible [84]. There are many explanations as to why it is so, but normally it is due to the higher rate of cell differentiation. An erratic and uncontrolled growth occurs where the oxygen supply becomes low. Then the tumor cells have no option but to undergo anaerobic respiration resulting in the formation of lactic acid. This process changes the pH profile of the tumor cell. This change is pH can be used to initiate a mechanism of targeted drug delivery and slowly releasing under acidic pH conditions.

1.5.10 Nucleic Acid/ Peptide based

Peptides are short chains of amino acid monomers (lesser than 50 amino acids) connected by peptide (amide) bonds. The covalent chemical bonds are formed from the reaction of carboxyl group of one amino acid with the amino group of another. Dipeptides are the shortest, consisting of 2 amino acids joined by a single peptide bond. Tripeptides, tetrapeptides can be synthesized by the linkage of respective amounts of amino acids reacting with each other. A polypeptide is a long, continuous, and unbranched peptide chain [85].

With the development and the popularization of recombinant proteins and effective protein purification methods, exquisite potency of the peptide based drug delivery systems has been realized. A new protein-based drug classification was introduced. It is referred to as 'Biologics' which include molecules such as engineered antibodies, insulin hormone, *etc*. Peptides and proteins bind with exquisite specificity to their *in vivo* targets. This reduces unnecessary side effects. Huge array of structural and functional diversity of these molecules possess high degree of selectivity in their specific interactions. So, it is easy to fine tune the peptide-based molecules for binding with biologically specific targets. Normally, injection methods are used to deliver current peptide therapeutics. Some examples for the peptide based drugs currently used are oxytocin, Fuzeon (antiretroviral), calcitonin (hypercalcemia, osteoporosis), teriparatide (parathyroid hormone analog, osteoporosis) and growth-hormone releasing hormone. However, applications of chemically synthesized different peptides have been severely restricted due to factors such as their low systemic stability, poor membrane permeability, and so on [86]. But, in a work done by the Kessler group, a research on cyclic N-methylated somatostatin analogs associated to the Veber-Hirschmann peptides were developed (Fig. **11**). They were able to

synthesize about 30 compounds by varying degrees of methylation of the secondary amides enclosed in the starting macrocycle [87]. Furthermore, in vitro evaluation studies have shown that specific methylation of D-Trp8, Lys9, and Ph11 considerably enhances the cell membrane permeability. This is also considered as an oral biocompatible compound according to rat studies.

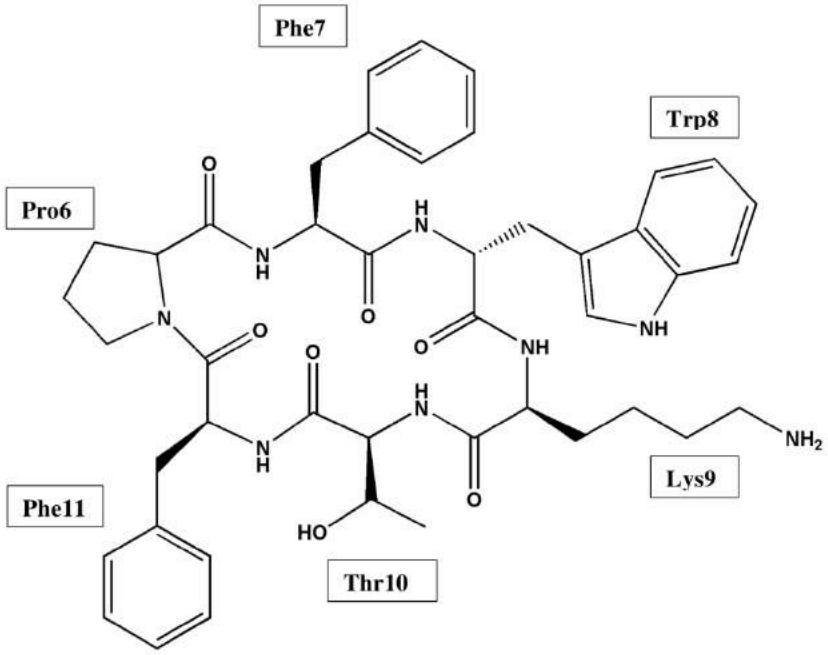


Figure 11: General structure of the Veber–Hirschmann peptides.

1.5.11 Transdermal approach in drug Transportation

Transdermal drug delivery systems, such as the use of patches, ointments and creams, have been around for several years. These systems enhance the skin permeation of low molecular weight usually < 500 Da [88], lipophilic drugs that are effective at low doses. However, improvements to this approach is required for hydrophilic molecules and macromolecules. In order to make the transdermal drug delivery methodology suitable for large, hydrophilic molecules and macromolecules, nano-carriers made of lipids, metals, or polymers have been successfully used. Nanocarriers increase penetration of drugs or vaccines. In this way, it is possible to achieve

controlled drug release and also to target drugs to specific areas of skin *in vivo* [89]. A transdermal drug delivery carrier can be of a passive design or an active design. It provides an alternative pathway for administering drug to specific site where the drug is delivered across the skin barrier. The passive approach relies on the optimization of formulation or drug carrying vehicle to increase skin permeability. However, passive methods are not very suitable for large drug molecules of over 500 Da molecular weights. Active methods rely on physical or mechanical methods of enhancing drug delivery and hence active methods have been shown to be much superior to passive methods. Active methods have been used for the delivery of drugs of differing lipophilicity and molecular weight. These include proteins, peptides, and oligonucleotides. Electrical methods such as iontophoresis, electroporation, mechanical methods such as abrasion, ablation, perforation, and other energy-related techniques such as ultrasound and needless injection have been successfully used in active transdermal drug delivery [89]. Transdermal delivery id associated with significant advantages compared with the oral pathway. However, hypodermic injections could be painful and may produce hazardous medical waste [90]. They are non-invasive and can also be self-administered. They can facilitate release for long periods of time, up to about a week. They also improve patient compliance and the systems are usually inexpensive. As described earlier, one of the important problems of transdermal delivery is that the method I compatible with only a limited number of drugs. Delivery of vaccines via transdermal route is another area of great interest. It has been reported that transdermal vaccine delivery can improve immune responses by targeting delivery to immunogenic Langerhans cells in the skin [91]. Brown and co-workers have reviewed Dermal and Transdermal Drug Delivery Systems: Current and Future Prospects, in particular, in 2006, and more information on this particular subject can be obtained from this excellent review [92-94].

1.5.12 Folate Targeting

Folate targeting is a method invented by Christopher P. Leamon and Philip S. Low for TDD process [95]. This involves the attachment of the vitamin, folic acid (Structure of folic acid is given in Fig. **12**) to a molecule or drug to form folate conjugates Folates are a kind of B vitamin which are involved in purine synthesis. Most cells get the folate they need *via* reduced folate

carrier anion channel which has a low affinity for folates. As such, there is only very little or no expression of folate receptors in most normal cells. However, cancer cells require a large amount of folate and hence they have excess folate receptors on their surfaces. As such, folate receptor proteins (FRPs) are commonly overexpressed in the surfaces of many human cancers. Folic acid has a specific binding ability to these FRPs. When folic acid is bound to drugs forming drug-folate conjugates they also have high affinity for FRPs in human cancer cell surfaces and trigger cellular uptake *via* endocytosis.

Among cellular surface drug targeting methods, folate receptor (FR) - α stands out as the main and one of the most explored epithelial cancer markers [96]. Currently, the potential importance of FR- β as a cellular target has also been identified. This has expanded the range of disease targets to chronic inflammatory diseases including rheumatoid arthritis and myelogenous leukemia. FRs, also called as folate-binding proteins (FBP), which are N -glycosylated proteins, hsving high binding affinity to folate. FRs consist of four isoforms, α, β, γ / γ ′ and δ. The α, β, and δ isoforms are glycosyl phosphatidylinositols (GPIs) which are anchored membrane proteins . FR- γ / γ′ is secreted by lymphoid cells. FR- δ has been found to be expressed on regulatory T cells. FR- δ has recently been proposed as a potential therapeutic target [95, 97]. However, most significant attention has been focused on FR- α and FR- β. These two isoforms are distinguishable by differences in their affinities for folic acid [98].

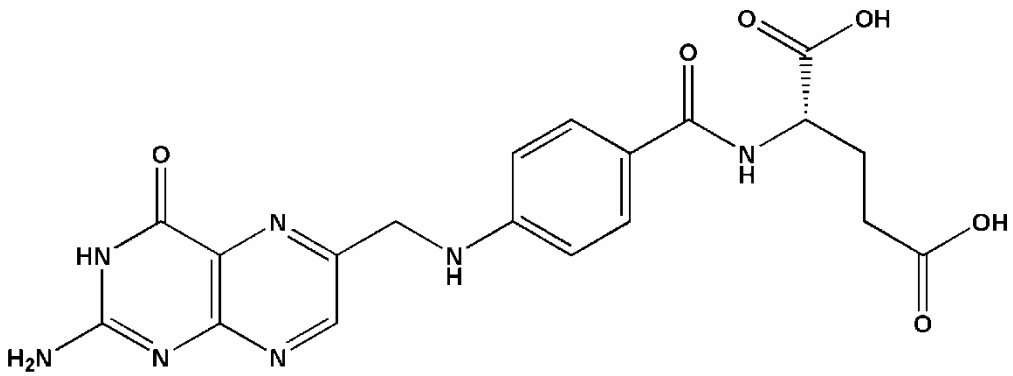


Figure 12: Chemical structure of folic acid.

2. CONCLUSIONS

Targeted drug delivery is developing as one of the most advanced technique in the medical sciences in the diagnosis and treatment of diseases. TDD is associated with many advantages which include minimal dosage requirement and minimal side effects with maximal bioavailability and high efficacy of the drugs. In this review, we attempted to highlight problems associated with conventional drug administration methods and shown that targeted delivery as a solution to these problems. We have reviewed, as much as possible, the main literature associated with targeted drug delivery though the database seems to be unlimited. We have focused mainly on cancer treatment, though TDD used in treating other diseases have also been discussed. Different carriers used in TDD were highlighted with their advantages, limitations and based on which their most useful practical applications were highlighted. With these target specific treatments, it is envisaged that safe, effective and efficient chemotherapeutic treatment methodologies will be realized for diseases such as cancers in the near future.

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