IJPSR (2019), Volume 10, Issue 8 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 December 2018; received in revised form, 16 February 2019; accepted, 07 March 2019; published 01 August 2019

NANOCARRIERS AS DELIVERY SYSTEMS FOR THERAPEUTICS AGENTS

Farah Hamad Farah

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman, PO Box 346, United Arab Emirates.

Keywords:

Nanocarriers, Delivery systems, Therapeutic agents, Drug targeting

Correspondence to Author:
Farah Hamad Farah

Associate Professor,
Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman, PO Box 346, United Arab Emirates.

E-mail: f.hamad@ajman.ac.ae

ABSTRACT: Nanotechnology is emerging as a field in pharmacy and medicine that is expected to elicit significant therapeutic benefits especially in the field of drug targeting. The development of effective nanocarriers capable of carrying therapeutic agents specifically and safely to a desired site of action is one of the most challenging tasks facing drug formulation researchers. Serious research attempts had been conducted to reformulate and add new dimensions to the existing blockbuster therapeutic agents to achieve and maintain therapeutic breakthroughs. Integration of nanocarriers therapeutic agent delivery technologies in pre-formulation work accelerate the development of new therapeutic moieties and help in the reduction of attrition of new molecular entities caused by undesirable biopharmaceutical and pharmacokinetic properties. Careful modification of physicochemical properties of nanocarriers provides improved control over the pharmacokinetics and pharmacodynamics of the encapsulated therapeutic agents relative to free drugs that would typically lead to a superior therapeutic index of the encapsulated agent. Nanocarriers vary from biological substances such as albumins, proteins, peptides, and phospholipid liposomes, to chemical substances such as bio-degradable hydrogels, dendrimers, nanoemulsions, silicon or carbon nanotubes, quantum dots, nanoshells, and magnetic nanocarriers.

INTRODUCTION: A wide spectrum of therapeutic nanocarriers has been extensively investigated to address the emerging need to improve the therapeutic properties of drugs to treat a wide variety of diseases. Nanotechnology involves the engineering of functional systems at the molecular scale.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(8).3487-07

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(8).3487-07

Such systems are characterized by unique physical, optical and electronic features that are attractive for disciplines ranging from materials science to nanomedicine that constitutes one of the most active research areas, which applies nano-technology to highly specific medical interventions for the prevention, diagnosis, and treatment of diseases [1-3]. Currently, nanomedicine is dominated by drug delivery systems, accounting for more than 75% of total sales [4].

The main objective of this review is to focus on recent advances and trends related to formulation and characterization of nanocarriers therapeutic agents delivery systems (NTADS) with special emphasis on their vital role in cancer targeted

therapeutic agent delivery. Also, future prospects, big impact, priority areas and challenges of nanocarriers, shall be covered.

1. Definition: Nanocarriers can be defined as nanoparticles having dimensions ranging from 1 to 100 nm (1 nm = 1 billionth of a meter = 10^{-9}). However, the prefix "nano" is commonly used for particles that are up to several hundred nanometers in size [5].

Nanocarrier's dimensions with relation to other scales are shown in **Fig. 1**. [5]

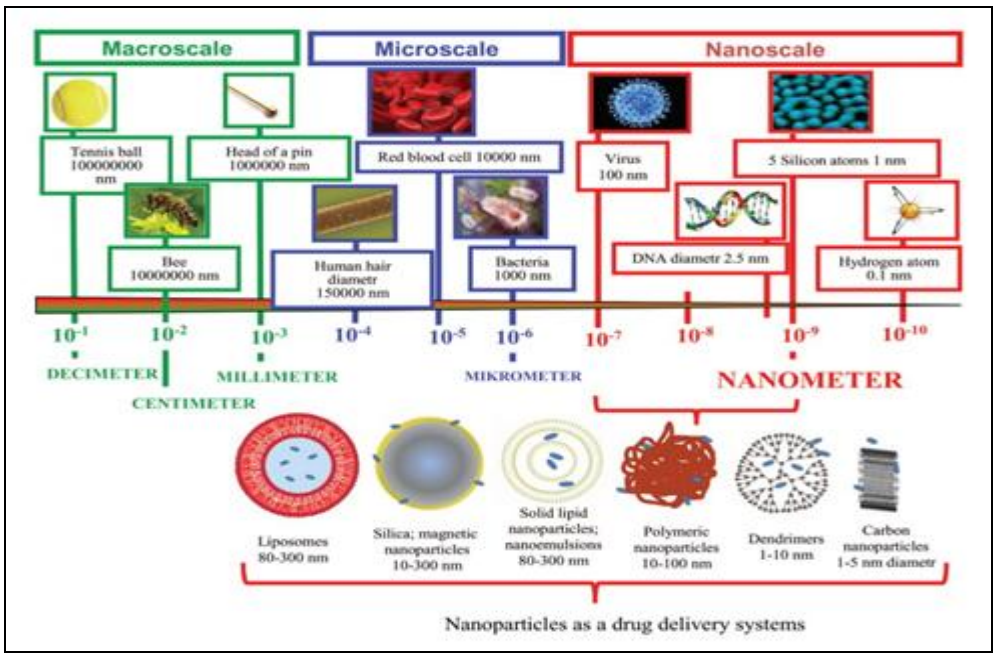

FIG. 1: NANOCARRIERS DIMENSIONS WITH RELATION TO OTHER SCALES

2. Therapeutic Agent Targeting of Nano-carriers: Delivering a therapeutic agent to the target site is a major problem in the treatment of many diseases. A conventional application of therapeutic agents is characterized by limited effectiveness, poor bio-distribution, and lack of selectivity. These limitations can be overcome by controlling therapeutic agent delivery. In controlled therapeutic agent delivery systems (TADS) the therapeutic agent is transported to the place of action; thus, its influence on vital tissues and undesirable side effects can be minimized. Also, TADS protects the therapeutic agent from rapid degradation or clearance and enhances therapeutic agent concentration in target tissues; therefore, lower doses of therapeutic agent are required. This modern form of therapy is especially important when there is a discrepancy between a dose or concentration of a therapeutic agent and its therapeutic results or toxic effects [6]. Cell-specific targeting can be achieved by attaching therapeutic agents to individually designed carriers. Recent developments in nanotechnology have shown that nanocarriers, due to their small sizes, exhibit optimized physicochemical and biological properties that make them easily taken up by cells so that they can be successfully used as delivery tools for currently available therapeutic agents [7].

2.1. Mechanism of Therapeutic Agent Targeting of Nanocarriers: Two basic requirements should be realized in the design of nanocarriers to achieve effective therapeutic agent delivery. First, therapeutic agents should be able to reach the desired tumor sites after administration with minimal loss to their activity in blood circulation. Second, they should selectively kill tumor cells without harming healthy tissues. These requirements may be enabled using two strategies: passive and active targeting of therapeutic agents.

2.1.1. Passive Targeting: Passive targeting takes advantage of the unique pathophysiological characteristics of tumor vessels, enabling therapeutic agents to accumulate in tumor tissues. Typically, tumor vessels are highly disorganized and dilated with a high number of pores, resulting in enlarged gap junctions between endothelial cells

and compromised lymphatic drainage. The 'leaky' vascularization, which refers to as enhanced vascular permeability and retention (EPR) effect, allows migration of macromolecules up to 400 nm in diameter into the surrounding tumor region. One of the earliest nanocarriers for passive targeting of drugs was based on the use of liposomes. More advanced liposomes are coated with a synthetic polymer that protects the agents from immune destruction or phagocytosis.

2.1.2. Active Targeting: Active therapeutic agent-targeting employs the attachment of affinity ligands (antibodies or peptides (arginine-glycine-aspartic acid) or folate and some vitamins), that only bind to specific receptors on the cell surface, to the surface of the nanocarriers by conjugation. Nanocarriers will recognize and bind to target cells through ligand-receptor interactions. To achieve high specificity, those receptors should be highly expressed on tumor cells, but not on normal cells. Active targeting can also be obtained through manipulation of the physiological environment or physical stimuli (*e.g.*, temperature, pH, magnetism, osmolality, or *via* an enzymatic activity) [6].

An illustration showing the mechanism of passive and active targeting is given in **Fig. 2**.

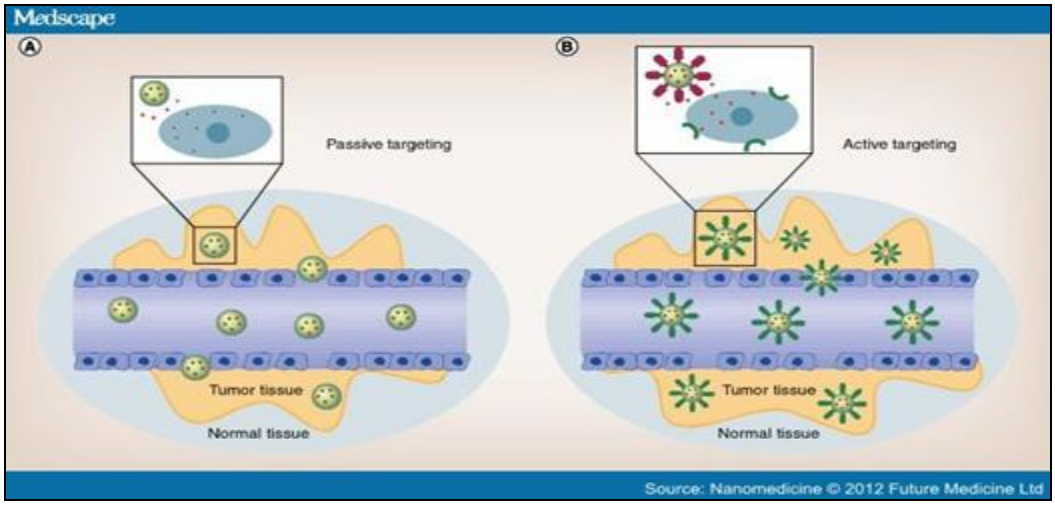

FIG. 2: AN ILLUSTRATION SHOWING THE MECHANISM OF PASSIVE AND ACTIVE TARGETING

3. Characteristics of Nanocarriers: Nanocarriers used to deliver therapeutic agents have to be biocompatible (do not elicit the immune response) and nontoxic (harmless to biological systems). Undesirable effects of nanocarriers strongly depend on their hydrodynamic size, shape, amount, surface chemistry, the route of administration, reaction of the immune system (especially uptake by macrophages) and residence time in the bloodstream. Due to some factors which may affect the toxicity of nanocarriers, then toxicological studies of new TADS formulation are needed. However, generally concerning their size, smaller particles have a greater surface area, thus, they are more reactive and, in consequence, more toxic [8]. It is generally accepted that nanocarriers with a hydrodynamic diameter of 10-100 nm have optimal pharmacokinetic properties for *in-vivo* applications. Smaller nanocarriers are subjects to tissue extravasations and renal clearance whereas larger nanocarriers are quickly opsonized and removed from the bloodstream via the macrophages of the reticuloendothelial system [9].

4. Release Pattern of Nanocarriers: To develop a successful nanocarrier TADS, both therapeutic agent release, and polymer biodegradation are important consideration factors. In general, therapeutic agent release rate depends on (i) solubility of therapeutic agent; (ii) desorption of the surface-bound/adsorbed therapeutic agent; (iii) therapeutic agent diffusion through the nanocarrier matrix; (iv) nanocarrier matrix erosion/degradation; and (v) combination of erosion/diffusion process.

Thus, solubility, diffusion, and biodegradation of the matrix materials govern the release process. In the case of nanospheres, where the therapeutic agent is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the therapeutic agent is faster than matrix erosion, the mechanism of

release is largely controlled by a diffusion process. The rapid initial release or "burst" is mainly due to therapeutic agent particles over the surface, which diffuse out of the therapeutic agent-polymer matrices [10].

4.1. Kinetics of Drug Release from Nanocarriers: Kinetics of drug release is an important evaluation parameter. The knowledge of the mechanism and kinetics of therapeutic agent release from these nanocarriers indicates their performance and gives proof of adequateness of their design. Drug release from nanocarriers involves mass transfer phenomenon involving diffusion of the therapeutic agent from higher to low concentration regions in the surrounding liquid.

Therapeutic agent release data is applied mainly for (i) quality control; (ii) understanding of physicochemical aspects of therapeutic agent delivery systems; (iii) understanding release mechanisms; and (iv) predicting the behavior of systems *in-vivo*. However, there are difficulties in modelling therapeutic agent release data, as there is a great diversity in the physical form of nanocarriers with respect to size, shape, arrangement of the core and the coat, properties of core-like solubility, diffusivity, partition coefficient, properties of coat-like porosity, thickness, crystallinity, inertness, *etc*. [11] Similar to other sustained release delivery systems, the release kinetics and the mechanism of therapeutic agent release from nanocarriers can be assessed by fitting the therapeutic agent *in-vitro* release data to zero order, first order, Higuchi's and Korsmeyer-Peppas models [12].

4.2. Methods used to Study the *in-vitro* Release of the Therapeutic Agent from Nanocarriers: Some methods have been used to study the *in-vitro* release of the therapeutic agent from nanocarriers, some of these include:

- **i.** Side-by-side diffusion cells with artificial or biological membranes.
- **ii.** Dialysis bag diffusion technique.
- **iii.** Reverse dialysis bag technique.
- **iv.** Agitation followed by ultracentrifugation/ centrifugation.
- **v.** Ultrafiltration or centrifugal ultrafiltration techniques.

Usually, the release study is carried out by controlled agitation followed by centrifugation.

Duetothetime-consuming nature and technical difficulties encountered in this parathion of nanocarriers from release media, the dialysis technique is generally preferred. Various researchers have proposed different methods with one common strategy of using synthetic membrane bag with specified porosity to hold the sample. The bag containing the sample is immersed in the recipient fluid, which is stirred at a specified rpm. The samples are withdrawn at regular intervals and are analyzed for the drug content [12].

5. *In-vitro* Blood Interaction and Toxicological Characterization of Nanocarriers: Immuno-logical evaluation includes both immuno-suppression and immune stimulation and applies to nanocarriers intended to be used as drug candidates and as drug delivery platforms. Short-term *in-vitro* assays are developed for quick evaluation of biocompatibility of nanocarriers, which includes analysis of plasma protein binding by polyacrylamide gel electrophoresis (PAGE), haemolysis, platelet aggregation, coagulation, complement activation, colony-forming unit–granulocyte macrophage (CFU-GM), leukocyte proliferation, phagocytosis, cytokine secretion by macrophages, chemotaxis, oxidative burst, and evaluation of cytotoxic activity of natural killer (NK) cells.

In addition to these methods, in vitro test may also include sterility assessment and pyrogenic contamination test by Limulus amebocyte lysate assay. These assay cascades are based on several regulatory documents recommended by the U.S. FDA for immune-toxicological evaluation of new investigational drugs, medical devices, and biotechnology-derived pharmaceuticals [1-5]. An essential aspect of this testing is to ensure the absence of toxicity to blood elements when nanocarriers are injected into the patients. The test protocols are developed in general, and when the same is applied for nanocarriers, there can be specific problems that are not generally anticipated. However, some have reported that interactions would act as a guideline in carrying out these tests with nanocarriers [13].

Nanocarriers toxicity include oxidative stress (an imbalance between the production of free radicals and the ability of the body to detoxify their harmful effects), apoptosis, (the genetically directed process of cell self-destruction/death) and mitochondrial dysfunction. Using an appropriate model, chemo-therapeutic efficacy can be examined *in-vitro* and, in certain cases, targeting of chemotherapeutic agent may be demonstrated, using optimized treatment/wash out schemes in celllines expressing the targeted receptor. Although nanocarrier metabolism or enzyme induction is yet to be demonstrated, specific nanoparticles with appropriate chemistries are believed to be subjected to phase I and II metabolism, as demonstrated by induction studies using cell-based microsomal and recombinant enzyme systems [13].

6. Pharmacokinetics and Pharmacodynamics of Therapeutic Agents from Nanocarriers: Careful modification of the elastic physicochemical properties of nanocarriers provides improved control over the bio-distribution, pharmacokinetics, and pharmacodynamics of the encapsulated agents relative to free therapeutic agents that would typically lead to a superior therapeutic index of the encapsulated agent [14]. Once the therapeutic agents are associated with their nanocarriers, the overall properties of their formulations would depend primarily on the nanocarrier design as a sustained-release delivery system. Hence, the manipulation of nanocarrier properties such as particle diameter, surface charge, packing and fluidity of the carrier matrix/shell, drug release rate, steric stabilization bioavailability, bio-distribution, and dosing schedule can significantly influence the therapeutic outcome of the encapsulated agents.

Therefore, the PK disposition of these agents is dependent upon the carrier and not the parent therapeutic agent until the agent is released from the carrier. The therapeutic agent that remains encapsulated in the nanocarrier is considered an inactive agent moiety and, thus, the therapeutic agent must be released from the carrier to be active. Logically, one can recognize that therapeutic agent release kinetics from the nanocarrier is of primary importance. Delayed and sustained release rate of the agent from the nanocarriers is often required for almost all systemic administrations of nanocarrier TADS.

Several formulation factors can influence the nanocarrier release rate and bioavailability, including size, matrix erosion rate, as well as diffusion of drug through the matrix or wall of the nanocarrier. Well-packed polymeric or lipoid nanocarriers TADS should have appreciably small diameters (few to several hundreds of nanometers) that would allow for both incorporation of sufficient amounts of small therapeutic agent molecules and also important thermodynamic and mechanical stability, for up to periods of several hours/days in the physiological systems. Many reports indicated that smaller diameters for the liposomal doxorubicin formulations resulted in superior therapeutic agent localization in tumors and improved therapeutic outcome. Despite an agreement that smaller diameter nanocarriers have improved plasma and tissue bio-distribution, attention must be balanced between smaller size and stability of the TADS internal and wall structure, to avoid particle collapse and burst/immediate release of therapeutic agent before reaching its target [15].

7. Nanocarriers as Delivery Systems for Therapeutic Agents: Nanocarriers have unusual properties that can be used to improve therapeutic agent delivery. Some of the challenges of most therapeutic agent delivery systems include poor bioavailability, *in-vivo* stability, solubility, intestinal absorption, sustained and targeted delivery to the site of action. Most of these challenges can be overcome by formulating therapeutic agents as nanocarriers, to enhance therapeutic effectiveness and reduce side effects & hence improve patient compliance.

Also, nanocarriers can potentially provide zero-order release to sustain therapeutic agents action and control plasma fluctuations of these agents to avoid possible ineffective or toxic response. Generally, nanocarriers have the ability to protect therapeutic agents encapsulated within them from hydrolytic and enzymatic degradation in the gastrointestinal tract; target the delivery of a wide range of therapeutic agents to various areas of the body for sustained release and thus are able to deliver therapeutic agents, proteins and genes through the per-oral route of administration. They deliver therapeutic agents that are highly water insoluble; can bypass the liver, thereby preventing

the first pass metabolism of the incorporated agent [16]. They increase oral bioavailability of therapeutic agents due to their specialized uptake mechanisms such as absorptive endocytosis and can remain in the blood circulation for a longer time, releasing the incorporated therapeutic agent in a sustained and continuous manner leading to fewer plasma fluctuations thereby maximizing therapeutic outcomes and minimizing side effects [16].

Due to the size of nanocarriers, they can penetrate tissues and are taken up by cells, allowing efficient delivery of drugs to sites of action. The uptake of nanocarriers was found to be 15-250 times greater than that of micro-particles in the 1-10 μm range [16]. Through the manipulation of the characteristics of nanocarriers, the release of therapeutic agents can be controlled to achieve the desired therapeutic concentration for the desired duration.

Nanocarriers can be applied to reformulate existing therapeutic agents, thereby enhancing their effectiveness, as well as increasing safety and patient compliance, and ultimately reducing health care costs. Nanocarriers can also act as potential delivery systems for treatment and management of chronic diseases such as cancer, HIV/AIDS and diabetes [17].

7.1. Some Examples of Nanocarriers used as Therapeutic Agent Delivery Systems: General common properties of nanocarriers include:

- Improving the solubility/stability of hydrophobic drugs, rendering them suitable for administration.
- Improving bio-distribution and pharmaco-kinetics, resulting in improved efficacy.
- Reducing adverse effects as a consequence of favored accumulation at target sites.
- Decreasing toxicity by using biocompatible nanocarriers.

Nanocarriers with optimized physicochemical and biological properties are taken up by cells more efficiently than larger molecules so that they can be successfully used as delivery tools for currently available therapeutic agents [7].

Some examples of nanocarriers that have been tested as therapeutic agent delivery systems include; nanocrystals, liposomes, polymeric nanocarriers, polymeric micelles, solid lipid nanocarriers, protein-based nanocarriers, dendrimers, carbon nanotubes, and magnetic nanoparticle. Some of these nanocarriers are illustrated in **Fig. 3**.

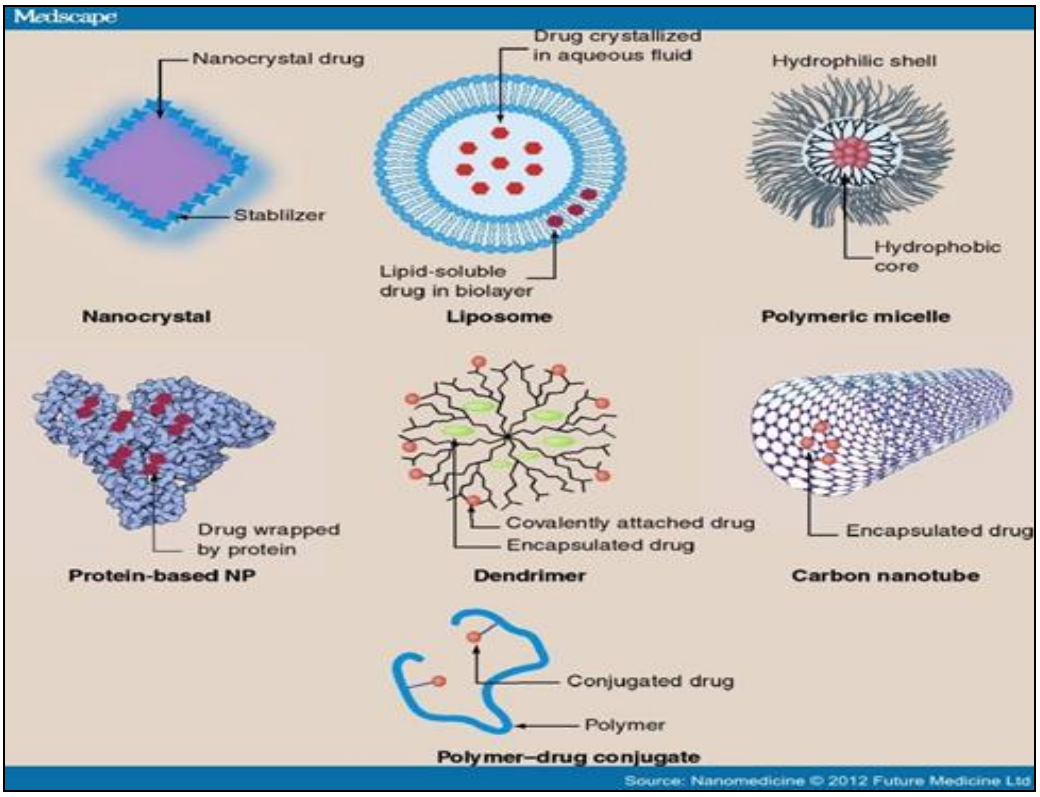

FIG. 3: ILLUSTRATIONS OF SOME NANOCARRIERS USED AS THERAPEUTIC AGENT DELIVERY SYSTEM

7.1.1. Nanocrystals: This is a nanotechnology technique used to convert existing therapeutic agents with poor water solubility and dissolution rate into readily water-soluble dispersions by turning them into nano-sized-particles [18, 19] **Fig. 4**.

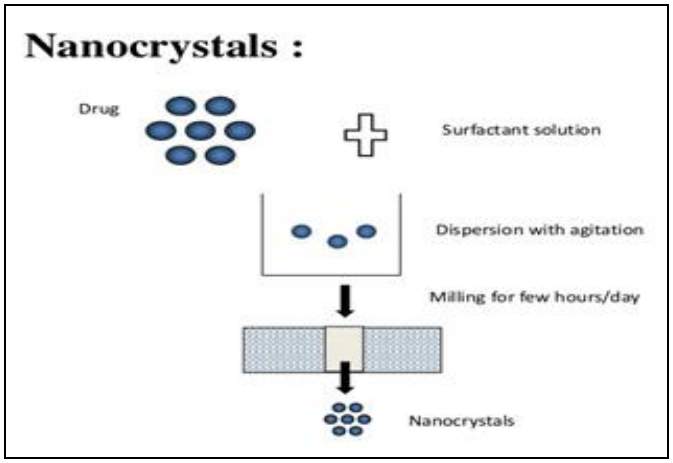

FIG. 4: DIAGRAM ILLUSTRATING SURFACTANT STABILIZED DRUG NANOCRYSTALS

The therapeutic agent itself may be formulated at a nanoscale such that it can function as its own 'carrier' [20]. Usually, after nano-sizing the particles of the therapeutic agent, the particles surface is stabilized using non-ionic surfactants or polymeric macromolecules [19]. By reducing the particle size of the therapeutic agent, the agent's surface area is increased considerably, thereby improving its solubility and dissolution and consequently increasing both the maximum plasma concentration and area under the curve. Once the therapeutic agent is nano-sized, it can be formulated into various dosage forms, such as oral, nasal and injectable. These nanocrystal therapeutic agents may have advantages over association colloids (micelle solutions) because the level of surfactant per amount of drug can be significantly minimized, using only the amount that is necessary to stabilize the solid surface [20].

Furthermore, recent studies have shown that stabilizing agents, such as surfactants, for nanocrystal therapeutic agent delivery can be eliminated. For example, a method was recently developed for the delivery of a hydrophobic photosensitizing anticancer agent in its pure form using nanocrystals, synthesized by the re-precipitation method; the resulting drug nanocrystals were stable in aqueous dispersion, without the necessity of any additional stabilizer [21].

Some representative examples of marketed nanocrystal-based therapeutic agents are shown in **Table 1** [22].

TABLE 1: SOME REPRESENTATIVE EXAMPLES OF MARKETED NANOCRYSTALS-BASED THERAPEUTIC AGENTS

Brand name	Therapeutic agent	Indications
Rapamune®	Rapamycin	Immunosuppressive[5]
Emend®	Aprepitant	Anti-emetic[5]
Tricor®	Fenofibrate	Hypercholesterolemia[5]
Megace®	Megestrol	Anti-anorexia[5]

7.1.2. Liposomes: Liposomes are the most clinically established nanocarriers for therapeutic agent delivery. They are self-assembled artificial vesicles developed from amphiphilic phospholipids. These vesicles consist of a spherical bilayer structure surrounding an aqueous core domain **Fig. 5**, and their size can vary from 50 nm to 300 nm.

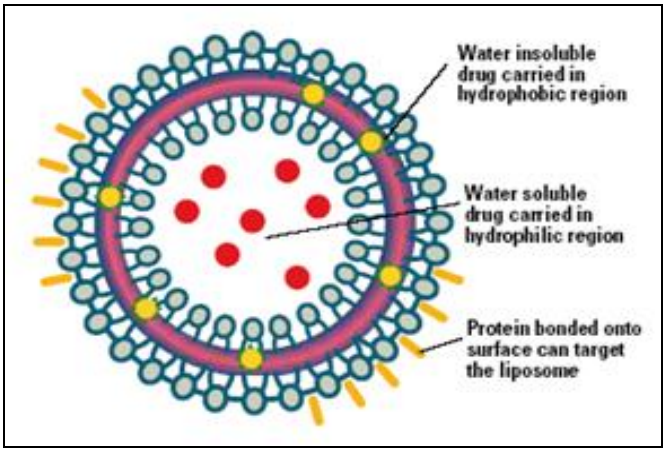

FIG. 5: THE ENCAPSULATION OF THERAPEUTIC AGENTS WITHIN LIPOSOMAL STRUCTURE

Liposomes have desirable biological properties, including biocompatibility, biodegradability, isolation of drugs from the surrounding environment and the ability to entrap both hydrophilic and hydrophobic drugs. Through the addition of agents, such as cholesterol to the lipid membrane, or the alteration of the surface chemistry, liposome properties, such as size, surface charge, and functionality, can be easily modified [23]. Liposomes have been reported to increase the solubility of drugs and improve their pharmacokinetic properties, such as the therapeutic index of chemotherapeutic agents, rapid metabolism, reduction of harmful side effects and increase of *in-vitro* and *in-vivo* anticancer activity

[24]. The encapsulation of therapeutic agents within the liposomal structure is shown in **Fig. 5**.

The *in-vivo* release of a therapeutic agent from liposomes is illustrated in **Fig. 6**.

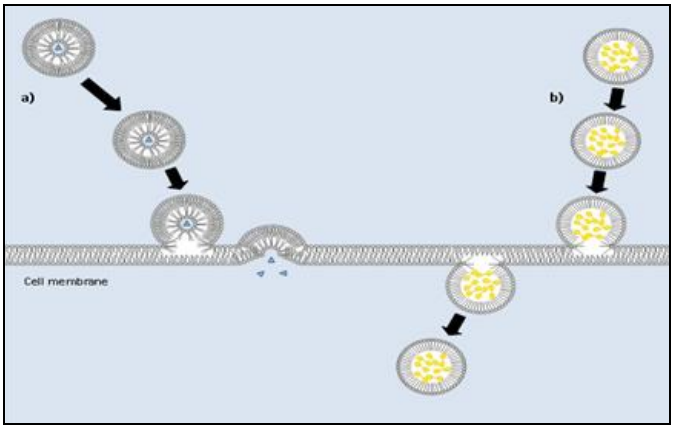

FIG. 6: *IN-VIVO* THERAPEUTIC AGENT DELIVERY BY LIPOSOMES

The release depends on the liposome composition, pH, osmotic gradient, and the surrounding environment. Additionally, a prolonged residence time increases the duration of action of such particles but decreases their number. Interactions of liposomes with cells can be realized by adsorption, fusion, endocytosis, and lipid transfer **Fig. 7**. [5]

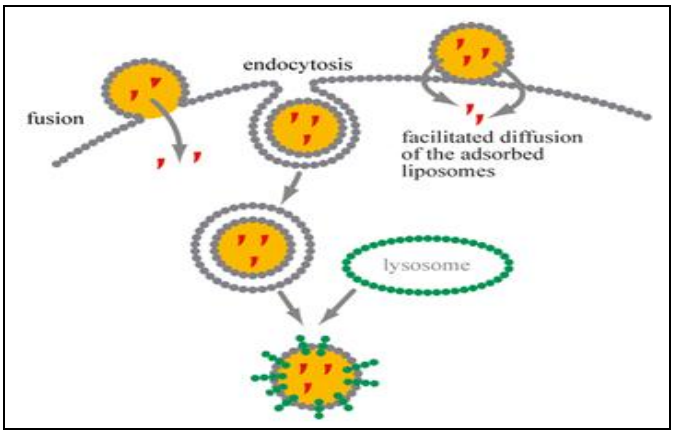

FIG. 7: INTERACTIONS OF LIPOSOMES WITH CELLS BY ADSORPTION, FUSION, ENDOCYTOSIS, AND LIPID TRANSFER

Cationic liposomes can be used as a gene delivery carrier. They are better than neutral or anionic liposomes for gene transfer [25]. Also, recently modified cationic liposomes using triphenyl-phosphonium-polyethylene glycol-phosphatidyl-ethanolamine conjugate loaded with an anticancer agent, paclitaxel, was found to target the mitochondria with minimum toxicity specifically [26].

7.1.2.1. Advantages of Liposomes as Therapeutic Agent Delivery Systems: [27]

- Can encapsulate both hydrophilic and lipophilic therapeutic agents.
- Provides selective passive targeting to tumor tissues.
- Increased efficacy and therapeutic index.
- Increased stability *via* encapsulation.
- Reduction in toxicity of the encapsulated agent.
- Used as carriers for controlled and sustained therapeutic agent delivery.
- Can be made into a variety of sizes.

7.1.2.2. Disadvantages of Liposomes: [28]

- Low encapsulation efficiency
- Leakage of encapsulated hydrophilic therapeutic agents during storage.
- Uptake of liposomes by the reticuloendothelial system
- Poor storage stability.
- Once administered, liposomes cannot be easily removed
- The possibility of dumping, due to faulty administration.

Some representative examples of marketed liposome-based therapeutic agents are shown in **Table 2**.

TABLE 2: SOME REPRESENTATIVE EXAMPLES OF MARKETED LIPOSOME-BASED THERAPEUTIC AGENTS

Brand name	Therapeutic agent	Indications
AmBisome®	Amphotericin B	Fungal infections[29]
Doxil®	Doxorubicin	Ovarian cancer, Kaposi's sarcoma and breast cancer[30]
Caelyx®	Doxorubicin	Ovarian cancer, Kaposi's sarcoma, and breast cancer[31]
Depocyt®	Cytarabine	Lymphomatous meningitis[32]
Daunoxome®	Daunorubicin	Kaposi's sarcoma[33]

7.1.3. Polymeric Nanocarriers: Polymeric nanocarriers (PNCs) are colloidal particles with a size range of 10-1000 nm, and they can be spherical, branched or core-shell structures. They have been fabricated using biodegradable synthetic polymers, such as polylactide-polyglycolide

copolymers, polyacrylates, and polycaprolactones, or natural polymers, such as albumin, gelatin, alginate, collagen and chitosan [34]. Various methods, such as solvent evaporation, spontaneous emulsification, solvent diffusion, salting out/ emulsification-diffusion and polymerization, have been used to prepare PNCs [35]. An illustration of PNCs is sown in **Fig. 8**.

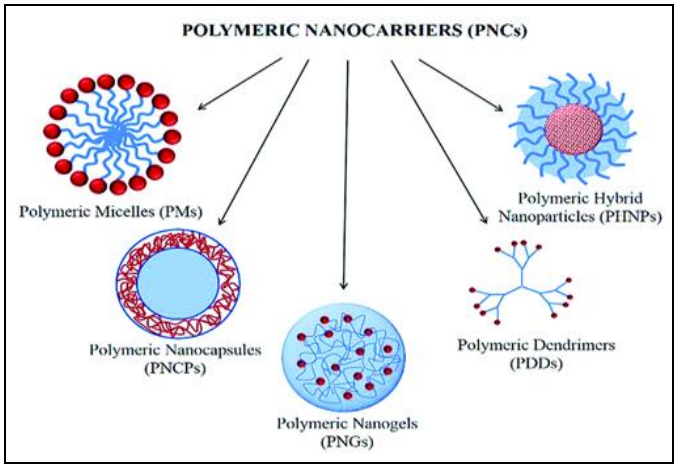

FIG. 8: POLYMERIC NANOCARRIERS (PNCs)

Advances in polymer science and engineering have resulted in the development of smart polymer (stimuli-sensitive polymer), which can change its physicochemical properties in response to environmental signals. Physical (temperature, ultrasound, light, electricity and mechanical stress), chemical (pH and ionic strength) and biological signals (enzymes and biomolecules) have been used as triggering stimuli. Various monomers having the sensitivity to specific stimuli can be tailored to a homopolymer in response to a particular signal or copolymers answering multiple stimuli. The versatility of polymer sources and their easy combination make it possible to tune up polymer sensitivity in response to a given stimulus within a narrow range, leading to more accurate and programmable drug delivery. PNCs can be categorized based on three therapeutic agent-incorporation mechanisms. The first includes polymeric carriers that use covalent chemistry for direct therapeutic agent conjugation (*e.g.*, linear polymers). The second group includes hydrophobic interactions between therapeutic agents and nanocarriers (*e.g.*, polymeric micelles from amphiphilic block copolymers). Polymeric nanocarriers in the third group include hydrogels, which offer a water-filled depot for hydrophilic therapeutic agent encapsulation [24].

Therapeutic agents may be released from PNCs by desorption, diffusion, or erosion in the target tissue. The mechanism of 5-fluorouracil controlled release from the biodegradable thermo-responsive chitosan-g-poly (N-vinyl caprolactam)-bio-polymeric nanocarrier was assumed to occur by swelling followed by conformational changes during a lower critical solution temperature transition (LCST). The *in-vitro* drug release showed a significant release above LCST. High toxicity to cancer cells, compared to normal cells, was observed [36]. PNCs can be coated with nonionic surfactants to reduce immunological interactions [37].

Some representative examples of marketed polymeric nanocarriers-based therapeutic agents are shown in **Table 3**.

TABLE 3: SOME REPRESENTATIVE EXAMPLES OF MARKETED POLYMERIC NANOCARRIERS-BASED THERAPEUTIC AGENTS

Brand name	Therapeutic agent	Indications
Adagen®	Adenosine deaminase	Adenosine deaminase enzyme deficiency[38]
Onscaspar®	L-asparaginase	Acute lymphoblastic leukemia[39]
Pegasys®	Polyethylene gylated IFN-α-2a	Hepatitis C[40]

7.1.3.1. Polymeric Micelles: Polymeric micelles can be employed to administer chemotherapeutics in a somewhat controlled and targeted manner with a high concentration in the tumor cells and reduced side effects. As they can accumulate in tumor tissues due to increased vascular permeability. However, the targeting ability of polymeric micelles is limited due to low therapeutic agent loading capabilities, which cause the loaded therapeutic agent to be released before getting to the site of action [41]. Micelles are formed when an amphiphilic surfactant or polymeric molecules spontaneously associate in an aqueous medium to form core-shell structures or vesicles **Fig. 8**.

Polymeric micelles are formed from amphiphilic copolymers, such as poly (ethylene oxide)-poly (benzyl-L-aspartate) and poly (N-isopropyl acrylamide)-polystyrene, and are more stable than surfactant micelles in physiological solutions [42]. The size of polymer micelles generally ranges from 20 nm to 100 nm, and recognition by reticuloendothelial systems, the primary reason for

the removal of particles from the blood compartment, is considerably lowered for particles less than 100 nm.

Another advantage arises from the specific core-shell structure of the micelles [43]. Polymeric micelles seem to be one of the best carriers for delivering hydrophobic drugs. The functional polymer micelles possess several advantages such as high drug efficiency, targeted delivery, and minimized cytotoxicity as well as less tendency to be cleared by the reticuloendothelial systems. While low therapeutic agent loading capabilities pose a disadvantage [44].

A representative example of a marketed polymeric micelle-based therapeutic agent is shown in **Table 4**.

TABLE 4: A REPRESENTATIVE EXAMPLE OF MARKETED POLYMERIC MICELLE-BASED THERAPEUTIC AGENT

Brand name	Therapeutic agent	Indications
Genexol-PM®	Paclitaxel	Cancer chemotherapy[45]

7.1.3.2. Dendrimers: Dendrimers are a class of regularly and highly branched spherical nanocarriers polymers, with a unique tree-like structure. Their size and shape can be precisely controlled. Dendrimers are very uniform, and they are commonly created with dimensions ranging from 1 to 10 nm. Their globular structures and the presence of internal cavities enable drugs to be encapsulated within the macromolecule interior and are used to provide controlled release from the inner core [46].

Schematic illustration of Dendrimers is shown in **Fig. 9**.

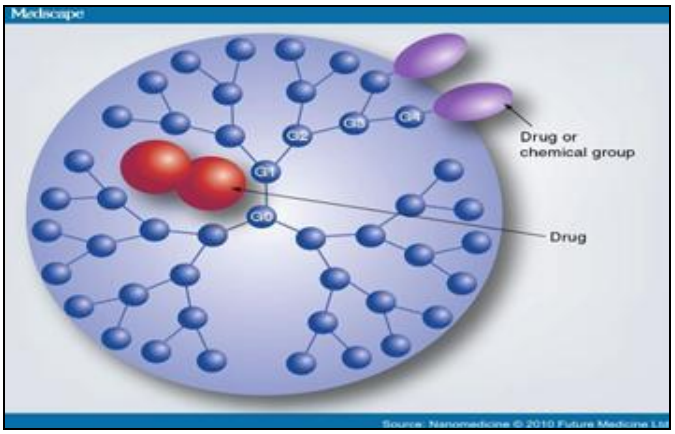

FIG. 9: SCHEMATIC ILLUSTRATION OF DENDRIMERS

Although the small size of dendrimers limits high therapeutic agent incorporation, their highly branching nature allows therapeutic agent loading onto the outside surface of the structure *via* covalent binding or electrostatic interactions [47].

Either divergent or convergent approaches can synthesize dendrimers. In the divergent approach, dendrimers are synthesized from the core and further built to other layers called generations. However, this method provides a low yield because the reactions that occur must be conducted on a single molecule processing a large number of equivalent reaction sites. Also, a large amount of reagents is required for the latter stages of synthesis, resulting in complication of purification. For the convergent method, synthesis begins at the periphery of the dendrimer molecules and stops at the core. In this approach, each synthesized generation can be subsequently purified [48].

Some examples of dendrimers include, polyamidoamine (PAMAM), poly propylene-imine (PPI) and biomolecules derived dendrimers such as amino acid, carbohydrate-modified, nucleic acids–nucleobases and polyester dendrimers. Advantages of dendrimers include the possession of a three-dimensional architecture, with high structural and chemical homogeneity, controlled degradation and high ligand density. The step-by-step synthesis of dendrimers allows for site-selective functionalization. The choice of polymer used in the dendritic system plays heavily into its utility as a therapeutic agent carrier owing to the association between the polymer and agent molecule. Bio-distribution and pharmacokinetic properties of dendrimers can be modified by controlling dendrimer size and confirmation [49-51].

Dendrimers can be used as nanocarriers for anti-cancer agents, as they enhance solubility, intracellular permeability and therapeutic agent delivery [52-54]. Therapeutic agents can be encapsulated inside the dendrimer network or form linkages (covalently or non-covalently) on the dendrimer surface [55]. Furthermore, selective functionalization of the dendrimer surface with specific ligands can enhance potential targeting. For example, *in-vitro* and *in-vivo* results of polyamidoamine dendrimers conjugate containing folic acid as the targeting agent and methotrexate as

the therapeutic agent revealed that the dendrimers conjugate was preferentially cytotoxic to the target cells [56]. The polyamidoamine dendrimer conjugated with an anti-prostate specific membrane antigen antibody was also demonstrated. The Antibody-dendrimer conjugate specifically bound to anti-prostate specific membrane antigen-positive, but not negative; cell lines [57]. However, dendrimer toxicity and immunogenicity are the main concerns when they are applied for drug delivery. Since the clinical experience with dendrimers has so far been limited; it is hard to tell whether the dendrimers are intrinsically 'safe' or 'toxic' (23). PAMAM dendrimers have also been tested as genetic material carriers. They have terminal amino groups, which can interact with phosphate groups of nucleic acids [58, 59].

7.1.4. Solid Lipid Nanocarriers (SLN): SLN general ingredients include solid lipid, emulsifier, and water. The term lipid is used generally in a very broad sense and includes triglycerides (*e.g.* tristearin, hard fat), partial glycerides (*e.g.*, Imwitor), polyethylene gylated lipids, fatty acids (stearic acid), steroids (*e.g.*, cholesterol) and waxes (*e.g.*, cetyl palmitate). SLN combine the advantages yet without inheriting the disadvantages of other colloidal carriers [60]. Advantages of SLN are the use of physiological lipids, the avoidance of organic solvents, a potentially wide application spectrum and the high-pressure homogenization as an established production method. Additionally, improved bioavailability, protection of sensitive drug molecules from the external environment (moisture, light) and even controlled release characteristics were claimed by incorporation of poorly water-soluble therapeutic agents in the solid lipid matrix. Common disadvantages of SLN are their unpredictable gelation tendency, their unexpected dynamics of polymorphic transitions and their inherent low incorporation rate due to the crystalline structure of the solid lipid [61].

Similar to microemulsions and liposomes, SLN is composed of toxicologically acceptable excipients and can be manufactured by high-pressure homogenization on a large industrial scale. High-pressure homogenization is an essential technique widely used in various industries and provides distinct advantages, compared to lipid particle production by sonication or *via* microemulsions [62].

As shown in **Table 1**, SLN joins the advantages of colloidal lipid emulsions with those of solid matrix particles. Their matrix should be able to defend labile agents from degradation and to regulate drug release profiles [63]. Because of the lipophilic nature of their matrix, solid triglyceride nanoparticles are found useful especially for the management of lipophilic therapeutic agents. Moreover, SLN can be employed to increase the specificity towards cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes and to protect them against enzyme inactivation [64].

A representative example of marketed solid lipid nanocarriers-based therapeutic agent is shown in **Table 5**.

TABLE 5: A REPRESENTATIVE EXAMPLE OF MARKETED SOLID LIPID NANOCARRIERS-BASED THERAPEUTIC AGENT

Brand name	Therapeutic agent	Indications
Amphotec®	Amphotericin B	Fungal infections [65]

7.1.5. Protein-based Nanocarriers: Being biocompatible and safe for human applications, protein polymers from animal and plant sources are promising materials for designing nanocarriers. However, it is essential to ensure that there is batch-to-batch consistency concerning purity and composition. This can be addressed using recombinant technology, in which the composition of the protein can be precisely defined and tailored for specific therapeutic agent delivery applications such as therapeutic agent release, and targeting. Alternatively, the protein polymers can also be combined with other synthetic polymers to suit specific drug delivery applications. An important issue in protein polymers is the possibility of inducing an immune or inflammatory response. The protein may behave differently in a particulate form as opposed to the protein in the soluble form.

Furthermore, the nanocarrier characteristics such as size, charge, and hydrophobicity may play a significant role in phagocytic uptake and initiating a subsequent immune response. This remains to be investigated systematically. Although protein polymers are biodegradable, it is essential to ensure that there is no premature enzymatic break down of the protein nanoparticles in the systemic

circulation. Surface modification of the protein nanoparticles can be used to address this issue. Of the various proteins, gelatin and albumin have been widely studied for drug delivery applications. The commercial success of albumin-based nano-carriers has created an interest in other proteins. An increased understanding of the physicochemical properties coupled with the developments in rDNA technology will open up new opportunities for protein-based nanoparticulate systems [66].

Hydrophobic drugs, such as taxanes, are highly active and widely used in a variety of solid tumor therapies. Both paclitaxel and docetaxel, which are the commercially available taxanes for clinical treatments, are hydrophobic. Because of their solubility problems, they have been formulated as suspensions using nonionic surfactants. However, these surfactants are associated with hypersensitivity reaction and toxic side effects on tissues. To decrease toxicity, albumin conjugated with paclitaxel has been formulated, yielding nano-carriers approximately 130 nm in size and approved by the FDA for breast cancer treatment. In addition to reduced toxicity, albumin-paclitaxel has been found to bind with the albumin receptor (gp60) on endothelial cells, with further extravascular transport, resulting in an increase in drug concentration at tumor sites without hypersensitivity reactions [67-71]. The albumin-paclitaxel complex is approved for the treatment of metastatic breast cancer [72-73].

A representative example of a marketed albumin-based therapeutic agent is shown in **Table 6**.

TABLE 6: A REPRESENTATIVE EXAMPLE OF MARKETED ALBUMIN-BASED THERAPEUTIC AGENT

Brand name	Therapeutic agent	Indications
Abraxane®	Paclitaxel	Metastatic breast cancer [72-73]

7.1.6. Carbon Nanotubes (CNTs): CNTs are characterized by unique architecture formed by rolling of single (single-walled carbon nanotubes (SWNCTs) or multi-walled carbon nanotubes (MWCNTs) layers of graphite with an enormous surface area and an excellent electronic and thermal conductivity [74].

Biocompatibility of nanotubes may be improved by chemical modification of their surface [75]. Such adjustment can be implemented by covalent anchoring of polyamidoamine (PAMAM) dendrimers [76], amphiphilic di-block copolymers [77], or PEG layers [78] on CNTs surface or dispersion within a hyaluronic acid matrix. Due to their mechanical strength, SWCNTs have been used as a support to improve properties of other carriers, *e.g.*, polymeric or non-polymeric composites [79].

CNTs have been extensively studied for delivery applications, because they can be surface functionalized for the grafting of nucleic acids, peptides and proteins [80, 81]. The size, geometry and surface characteristics of single-wall nanotubes (SWNTs), multiwall nanotubes (MWNTS) and C60 fullerenes make them appealing for therapeutic agent carrier. For example, paclitaxel-conjugated SWNTs have shown promising results for *in-vivo* cancer treatment, as evidenced by its ability to slow down tumor growth at a low paclitaxel [73].

However, the primary drawback of CNTs appears to be their toxicity. Experiments have shown that CNTs can lead to cell proliferation inhibition and apoptosis (cell death). The toxicity of CNTs increases significantly when carbonyl, carboxyl and hydroxyl functional groups are present on their surface [82-83]. To promote the application of CNTs for therapeutic agent delivery, researchers have functionalized their surface, rendering them benign [84]. Unfortunately, concerns that functionalized CNTs may revert to a toxic state if the functional group detaches has limited the use of these modified CNTs for biomedical applications. Given the mounting evidence demonstrating the toxicity of carbon CNTs, the enthusiasm to develop them for therapeutic agent delivery has decreased significantly in recent years [23].

There are three ways of drug immobilization in carbon nanocarriers, which are encapsulation of a drug in the carbon nanotube [85, 86], chemical adsorption on the surface or in the spaces between the nanotubes (by electrostatic, hydrophobic and hydrogen bonds) [87], and attachment of active agents to functionalized carbon nanotubes (f-CNTs).

Encapsulation has the advantage over the two remaining methods as the drug is protected from degradation during its transport to the cells and is released only in specific conditions [88].

Some examples of therapeutic agents that were attached to CNTs are listed in **Table 8**.

TABLE 8: CARBON NANOTUBES AS THERAPEUTIC AGENT DELIVERY SYSTEMS

Type of CNTs	Therapeutic agent	Method of immobilization
MWCNTs	Cisplatin	Encapsulation via capillary forces [89]
f-CNTs	Amphotericin B	Conjugated to carbon nanotubes [90]
SWCNTs	Cisplatin-EGF	Attachment to carbon nanotubes *via* amide linkages [91]
MWCNTs	Dexamethasone	Encapsulation [92]

MWNTs = multi-walled nanotubes; f-CNTs = functionalized carbon nanotubes; SWCNTs single-walled nanotubes.

Schematic illustration of the therapeutic agent delivery process from CNTs is described in **Fig. 10**.

(a) CNTs surface is linked with a chemical receptor (Y) & therapeutic agent (•) are loaded inside, (b) open end of CNTs is capped, (c) drug-CNTs carrier is introduced in the body & reaches the target cells due to chemical receptor on CNTs surface, (d) cell internalizes CNTs *via* endocytosis pathway (for example), (e) capsule is removed or biodegrades inside the cell, the a therapeutic agent is released.

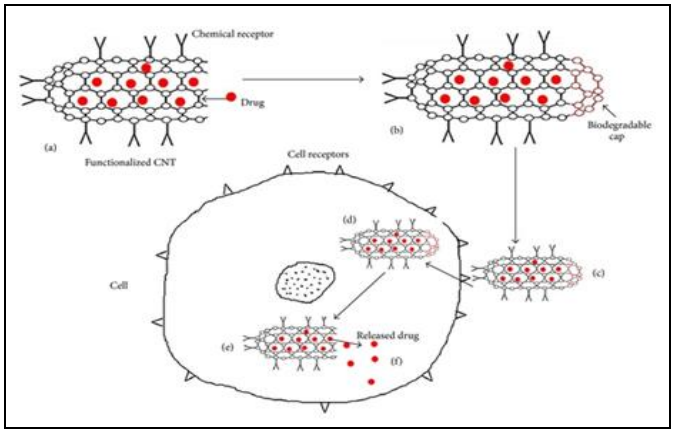

FIG. 10: SCHEMATIC ILLUSTRATION OF THERAPEUTIC AGENT DELIVERY PROCESS FROM CNTs

7.1.7. Magnetic Nanoparticles (MNPs): MNPsexhibit a wide variety of properties that make them highly promising carriers for therapeutic agent delivery. These properties include easy handling with the aid of an external magnetic field, the possibility of using passive and active therapeutic agent delivery strategies, the ability to enhance the uptake by the target tissue resulting in effective treatment at the therapeutically optimal doses [87]. However, certain disadvantages lie with magnetic nanocarriers which are associated with inappropriate features of MNPs or inadequate magnet system. MNPs, for instance, tend to aggregate into larger clusters losing the specific properties connected with their small dimensions and making physical handling difficult. In turn, the magnetic force may not be strong enough to overcome the force of blood flow and to accumulate magnetic therapeutic agents only at the target site. Therefore, designing magnetic therapeutic agent delivery systems requires taking into consideration many factors, *e.g.*, magnetic properties and size of particles, the strength of magnetic field, therapeutic agent loading capacity, the place of accessibility of target tissue, or the rate of blood flow [93].

Depending on magnetic properties, MNPs can be divided into pure metals such as cobalt, nickel [94], manganese [95], and iron [96]. Iron oxide nanoparticles, due to the favorable features they exhibit, are the only type of magnetic nanoparticles approved for clinical use by the FDA. These features include facile single step synthesis by alkaline co-precipitation of Fe^{2+} and Fe^{3+}, [97] chemical stability in physiological conditions [98] and possibility of chemical modification by coating the iron oxide cores with various shells, *i.e.*, silane [99], golden [100], polymers [101], or dendrimers [102] **Fig. 11**.

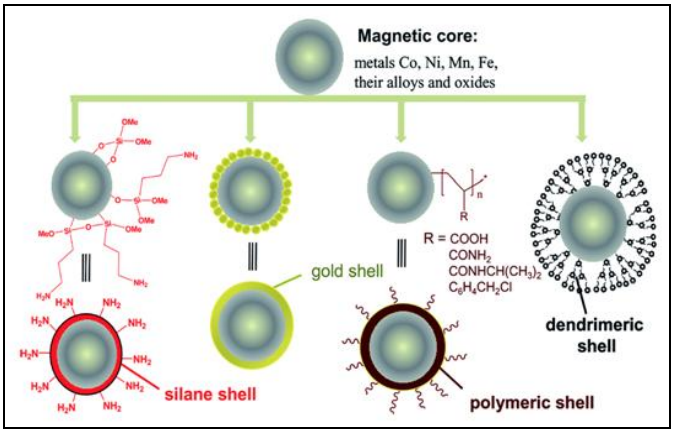

FIG. 11: MAGNETIC NANOPARTICLES WITH VARIOUS SHELLS

Also, iron oxides-magnetite and magnemite-occur naturally in human heart, spleen and liver [103], which indicates their biocompatibility and non-toxicity at a physiological concentration. Connecting a therapeutic agent with MNPs may be achieved by covalent binding, electrostatic

interactions [99], adsorption [104], or encapsulation process [105]. Targeting of therapeutic agent-MNPs conjugates to diseased tissues, depending on their size and surface chemistry, can be carried out by a passive or active mechanism. Passive targeting is a result of enhanced vascular permeability and retention (EPR) of tumor tissues. The active strategy relies on the attraction of nanoparticles to the affected site by using recognition ligands (*e.g.*, antibodies) attached to the surface of MNPs and by the handling of an external magnetic field [97].

Mechanisms of bio-distribution of MNPs are closely associated with their surface chemistry and hydrodynamic sizes [106]. Plasma proteins can quickly opsonize magnetic nanoparticles, and subsequently removed from the bloodstream by macrophages of the reticuloendothelial system [107]. The greatest overall uptake of nanoparticles can be observed in liver and spleen [108]. Therapeutic activity of some therapeutic agents incorporated into iron oxide nanocarriers has been tested and reported **Table 9**.

TABLE 9: SOME EXAMPLES OF THERAPEUTIC AGENTS INCORPORATED INTO IRON OXIDE NANOCARRIERS

Therapeutic agent	Therapeutic activity	Nanocarrier (core @ shell)
Ciprofloxacin	antibiotic	Fe_3O_4 @ poly(vinyl alcohol)-poly(methyl methacrylate) [109]
5-Fluorouracil	anticancer	Fe_3O_4 @ ethyl cellulose[110]
Cisplatin	anticancer	Fe_3O_4 @ poly e-caprolactone[111]
Doxorubicin	Antineoplastic	Fe_3O_4 @ gelatin[112]
Dopamine	Anti-Parkinsonian	Fe_3O_4 @ silica (diatom)[113]

8. The Role of Nanocarriers in Cancer Targeted Therapeutic Agent Delivery: The use of nanocarriers as drug delivery systems for chemotherapeutic agents can improve the overall pharmacological properties of commonly used drugs in chemotherapy. The clinical success, as well as the ease with which surface modifications can be made to nanocarriers to accommodate targeting ligands, have made them in particular attractive candidates for future work involving targeted drug delivery [114].

Nanocarriers can serve as customizable, targeted delivery vehicles capable of carrying large doses of chemotherapeutic agents into malignant cells while sparing healthy cells, hence greatly reducing side effects that are associated with many cancer therapies. Some nanocarriers, such as liposomes, nanoemulsions, dendrimers, carbon nanotubes, and polymeric micelles can be targeted to cancer cells. Such an increase in the selectivity of therapeutic agents towards cancer cells will reduce the toxicity to normal tissues. Local therapeutic agent-targeting results in increased local concentrations and provides strategies for more specific therapy. Nanocarriers have specific characters as tools to implement such targeting strategies. Such characters include their small size which facilitates penetration of cell membranes, binding and stabilization of proteins, and lysosomal escape after endocytosis. The entrapment of chemotherapeutics in nanocarriers like liposomes has been extensively studied [115-116]. Liposomes as nanocarriers have the advantage of being small, flexible and biocompatible thus being able to pass along the smallest arterioles and endothelial fenestrations without causing clotting [116]. In principle, the incorporation of polyethylene glycol to liposomes (Doxil®) causes the nanocarriers to remain in the blood circulation for an extended period of time, allowing for frequent passages on compromised endothelia surrounding tumor tissues and subsequent continuous accumulation at target tumor tissue in the phenomenon known as enhanced permeability and retention (EPR) effect.

In this scheme, most of the dose remains in the central compartment (the blood), and only less than 20% of the dose is delivered to the liver, along with further significant time-dependent bio-distribution into the tumor site. There is also established clinical evidence demonstrating that PEGylated liposomal doxorubicin (Doxil®) is less cardiotoxic than conventional doxorubicin, and direct comparisons between PEGylated liposomal doxorubicin and conventional doxorubicin showed comparable efficacies, but a significantly lower risk for cardiotoxicity with the polyethylene gylated liposomal formulations of doxorubicin [117]. A similar long-circulating liposomal platform (Marqibo®) was also demonstrated to be successful in achieving higher exposures in tumors and lymph

nodes than in nerves, proving to be less neurotoxic and more active than non-liposomal vincristine in preclinical models and relapsed lymphoma patients [14]. On the other hand, administration of drugs in nanoformulations may also result in new toxicities. The most common adverse events associated with PEGylated liposomal doxorubicin are hand-foot syndrome and stomatitis, which have not been reported with conventional free doxorubicin. Since these toxicities are schedule and dose-dependent, they were suggested to be related to lateral extravasation of the stealth liposomal carriers into skin and GI tract mucosa, followed by slow leakage of vesicant doxorubicin. PEGylated liposomal doxorubicin is generally well tolerated, and its side-effect profile compares favorably with those of other chemotherapies used in indicated treatment protocols [118]. Recently, polyethylene glycol-phosphatidylethanolamine liposomes conjugated with triphenylphosphonium, have been examined using paclitaxel (anti-tumor) as a model drug. It was found that such liposomal delivery system provided an efficient mitochondrial targeting and highly reduced toxicity [5].

The formulation of the chemotherapeutic agent paclitaxel (Taxol), as nanoemulsions have resulted in enhanced cytotoxicity for tumor cells *in-vitro*, and at the same time an increased sustainable therapeutic efficacy, as reflected in an increased area under the curve (AUC), in an *in-vivo* animal model [119]. To target drugs to the site of action, the drug can be conjugated to a tissue or cell specific ligand that reaches the target organs. Such ligands, being coupled to nanocarriers, will facilitate recognition of their receptors on target neoplastic cells with greater specificity than normal cells, and thus, targeted delivery of the chemotherapeutics into cancer cells. Ligands capable of recognizing tumors include antibodies, peptides, saccharides, hormones, and some low-molecular-weight compounds such as folate and some vitamins [120].

In an attempt to decrease the toxicity of paclitaxel, the drug has been conjugated with albumin, yielding nanoparticles, approximately 130 nm in size that has been approved by the FDA for breast cancer treatment [52-54]. The albumin-paclitaxel conjugate (Abraxane®), has been found to bind with the albumin receptor (gp60) on endothelial cells, with further extravascular transport, resulting in an increase in drug concentration at tumor sites without hypersensitivity reactions [54-56].

Drug molecules associated with dendrimers have been used for cancer treatment [121]. Selective functionalization of the dendrimer surface with specific ligands can enhance potential targeting. For example, *in-vitro* and *in-vivo* results of polyamidoamine dendrimers encapsulating methotrexate conjugated with folic acid as the targeting agent revealed that the dendrimers conjugate was preferentially cytotoxic to the target cells [54]. Similarly, the encapsulation of the anticancer cisplatin in polyamidoamine dendrimer was observed to exhibit several advantages, such as sustained drug release, higher accumulation of the drug in solid tumors, and lower toxicity in all organs compared with free cisplatin [122, 123].

The size, geometry and surface characteristics of single-wall nanotubes (SWNTs) make them appealing for chemotherapeutic carrier usage. For example, paclitaxel-conjugated SWNTs have shown promising results for *in-vivo* cancer treatment. SWNT delivery of paclitaxel provides markedly improved treatment efficacy as evidenced by its ability to slow down tumor growth at a low drug dose [59]. The superparamagnetic properties of iron (II) oxide nanoparticles can be used to guide microcapsules in place for delivery by external magnetic fields. Another advantage of using magnetic nanoparticles is the ability to heat the particles after internalization, which is known as the hyperthermia effect.

For example, a grafted thermos-sensitive polymeric system had been developed by embedding Fe-Pt nanoparticles in poly (N-isopropyl acrylamide)-based hydrogels, which can be triggered to release the loaded therapeutic agent by inducing an increase in temperature based on a magnetic thermal heating event [124]. The main benefits of superparamagnetic nanoparticles over classical cancer therapies are minimal invasiveness, accessibility of hidden tumors and minimal side effects. Also, targeted paramagnetic particles provide a powerful strategy for localized heating of cancerous cells compared to conventional heating of a tissue by, for example, microwaves or laser light that results in the destruction of healthy tissue surrounding the tumor [23].

Polymeric micelles can reach parts of the body that are poorly accessible to liposomes; accumulate more than free drugs in tumor tissues due to increased vascular permeability [125]. Thus, polymeric micelles can be employed to administer chemotherapeutics in a controlled and targeted manner with a high concentration in the tumor cells and reduced side effects.

However, the targeting ability of polymeric micelles is limited due to low drug loading and low drug incorporation stability that cause the loaded drug to be released before getting to the site of action. Consequently, manipulation of the production parameters and the design of the inner core can improve drug loading and drug incorporation stability, respectively. Lipid moieties, such as cholesterol and fatty acylcarnitines, can also be employed to impart good stability to the polymeric micelles. This is based on increased hydrophobic interaction between the polymeric chains in the inner core due to the presence of fatty acid acyls [126].

Some examples of nanocarrier-based chemo-therapeutics that are clinically approved, for cancer treatment are shown in **Table 9**.

TABLE 9: SOME EXAMPLES OF NANOCARRIER-BASED CHEMOTHERAPEUTICS THAT ARE CLINICALLY APPROVED, FOR CANCER TREATMENT

Nanocarrier	Therapeutic agent	Therapeutic activity
Liposomes	Doxorubicin (Doxil®)	Ovarian cancer, Kaposi's sarcoma and breast cancer [33]
Liposomes	Doxorubicin (Caelyx®)	Ovarian cancer, Kaposi's sarcoma and breast cancer [34]
Liposomes	Cytarabine (DepoCyt®)	Lymphomatous meningitis [35]
Liposomes	Daunorubicin (Daunoxome®)	Kaposi's sarcoma [36]
Polymeric micelle nanocarriers	Paclitaxel (Genexol-PM®)	Metastatic breast cancer [48]
Albumin-based nanocarrier	Paclitaxel (Abraxane ®)	Metastatic breast cancer [71-72]
Polymeric nanocarrier (polylactide-co-glycolide)	Goserelin acetate (Zoladex®)	Prostatic carcinoma [127]
Polymeric nanocarrier (polylactide-co-glycolide)	Leuprolide acetate (Lupron Depot®)	Advanced prostatic carcinoma [128]
Polymeric nanocarrier (polyethylene glycol)	L-Asparaginase (Oncaspa®)	Acute lymphoblastic leukaemia [129]
Polymeric nanocarrier (polyethylene glycol) –pegylated-	α-Interferon (PEG intron®)	Chronic hepatitis C in adults & melanoma [130]
Polymeric nanocarrier (styrene maleic anhydride)	Neocarzinostatin (Zinostatin®)	Hepatocellular carcinoma [131]
IL2 Fusion Protein-based nanocarrier	Diptheria toxin (Ontak®)	Lymphoma [132]
Anti-CD20	Yttrium-90/Indium-111 (Zevalin®)	Lymphoma [133]
Anti-CD20	Iodine-131(Bexxar®)	Lymphoma [134]

9. Challenges and Impact of Nanocarriers: The use of nanotechnology in drug delivery is set to spread rapidly. For decades' pharmaceutical scientists have been using nanocarriers to reduce toxicity and side effects of drugs. Up to recently, it was not realized that these carriers themselves might impose risks to the patient. The type of hazards that are introduced by using nanoparticles for drug delivery are beyond that posed by conventional hazards imposed by chemicals in delivery matrices. However, so far, the scientific paradigm for the possible (adverse) reactivity of nanoparticles is lacking, and we have little understanding of the basics of the interaction of nanoparticles with living cells, organs and organisms. A conceptual understanding of biological responses to nanomaterials is needed to develop and apply safe nanocarriers in drug delivery in the future. Furthermore, a close collaboration between those working in drug delivery and particle toxicology is necessary for the exchange of concepts, methods, and expertise to move this issue ahead [116].

Although there are several nanocarrier-based therapeutic agents which are currently being developed and are under preclinical evaluation, only a handful of nanocarriers drug delivery systems are available on the market, *e.g.,* liposomal conjugates: Doxil® (doxorubicin) or Daunoxome®

(daunorubicin). This is because nanocarrier-based drug delivery systems do have some drawbacks and limitations. Some of them arise from scaling up problems. For instance, small size and large surface area of nanocarrier-based targeting system can lead to aggregation, making physical handling difficult. Nanocarrier-conjugates can be phagocytosed by cells whereas their intracellular degradation may cause cytotoxic effects. Other issues include low drug loading capacity and poor ability to control the size distribution of carriers. Furthermore, there is a lack of technological methods, which will lead to nanodevices of approvable quality. Despite all the limitations and shortcomings, nanocarriers, which respond to slight changes in the local cellular environment, have the potential to resolve many of the current drug delivery problems. However, before the ongoing research brings a clinically useful drug delivery system, challenges which include developing toxicity testing protocols, improving biocompatibility, drug loading, targeting, transport, and release, controlling interaction with biological barriers, detecting and monitoring exposure level and assessing the impact on the environment have to be met [5].

10. Future Prospects: The ultimate goal of nanocarriers as delivery systems is to develop clinically useful formulations for treating diseases. As nanomedical applications for personalized medicine become more advanced and multifunctional, they may increasingly challenge traditional regulatory categories and criteria. Therefore, it will be critical for regulatory systems to provide oversight and well-defined evaluation pathways for nanomedicine products, while remaining adaptive to rapidly emerging nanomedical technologies and products [24].

To transform nanotechnologies from basic research into clinical products, it is essential to understand how the bio-distribution of nanocarriers, which is primarily governed by their ability to negotiate biological barriers, affects the body's complex biological network, as well as mass transport across compartmental boundaries in the body. Moreover, the healthy growth of this field depends on establishing a toxicology database to support safety determinations and risk assessments. The database should include toxicity as a function of material, size, shape, cell type or animal, duration of exposure and the methods used to assay toxicity. Also, the ability to scale up the production of drug particles is required. The manufacturing complexity of nanocarriers may be an obstacle to confronting generic drug companies. Lastly, storage and handling protocols must be considered. With such a database, the translation of biomedical nanotechnology from the laboratory to the general public will be significantly accelerated.

Realizing such a goal requires harmonized efforts among scientists in various disciplines, including medicine, materials science, engineering, physics, and biotechnology. Better cross training would produce better proposals with a higher likelihood of success. Experts from different disciplines need to work together to translate novel laboratory innovation into commercially viable medical products. Also, continuous cooperation between regulatory agencies and the pharmaceutical industry is necessary [24].

Nanocarriers can also be applied to reformulate existing therapeutic agents, thereby enhancing their performance, improving their acceptability by increasing effectiveness, as well as increasing safety and patient compliance, and ultimately reducing health care costs [69, 74]. Nanocarriers can also act as potential delivery systems for treatment and management of chronic diseases such as cancer, HIV/AIDS and diabetes [54]. Among the essential prospects of nanotechnology are the fabrication of devices and drug delivery systems for better monitoring, diagnosis, and treatment of chronic diseases.

CONCLUSION: The application of nano-technology to drug delivery is widely expected to create novel therapeutics, capable of changing the landscape of pharmaceutical and biotechnology industries. Nanocarriers drug delivery strategies are beginning to make a significant impact on global pharmaceutical planning and marketing. Therefore, there is a great need to develop suitable and safe drug delivery systems that distribute the therapeutically active drug molecule only to the site of action, without affecting healthy organs and tissues. Nanocarrier drug delivery systems should also have the ability to improve the pharmacokinetics and increase the bio-distribution of therapeutic agents to target organs, which will

result in improved efficacy. The field of nanotechnology has a bright future with the emergence of several promising approaches for delivery of therapeutic agents and using the advantages of the nanocarriers.

ACKNOWLEDGEMENT: I acknowledge the support of the College of Pharmacy and Health Sciences, Ajman University.

CONFLICT OF INTEREST: The author declared no conflict of interest.

REFERENCES:

1. Lobatto M, Fuster V, Fayad Z and Mulder W: Perspectives and opportunities for nanomedicine in the management of atherosclerosis. Nat Rev Drug Disc 2011; 10(11): 835-52.
2. Riehemann K, Schneider SW, Luger TA, Godin B, Ferrari M and Fuchs H: Nanomedicine - challenge and perspectives. Ange Chem Int Ed Engl 2009; 48(5): 872-97.
3. Wagner V, Dullaart A, Bock A and Zweck A: The emerging nanomedicine landscape. Nat Biotechnol 2006; 24(10): 1211-17.
4. NIH Roadmap Initiatives. http://nihroadmap.nih.gov /initiatives.asp
5. Wilczewska AZ, Niemirowicz K and Karolina H: Markiewicz, and Halina Car. Nanoparticles as drug delivery systems. Pharmacological Reports 2012; 64: 1020-37.
6. Nevozhay D, Kañska U, Budzyñska R and Boratyñski J: Current status of research on conjugates and related drug delivery systems in the treatment of cancer and other diseases. Postepy Hig Med Dosw 2007; 61: 350-60.
7. Suri SS, Fenniri H and Singh B: Nanotechnology-based drug delivery systems. J Occup Med Toxicol 2007; 2: 16.
8. Ai J, Biazar E, Montazeri M, Majdi A, Aminifard S, Safari M and Akbari HR: Nanotoxicology and nanoparticle safety in biomedical designs. Int J Nanomedicine 2011; 6: 1117-27.
9. Shi L, Fleming CJ, Riechers SL, Yin NN, Luo J, Lam KS and Liu GY: High-resolution imaging of dendrimers used in drug delivery *via* scanning probe microscopy. J Drug Deliv 2011; 2011: 254095. (doi: 10.1155/2011/254095).
10. Dhawan S, Singla AK and Sinha VR: Evaluation of mucoadhesive properties of chitosan microspheres prepared by different methods. AAPS Pharm Sci Tech 2004; 5(4): e67.
11. Washington C: Drug release from microparticulate systems in: Microencapsulation: Methods and Industrial Applications. Edited by Benita S, New York: Marcel Dekker, 2nd edition, 1996: 156-75.
12. Murthy RSR: *In-vitro* evaluation of NPDDS, drug delivery nanoparticles formulation and characterization edited by Yashwant Pathak Sullivan and Deepak Thassu, Informa Healthcare USA, Inc., 1st edition, 2009; Chapter 10: 156-68.
13. Murthy RSR and Pathak Y: *In-vitro* blood interaction and pharmacological and toxicological characterization of nanosystems, drug delivery nanoparticles formulation and characterization edited by Yashwant Pathak Sullivan and Deepak Thassu, Informa Healthcare USA, Inc, 1st edition, 2009; Chapter 12: 190-18.
14. Elbayoumi TA and Torchilin VP. Current trends in liposome research. Methods Mol Biol 2010; 605: 1-27.
15. Damajanov N, Fishman MN and Steinberg JL: Final results of a Phase I study of liposome-entrapped paclitaxel (LEP-ETU) in patients with advanced cancer. Proc Am Soc Clin Oncol 2005; 23: 147s.
16. Cheisa M, Garg J, Kang YT and Chen G: Thermal conductivity and viscosity of water-in-oil nanoemulsions. Colloids and Surfaces A: Physicochemical and Engineering Aspects 2008; 326(1-2): 67-72.
17. Orive G, Hernandez RM, Gascon AR and Pedraz JL. Micro and nano drug delivery systems in cancer therapy 2005; 3: 131-38.
18. Kharb V, Bhatia M, Dureja H and Kaushik D: Nanoparticle technology for the delivery of poorly water-soluble drugs. Pharm Technol 2006; 30(2): 82-92.
19. Merisko-Liversidge E, Liversidge GG and Cooper ER: Nanosizing: a formulation approach for poorly-water-soluble compounds. Eur J Pharm Sci 2003; 18: 113-20.
20. Kipp JE: The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. Int J Pharm 2004; 284: 109-22.
21. Baba K, Pudavar HE and Roy I: A new method for delivering a hydrophobic drug for photodynamic therapy using pure nanocrystal form of the drug. Mol Pharm 2007; 4(2): 289-97.
22. Junghanns JA and Muller RH: Nanocrystal technology, drug delivery, and clinical application. Int J Nanomed 2008; 3: 295-10.
23. Bamrungsap S, Zhao Z, ChenT, Wang L, Chunmei Li C, Ting F and Weihong T: Nanotechnology in therapeutics: a focus on nanoparticles as a drug delivery system. Nanomedicine 2012; 7(8): 1253-71.
24. Dos Santos Giuberti C, de Oliveira Reis EC, Ribeiro Rocha TG, Leite EA, Lacerda RG, Ramaldes GA and de Oliveira MC: Study of the pilot production process of long-circulating and pH-sensitive liposomes containing cisplatin. J Liposome Res 2011; 21: 60-69.
25. Xiong F, Mi Z and Gu N: Cationic liposomes as gene delivery system: transfection efficiency and new application. Pharmazie 2011; 66: 158-64.
26. Biswas S, Dodwadkar NS, Deshpande PP and Torchilin VP: Liposomes loaded with paclitaxel and modified with novel triphenylphosphonium-PEG-PE conjugate possess low toxicity, target mitochondria and demonstrate enhanced antitumor effects *in-vitro* and *in-vivo*. J Control Release 2012; 159: 393-02.
27. Zamboni CW: Liposomal nanoparticle and conjugated formulations of anticancer agents. Clin Cancer Research 2005; 23: 8230-34.
28. Lim HJ, Cho EC, Shim J, Kim DH, An EJ and Kim J: Polymer-associated liposomes as a novel delivery system for cyclodextrin-bound drugs, J Colloid and Interface Science 2008; 320(2): 460-68.
29. Davidson RN, Croft SL, Scott A, Maini M, Moody AH and Bryceson AD: Liposomal amphotericin B in drug-resistant visceral leishmaniasis. Lanc 1991; 337: 1061-62.
30. Rivera E: Current status of liposomal anthracycline therapy in metastatic breast cancer. Clin Breast Cancer 2003; 4: S76-S83.
31. Gabizon A, Peretz T and Sulkes A: Systemic administration of doxorubicin-containing liposomes in cancer patients: Phase I study. Eur J Cancer Clin Oncol 1989; 25(12): 1795-03.
32. Glantz MJ, Jaeckle KA, Chamberlain MC: A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in

patients with neoplastic meningitis from solid tumors. Clin. Cancer Res 1999; 5(11): 3394-02.
33. Guaglianone P, Chan K and DelaFlor-Weiss E: Phase I and pharmacologic study of liposomal daunorubicin (DaunoXome). Invest N Drugs 1994; 12: 103-110.
34. Panyam J and Labhasetwar V: Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 2003; 55: 329-47.
35. Soppimath KS, Aminabhavi TM, Kulkarni AR and Rudzinski WE: Biodegradable polymeric nanoparticles as drug delivery devices. J Cont Rel 2001; 70(1-2): 1-20.
36. Rejinold NS, Chennazhi KP, Nair SV, Tamura H and Jayakumar R: Biodegradable and thermo-sensitive chitosan-g-poly(N-vinylcaprolactam) nanoparticles as a 5-fluorouracil carrier. Carbohydr Polym 2011; 83: 776-86.
37. Torchilin V: Multifunctional Pharmaceutical Nanocarriers, Springer Science& Business Media, LLC, NY, 1st edition, 2008.
38. Bory C, Boulieu R, Souillet G, Chantin C, Guibaud P and Hershfield MS: Effect of polyethylene glycol-modified adenosine deaminase (PEG-ADA) therapy in two ADA-deficient children: measurement of erythrocyte deoxyadenosine triphosphate as a useful tool. Adv Exp Med Bio 1991; 309A: 173-76.
39. Rosen O, Muller HJ and Gokbuget N: Pegylated asparaginase in combination with high-dose methotrexate for consolidation in adult lymphoblastic leukaemia in first remission: a pilot study. Br J Haematol 2003; 123(5): 836-41.
40. Glue P, Pouzier-Panis R and Raffanel C: A dose-ranging study of pegylated interferon α-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Therapy Group. Hepatology 2000; 32(3): 647-57.
41. Nishiyama N and Kataoka K: Current state achievements and prospects of polymeric micelles as nanocarriers for drug and gene delivery. Pharmacology and Therapeutics 2006; 112: 630-48.
42. Yamamoto T, Yokoyam M, Opanasopit P, Hayama A, Kawano K and Maitani Y: What are determining factors for stable drug incorporation into polymeric micelle carriers? Consideration on physical and chemical characters of the micelle inner core. J Controlled Release 2007; 123: 11-18.
43. Liu M, Kono K and Frechet JMJ: Water-soluble dendritic unimolecular micelles: their potential as drug delivery agents, Journal of Controlled Release 2000; 65: 121-31.
44. Wang C and Hsiue G: Polymeric micelles with a pH-responsive structure as intracellular drug carriers, Journal of Controlled Release 2005; 108: 140-49.
45. Kim TY, Kim DW and Chung JY: Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. Clin Cancer Res 2004; 10(8): 3708-16.
46. Namazi H and Adeli M: Dendrimers of citric acid and poly (ethylene glycol) as the new drug delivery agents, Science Direct 2005; 26: 1175-83.
47. Svenson S and Tomalia DA: Dendrimers in biomedical applications - reflections on the field. Adv Drug Deliv Rev 2005; 57(15): 2106-29.
48. Hawker CJ and Frechet JMJ: Preparation of polymers with controlled molecular architecture. A new convergent approach to dendritic macromolecules. J Am Chem Soc 1990; 112: 7638-7647.
49. Jang W, Selim K, Lee C and Kang I: Bioinspired application of dendrimers: from bio-mimicry to biomedical applications, Progress in Polymer Science 2009; 34: 1-23.
50. Lee C, Mackay J, Frechet J and Szoka F: Designing dendrimers for biological applications. Nature Biotechnology 2005; 12: 1517-26.
51. Zuckerman S and Kao JW: Nanomaterials and biocompatibility bio-MEMS and dendrimers, Nanotechnology in Drug Delivery. Springer Science & Business Media, LLC, NY. Chapter 7, 2009: 193-28.
52. Wolinsky JB and Grinstaff MW: Therapeutic and diagnostic applications of dendrimers for cancer treatment. Adv Drug Deliv Rev 2008; 60: 1037-55.
53. Najlah M, Freeman S, Attwood D and D'Emanuele A: *In-vitro* evaluation of dendrimer prodrug for oral drug delivery. Int J Pharm 2007; 336(1): 183-90.
54. Najlah M and D'Emanuele A: Crossing cellular barriers using dendrimer nanotechnologies. Curr Opin Pharmacol 2006; 6(5): 522-27.
55. El-Sayed M, Kiani MF, Naimark MD, Hikal AH and Ghandehari H: Extravasation of poly(amidoamine) (PAMAM) dendrimers across microvascular network endothelium. Pharm Res 2001; 18(1): 23-28.
56. Myc A, Kukowska-Latallo J and Cao P: Targeting the efficacy of a dendrimer-based nanotherapeutic in heterogeneous xenograft tumors *in-vivo*. Anticancer Drugs 2010; 21(2): 186-92.
57. Patri AK, Myc A, Beals J, Thomas TP, Bander NH and Baker JR: Synthesis and *in-vitro* testing of J591 antibody–dendrimer conjugates for targeted prostate cancer therapy. Bioconjug Chem 2004; 15(6): 1174-81.
58. Bielinska AU, Kukowska-Latallo JF, Johnson J, Tomalia DA and Baker JR: Regulation of *in-vitro* gene expression using antisense oligonucleotides or antisense expression plasmids transfected using starburst PAMAM dendrimers. Nucleic Acids Res 1996; 24: 2176-82.
59. Kukowska-Latallo JF, Raczka E, Quintana A, Chen CL, Rymaszewski M and Baker JR: Intravascular and endobronchial DNA delivery to murine lung tissue using a novel, non-viral vector. Hum Gene Therapy 2000; 11: 1385-95.
60. Mehnert W and Mäder K: Solid lipid nanoparticles: Production, characterization and applications. Adv Drug Deliv Rev 2001; 47: 165-96.
61. Jores K, Mehnert W, Bunjes H, Drechsler M and Mader K: From solid lipid nanoparticles (SLN) to nanospoons: visions and reality of colloidal lipid dispersions, Controlled Release Society, 30th Annual Meeting Proceedings 2003.
62. Dingler A and Gohla SH: Production of solid lipid nanoparticles (SLN): scaling up feasibilities. J Microencapsul 2002; 19: 11-18.
63. Muller RH, Mader K and Gohla S: Solid lipid nanoparticles (SLN) for controlled delivery: a review of state of the art. Eur J Pharm Biopharm 2000; 50: 161-77.
64. Esposito E, Fantin M, Marti M, Drechsler M, Paccamiccio L and Mariani P: Solid lipid nanoparticles as delivery systems for bromocriptine. Pharmaceutical Research 2008; 7: 1521-30.
65. Alder-Moore J: AmBisome targeting to fungal infections. Bone Marrow Transplant 1994; 14(S5): S3-S7.
66. Podaralla SK and Perumal OP and Kaushik RS: Design and formulation of protein-based NPDDS. Drug delivery nanoparticles formulation and characterization edited by Yashwant Pathak Sullivan and Deepak Thassu. Informa Healthcare USA, Inc 2009; Chapter 6: 69-88.
67. Wang G and Uludag H: Recent developments in nanoparticle-based drug delivery and targeting systems with emphasis on protein-based nanoparticles. Expert Opin Drug Deliv 2008; 5(5): 499-15.

68. Green MR, Manikhas GM and Orlov S: Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol 2006; 17(8): 1263-68.
69. Gradishar WJ: Albumin-bound paclitaxel: a next-generation taxane. Expert Opin Pharmacother 2006; 7: 1041-53.
70. Paal K, Muller J and Hegedus L: High-affinity binding of paclitaxel to human serum albumin. Eur J Biochem 2001; 268: 2187-91.
71. Purcell M, Neault JF and Tajmir-Riahi HA: Interaction of taxol with human serum albumin. Biochim Biophys Acta 2000; 1478: 61-68.
72. Ibrahim NK, Desai N and Legha S: Phase I and pharmacokinetic study of ABI-007, a cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clin Cancer Res 2002; 8(5): 1038-44.
73. Nyman DW, Campbell KJ and Hersh E: Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol 2005; 23(31): 7785-93.
74. Beg S, Rizwan M, Sheikh AM, Hasnain MS, Anwer K and Kohli K: Advancement in carbon nanotubes: basics, biomedical applications and toxicity. J Pharm Pharmacol 2011; 63: 141-63.
75. Foldvari M and Bagonluri M: Carbon nanotubes as functional excipients for nanomedicines: I. Pharmaceutical properties. Nanomedicine 2008; 4: 173-82.
76. Zhang B, Chen Q, Tang H, Xie Q, Ma M, Tan L, Zhang Y and Yao S: Characterization of and biomolecule immobilization on the biocompatible multi-walled carbon nanotubes generated by functionalization with polyamidoamine dendrimers. Colloids Surf B Biointerfaces 2010; 80: 18-25.
77. Di Crescenzo A, Velluto D, Hubbell JA and Fontana A: Biocompatible dispersions of carbon nanotubes: a potential tool for intracellular transport of anticancer drugs. Nanoscale 2011; 3: 925-28.
78. Bhirde AA, Patel S, Sousa AA, Patel V, Molinolo AA, Ji Y and Leapman RD: Distribution and clearance of PEG-single-walled carbon nanotube cancer drug delivery vehicles in mice. Nanomedicine 2010; 5: 1535-46.
79. Shin US, Yoon IK, Lee GS, Jang WC, Knowles JC and Kim HW: Carbon nanotubes in nanocomposites and hybrids with hydroxyapatite for bone replacements. J Tissue Eng 2011; 2011: 674287.
80. Kukowska-Latallo JF, Raczka E, Quintana A, Chen CL, Rymaszewski M and Baker JR: Intravascular and endobronchial DNA delivery to murine lung tissue using a novel, nonviral vector. Hum Gene Therapy 2000; 11: 1385-95.
81. Cui D, Tian F and Coyer SR: Effects of antisense-myc-conjugated single-walled carbon nanotubes on HL-60 cells. J Nanosci Nanotechnol 2007; 7: 1639-46.
82. Kateb B, Van Handel M and Zhang L: Internalization of MWCNTs by microglia: possible application in immunotherapy of brain tumors. Neuroimage 2007; 37(S1): S9-S17.
83. Sinha R, Kim GJ, Nie S and Shin DM: Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. Mol. Cancer Ther 2006; 5(8): 1909-17.
84. Smith AM, Duan H, Mohs AM and Nie S: Bioconjugated quantum dots for *in-vivo* molecular and cellular imaging. Adv Drug Deliv Rev 2008; 60(11): 1226-40.
85. Papahadjopoulos D, Allen TM and Gabizon A: Sterically stabilized liposomes: improvements in pharmacokinetics and antitumor therapeutic efficacy. Proc Natl Acad Sci USA 1991; 88: 11460-464.
86. Arsawang U, Saengsawang O, Rungrotmongkol T, Sornmee P, Wittayanarakul K, Remsungnen T and Hannongbua S: How do carbon nanotubes serve as carriers for gemcitabine transport in a drug delivery system? J Mol Graph Model 2011; 29: 591-96.
87. Tripisciano C, Costa S, Kalenczuk RJ and Borowiak-Palen E: Cisplatin filled multiwalled carbon nanotubes-a novel molecular hybrid of anticancer drug container. Eur Phys J B 2010; 75: 141-46.
88. Chen Z, Pierre D, He H, Tan S, Pham-Huy C, Hong H and Huang J: Adsorption behavior of epirubicin hydrochloride on carboxylated carbon nanotubes. Int J Pharm 2011; 28(405): 153-61.
89. Zhang D, Pan B, Wu M, Wang B, Zhang H, Peng H, Wu D and Ning P: Adsorption of sulfamethoxazole on functionalized carbon nanotubes as affected by cations and anions. Environ Pollut 2011; 159: 2616-21.
90. Perry JL, Martin CR and Stewart JD: Drug-delivery strategies by using template-synthesized nanotubes. Chemistry 2011; 17: 6296-02.
91. Prajapati VK, Awasthi K, Gautam S, Yadav TP, Rai M, Srivastava ON and Sundar S: Targeted killing of Leishmania donovani *in-vivo* and *in-vitro* with amphotericin B attached to functionalized carbon nanotubes. J Antimicrob Chemother 2011; 66: 874-79.
92. Bhirde AA, Patel V, Gavard J, Zhang G, Sousa AA, Masedunskas A and Leapman RD: Targeted killing of cancer cells *in-vivo* and *in-vitro* with EGF-directed carbon nanotube-based drug delivery. ACS Nano 2009; 3: 307-16.
93. Luo X, Matranga C, Tan S, Alba N and Cui XT: Carbon nanotube nanoreservior for controlled release of anti-inflammatory dexamethasone. Biomaterials 2011; 32: 6316-23.
94. Arruebo M, Fernández-Pacheco R, Ibarra, MR and Santamaría J: Magnetic nanoparticles for drug delivery. Nano Today 2007; 2: 22-32.
95. Neuberger T, Schopf B, Hofmann H, Hofmann M and Von Rechenberg B: Superparamagnetic nanoparticles for biomedical applications: possibilities and limitations of a new drug delivery system. J Magn Magn Mater 2005; 293: 483-96.
96. Cao Q, Han X and Li L: Enhancement of the efficiency of magnetic targeting for drug delivery: Development and evaluation of magnet system. J Magn Magn Mater 2011; 323: 1919-24.
97. Kale SN, Jadhav AD, Verma S, Koppikar SJ, KaulGhanekar R, Dhole SD and Ogale SB: Characterization of biocompatible $NiCo_2O_4$ nanoparticles for applications in hyperthermia and drug delivery. Nanomedicine 2012; 8: 452-59.
98. Sayed FN, Jayakumar OD, Sudakar C, Naik R and Tyagi AK: Possible weak ferromagnetism in pure and M (Mn, Cu, Co, Fe and Tb) doped $NiGa_2O_4$ nanoparticles. J Nanosci Nanotechnol 2011; 11: 3363-69.
99. Smolensky ED, Park HY, Berquó TS and Pierre VC: Surface functionalization of magnetic iron oxide nanoparticles for MRI applications - an effect of anchoring group and ligand exchange protocol. Contrast Media Mol Imaging 2011; 6: 189-99.
100. Figuerola A, Di Corato R, Manna L and Pellegrino T: From iron oxide nanoparticles towards advanced iron-based inorganic materials designed for biomedical applications. Pharmacol Res 2010; 62: 126-43.
101. Asmatulu R, Zalich MA, Claus RO and Riffle J: Synthesis, characterization and targeting of biodegradable magnetic

nanocomposite particles by external magnetic fields. Journal of Magnetism and Magnetic Materials 2005; 292: 108-19.
102. Chang JH, Kang KH, Choi J and Jeong YK: High-efficiency protein separation with organosilane assembled silica-coated magnetic nanoparticles. Superlattice Microst 2008; 44: 442-48.
103. Tamer U, Gundogdu Y, Boyaci IH and Pekmez K: Synthesis of magnetic core-shell Fe_3O_4– Au, nanoparticles for biomolecule immobilization and detection. J Nanopart Res 2010; 12: 1187-96.
104. Chomoucka J, Drbohlavova J, Huska D, Adam V, Kizek R and Hubalem J: Magnetic nanoparticles and targeted drug delivering. Pharm Res 2010; 62: 144-49.
105. Pan BF, Gao F and Gu HC: Dendrimer modified magnetite nanoparticles for protein immobilization. J Colloid Interface Sci 2005; 284: 1-6.
106. Grassi-Schultheiss PP, Heller F and Dobson J: Analysis of magnetic material in the human heart, spleen and liver. Biometals 1997; 10: 351-55.
107. Yallapu MM, Othman SF, Curtis ET, Gupta BK, Jaggi M and Chauhan SC: Multi-functional magnetic nanoparticles for magnetic resonance imaging and cancer therapy. Biomaterials 2011; 32: 1890-05.
108. Wu W, Chen B, Cheng J, Wang J, Xu W, Liu L and Xia G: Biocompatibility of Fe_3O_4/DNR magnetic nanoparticles in the treatment of hematologic malignancies. Int J Nanomedicine 2010; 5: 1079-84.
109. Yoo JW, Chambers E and Mitragotri S: Factors that control the circulation time of nanoparticles in blood: challenges, solutions and prospects. Curr Pharm Des, 2010; 16: 2298-07.
110. Shubayev VI, Pisanic TR and Jin S: Magnetic nanoparticles for theragnostics. Adv Drug Deliv Rev 2009; 61: 467-77.
111. Wang J, Chen Y, Chen B, Ding J, Xia G, Gao C and Cheng J: Pharmacokinetic parameters and tissue distribution of magnetic Fe_3O_4 nanoparticles in mice. Int J Nanomedicine 2010; 5: 861-66.
112. Bajpai AK and Gupta R: the Magnetically mediated release of ciprofloxacin from polyvinyl alcohol-based superparamagnetic nanocomposites. J Mater Sci Mater Med 2011; 22: 357-69.
113. Arias JL, López-Viota M, Delgado AV and Ruiz MA: Iron/ethylcellulose (core/shell) nanoplatform loaded with 5-fluorouracil for cancer targeting. Colloids Surf B Biointerfaces 2010; 77: 111-16.
114. Yang J, Park SB, Yoon HG, Huh YM and Haam S: Preparation of poly e-caprolactone nanoparticles containing magnetite for magnetic drug carrier. Int J Pharm 2006; 324: 185-90.
115. Gaihre B, Khil MS, Lee DR and Kim HY: Gelatin-coated magnetic iron oxide nanoparticles as carrier system: drug loading and *in-vitro* drug release study. Int J Pharm 2009; 365: 180-89.
116. Losic D, Yu Y, Aw MS, Simovic S, Thierry B, and Addai-Mensah J: Surface functionalization of diatoms with dopamine modified iron-oxide nanoparticles: toward magnetically guided drug microcarriers with biologically derived morphologies. Chem Commu (Camb) 2010; 46: 6323-25.
117. Khan DR: The use of nanocarriers for drug delivery in cancer therapy. J Cancer Sci Ther 2010; 2(3): 058-062.
118. Metselaar JM and Storm G: Liposomes in the treatment of inflammatory disorders. Ex Opi Drug Del 2005; 2: 465-76.
119. Minko T, Pakunlu RI and Wang Y: New generation of liposomal drugs for cancer. Anticancer Agents Med Chem 2006; 6: 537-52.
120. Jong WHD and Borm PJA: Drug delivery and nanoparticles: Applications and hazards. International Journal of Nanomedicine 2008; 3(2): 133-49.
121. Zamboni WC: Concept and clinical evaluation of carrier-mediated anticancer agents. Oncol 2008; 13(3): 248-60.
122. Win KY and Feng SS: *In-vitro* and *in-vivo* studies on vitamin E TPGS- emulsified poly (D, L-lactic-co-glycolic acid) nanoparticles for paclitaxel formulation. Biomaterials 2006; 27: 2285-91.
123. Mora-Huertas CE, Fessi H and Elaissari A: Polymer-based nanocapsules for drug delivery. Int J Pharm 2010; 385: 113-42.
124. Park JW, Hong K and Kirpotin DB: Anti-HER2 immunoliposomes: enhanced efficacy attributable to targeted delivery. Clin Cancer Res 2002; 8(4): 1172-81.
125. Malik N, Evagorou EG and Duncan R: Dendrimer-platinate: a novel approach to cancer chemotherapy. Anti-Cancer Drugs Des 1999; 10: 767-76.
126. Brazel CS, Ankareddi I, Hampel ML, Bagaria H, Johnson DT and Nikles DE: Development of magnetothermal-responsive delivery systems using FePt nanoparticles imbedded in poly(N-isopropylacrylamide)-based hydrogels. Control Rel Soc Trans 2006; 33: 762.
127. Yamamoto T, Yokoyam M, Opanasopit P, Hayama A, Kawano K and Maitani Y: What are the determining factors for stable drug incorporation into polymeric micelle carriers? Consideration on physical and chemical characters of micelle inner core. J Controlled Release 2007; 123: 11-18.
128. Jones MC and Leroux JC: Polymeric micelles –a new generation of colloidal drug carriers. Eur J Pharm Biopharm 1999; 48(2): 101-11.
129. Duncan R: Polymer conjugates as anticancer nano-medicines. Nat Rev Cancer 2006; 6: 688-01.
130. Dinndorf PA, Gootenberg J, Cohen MH, Keegan P and Pazdur R: FDA drug approval summary: pegaspargase (oncaspar) for the first-line treatment of children with acute lymphoblastic leukaemia (ALL). Oncologist 2007; 12: 991-8.
131. Bukowski RM, Tendler C, Cutler D, Rose E and Laughlin MM: Treating cancer with PEG Intron: pharmacokinetic profile and dosing guidelines for an improved interferon-alpha-2b formulation. Cancer 2002; 95: 389-96.
132. Okusaka T, Okada S, Ishii H, Ikeda M and Nakasuka H: Trans-arterial chemotherapy with zinostatin stimalamer for hepatocellular carcinoma. Oncology 1998; 55: 276-83.
133. Foss FM: DAB(389) IL-2 (ONTAK): a novel fusion toxin therapy for lymphoma. Clin Lymphoma 2000; 1: 110-6
134. Garber K: For Bexxar, FDA meeting offers a long-awaited chance at approval. J Natl Cancer Inst 2002; 94: 1738-9.

How to cite this article:
Farah FH: Nanocarriers as delivery systems for therapeutic agents. Int J Pharm Sci & Res 2019; 10(8): 3487-07. doi: 10.13040/IJPSR. 0975-8232.10(8).3487-07.