Smart Drug Delivery Systems in Cancer Chemotherapy

Y. J. Oyeniyi*[1], A. Abdulsamad[2]

[1]Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Usmanu Dan Fodiyo University, Sokoto.

[2]Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria.

Abstract: **The review is aimed at delivering current updates on the various applications of nanotechnology in cancer chemotherapeutics. This involves the use of nano scale technology to deliver anti-neoplastic agents directly to cancer cells. Specifically, considerable attention will be will be given to the various nanopharmaceutical formulations currently approved for clinical uses by Food and Drug Administration (FDA). Also merits inherent in these nano-pharmaceuticals as compared to conventional drug delivery system of same drugs molecule will be critically assessed. A detailed evaluation of the various types of nanopharmaceuticals used in cancer chemotherapy is essential to expand our current nanopharmaceutical repertoire. This review revealed that there is an increased effort by researchers to formulate anticancer drugs as nanopharmaceuticals using different formulation methods. These nano formulations offers improved bioavailability, smart drug delivery and reduced adverse drug reactions of most cytotoxic agents. There is therefore an increasing role and application of nanotechnology in smart drug delivery system.**

Keywords: **Nanotechnology, Nano-pharmaceuticals, cancer chemotherapeutics, drug delivery system.**

1.   INTRODUCTION

Cancer is a disease characterized by the uncontrolled growth and spread of abnormal cells, and is still the second most common cause of death worldwide (Haley and Frenkel, 2008). Cancer treatment includes surgery, radiation, hormone therapy, and chemotherapy. Chemotherapy is the use of cytotoxic agents to effect cancerous cells death, and this forms a major strategy for treating the disease. All cytotoxic drugs are highly non-specific in targeting only tumor cells making normal healthy cells vulnerable to the drug‟s undesirable effects. This significantly hampers the maximum allowable dose of the drug. Moreover, rapid elimination and non-specific distribution of drug molecules into all tissues and organs in the body necessitate the administration of large dose of drug, which is uneconomical and often results in unwanted toxicity issues (Cho *et al*., 2008).

Nanotechnology is the science and study of matter in nano scale size of less than 100 nm. Nanotechnology is dynamic and with various applications. It is sometimes referred to as a general-purpose technology, because in its advanced form, it offers significant impact on almost all industries and all areas of the society. It offers better built, longer lasting, cleaner, safer, and smarter products for the home, for communications, for medicine, for transportation, for agriculture, and for industry in general (Bainbridge and Mihail, 2001). The term „nanotechnology‟ can be traced back to 1974. It was first used by Norio Taniguchi, in which he describe nanotechnology as the technology to get the extra high accuracy and ultra fine dimensions, i.e., the preciseness and fineness of the order of 1 nm (nanometer), in length, (Taniguchi, 1974). Taniguchi discussed his concept of „nanotechnology‟ in material processing, basing his arguments on the microscopic behavior of materials. Taniguchi imagined that ion sputtering would be the most promising process for the technology.

Nanotechnology present various applications mostly especially in pharmacotherapeutics, electronics, food, fuel cells, solar cells etc. The use of nanotechnology principles to address some of the problems associated with clinical uses of some conventional pharmaceutical products is the focus of many formulation scientists today. Based on major advances in nanoscale material science, the American government through the National Institute of Health (NIH) started in the year 2000 the National Nanotechnology Initiative (NNI) as a Federal Government program in order to promote nanoscience-related research and development. This launch of a broad program generously supporting and coordinating the design, study, and exploration of nanomaterials has had a quick impact on health-science related research and development. Extensive governmental financial support greatly stimulated the launch of interdisciplinary research. The new concept of Nanomedicine arose from merging nanoscience and nanotechnology. Pharmaceutical scientists quickly adopted nanoscience terminology, thus "creating" "nanopharmaceuticals" (Babu *et al.*, 2014).

Nanopharmaceuticals have received a lot of attention due to their potential to revolutionize drug delivery systems, especially in cancer chemotherapy where accurate dose of anti neoplastic agents must be made available selectively to the target cancer cells and not to the normal healthy cells. This is the most critical aspect in drug delivery systems as it relates to cancer chemotherapy. This also ensures reduction in toxic effects of cytotoxic drugs, as well as to optimize the therapeutic effect of the active agent as compared to the classic draw backs of traditional chemotherapeutics (Hossain-Saad et *al.,* 2012). In other words, nanopharmaceuticals selectivity of the diseased tissue or lesion also improved the uptake of poorly soluble drugs which also leads to an improvement in drug bioavailability and drug kinetics. The annual global R&D investment of drug companies in nanopharmaceuticals is over 40 billion dollars today, with an estimated global market of 50.1 billion US$ in 2011 and expected to expand to about 96.9 billion US$ in 2016. Nanopharmaceutical comprises of various formulations of active pharmacological compounds at nanoscale which offer the following advantages:

☐ Increase drug targeting ability since most nanopharmaceuticals incorporates receptor specific ligands.

☐ Reduction in the dose of active pharmaceutical ingredient needed to elicit pharmacological responses

☐ Enhance oral bioavailability of the drug

☐ Decrease systemic toxicity since the dose of drug administered are delivered directly at the receptor site

☐ Enhance drug solubility

☐ Increase the stability of drug and formulation

☐ Increased surface area

☐ Enhanced rate of dissolution

☐ Decreased drug resistance

☐ Increase patient compliance (Babu *et al.*, 2014)

Nanopharmaceutical formulations may be used to fabricate gene and monoclonal antibody delivery system, reported to be very effective in cancer chemotherapy (Hossain-Saad *et al.,* 2012).

Types and classifications of nanopharmaceuticals

From a material science perspective, nanopharmaceuticals can be simply classified as soft and hard nanopharmaceuticals depending on the nature of the end products. Soft nano-pharmaceuticals includes liposomes, nano-emulsions, submicron lipid emulsions, nano-gels and polymeric micelles which can be deformed and reformed to varying degrees by external or internal stress. Soft nanopharmaceuticals in contrast to hard nanopharmaceuticals are better able to navigate capillary beds and tissue extracellular spaces. Hard-type nanopharmaceuticals include polymeric nanoparticles, quantum dot, nanocrystal and solid lipid nanoparticles. Generally they are less flexible and elastic. Size selection during the formulation is critical to their performance since they can block capillaries that have dimensions similar to the particles (Von Werne and Patten, 1999; Jain, 2005; Park, 2007; Pridgen *et al.*, 2007). This review will focus on each of the various sub-classes of nanopharmaceuticals and their ability in selective delivery of antineoplastics to tumor cells.

Liposomes

Liposomes were first introduced for drug delivery in 1965. In simple term, they are nanopharmaceutical formulations containing phospholipids as the drug carrier. They are spherical vesicles comprised of an outer phospholipid membrane with an internal aqueous compartment. Water-soluble drugs can be entrapped in the aqueous compartment while hydrophobic drugs are incorporated within the lipid bilayer. In particular, liposomes have been recognized as an effective nano drug delivery system used extensively in formulating cytotoxic agents with profound therapeutic applications.

The amphipathic property of liposomes has made them a versatile drug molecule carrier, i.e. they can be used to deliver both lipophilic and hydrophilic drug molecule to the desired pharmacological site. Also entrapped drug molecules are protected from enzymatic and metabolic degradation; thereby increasing the biological half-life of the incorporated drugs. The increased uses of liposome as nano drug delivery system is often said to be due to its ability to increase drug concentration at targeted site thereby decreasing drug concentration at other sensitive normal healthy tissues resulting in reduction in unwanted adverse effects. Because liposomes are formulated using natural biocompatible and biodegradable material that shares some similarity with biological membranes and body tissues, they are generally safe, and can be
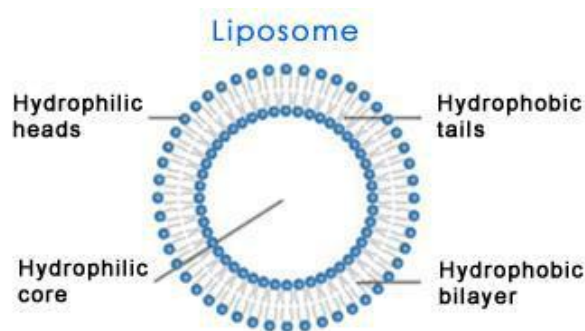

Figure 1: Liposome structure (Jain, 2005).

fabricated to selectively deliver drug molecules to only tumor cells (Hussain *et al.,* 2006).

Liposomes offer the following advantages:

1. Drug encapsulation versatility in their aqueous compartments (hydrophilic drugs), in their bilayers (lipophilic drugs) or both (amphiphilic drugs);

2. Potential to offer a high level of safety due to their inherent nontoxic, non-immunogenic and biodegradable property;

3. Liposomes can be engineered to efficiently encapsulate and effectively transport a variety of drugs. Small changes in these parameters can also have profound effects on the pharmacokinetic and pharmacodynamic profiles of a drug (VanVlerken and Amiji, 2006).

Liposome and cancer chemotherapeutics

It must be noted that majority of conventional anticancer drugs are nonspecific, and cytotoxic drugs that kills tumor cells will as well damage normal healthy tissues. Also most cytotoxic agents have narrow therapeutic index, with high potential for serious side effects. A variety of drug delivery systems are currently being investigated in an effort to make anticancer drugs delivery more efficient, smart and less toxic. Liposomal encapsulation of chemotherapeutic agents represents one major method of achieving this goal (Rakesh *et al.,* 2012). The advancement of liposomal drug delivery system in the oncology field was predicated on preclinical and clinical data demonstrating the benefits of liposome over others. Some of the liposomal preparations significantly increase the half-life of the incorporated agent as compared with that of the free drug (Bangham *et al.,* 1965; Hwang, 1987; Papahadjopoulos *et al.,* 1991; Samad *et al.,* 2007). Liposomal formulations also shield the incorporated drugs such that it prevents enzymatic and metabolic degradation of the encapsulated drug. As a result, the pharmacokinetic parameters of the conventional drug are improved by liposomal formulations. Clinically, chemotherapeutic agents formulated as liposomes exhibit increased circulation times with a corresponding increase in area under the curve (AUC), lower rate of clearance, and smaller volume of distribution as compared with that of the free drugs. The narrow therapeutic index of many cytotoxic drugs is, in part, a consequence of their large volume of distribution. Incorporating them into liposomes significantly reduces the volume of distribution, thereby decreasing the

toxicity to normal tissue and increasing the amount of drug that can be effectively delivered to the tumor (Pestalozzi *et al.,* 1992; Allen *et al*., 1995; Allen and Stuart, 1999). The following are good examples of cancer chemotherapeutic agents formulated as liposomes:

☐ Pegylated liposomal doxorubicin (Doxil/Caelyx® by Alza/Johnson and Johnson in the US and Schering-Plough outside the US),

☐ Non-pegylated liposomal doxorubicin (Myocet® by Elan),

☐ Liposomal daunorubicin (DaunoXome ® by Gilead),

☐ Liposomal cytarabine (DepoCyte® by Skye Pharma/Enzon/Mundipharma)

☐ Liposomal cisplatin (Lipoplatin® by Regulon), also

☐ Liposomal formulations of anthracyclines are used for the treatment of ovarian and breast cancer or HIV associated Kaposi¨s sarcoma.

DepoCyte® was approved for the treatment of lymphomas with meningeal spread and is the only liposomal drug administered by intrathecal infusion. Lipoplatin® is used for the treatment of epithelial malignancies. The clinical use of liposomal formulations of conventional cytostatic® drugs was focused initially on anthracyclines since these cationic amphiphiles allow for an efficient and stable liposomal entrapment. For example, conventional formulation of anthracyclines bear a high risk for acute and cumulative cardiotoxicity (resulting in cardiomyopathy) limiting their use. This problem was however addressed using appropriate liposomal formulations since an altered pharmacokinetics of liposomal anthracyclines offers the possibility to avoid high plasma peaks owing to the drug retention within the liposomal formulation. In addition, a reduced distribution of the liposomal anthracyclines to the heart muscle is observed using pegylated liposomes, (Gill *et al.,* 1995; Newman *et al.,* 1999; Gabizon, 2001; Waterhouse *et al.,* 2001; Gabizon *et al.,* 2006).

Liposomes tumor selectivity (targeting) and monoclonal antibodies therapy

Tumor cells are often characterized by a specific expression pattern of membrane associated proteins such as receptors, membrane transport systems or adhesion molecules. Provided that these structures are accessible from the extracellular space, such properties can be exploited for an active targeting of diseased cells and tissues using specific effector molecules. The concept of active targeting has the potential to combine the advantage of an increased therapeutic efficacy with a reduced risk of adverse drug effects in non-diseased tissues. And with the arrival of genetic engineering technologies, which made it possible to design chimeric mouse-human monoclonal antibodies or recombinant peptidic receptor ligands, the clinical use of these active tumor targeting strategies has become reality. During the last years, several monoclonal antibodies were developed and approved by FDA for active targeting of various tumors (Stathopoulos *et al.,* 2005). Examples include:

☐ Trastuzumab (Herceptin), a monoclonal antibody for the treatment of HER-2/neu-positive breast cancer (Stathopoulos *et al.,* 2005)

☐ Rituximab (Mabthera) for the treatment of CD20 expressing lymphoproliferative cells (Imai and Takaoka, 2006)

☐ Alemtuzumab (Campath) for the treatment of B- and T-cell hematological tumors being characterized by the expression of the CD52 surface antigen (McLaughlin *et al.,* 1998;

Baselga, 2000; Flynn and Byrd 2000).

The mechanisms of this antibody-based cancer therapy can be explained in twofold: First, a direct action by blocking or stimulating the function of target receptors, e.g., inhibition of signaling by the human epidermal growth factor receptor 2 (HER-2/neu) by Herceptin leading to cell growth inhibition and apoptosis of the target cell. Secondly, immune-mediated elimination of tumor cells by IgG mediated mechanisms including antibody-dependent cellular toxicity, complement-dependent cytotoxicity and cell mediated cytotoxicity (e.g., phagocytosis by macrophages or cytolysis by natural killer cells after recruitment of these immune-effector cells). The efficacy of such therapeutic antibodies can be increased by combination with a conventional chemotherapy. Alternatively, the antibodies can be linked directly to a toxin in order to guide the cytotoxic drug to the target tumor tissue. Experimental systems were used to study conjugates between targeting antibodies and small molecules such as the antineoplastic drug daunomycin (Flynn and Byrd, 2000). Clinical trials have

explored the pharmacological effects of conjugates between antibodies and potent plant toxins such as a deglycosylated ricin A-chain (Imai and Takaoka, 2006). Such targeting strategies using specific monoclonal antibodies as targeting vectors are of great interest. However, a major draw-back of these technologies is the limited carrying capacity of the monoclonal antibody vector since a very limited amount of effector molecules only can be coupled directly to a targeting vector without interfering with the antigen-recognition by the antibody and availability of suitable linking agents (Stathopoulos *et al.,* 2005; Imai and Takaoka, 2006).

Solid Polymeric Nanoparticles (SPN)

In the recent decades, various polymers are widely used as nano drug carriers due to their favorable properties such as good biocompatibility, biodegradability, flexibility of design and preparation. In the field of nano drug delivery, polymers played a significant role because it can deliver therapeutic agents directly into the intended site of action, with superior efficacy.

Polymeric nanoparticles are defined as solid colloidal particles composed of polymeric materials ranging in size from 1–100 nm. They can be sub-classified as;

□ Nano- capsules, which are vesicular systems with a polymeric shell and an inner core.

□ Nano-spheres are a polymeric matrix (Tiwari and Amiji, 2006).

□ Polymeric micelles are nanoscopic therapeutic systems that incorporate therapeutic agents, molecular targeting and diagnostic imaging capabilities that are emerging as the next generation of multifunctional nanopharmaceuticals intended to improve the therapeutic outcome of drug therapy. Polymeric micelles are self-assembled nano-materials of amphiphilic block copolymers containing hydrophobic and hydrophilic blocks (Vinogradov *et al.,* 2005).
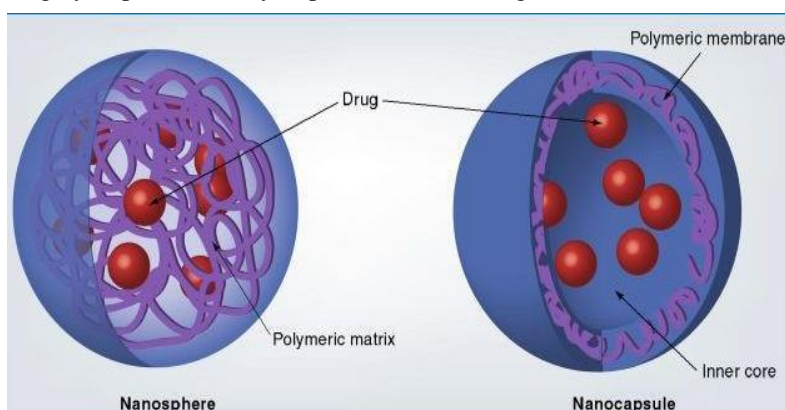

Figure 2: Images of Nanosphere and Nanocapsule (Tiwari and Amiji, 2006).
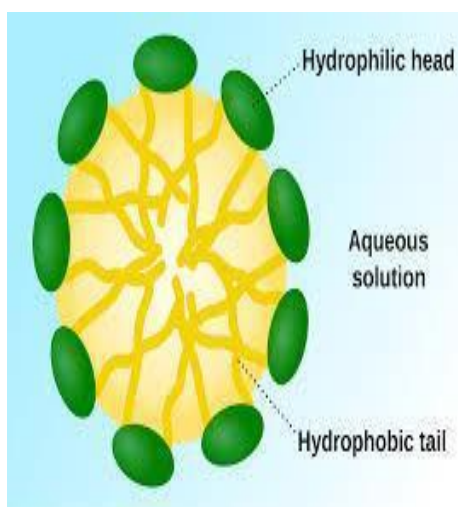

Figure 3: Polymeric Micelles (Tiwari and Amiji, 2006).

There are two basic types of polymers used as carriers of drug molecules in the formulation of nanopharmaceuticals (i.e. natural and synthetic). Natural polymers or biopolymers are naturally occurring materials which are formed during the life cycles of green plants, animals, bacteria and fungi. Table 1 shows example of natural and synthetic polymers approved for used in the formulation of nanopharmaceuticals while Table 2 shows the advantages and disadvantages of these natural and synthetic polymers.

Table 1: Some selected Polymers used in formulations of nanopharmaceuticals

Natural	Synthetic
Cellulose, Starch, Chitosan, Carrageenan, Alginates, Xantham gum, Gellan gum, Pectins	Poly (lactic acid) **PLA**, poly (cyanoacrylates) **PACA**, poly (acrylic acid) **PAA,** Poly (anhydrides), poly (amides), poly (ortho esters), poly (ethylene glycol), poly (vinyl alcohol) **PVA** , poly (lactic-co-glycolic acid) **PLGA**

Table 2: Merits and demerits of natural and synthetic Polymers

Advantages	**Natural** • Less toxic • Biocompatibility • Biodegradable • Easily available **Synthetic** • Biocompatibility
Disadvantages	**Natural** • High degree of variability in natural materials derived from animal sources • Structurally more complex • Extraction process very complicated and high cost **Synthetic** • Toxic • Non degradable • Synthetic process is very complicated and high cost

Various methods such as entrapment, encapsulation, dissolution and simple dispersion are available for loading drugs into solid polymeric nanoparticles, which may be released from the matrix by diffusion, swelling, erosion, or degradation (Du-Toit *et al.,* 2010). A wide spectrum of hydrophobic and hydrophilic drugs can be incorporated as nanoparticles for drug delivery system. Examples of anticancer drugs formulated as polymeric nanoparticles are;

☐ Paclitaxel (Taxol ®) a PLGA nanoparticle formulation containing vitamin E for the treatment of breast cancer.

☐ Oncaspar® (PEG-L-asparaginas) for the treatment of acute lymphoblastic leukemia.

☐ Others are Docetaxel and Curcumine nanoparticles (Zhang *et al.,* 2008; Heidel and Davis, 2011; Sanna *et al.,* 2011; Thakor and Gambhir, 2013; Wang *et al.,* 2014).

The following are among the important pharmaceutical advantages of nanoparticles as drug carriers:

☐ High stability (i.e., long shelf life). Stability of nanoparticles offers the possibility of oral administration. The fate of nanoparticles in the gastrointestinal tract is well documented.

☐ High carrying capacity (i.e., many drug molecules can be incorporated in the particle matrix)

☐ Possibility of incorporation of both hydrophilic and hydrophobic substances

☐ Possibility of variable routes of administration, including oral administration and inhalation.

☐ These carriers can also be designed to enable controlled (sustained) drug release from the matrix.

Solid Lipid Nanoparticle (SLN)

In the 1990"s solid lipid nanoparticles (SLN) were developed as an alternative colloidal carrier system for emulsions, liposomes and polymeric nanoparticles in controlled drug delivery. These particles are advantageous compared to other nanopharmaceuticals as they offer, physical stability, protection of incorporated labile drugs from degradation, controlled release, and excellent tolerability. SLN consist of a solid lipid core matrix that can solubilize lipophilic drugs which is stabilized by surfactant layer at room temperature. The drug is normally incorporated in the submicron size range, usually between 10 to 1000 *nm*. SLN are composed of physiological lipids and the surfactants that have an accepted GRAS (Generally Recognized as Safe status). SLN can be produced in large scales by high-pressure homogenization without using organic solvents, and have been used in parenteral, pulmonary and transdermal delivery of anticancer agents (Damascelli *et al.,* 2001; Sparreboom *et al.,* 2005; Weber *et al.,* 2008). A good example of solid lipid nanoparticles formulations recently evaluated for clinical use is methotrexate-loaded solid lipid nanoparticle (MTX-SLN), formulated and evaluated for topical treatment of psoriasis (Misra *et al.,* 2004).
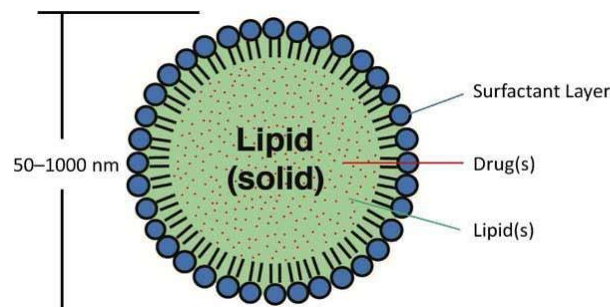

Figure 4: Basic structure of Solid lipid nanoparticle (Misra *et al.,* 2004).

The formulation and preparation of MTX-SLN gel were optimized using the cetyl alcohol lipid, Tween 80 as surfactant and sodium tauroglycocholate as co-surfactant. The optimized SLN particle size was 123 nm and an entrapment efficiency of 52% was obtained. The use of MTX-SLN improves the therapeutic response and the MTX-SLN base gel was observed to reduce adverse effects of therapy, promoting better patient compliance. It is therefore possible to consider it as a supplementary to oral therapy, particularly in the final stage of psoriasis treatment.

Dendrimers

Dendrimers are a versatile class of well-defined and highly branched nano-scale structures with several surface-active groups. Due to their smaller size (<100 nm), narrower molecular weight distribution, greater functionality, higher quantity of surface groups and relatively easier incorporation of targeting ligands, they are very good candidates for drug delivery.

The main characteristics which make dendrimers special are three different topological sites

☐ Poly-functional core

☐ interior layers and

☐ Multivalent surface (Bai *et al.,* 2007).

Several anticancer agents and brain specific drugs can be easily incorporated and delivered by Dendrimers. The most widely explored and used dendrimers are Poly-Amido-Amine (PAMAM) dendrimers. PAMAM dendrimers can facilitate transport through epithelial barrier which show their potential as a carrier for oral delivery, (Bai *et al.,* 2007). These are also efficient as gene delivery systems and in fact they have at least equal efficacy as other cationic carriers like polylysine (Qin *et al.,* 1998). Cationic dendrimers (G2 PAMAM, G3 PAMAM, PEGylated G3) can also be used as

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pulmonary delivery carriers to administer large molecular weight anionic drug like low molecular weight heparin (Ziady *et al.,* 2003). Pulmonary delivery of Plasmid DNA by G9 PAMAM dendrimer was also reported (Kitchens *et al.,* 2006). PAMAM dendrimers are also used for ocular insert or patches (Ke, *et al.,* 2009).
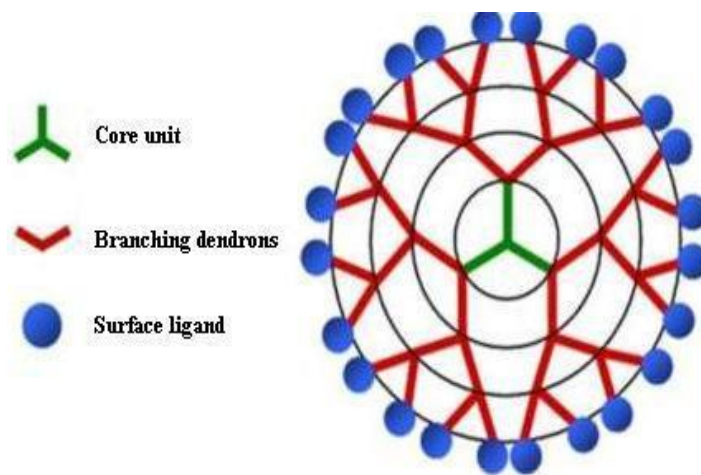

Figure 5: Basic structure of dendrimer (Dutta *et al.,* 2008)

Commercial dendrimer products for biomedical applications has also been produced i.e. VivaGel™, for prevention of sexually transmitted diseases and **SuperFect®** for gene transfection. Incorporation of large amount of drug is possible into dendrimers because of its structural configuration. Various techniques like (a) adsorption to the surface, (b) encapsulation in hydrophobic microcavities and (c) direct covalent conjugation with surface active groups can be employed to do so. Due to these properties dendrimer can be used as a carrier for water-soluble and water- insoluble drugs simultaneously (Bushrab and Müller, 2003; Cinzia De-Vita, 2004).

Nanocrystal

Since the beginning of the 90s, Elan Nanosystems (San Francisco, CA, USA) propagated the use of nanocrystals instead of microcrystals for the improvement of bioavailability of orally administered drugs. Drug nanocrystals are crystals with a size in the nanometer range, which means they are nanoparticles with a crystalline character. A unique characteristic of nanocrystal is that nanocrystal drugs are composed of 100% drug; i.e. there is no carrier material as in polymeric nanoparticles. Dispersion of drug nanocrystals in liquid media gives nanosuspensions (in contrast to "microsuspensions" or "macrosuspensions"), (Bushrab and Müller 2003; Cinzia De-Vita, 2004). There are different methods such milling, precipitation and homogenization that are available today for producing nanocrystal drug formulations in the desired shape and size. A good example of anticancer drug formulated as nanocrystal is Megestrol® a synthetic progestin.

Megestrol® also has direct cytotoxic effects on breast cancer cells in tissue culture and suppresses luteinizing hormone release from the pituitary. Megestrol® nanocrystal suspension bioavailability is improved due to increase rate of drug dissolution (Femia, 2005).

2. CONCLUSION

The role of nanotechnology will remain vital in the delivery of potent cytotoxic agents for the treatment of various forms of cancer. Nanopharmaceuticals of anticancer agents have been used in the clinic for some time and there are clear advantages of nanopharmaceuticals in cancer chemotherapy with regard to reducing the side-effects of drug, enhancing tumor targeting, and, in some cases, improving the therapeutic efficacy. Newer nanopharmaceutical formulations with increased active tumor cell targeting properties are making their way into clinical trials. In addition, an increased number of different nanopharmaceutical formulations sub-types are gaining approval and being tested in humans. Thus, the armamentarium of approved nanopharmaceutical formulations will certainly increase as regulatory agencies and clinicians become more familiar with their safety profiles and efficacy of these diverse nanopharmaceutical formulations. Certainly, the need for new cancer chemotherapy is significant and nanopharmaceutical-based formulations will find an ever-increasing presence in the clinic, hopefully, to the benefit of cancer patients worldwide.

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