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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(2): 240-248

ISSN No: 0975-7384

Bucky balls: A novel drug delivery system

Darshana Nagda, K. S. Rathore*, M. Bharkatiya, S. S. Sisodia and Nema R. K.

B. N. Girls College of Pharmacy, Udaipur, Rajasthan, India

Abstract

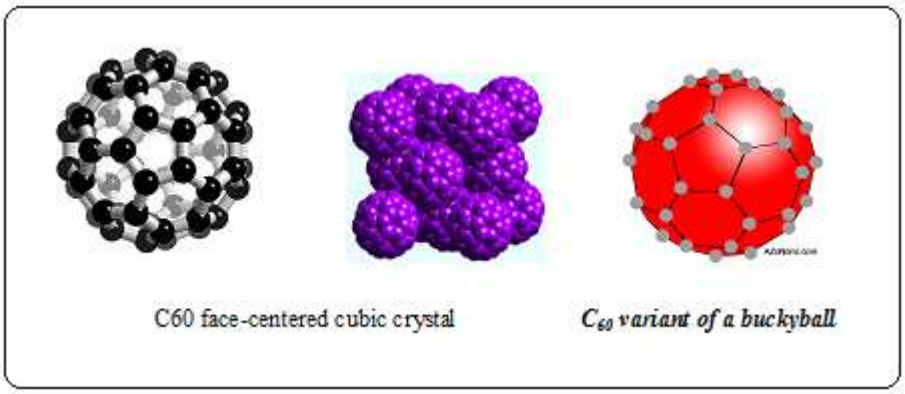
Nanotechnology means that what we are working with is very small. It generally means that we are working on the molecular level or, at least, in sizes of a few nanometers in the semiconductor industry Smaller…smaller….smaller mantra translates to Faster….. Faster…faster. . What is new is that we are learning to manipulate nanoparticles and even molecules to achieve great benefit. Nanotechnology deals with the study, development and practical application of structures and devices at molecular scale (between 1 and 100 nanometers, one nanometer is equivalent to 1 in 10^{-9} meters. Nanotechnology employs devices with dimensions of one to 1,000 nanometers. To put this in perspective, consider the following: a nanometer is 1/80,000th the width of a human hair; it is the length of 10 hydrogen atoms placed end to end; and it is less than one third the height of a single twist on a strand of DNA. At these sizes it is no wonder that scientists have seized upon nanotechnology for myriad medical applications….

Key words: Buckyballs, C60, Buckminsterfullerene, fullerenes, quantum dots.

Introduction

Buckyballs – a new sphere of science

"Buckyball" is the common name for a molecule called Buckminsterfullerene, which is made of 60 carbon atoms formed in the shape of a hollow ball. British scientist Harry Kroto discovered it in 1985. The arrangement of the atoms resembled the shape of the geodesic domes invented by architect Buckminster Fuller, hence the name. Along with American researchers Richard Smalley and Robert Curl, Kroto was able to create buckyballs in the laboratory. For this work, the three were awarded a Nobel Prize in Chemistry in 1996. These researchers found that buckyballs had many interesting properties [1]. They were very hard to break apart, even at temperatures of nearly 1000 °C, and would bounce back if squeezed or slammed against a solid object…



The discovery of "buckminsterfullerene"

Nobel Prize in 1996 for Chemistry was awarded for the discovery of fullerenes. The discovery of the buckyball can be likened to the discovery of benzene in 1825. Benzene is made up of a six carbon ring along with six hydrogen atoms (C_6H_6).The molecule was named for Richard Buckminster Fuller, a noted architect who popularized the geodesic dome. It was discovered in 1985 by Professor Sir Harry Kroto, and two Rice University professors, chemists Dr. Richard E. Smalley and Dr. Robert F. Curl Jr., [for which they were jointly awarded the 1996 Nobel Lauriate for chemistry] and is the only molecule composed of a single element to form a hollow spheroid which gives the potential for filling it, and using it for novel drug-delivery systems [2].

Chemical and physical properties of buckyballs

Buckyballs and other fullerenes because of their chemistry and their unusual hollow, cage-like shape extremely stable and can withstand very high temperatures and pressures. The carbon atoms of buckyballs can react with other atoms and molecules, leaving the stable, spherical structure intact. Researchers are interested in creating new molecules by adding other molecules to the outside of a buckyball and also in the possibility of trapping smaller molecules inside a buckyball[1].

Classification of nanomaterials

1. Nanotubes: Nanotubes are hollow cylinders made of carbon atoms. They can also be filled and sealed, forming test tubes or potential drug delivery devices.

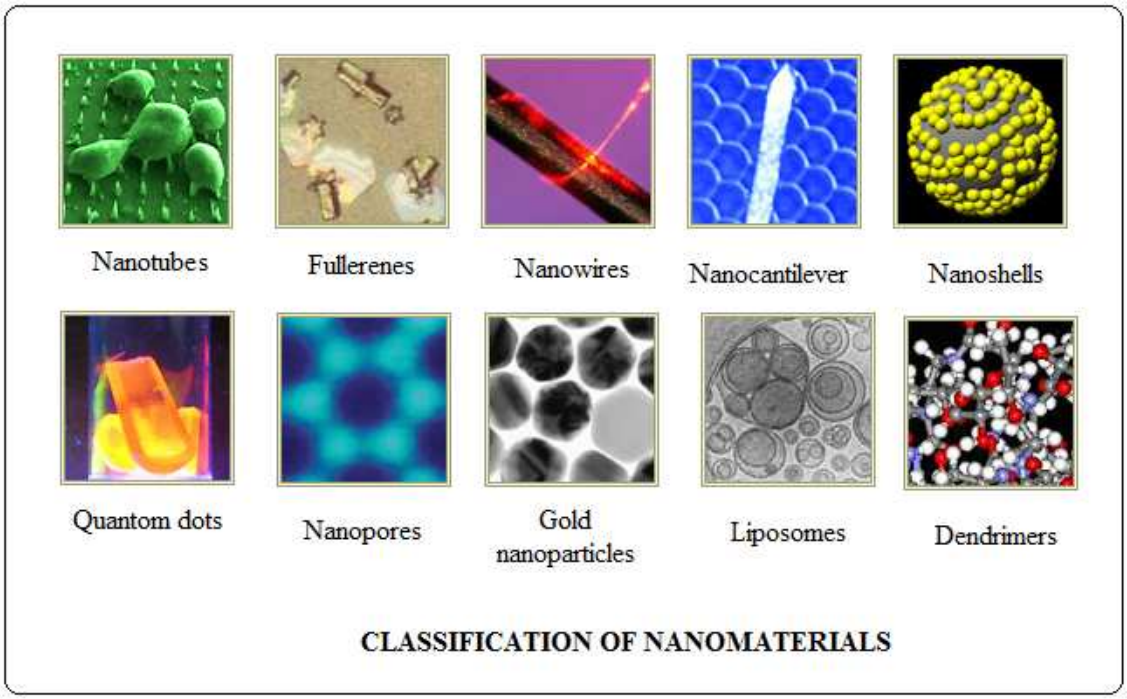
2. Fullerenes: These crystalline particles are a form of carbon atom whose molecular architecture is arranged in a soccer ball-like structure. Also known as buckyballs, they were discovered in 1985 among the detritus of laser-vaporized graphite. Unlike other molecules that have applications as cancer drug delivery vehicles, fullerenes don't break down in the body and are excreted intact. This trait can be important for some cancer treatment compounds that are dangerous to healthy cells. For example, fullerene drug delivery particles that contain radioactive atoms would allow for the complete removal of radiation from the body following treatment [2].

3. Nanowire : This glowing silica nanowire is wrapped around a single strand of human hair. It looks delicate—it is about five times smaller than a virus application for nanowires include the early sensing of breast and ovarian malignancies.

4. Nanocantilever: The honeycomb mesh behind this tiny carbon cantilever is the surface of a fly's eye.Cantilevers is beams anchored at only one end. In the nanoworld, they function as sensors ideal for detecting the presence of extremely small molecules in biological fluids.

5. Nanoshells: Nanoshells are hollow silica spheres covered with gold. Scientists can attach antibodies to their surfaces, enabling the shells to target certain cells such as cancer cells. Nanoshells could one day also be filled with drug-containing polymers.

6. Quantum Dots: Quantum dots are miniscule semiconductor particles that can serve as signposts of certain types of cells or molecules in the body. They can do this because they emit different wavelengths of radiation depending on the type of cadmium used in their cores: cadmium sulfide for ultraviolet to blue, cadmium selenide for most of the visible spectrum, and cadmium telluride for the far red and near-infrared [3].



7. Nanopores: Nanopores have cancer research and treatment applications. Engineered into particles, they are holes that are so tiny that DNA molecules can pass through them one strand at a time, allowing for highly precise and efficient DNA sequencing..By engineering nanopores into the surface of a drug capsule that are only slightly larger than the medicine's molecular structure, drug manufacturers can also use nanopores to control the rate of a drug's diffusion in the body.

8. Gold Nanoparticles: These nanoparticles, seen in a transmission electron micrograph image, they have a solid core. Researchers at Northwestern University are using gold nanoparticles to develop ultrasensitive detection systems for DNA and protein markers associated with many forms of cancer, including breast and prostate cancer.

9. Liposomes: Tiny pouches made of lipids, or fat molecules, surrounding a water core—widely used for clinical cancer treatment. Several different kinds of liposomes are also widely employed against infectious diseases and can deliver certain vaccines. During cancer treatment they encapsulate drugs, shielding healthy cells from their toxicity, and prevent their concentration in vulnerable tissues such as those of a patient's kidneys and liver. Liposomes can also reduce or eliminate certain common side effects of cancer treatment such as nausea and hair loss.

10. Dendrimer: This fascinating particle holds significant promise for cancer treatment. Its many branches allow other molecules to easily attach to its surface. Researchers have fashioned

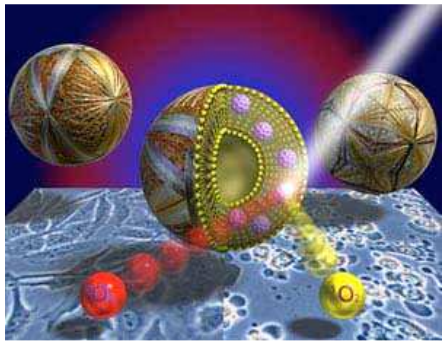
dendrimers into sophisticated anti-cancer machines carrying five chemical tools-a molecule designed to bind to cancer cells, a second that fluoresces upon locating genetic mutations, a third to assist in imaging tumor shape using X-rays, a fourth carrying drugs released on demand, and a fifth that would send a signal when cancerous cells are finally dead. The creators of these dendrimers have had successful tests with cancer cells in culture and plan to try them in living animals soon.

Applications of Buckyballs as Nanomedicine

Buckyballs may see widespread use in future products and applications, from drug-delivery vehicles for cancer therapy to ultra hard coatings and military armor, chemical sensors and hydrogen-storage technologies for batteries and automotive fuel cells and few are described here [4]-

- Hollow success - buckyballs for cancer treatment.
- Buckyball-Antibody Combination Delivers Antitumor Drugs
- Buckyballs to Fight Allergy
- Buckyballs as powerful anti-oxidant
- Buckyballs as inhibitor of HIV

1. Hollow success- buckyballs for cancer treatment:



C60 trapped in lipid membrane releases toxic singlet oxygen to kill cancer

Researcher says Trapping C60 Buckyballs in lipid globes could deliver improved cancer treatments, Atsushi Ikeda and colleagues from the Nara Institute of Science and Technology in Ikoma showed that the carbon isotope C60 could be delivered into human cancer cells by hollow lipid spheres and used to induce cell death under visible light irradiation. Combining a light source with a light-sensitive drug - a photosensitiser - to destroy cancer cells in this way is the principle behind photodynamic therapy (PDT). C60 yields singlet oxygen under irradiation and it is this that induces cell death. The problem facing Ikeda was how to dissolve the insoluble C60 in water and so open the possibility of transporting the compound into the cancer cells. Whilst some C60 derivatives are soluble in water, unmodified C60 yields singlet oxygen more efficiently[2].

The group used various lipids, including phospholipids and aminolipids, to make the lipid membrane-C60 structures, called LMI [60] fullerenes. The LMI [60] fullerene with a cationic surface was found to have a considerably higher PDT activity than the structures with anionic and neutral surfaces; Ikeda said that a future challenge will be to develop PDT photosensitizes with specific tissue distribution properties. His plan is to study the enhanced permeability and retention effects of LMI [60] fullerenes and also to tune the lipid membrane surface using various lipids with functional groups.. 'LMI [60] fullerenes will be used not only as a new cancer therapy, but also as antibacterial or antifungal agents,'

2. Buckyball-Antibody Combination Delivers Antitumor Drugs

Combining a monoclonal antibody known to target melanoma tumors with multiple C60 buckyballs, researchers at University of Texas M.D. Anderson Cancer Center have developed a new way to deliver multiple drugs simultaneously to tumors. Unlike other methods that use multiple targeting agents, such as antibodies, to deliver individual drug-loaded nanoparticles to malignant cells, this new approach attaches multiple nanoparticles to an individual tumor-targeting antibody. The M. D. Anderson Cancer Center investigators shown that ***ZME-018,*** which binds to a tumor protein known as ***gp240,*** will deliver anticancer drugs into melanoma tumors, while the Rice group has been developing buckyballs as drug delivery agents[1].

3. Buckyballs to Fight Allergy

Allergic disease is the sixth leading cause of chronic disease in the United States, and while various treatments have been developed to control allergy, no cure has been found. These findings advance the emerging field of medicine known as nanoimmunology. US researchers has identified a new biological function for a soccer ball-shaped nanoparticle called a buckyball or fullerene– the ability to block allergic response, setting the stage for the development of new therapies for allergy.

Biological Activities:

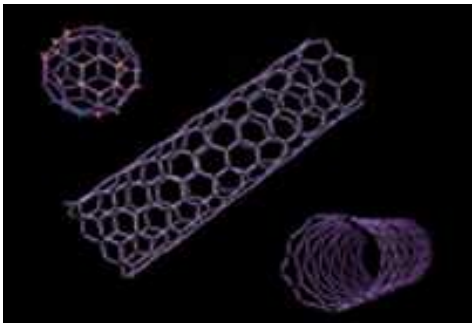
The list of exciting biological activities of water-soluble fullerene derivatives includes the inhibition of enzymes of -

- human immunodeficiency (HIV)
- hepatitis A, B and C viruses,
- anticancer action,
- antiproliferative effects,
- photodynamic therapy And efficient neuroprotective activity.

Some fullerene derivatives can be successfully applied as advanced bacteriostatic agents and contrast materials in X-ray and magnetic resonance imaging.

Buckyballs and Carbon Nanotubes in Cancer Therapies and Medical Treatment

Unlike other molecules that are used to encapsulate drugs, fullerenes resist breakdown by the body. This stability is especially important for holding compounds that would cause harm if released in healthy cells, for example, radioactive metal atoms. L. Wilson have modified 60-carbon fullerenes, called buckyballs, to home in on bone when injected into the body. Gonzalez an Wilson designed their compound to stick to hydroxyapatite. They also got a surprise when characterizing the compound: The molecule has one unpaired electron, making it magnetic. This property makes the compound a potential contrast agent for magnetic resonance imaging (MRI). A contrast agent injected into a patient can sharpen an MRI picture, revealing otherwise invisible features [5].



S. R. Wilson is working on fitting radioactive metals inside the buckyball, which as they travel through the bloodstream, will emit radiation. But since they are excreted intact, they will completely remove the radiation from the body after the procedure. He is also working on fullerenes that will deliver bone-building drugs for osteoporosis. Currently, most of those drugs are not well absorbed and are toxic. Buckyballs might offer a non-toxic molecular ship to deliver the materials safely to fragile bones. And on a more distant horizon,

Buckyballs Can Be Nontoxic.

Buckminsterfullerene, a form of carbon containing 60 atoms arranged like the facets of a soccer ball and one of the first and best studied nanoscale structures, has come under scrutiny in recent years over concerns that it may be toxic to living organisms. While media headlines have largely focused on studies showing that C60-fullerenes, or buckyballs, are toxic to bacterial, algae, and fish, other studies have failed to find such toxicities. Now, a new study from an international team of researchers suggests that the toxic effects of these molecules may result from the polar organic solvents used to dissolve them

Buckyballs Found in Nature

The Carbon 60 molecules, shaped like a geodesic sphere, were first synthesized in laboratories in 1985. This is now the third form of pure carbon known to exist naturally (along with graphite and diamonds)...Fullerenes are similar in structure to graphite, which is composed of a sheet of linked hexagonal rings, but they contain pentagonal rings that prevent the sheet from being planar…The structure of C60 - buckminsterfullerene - is that of a truncated icosahedron, which resembles a round soccer ball of the type made of hexagons and pentagons, with a carbon atom at the corners of each hexagon and a bond along each edge [6].

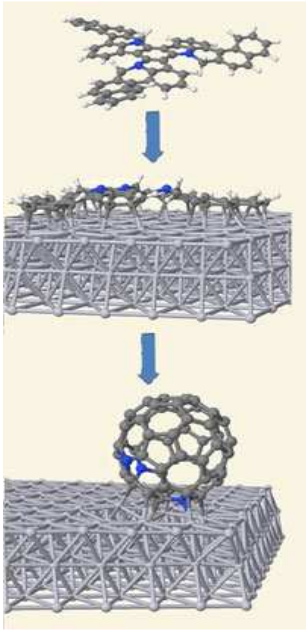
Advances and challenges of nanotechnology-based drug delivery systems

Nanoscale smart materials, such as carbon nanotubes, C_{60}, dendrimers and cyclodextrins, hold great promise for use in the development of better diagnostics, drug delivery and the alteration of biological function. The ability to deliver highly efficient therapeutic compounds specifically to diseased sites is crucial for effectively treating all human illnesses. Unfortunately, conventional therapeutic strategies require unnecessarily high systemic administration due to non-specific biodistribution and rapid metabolism of free drug molecules prior to reaching their targeted sites. Using the tools of nanotechnology, drug delivery systems within the nanometer size regime can be developed to alter both pharmacological and therapeutic effects of drug molecules. Due to their small size, these novel DDS offer superior advantages, such as altered pharmacokinetic behavior and improved payload, over traditional large-scale systems. In addition, the relative ease in modifying their surface chemistry permits the attachment of targeting and therapeutic molecules for specific therapeutic applications. Finally, complex nanostructures can be assembled using different building blocks with multiple functionalities ranging from targeting, detecting, imaging and therapeutic capabilities [3].

Buckyball synthesis under control

Fullerenes are formed when vaporized carbon condenses in an atmosphere of inert gas. The gaseous carbon is obtained e.g. by directing an intense pulse of laser light at a carbon surface. The released carbon atoms are mixed with a stream of helium gas and combine to form clusters of some few up to hundreds of atoms. The gas is then led into a vacuum chamber where it expands and is cooled to some degrees above absolute zero. The carbon clusters can then be analyzed with mass spectrometry. The Instituto de Ciencia de Materiales de Madrid (CSIC)-based team successfully synthesized fullerene, C_{60}, and triazafullerene, $C_{57}N_3$, with yields close to 100 per

cent. Their technique not only allows controlled heterofullerene synthesis, but could also be adapted to make buckyballs that encapsulate small molecules [7].



The fullerenes form on a platinum surface

Other shapes

The C_{60} buckyball is the most famous of the fullerenes but by no means the only one. In fact, scientists have now discovered hundreds of different combinations of these interlocking pentagon/hexagon formations. Examples include

- '**buckybabies**' – spheroid carbon molecules containing fewer than 60 carbon atoms,
- **'fuzzyballs'** – C_{60} buckyballs with 60 hydrogen atoms attached, There are many applications to fuzzyballs, one of which could create a slicker substance than teflon. A fully fluorinated buckyball would create the slickest molecular lubricant known to man, C60F60. The uses for a molecular lubricant are boundless, limited only by our imagination.
- **Metallofullerenes:** having metal atoms instead of carbon.
- **Gadofullerenes :** gadolinium-containing metallofullerenes, which are also termed gadofullerenes
- **Giant fullerenes** – fullerenes containing hundreds of carbon atoms, and
- **C_{70}** – molecules with 70 carbon atoms, shaped a bit like a rugby ball

Demerits

- **Buckyballs Hurt Cells**

A new study of the revolutionary nano-sized particles known as 'buckyballs' predicts that the molecules are easily absorbed into animal cells, providing a possible explanation for how the molecules could be toxic to humans and other organisms. "Buckyballs are already being made on a commercial scale for use in coatings and materials but we have not determined their toxicity studies showing that they can cross the blood-brain barrier and alter cell functions, which raise a lot of questions about their toxicity and what impact they may have if released into the environment." The resulting model showed that buckyball particles are able to dissolve in cell membranes, pass into cells and re-form particles on the other side where they can cause damage to cells [8].

- **Buckyballs' Have High Potential To Accumulate In Living Tissue**

Synthetic carbon molecules called fullerenes, or buckyballs, have a high potential of being accumulated in animal tissue, but the molecules also appear to break down in sunlight, perhaps reducing their possible environmental dangers "Because of the numerous potential applications, it is important to learn how buckyballs react in the environment and what their possible environmental. The researchers mixed buckyballs in a solution of water and a chemical called octanol, which has properties similar to fatty tissues in animals. Findings indicated buckyballs have a greater chance of partitioning into fatty tissues than the banned pesticide DDT. However, while DDT is toxic to wildlife, buckyballs currently have no documented toxic effects... When nanotechnology is referred to relative to therapeutics, it generally means that the active agent is targeted to specific locations in the body and that we are working on the molecular basis or with very small particles, such as, for example, gold nanoparticles [4].

- **Difficulty of targeting drug delivery to the location**

One major problem for current therapeutics is the difficulty of targeting drug delivery to the location where it is desired. The result of non-targeted delivery is that the drug can be active all over the body that means that large doses, larger than would otherwise be required, must be used, or that we realize a lot of peripheral damage to otherwise healthy parts, killing healthy cells or causing immune reactions. A second major problem for therapeutics is delivery of the active agent. This issue is related to the targeting problem but is broader than just that. Currently, we design active drugs and expect them to circulate through the body, pass through barriers such as the digestive system, the cell, and the blood-brain barrier, and still to be active as a drug after doing all that and it is not surprising that many drugs cannot effectively do this.

The issue is even more critical for cancer treatment where drugs often do great damage at the wrong locations. We are all aware of the major side effect problems with most cancer drugs. This issue will have to be solved by new delivery agents, materials which will do several jobs—that will direct the drug to the desired location, that will help the active agent get through the barriers, that will protect the drug from degradation during delivery, and, finally, that will release the drug once it is inside the cell or in the preferred location [9].

Uses

- Carbon nanotubes can be modified to circulate well within the body. Such modifications can be accomplished with either covalent or non-covalent bonding. And the modifications can be such that they increase or decrease circulation time within the body. Many current drugs, especially for cancer treatment, circulate for only short times before excretion.
- Carbon nanotube drug complexes are readily excreted from the body. Long-term data will be required, but initial studies indicate acceptable excretion.
- Carbon nanotubes show no significant toxicity when they have been modified so as to be soluble in aqueous, body-type fluids.
- Carbon nanotubes readily enter cells.
- A wide range of active agents can be attached to carbon nanotubes and carried into cells along with the nanotubes. It appears that stable structures are formed which protect the active agents during transport. The active agents which can be carried by carbon nanotubes include many cancer drugs and also include short interfering RNA, which may be the hottest current area within therapeutics research.
- Cancer cells in tumors are larger than normal cells and also exhibit leakage. This means that there is both leakage out of and leakage into the cells. Large molecules which

circulate slowly can leak into and accumulate in the cancer cells. Carbon nanotubes carrying active agents have been demonstrated in animal studies to do this and can be modified to increase circulation time and, therefore, the time for leakage into tumor cells [5].

- For cancer treatment, the active agent can be released once inside the cell, therefore returning that material to its active form. That means that the critical agent would be basically inactive during delivery but then become active inside the cancer cell. Cancer cells generally have a slightly lower pH than healthy cells, and it is the fractionally higher acidity which facilitates the release of the drug inside the cancer cells [7].
- Researchers have also used carbon nanotubes to deliver the precursors of an active drug, which they call a prodrug. The prodrug is then converted to its active form after it is inside the cancer cells e.g cisplatin, a common cancer drug. Using carbon nanotubes as the delivery agent, the prodrug is delivered with the platinum in its inactive oxidation IV state and then is reduced to the active oxidation II state inside the cancer cell. So, the active agent does not come into contact with other locations. It becomes active only inside the cancer cell [8].
- In one way of treating cancer, carbon nanotubes can even function as the active agent, themselves. They can enter cells and then be treated with external electromagnegic radiation such as radio frequency or near-infrared to heat the carbon nanotubes and kill the cancer cells [9].

References

[1] Jiang W, Kim BY, Rutka JT, Chan WC: *Expert Opin. Drug Deliv.* **2007,** 4, 621-633.
[2] Chan WCW: In: *Bio-Applications of Nanoparticles.* **2007,** Landes Bioscience, Austin, TX, USA.
[3] Kamal Singh Rathore, Rohit lowalekar, Dr.R.K.Nema, Dr.C.P.Jain, *The Pharma Review*, 2006, June, p.30-32.
[4] Sitharaman B, Tran LA, Pham QP *et al.*: *Contrast Media Mol. Imaging* **2007,** 2, 139-146.
[5] Bolskar RD, Benedetto AF, Husebo LO *et al.*: *J. Am. Chem. Soc.* **2003,** 125, 5471-5478.
[6] Toth E, Bolskar RD, Borel A *et al.*: *J. Am. Chem. Soc.* **2005,** 127, 799-805.
[7] Szoka F Jr, *Annu. Rev. Biophys. Bioeng.* **1980,** 9, 467-508.
[8] Hirsch LR, Gobin AM, Lowery AR *et al.*: *Ann. Biomed. Eng.* **2006,** 34, 15-22.
[9] Tomalia DA, Reyna LA, Svenson S: *Biochem. Soc. Trans.* **2007,** 35, 61-67.