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Bio-Medical Application of Fullerenes : An Overview

Chemistry

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ABSTRACT

Advancement in the field of medicine is undoubtedly remarkable in the 21st century. The discovery of these wonder carbon-spheres has brought about a revolution in the field of medical application, and has led to the new concept leading to truly un-conventional mode of therapeutics, using fullerenes as medical adjuvant with nearly negligible side effects. Many of the practical applications of fullerenes follow directly from their extraordinary properties. Relevant chemical, physical and the optical properties are assessed, which makes the Fullerenes as an essential component for the future of the nanoelectromechanical system. In many cases, the necessity of building novel organic compounds leads to the exploration of nanostructures, like fullerenes. These molecules bring flexibility to the world of engineering and provide promising applications in electrical, military and medical fields. Major attribute of fullerenes are their versatility, therefore, broadening and widening the horizons of their applications in the field of medicine. . This review paper explores the molecular structure of these molecules and different synthesis methods used nowadays and highlighting the major biomedical applications of fullerenes as anti cancer and anti diagnostic agents.

INTRODUCTION

Allotropism is the property of some chemical elements to exist in two or more different forms known as allotropes of these elements. Till mid of 1980's, only two allotropic forms of elemental carbons were known; Diamond and Graphite. In fact, six crystalline forms of the element carbon were known, namely, two kinds of graphite, two kinds of diamond, chaoit and carbon (VI). The latter two were discovered in 1968 and 1972, respectively. Fullerenes are the third allotropic form of carbon material after graphite and diamond.

Allotropes of carbon include diamond, graphite, fullerenes and graphene. In 1985, three scientists named Harold Kroto, Robert Kurl and Richard Smalley were trying to produce particles similar to those produced by giant stars in interstellar space. They subjected graphite to high energy pulsed LASER beam (LASER – Light amplified by stimulated emission of radiation) and passed vaporized fragments into mass spectrometer for analysis. They found an intense mass a spectral peak at very high mass 720, corresponding to C_{60} (C=12x60 = 720). Other less intense peaks were also discovered C_{70} (mass 840). For this, they got Nobel Prize in 1996 in Chemistry.

In 1990, W. Kratschmer, D. Huffman and their co-workers practically described the first synthesis of C_{60} by arc vaporization of graphite in a helium environment. The gaseous carbon is obtained by directing intense laser light at carbon surface. C_{60} was named as *buckminister fullerene,* a molecule shaped like a soccer ball, due to its resemblance of this shape to geodesic domes designed & built by architect engineer Richard Buckminister Fuller**.**

Due to their spherical shapes, they are sometimes called Bucky balls / Foot ballene / soccer ballene. An important property of C_{60} molecule is its high symmetry. In 1995, Kroto found that fullerenes C_{60} & C_{70} are highly stable aromatic compounds.

The precursor of C_{60} is graphite. Graphite consists of planar hexagonal carbon rings. Each carbon atom is connected to three other carbon atoms in the same layer by bonds of approximately same length (1.42Å) Thus, sheets in graphite are like infinite number of fused aromatic rings, two layers beings 3.4 Å apart, no covalent bonds between C-atoms in different layers only weak forces holds the layers together. If a graphite layer is blasted by applying energy, a carbon atom is expelled from one of hexagonal ring of graphite layer, ring becomes pentagonal and thus it does not remain flat, resulting polycyclic aromatic hydrocarbon .Carannulene consist of five benzene rings around pentagon. It is soccer shaped and is considered as fragment of Buckminster fullerene and is called "bucky ball" due to ball shape. Ejection of more carbon atoms from graphite layers leads to increasing curvature and eventfully closure to sphere structures.

Fullerenes have general formula C_{20+2n}, made up of 12 pentagons and 20 hexagons. C_{60} is icosahedrons with sixty vertices (one at each carbon) 32 faces with 12 pentagons and 20 hexagons. No two pentagons are adjacent to each other.C_{70} = 12 pentagons + 25 hexagons (n=25).Each carbon of fullerene is sp^2 hybridized and forms sigma bonds to three other carbon atoms. Fourth valence e^- of each carbon lies in p- orbital. These orbital overlap to form a π e^- cloud outside and inside the sphere (like π e^- cloud below ad above plane of benzene ring); thus structure is aromatic and exceptionally stable**.** Vander Waal's diameter of a C_{60} molecule is about 1 nm C_{60} and has two bond lengths between hexagon and hexagon 1.39 Å (6:6 double bonds) and between hexagon and pentagon 1.43 Å (6:5) .

REACTIONS

Characteristic reaction of fullerenes is electrophilic addition at 6:6 double bonds reducing the angle strain by charging sp^2 into sp^3 hybridized carbons.

$$C_{60} + Br_2 \text{----------} C_{60}Br_2 + C_{60}Br_4$$

They don't show electrophilic substitution since there are no H-atoms to substitute.

Fullerenes are insoluble in water and stable in air. Good solvents for fullerenes are CS_2, Toluene, and xylene. Due to π-π^* e^- transitions, fullerene solutions are coloured. On heating fullerenes under vacuum up to 1500°C, they transform to graphite. C_{60} crystals are electrically insulated but on doping with alkali metal, they acquire various semi-conductor, super conductor properties depending on doping concentration and temperature. Doping alkali atoms occupy vacant octahedral & tetrahedral sites**.**

If alkali metal is K or Rb, compound are super conductors i.e. below transition temperature (T_c), they conduct electric current without any resistance. T_c for alkali doped fullerides is 20- 40 K. They exist as ionic solids like - K_3C_{60}, K_2RbC_{60}, KRb_2C_{60}, Rb_4C_{60}, $Rb_{15}C_{60}$, etc.

Endohedral fullerenes:

Fullerenes have the characteristic of stuffing atoms into its empty space; such fullerenes are called endohedral. If metallic atom is present inside; they are called metallic fullerenes. For e.g. - Lanthanum, Yttrium, Scandium, noble gases etc.The fullerene family is ever growing and new members are added in large numbers.

Biomedical application of fullerenes

Fullerenes serves as a great diagnostic and therapeutic tool exhibiting dual benefits of specificity and reliability with number of biomedical applications. Use of fullerene as medical adjuvant with minimal side effects is the most remarkable discovery today. Keeping in mind the versatility of these materials, they found extensive applications as contrasting agents, diagnostic tools, drug and delivery agents, virus inactivators and various other applications.

1. Anti-diagnostic agents

Endohedral metallofullerenes are fullerenes with metal ion trapped inside fullerene cage. They have intense potential in diagnostics. Water solubilised endohedral gadofullerenes are being used as contrasting agents in MRI. Gadolinium is formulated in a chelate in order to prevent toxicity. Chelate agents is designed to stay in body for short span of time and is eliminated through renal duct .However, if patient suffers from kidney disease, the cleansing system is affected and slowed down. As a result, the chelate and gadolinium gets separated and expose the patient to toxic metals. The new trimetasphere endohedral fullerene based agent completely encapsulates gadolinium so that the toxic metal cannot escape .Such trimetasphere based contrasting agents are more sensitive and thus improves measurement of relativity .In this way , in coordination with cell targeting technology, improving relaxivity can intense detectability of disease conditions. Also such agents can promote the small potable MRI systems. Additionally in the case of patients suffering with CAD (coronary artery disease) ,such trimetaphase MRI contrasts can help in detecting atherosclerotic plague built up in blood vessel walls. This wound help in earlier detection providing physician and the patient pre-emptive information before myocardial infarction stroke event.

2. Anti-cancer agents

Atushi Ikeda et al., Ikoma (Nara institute of science and technology reported that C60 could be delivered into human cancer cells by trapping them into human cancer cells and can induce cell death under visible light irradiation. Advent of this technique has opened new avenues to new area of targeted drug delivery called PDT. In PDT photo dynamic therapy, the fullerene is coated with antibodies specific to membrane proteins on cancerous cells and is tagged with a magnetic nano particle. A fullerene contains an entrapped cyto toxic drug molecule. When exposed to near IR LASER radiation, it binds to target cell and changes into carbon nano tube conformation and thus allows easy passage of drug on target cell surface.

The magnet nano particles tagged on fullerene oscillates on exposure to LASER ,thus creates a magnetic field at target site which further attracts more fullerenes toward target site, thus achieving target cytotoxic drug delivery specific to career cells. Also, it was observed that when fullerenes are tagged with nucleotide chain, preferably guanidine residue ,it induces cell death forming a trihelical aggregate in conjunction with specific nucleotide sequence in DNA. On exposure to near IR LASER, DNA photo cleavage in induced by means of generation of reactive oxidising species. On exposure to low power visible light, water soluble fullerene carboxylic derivative was reported to be cytotoxic i.e. it killed the cancer cells. Later, it was shown that cytotoxicity of C_{60} derivatives was mediated by its ability to cleave DNA.

3. Anti-HIV activity

The enzyme aspartate protease specific to HIV-I is a viable target in antiviral therapy in AIDS. The active site of this enzyme can be described roughly as an open ended cylinder lined almost exclusively by hydrophobic amino acids except Asp -25 and Asp -125. Fullerenes with amino derivatives complimentary to aspartate residue on HIV protease bind specifically within the cavity of enzyme and inactivate it completely which inhibits the proliferation and replication mechanism of virus, thus significantly reducing its virulence. This development could bring a revolution in HIV treatment mechanisms in upcoming future.

4. As an Anti-oxidants and Bio-pharmaceuticals

Fullerenes are the powerful antioxidants, reacting readily, and at a high rate with free radicals, which are often the cause of cell damage or death. Fullerenes hold great promise in health and personal care applications where prevention of oxidative cell damage or death is desirable, as well as in non-physiological applications where oxidation and radical processes are destructive (Food spoilage, Plastics deterioration, metal corrosion etc).

Fullerenes are known to behave like a "radical sponge," as they can sponge-up and Neutralize 20 or more free radicals per fullerene molecule. They have shown performance 100 times more effective than current leading antioxidants such as Vitamin E. Fullerene is highly soluble in almond oil and thus it can be used for screening test for ocular tissue toxicity indicating no adverse effect.

A dendrimer containing 18 carboxylic acid groups was added as an addend to C_{60} to give rise to a dendro[60]fullerene also known as DF-1. This novel functionalized fullerene has shown remarkable antioxidant properties against the dangerous effects of ionizing radiation.

Conclusion:

Major pharmaceutical companies are exploring the use of fullerenes in controlling the neurological damage of such diseases as Alzheimer's disease and Lou Gehrig's disease (ALS), which are a result of radical damage. Drugs for atherosclerosis, photodynamic therapy, and anti-viral agents are also in development .Interest of scientists in water-soluble fullerene compounds are directly related to their biological activity. Dendrimer 4p containing 18 carboxyl groups is the more promising today.

Thus this study gives the basic knowledge of structure of fullerenes and their applications. The fullerenes can be used as organic photovoltaic's (OPV). Other uses of C60 like catalysts, in water purification and biohazard protection are also under extensive studies.

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