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# Water Soluble Nanocarbon Materials: A Panacea for All?

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Dedicated to: the memory of my father, late Mr V. Sambasivan on his birth centenary.

**Abstract**

Fictionalizations (fullerenes, CNTs & grapheme) help overcome the limitation of nanocarbon materials, making them soluble. Recently the emphasis has shifted to make water soluble Fullerenes (FWS). Much work has been documented showing the use of FWS in treating cancer (e.g. breast cancer), tumors, arthritis, Parkinson's, Influenzas & HIV-AIDS. Even an aqueous nasal spray to combat Alzheimer's has been advocated. A recent US patent shows that FWS is a powerful Radical Oxygen Scavenger (ROS) and thus shows anti-oxidant activity. FWS have been used in X-ray imaging, as MRI Contrast Agents (MRI-CA), to make solar cells and are expected to help produce nano-devices and biosensors.

**Keywords:** Nano biotechnology; Theranostics; Nanomaterials; Targeted drug delivery; Radical Oxygen Scavenger (ROS)

## Introduction

Nanocarbon materials (NCMs) include fullerenes, carbon nanotubes and graphene, which have been recognized by the award of Nobel prizes in 1996 and 2010. However, limited solubility restricts their widespread use. Functionalization of NCMs make them soluble and thus in recent years the emphasis has shifted to water soluble derivatives, which are relatively safe. Soluble NCMs have been shown to possess activity against cancer (e. g. breast cancer), tumors, arthritis, HIV-AIDS, Influenzas, etc. There are even reports of their possible use in aqueous nasal sprays (containing up to 0.0002mg per 100 ml water) for treatment of Alzheimer's disease. The poster boy fullerene derivative, C3-tris malonic acid possesses activity against Parkinson's disease in mice. A recent patent documents their use as antioxidants, as these are Radical Oxygen Scavengers (ROS), which are expected to serve as good theranostic platforms.

Is it true that water soluble NCMs are a panacea for all diseases? While very recent work seems to suggest this to be true yet these claims need to be very carefully evaluated. Water solubility would allow intravenous injections to patients, permitting targeted delivery to the cancer/tumor sites rather than to spread it all over the body. These are thus good candidates for personalized medicine but toxicity issues should not be overlooked. We must remember that the public perception and expectation could differ considerably from the expert's viewpoint.

Soluble NCMs have been used in making solar cells, as MRI, contrasting agents and in X-Ray imaging. Nano devices hold great promise, but just like the nanocarbon materials themselves, these still remain restricted to the research laboratories, occasionally catching the media attention. However, no one can deny that the time is ripe for them to reach the market soon.

## Synthesis and characterization of nanocarbon derivatives

Buckminsterfullerene was discovered in 1985 by W. Kroto and others who received the Nobel Prize 11 years later. Fullerene $C_{60}$ is spherical molecule containing six member aromatic rings and five members radicalize rings. It is a good electron acceptor and it has been studied using cyclic voltammetry. Limited solubility has, however, hampered their industrial use. The molecule has a diameter of 0.7 nm & since it does not contain any hydrogen atom it shows no signal in the $^{1}H$- NMR, except for the proton present on the substituent. It shows only one signal in its $^{13}C$- NMR spectrum at 145 ppm, showing that all 60 carbon atoms are equivalent. Fictionalization by different methods of derivatizationmakes it soluble and derivative fullerenes show no cytotoxicity. However, on derivatization the $^{13}C$-NMRC spectrum is characterized by the presence of up to 60 peaks or 16 peaks between 137-143 ppm, depending on the symmetry of the product. Cost of production of fullerene in the past has also been a limiting factor. In recent years, an Arizona based company is selling $C_{60}$at $20 per gram, when a minimum of 100 gm of this fullerene is purchased. The cost is expected to drop dramatically, when fullerene based products reach the market and are found to be useful. FT-IR spectra & thermo gravimetric analysis (TGA) are also used for their characterization. The FT-IR shows of $C_{60}$ shows peaks just like alkenes or aromatic rings. Two methods of preparing derivatives are the Prato reaction (reaction with nitrenes) and the Bingel reaction (reaction with carbenes) is commonly used for this purpose.

UV-Vis spectrum of $C_{60}$ shows bands 213, 230, 257, 329 and 406 nm. After the Prato and Bingel reaction a weak peak due to at singlet-singlet forbidden transition is seen at 430 nm. Modern mass spectrometric methods are extremely useful for characterizing fullerene adducts when precise molecular weight up to the fourth decimal place can be obtained. The unreacted fullerene can be eluted from silica gel columns on elution with toluene followed by elution with 3:1 methylene dichloride: toluene. However, the nano adducts of fullerene can be precipitated from toluene/ orthro-dicholobenzene using petroleum ether or acetone. Both the Bingel reaction, the Proto reaction have 80-90% success rate.

Common functionalization methods include heating with concentrated $HNO_3$ and $H_2SO_4$ in temperature range of 85 °C to 115 °C. This could partially damage the nanostructure. The carboxylic groups, thus generated make the material more water soluble and serve as points where further reaction ($SOCl_2$) and attachment of other molecules like peptides and drugs can be carried out. However, the harsh acidic conditions used are better avoided. Instead, it would be prudent to use the Prato or Binglel reaction, which could then be followed by the functionalization of the substituent thus added to the Nanocarbon. This would permit this functionalization to be carried out with less damage to the NCMs.

An exceptionally quick method for preparing water soluble poly hydroxylated fullerenes involves reaction in 3 minutes with aqueous sodium hydroxide and a small amount of tert-butyl ammonium hydroxide as a catalyst. An average 26 hydroxyl groups are thus attached, leading to greater water solubility. Characterization of derivatives of other Nanocarbon materials, viz. CNTs and Grapheme is done using FT-IR and UV-vis, TGA, TEM, SEM, cyclic voltammetry and Raman spectroscopy are more commonly used.

## Water soluble fullerenes for medical applications

It is known that fullerene shows little toxicity in its functionalized form. This is in spite of the possible cytotoxicity arising from the efficient generation of singlet oxygen Fullerenes are powerful antioxidants due to their ROS activity [1] and can serve as multifunctional Theranostics (therapy+diagnostics) platforms"demonstrating the beauty and power on nanotechnology". It is nessecery to emphasize that fullerene is homogeneous as it represents a single molecular structure with precise molecular weight and 3D structure, which is very important for the pharmaceutical industry. Unlike fullerene, "the length and chirality of CNTs may vary" and grapheme sheets may be "in different size and termination".

The use of water soluble $C_{60}$ fullerene in anticancer therapy has been described [2]. Being water soluble it could be used for intravenous administration and the Active agent being made available only at the desired site and not circulate throughout the body [3]. These workers transplanted a tumor in mice and studied anticancer activity this mice. Histological sections of mice lung carcinoma in male after 34 days after transplantation were studied. They divided the study into two parts: The $C_{60}$ derivative was injected into the animals before tumor transplantation was called "the protective effect" and when it was injected after the transplantation of the tumor being called "the inhibitive effect". It is noted that in "the protective effect", the C60 derivative activated mitosis and apoptosis of tumor cells. As against this in "the inhibitive effect", $C_{60}$ activated necrosis of tumor cell. When treated with 5mg/kg in lung male carcinoma in male mice C57BL: J in "the protective effect", 35.3 % of tumor growth inhibition was observed. In "the inhibitory effect", 25.1% tumor growth was observed and extension of life by 21.8%. In the metastasis ingestion effect, 96% for "protective" and 48% for "inhibitive" effect of $C_{60}$ were observed, which "is promising for clinical oncology".

A US patent in 2016 establishes the antioxidant property of water soluble fullerenes [4]. In addition to FT-IR, UV-Vis, Zeta potential, MTT assay (cytotoxicity assay), TEM, AFM, SEM have all been recorded. Electron paramagnetic resonance (EPR) measurements are particularly noteworthy for establishing the radical quenching property. The superoxide generated was quenched by $C_{60}$ completely abolishing the EPR spectrum. The MTT assay established the carbon nanomaterials are not toxic. Chemotherapy of breast cancer depends on whether it is carried out before surgery (neo-adjuvant) or after surgery (adjuvant) or whether the cancer is in an advanced stage. Currently used drugs include, Doxorubicin (Adriamycin), Taxotere and Carboplatin. However, all these drugs have severe side effects. Doxorubicin shows severe cardiotoxicity leading to permanent heart damage (cardiomyopathy). However, soluble fullerene C60 modulates such side effects of Doxorubicin. Gadolinium metallo-fullerenol nanomaterials was found as nontoxic breast cancer stem cell specific inhibitor, showing higher anticancer activity than Isplatinum. Intracellular release of doxorubicin is tracked by fluorescence quenching by $C_{60}$. Photodynamic therapy (PDT) has also been considered but $C_{60}$ has a low efficiency at the


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commonly used wavelength of 532nm. Though it absorbs well in UV range, but poorly so at the red end of the spectrum.

The Poster boy of fullerene adducts, the $C_3$ tris-malonic ester $C_{60}$ at 14-15μM) completely eliminated all superoxide radicals generated in situ and this one derivative is thus pushing the field "closer to the market". This compound when administered to non-human primates with Parkinson's disease improved their motor function [5].

"Fullervir", the sodium salt of polyhydroxy fullerene poly-amino-caproic acid, manufactured by Intel firm company showed anti-retroviral properties in human cell cultures infected by human immunodeficiency virus (HIV-AIDS). This agent was able to protect the cell form the cytopathic action of HIV [6]. Fullerene Water Solutions (FWS) containing 0.002%mg C60per 100ml 0.002mg/100mL of water has been approved as dietary supplement by the Ukrainian Ministry of Health. Patients may spray this water as nasal spray and drink certain amounts of this water to overcome ill effects of Alzheimer's disease. Is "Fullervir", an Elixir? Beneficial effects of water soluble $C_{60}$ has been demonstrated in the rat model of arthritis as it arrests arthritis in ankle joints [7]. Should these results be extendable to Humans, suffering and swelling pain and inability to move joints could be consider ably reduced? Inhibition of HIV-1 protease by fullerene based inhibitor has been demonstrated very recently [8]. Water soluble fullerene (FWS) shows beneficial effects on growth and diverse biological models. Effects of NCMs on plants have been documented in *Arabidopsis thaliana*. Interestingly seed germination is promoted and increased lengths of hypo-cotyledons have been observed. This augurs well for agriculture as the seeds could now be sown at greater depth and stronger plants could emerge from the soil. The distribution of nano substances in different parts of the plant body has also been documented. This must caution us about possible distribution of nano-substances in plant bodies, soils and the environment. Presence of fullerene like structures in Chinese's hibiscus (*Hibiscus rosasinensis*) with putative function for mechanical stability and adductive property has recently been established [9].

### SWCNTs and Graphene

Preliminary studies by Romanian scientists have shown that attachment of doxorubicin to NCMs could be used for targeted release of doxorubicin. Though they show TEM, SEM pictures and have studied the release of the anticancer drug but their results are at best indicative in nature. A recent study from the Amrita Hospital, Edapally, Kerala, India conclusively proves the drug like this could be attached to graphene and combined with Photodynamic therapy (PDT) [10]. In these studies Rao et al. [11] the celebrated Indian scientist is also a co-author, lending great credibility to these results. The regression of tumors by this combined PDT, graphene drug therapy is thus well established by this group.

## Application to Materials Science

Efficient solar cell have been fabricated using water soluble Fullerene. Similarly Gadolinium $C_{60}$ adducts have been found useful as MRI contrast agents [12]. FWS containing multiple carboxylic shows excellent magnetic properties and have also been used for nanolithography. Gadolinium chelates are commonly used for MRI scans in Hospitals but the toxic gadolinium can be released from the chelate inside the patient's body. Fullerene-Gadolinium adducts do not suffer from any such limitation. It is thus expected that very soon this that Gd-$C_{60}$ will soon replace Gd-chelates. Hydrogen absorption ability of the FWS is very superior to other alterative s and may, in future, be used to fuel automobiles. A car of nanodimensions with fullerene as wheels has also been conceived! Indeed, using infrared spectroscopy, fullerenes/ fullerene adducts have been detected "in the circumstellar envelopes around low-mass evolved stars (the so-called planetary nebulae [13].

## Fullerene Based Sensors

Soluble derivatives of Fullerene add a new dimension to the construction of highly sensitive biosensors [14]. These have been used to detect glucose levels in blood serum, urea level in urine, hemoglobin, immunoglobulin, glutathione in sample for pathological purposes, to identify doping abuse, to analyze pharmaceutical preparations and even to detect cancer and tumor cells at an earlier stage Thus theranostic applications of water soluble fullerenes in photo-acoustic imaging have been described [15].. Questions are raised as to how far have we progressed with nano devices? Yes, they make good headlines in the media and are good materials for research proposals, but what is the reality? How far are we away from marketable useful nano devices? It is to be hoped that both in medical and materials science applications of water soluble Fullerenes there is much progress in coming years.

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