NANODIAMONDS: A NEW-FANGLED DRUG DELIVERY SYSTEM

Nanodiamonds drug delivery system is a new path to the medical science. The unique nanodiamond properties have demonstrated exceptional performance in various fields especially in pharmaceutical as drug delivery system and biotechnology. As compared to other nanoparticle, nanodiamonds have purity, size selectivity, retention of aggregation, colloidal stability and surface functionality. An approach is made herein to review the concept of nanodiamonds, their advantages, and methods of preparation. Also their wide applications in various fields of drug delivery are reported. Nanodiamond having a coat of the drug and proteins that targets the cancer cell in body and destroy the cancerous cells without affecting any normal cell and they can bind tightly to a variety of molecules and deliver them right into a tumor. This review concludes with an evidence for the future directions and challenges involved in maximizing the potential of these exciting little carbon-based gems in the field of medicine and biotechnology.

INTRODUCTION-
Nanodiamonds are members of the diverse structural family of nanocarbons, which include nano-sized amorphous carbon, fullerenes, diamondoids and tubes. First detailed study about nanodiamonds was conceded in the 1960s in Russia, nanodiamonds have now gained world-wide attention due to their inexpensive large scale synthesis based on the detonation of carbon-containing explosives, small primary particle size (4 to 5 nm) with narrow size distribution, facile surface functionalization including bioconjugation, as well as high biocompatibility [1].

![Figure 1 - Nanodiamonds](image1.jpg)

It is anticipated that the attractive properties of nanodiamonds will be exploited in a similar manner to other carbon nanoparticles, quantum dots, and metallic nanoparticles, for the development of therapeutic agents for diagnostic probes, delivery vehicles, gene therapy, anti-viral and anti-bacterial treatments, and the development of novel medical devices such as nanorobots [2]. This has been used to immobilize proteins and deliver drug molecules. It has also sensing, imaging, and drug delivery properties. The study associated with the interface between Nanodiamond and life sciences which is important for development of effective drug delivery systems. The nanodiamond-insulin clusters hold promise for wound-healing applications and could be integrated into gels, ointments, bandages or suture materials. They are considered potential medical agents due to their high adsorption capacity, high specific surface area, and chemical inertness [3].

STRUCTURE OF NANODIAMONDS-
Nanodiamonds are an allotrope of carbon. Nanodiamonds are carbon-based materials approximately 2 to 8 nanometers in diameter. Each nanodiamond surface possesses functional groups that allow a wide spectrum of compounds to be attached to it, including chemotherapy agents. The crystal structure of nanodiamonds consists of two close packed interpenetrating face centered cubic lattices; one lattice is shifted with respect to the other along the elemental cube space diagonal by one-quarter of its length. Nanodiamond is often described as a crystalline diamond core with a perfect diamond lattice surrounded by an amorphous shell with a combination of sp2/sp3 bonds or onion-like graphite shell [4, 6].

![Figure 2 - Nanodiamond Structure](image2.jpg)

Nanodiamonds are clustered carbon atoms with both graphitic (sp2) and diamondoid (sp3) bonds. The two types of bonds can be interchangeable, for example, the stretched face of diamond is a graphene plane. In reverse, the puckered graphene may become a diamond surface [5].
SIGNIFICANCE OF NANODIAMONDS-
1. Drugs can be slowly released over time.
2. Nanodiamonds can trap nearly 5 times compared to conventional drug delivery.
3. The new system localizes the drugs to minimize and mitigate side effects.
4. It can be combined with a wide variety of drugs and RNA.
5. They’re nontoxic, and the body’s immune system doesn’t attack them. They can bind tightly to a variety of molecules and deliver them right into a tumor.
6. Using nanodiamonds, tiny particles of carbon, as a drug delivery system, to treating breast and liver cancer tumors that are resistant to chemotherapy.
7. The drug-nanodiamond complexes had no negative effect on the white blood cell count. This is especially important for cancer treatment: if the white blood cell count drops below a certain level, treatment is stopped due to the risk of major complications [5].

PROPERTIES OF NANODIAMONDS-
1. Surface area and solubility-
They have a larger surface area, so larger amounts of drugs can be placed on the particles. They are very soluble in water, thus allowing them to travel throughout the body easily. They are smaller, and can be used to target specific areas in the body. They can be easily produced and in large amounts [7].

2. Hardness-
Physical properties of diamond compared to Titanium and stainless steel. The hardness of diamond is about 50 times of Titanium and stainless steel. The toughness of diamond makes it suitable in applications in biomedical fields such as implant, cutting tools for surgeries etc [7].

3. Chemical inertness-
Chemical inertness is an important factor for ND to be applied in biology, since the biological environment is corrosive. Alloy of Ti6Al4V coated with ND films show that the diamond films have a very good chemical resistance to the corrosive liquid [8].

4. Excellent optical property-
Excellent optical property is necessary for diamond to be applied as a biomarker or a biolabel. There are impurity sites within core, defects in the diamond or sp2 clusters on the ND surface. With the light excitation, the ND will emit light with different frequency due to different type of impurity site [9].

5. Chemical modification-
Chemical modification of diamond surface is essential for diamond to be applied as potential biosensor or biochip or a substrate to immobilize biological molecules. With the hydrogen terminated nanocrystalline diamond, designed a chemical procedure to attach DNA onto the diamond surface. Recently, ND with the size of 5-100nm in diameter was carboxylated. It was found that carboxylated ND has good physical absorption properties including hydrophobic and hydrophilic interaction, which can be used to immobilize biomolecules [4].

BIOCOMPATABILITY OF NANODIAMONDS-
Biocompatibility is main aspect when diamond is applied to biology. Many researcher investigated that nanodiamond with small size of 2-10nm are not toxic to a variety of cells through mitochondrial function (MIT) and luminescent ATP production assays. It was found that after the incubation of cells with nanodiamonds, cell morphology is unaffected by the presence of nanodiamonds while nanodiamonds are seen surrounding the cell borders and attached to nitrite extensions [10].

Figure 3- Interactions nanodiamond (Nanodiamond) particles including biomolecular binding

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Before nanoparticles are fully integrated into biomedical applications, their unique interactions with biological systems demands special consideration. Compared with other nano-sized forms of carbon, nanodiamonds show greater biocompatibility irregardless of their purification method, concentration, or size [11]. For example, some researcher demonstrated differential biocompatibility between neuronal and lung cell lines after exposure to aqueous suspensions of carbon nanomaterials (nanodiamond, MWNT, SWNT) at concentrations from 25 to 100 μg/mL for 24 hours with the MTT assay. The trend for biocompatibility was ND>MWNT>SWNT. The lung cells (macrophages) were more greatly affected by the presence of carbon nanomaterials generating up to five times the amount of ROS compared with the neuroblastoma cells after exposure to either MWNTs or SWNTs. However, there was a lack of ROS generation from either cell line after incubation with the nanodiamonds as well as intact mitochondrial membranes further supporting the low toxicity of nanodiamonds [12].

TYPES OF NANODIAMONDS-
1. Commercial Nanocrystalline Diamond Particles
2. Commercial Ultrananocrystalline Diamond Particles
3. Diamondoids

1. Commercial Nanocrystalline Diamond Particles-
Nanocrystalline diamond particles with characteristic sizes of primary particles in the range of several tens of nanometers can be in the form of isolated monocrystalline particles or polycrystals as shown in figure no. 3. Monocrystalline nanoparticles are obtained by processing micron-sized monocrystalline diamond particles, which are, in turn, a byproduct of natural diamond. The processing of micron-sized diamond particles to smaller fractions includes grinding, purification, and grading of the powder [13].

![Figure 4 - Nanocrystalline Diamond Particulate](image)

Monocrystalline ground diamond particles have rather sharp edges compared with other forms of nanodiamond (Fig). Monocrystalline natural nanodiamond powder is the purest product within the class of nanodiamond materials. Synthetic HPHT type Ib monocrystalline diamond powders used for annealing for Bio-labeling applications. The polycrystalline nanodiamond powder is processed from micron-sized polycrystalline diamond particles obtained by shock synthesis (DuPont de Nemours’s method). Polycrystalline particles consist of nanometer-sized diamond grains (20 to 25nm). The finest diamond fraction produced by micronizing followed by grading has an average particle size of 25 nm. This type of nanodiamond has a high content of impurities and thus far has not been used for bio-applications. The shape of primary particles is more platelet like rather than spherical [14].

2. Commercial Ultrananocrystalline Diamond Particles-

![Figure 5 - Ultrananocrystalline Diamond Particulate](image)
Out of several types of ultrananocrystalline diamond particles only detonation nanodiamond has been commercialized. The size of primary detonation nanodiamond particles depends on the weight of explosive charge so, in principle, there is no specific maximum size, although most vendors produce particles with an average size of 3.5 to 6 nm. This type of nanodiamond is most frequently used for envisioned bio-applications such as broad drug delivery platforms for nanoscale medicine, protein adsorption, carriers of genetic material in gene gun ballistic delivery, as enter sorbents, as well as other applications. The cost factor is also an important issue for applications of nanodiamond particles. For example, HPHT nanodiamond with an average particle size 25 nm costs $75/gram. However, well purified DND powder costs only about $1 to $2/gram for polydispersed powder (200 nm average aggregate sizes) and about $10–20/gram for a fraction with 20 nm average aggregate size. Since detonation ND is the most popular starting material within the nanodiamond particle family for biomedical applications [15].

3. Diamondoids-
As highly rigid, well defined, readily derivatizable structures, these so-called “higher diamondoids” are valuable molecular building blocks for nanotechnology. With more than 3 crystal diamond cages, higher diamondoids are intermediate in size to the adamantane molecule, the smallest species of H-terminated cubic diamond containing only 10 carbon atoms, and ultrananocrystalline diamond particles with sizes more than 2 nm. Higher diamondoids are extracted from petroleum as diamond molecules in the form of nanometer-sized rods, helices, discs, pyramids, etc [15].

lower diamondoids
Adamantane (C_{10}H_{18}), Diamantane(C_{14}H_{29}), Triamantane (C_{18}H_{24}),

Higher diamondoids
Hydrogenated molecules with sizes 1-2 nm
Isolated from petroleum.

METHODS FOR SYNTHESIS OF NANODIAMONDS-
1. Detonation Nanodiamond-
2. Ultrasonic Cavitation Method-
3. Pulsed-laser Irradiation-

1. Detonation Nanodiamond-
Detonation Nanodiamond (DND), often also called ultradispersed diamond (UDD), is diamond that originates from a detonation. A nanodiamond can be created by detonating mixture of trinitrotoluene (TNT) and hexogen (RDX).

Figure 7- Two explosives most commonly employed for detonation synthesis
This idea is that pure nanodiamond can be produced by the detonation of a diamond blend and will then form by chemical purification. The soot left over actually contains tiny diamonds, which measure four nanometers in size. However, in order for these diamonds to shine and look anything like diamonds they must be exposed to a high-energy electron beam and then heated 800 degrees Celsius. The diamond yield after detonation crucially depends on the synthesis condition and especially on the heat capacity of the cooling medium in the detonation chamber (water, air, CO2, etc.). The higher the cooling capacity, the larger the diamonds yield, which can reach 90%. After the synthesis, diamond is extracted from the soot using high-temperature high pressure (autoclave) boiling in acid for a long period (1–2 days). The boiling removes most of the metal contamination, originating from the chamber materials, and non-diamond carbon. Various measurements, including X-ray diffraction and high-resolution transmission electron microscopy revealed that the size of the diamond grains in the soot is distributed around 5 nm. The grains are unstable with respect to aggregation and spontaneously form micrometer-sized clusters the adhesion is strong and contacts between a few nano-grains can hold a micrometer sized cluster attached to a substrate [16, 17].

2. Ultrasonic Cavitation Method-
Diamond nanocrystals can also be synthesized from a suspension of graphite in organic liquid at atmospheric pressure and room temperature using ultrasonic cavitation. The yield is approximately 10%. Phenomenon of cavitation can be occur when the emission of ultrasonic wave into the liquid. During formation of cavitation cavities filled with gas or their mixture. During the cavitation a relatively low average energy density of acoustic field is trans-formed into the high energy density inside and near the being begun to flap bubble. During this phenomenon pressure and temp 101k developed. The acoustic cavitation is expended on the emission of shock waves. The selection of this carbon-containing liquids hexane C₆H₁₄ and ethanol C₂H₅OH is caused by the fact that acoustic cavitation energy is compared with tensile energy of the connection between the atoms C and H, and hydrogen possesses a sufficient diffusion rate from the collapse medium of cavitation bubble for obtaining the nanodiamond [14, 17].

3. Pulsed-laser Irradiation-
An alternative synthesis technique is irradiation of graphite by high-energy laser pulses. Phase transformation from graphite to sp-bonded carbon chains carbine and nanodiamond has been induced by femtosecond laser pulses on graphite surface. The structure and particle size of the obtained diamond is rather similar to that obtained in explosion [17].

APPLICATIONS OF NANODIAMONDS-
Being extremely small and with high amount of surface atoms, nanodiamond has diversified applications. They include the preparation of composites and a coating, to modify surfaces, uses broad biomedical applications, in pharmaceutical formulation nanodiamond has two types application:
1. General application
2. Biomedical application

1. General applications-
   a) Cosmetic-
   As nanodiamond is non-poisonous, a big area of application is nanodiamond impregnated cosmetics. So, nanodiamond can be formulate as a dental filling, lotion, deodorant, toothpaste, shampoo, antibiotic, dermal strip, skin cleanser [18].
   
   b) Dental care-
   Nanodiamond may be formulated as a dental material. The dental material can be formulated for use as a filling, reconstruction, and the like. The nanodiamond particles can provide additional mechanical strength, as well as an appearance that approximates natural enamel when dry. Alternatively, the remedial healthcare composition can be formulated as toothpaste including an acceptable carrier and a plurality of nanodiamond particles. Nanodiamond added toothpaste has another advantage, as nanodiamond is known to cure gum disease [18].
c) Skin care-
Owing to unique adsorption capabilities of nanodiamond, their addition to skincare products enhances the effect of biologically active ingredients and facilitates their penetration into deeper skin layers. Nanodiamond makes all biologically-active additives “work” at their maximum efficiency. Also, due to their unique optical properties, nanodiamond is an excellent agent for skin protection from harmful UV radiation. The nanodiamond surface functional groups form powerful bonding with water molecules to provide an all-day-long moisturizing effect and to protect the skin from aging. At the same time, nanodiamond-base creams are fully and rapidly absorbed by the skin. The presence of nanodiamond particles can improve absorption of oils and undesirable deposits from the skin without abrasiveness associated with larger diamond particles [18].

2. Biological applications-

a) Nanodiamond in biomedical applications-
Due to its hardness, chemical inertness, thermal conductivity, and low cytotoxicity, nanodiamond could be applied as coating materials of implants, other surgery tools, etc. in biomedical fields. Implanted orthopedic screws, coated with nanocrystalline diamond film to a patient with a complex fracture of femoral bone After surgery, no ejection was observed. As such, diamond is ideal for use in medical applications [19].

b) Nanodiamond improves image resolution of MRI-
Magnetic resonance imaging (MRI) is a noninvasive medical imaging technique that uses an intravenous contrast agent to produce detailed images of internal structures in the body. Contrast agents are used in MRI because they improve image resolution. The coupling of MRI contrast agent to a nanodiamond results in dramatically enhanced signal intensity and thus bright image contrast. Gadolinium (Gd) is the material most commonly used as an MRI contrast agent, but its contrast efficacy can be improved by conjugation with nanodiamond. Gd (III)-ND complex demonstrated a greater than 10-fold increase in improvement of image resolution and, in turn, a significant increase in contrast enhancement [19].

c) Drug delivery vehicles-
The uptake of nanodiamond by living cell found in the biological nanodiamond research facilitated the use of nanodiamonds as drug carriers and delivery vehicles. Nanodiamonds possess numerous hallmarks of an ideal drug delivery system and are promising platforms for advancing cancer therapy. They’re nontoxic, and the body’s immune system doesn’t attack them. They can bind tightly to a variety of molecules and deliver them right into a tumor [19].

d) Applications as an excellent sorbent-
Materials like activated carbon have been known for long to possess good adsorptive properties, especially when they exhibit a large active surface. It may adsorb up to four times its own weight of water, so it is a suitable additive in certain areas of application. It is not only water, but also other substances (like with biological origin) that can be adsorbed to the nanodiamond surface. As biological materials are made of carbon compounds, almost all life sustaining chemicals can be absorbed by nanodiamond. Thus, nanodiamond is an excellent absorbent for amino acids, proteins, platelets, and DNA. Nanodiamonds are typically smaller than most viruses (10–100 nm) and bacteria (10–100μm). Therefore, nanodiamond can be used to penetrate the outer layers of viruses and bacteria and then attach to RNA, DNA or other groups within the organism to prevent the virus or bacteria from functioning. Human body contains about 1/4 of carbon by weight. Nanodiamond as carbon is non-poisonous. Moreover, it is not only cancer inactive, but also a catalyst for promoting drug effectiveness. For examples, nanodiamond has been used to treat burning skin infections, food poisons, and intestine malfunctions with good results [20].

e) Immobilization of biomolecules-
The chemical modification and physical absorption of diamond surface hold promises for nanodiamond to be applied in immobilization of protein and DNA for purification, separation, and further analysis. Using detonation nanodiamond successfully separated recombinant Ca2+-activated photoprotein apoobelin and recombinant luciferase from bacterial cells of Escherichia coli through physical absorption of proteins on nanodiamond. For traditional purification by chromatographic means, it usually takes several days. The procedures using nanodiamond, the whole process took 30–40 min with a yield of 35-60%. Kong and coworker applied the same principle to capture proteins and DNA for the matrix-assisted laser desorption/ ionization (MALDI) time of flight (TOF) mass spectrometry (MS). Carboxylated nanodiamond exhibits high affinity to proteins and polypeptides through hydrophobic and hydrophilic forces. Proteins in very dilute solution can be easily captured by nanodiamond and separated and directly analyzed by MALDI-TOF-MS [20].
f) **Nanodiamond-insulin administration**

One medical use for the nanoparticles is to administer insulin, which acts as a growth hormone, into the body to help fight infection after wounded. The nanodiamonds with insulin can then be put in gels, ointments, and bandages. Since nanodiamonds tend to cluster naturally after extraction, thus having a relatively large surface area, large amounts of insulin can be placed on the nanodiamonds. When nanodiamond-insulin clusters are in an environment with a slightly basic pH, the insulin releases itself from the nanodiamonds. Because a bacterially infected wound has a pH higher than the physiological pH of 7.4, the insulin will only release where the infected area is. Since localized release of therapeutic medicine is becoming more and more important [20].

g) **Safe gene therapy with Nanodiamonds**

Gene therapy holds promise in the treatment of a myriad of diseases, including cancer, heart disease and diabetes, among many others. However, developing a scalable system for delivering genes to cells both efficiently and safely has been challenging. The power of nanodiamonds as a novel gene delivery technology that combines key properties in one approach: enhanced delivery efficiency along with outstanding biocompatibility. A research team engineered surface-modified nanodiamond particles that successfully and efficiently delivered DNA into mammalian cells. The delivery efficiency was 70 times greater than that of a conventional standard for gene delivery. The new hybrid material could impact many facets of nanomedicine [19, 20].

h) **Nanodiamonds deliver on cancer treatment**

Cancer is usually treated with a number of chemotherapeutic agents but the results and outcomes are not 100%. But now a new shine have reached us giving a promise to our next generation about 100% and perfect cure of cancer. Attaching chemotherapy drugs to small particles called nanodiamonds can make the drugs more effective. Anticancer drugs tend to become ineffective because cancer cells quickly pump them out before they had to do their work. Nanodiamonds carbon based particles 2–8 nanometres in diameter with a truncated octahedral structure that gives it multiple facets not unlike a diamond's Each Nanodiamonds surface possesses functional groups that allow a wide spectrum of compounds to be attached to it, including chemotherapy agents overcome this problem because the cellular transport proteins that usually pump the drug out of the cell can't carry them. The drug therefore stays inside the cell. Delivery of drug using this system reduces the side-effects and improves the targets [19, 20]. One experiment had done on nanodiamond with anticancer drug. The anticancer drug doxorubicin attached to nanodiamonds. They had treated mice which have liver tumours with either this compound or with doxorubicin alone, and checked levels of the drug in the tumours two days later. They found that doxorubicin levels were ten times higher in mice treated with the nanodiamond compound compared with mice given doxorubicin alone, and remained high for seven days. The tumours of mice receiving nanodiamond-doxirubicin also shrank more and the mice survived longer [20].

**CONCLUSION**

Nanodiamonds drug delivery system shows a new path to the medical science. The unique nanodiamond properties have demonstrated exceptional performance in various fields, especially in pharmaceutical as drug delivery system and Biotechnology. As compare to other nanoparticle nanodiamond have that purity, size selectivity, retention of aggregation, colloidal stability, surface functionality. Recent work on cancer therapy shows that nanodiamond is good carrier for used in drug therapy. Nanodiamond doesn't harm to other system of our body and also having patient compliances. Nanodiamond having a coat of the drug and proteins that targets the Caner cell in body and destroy the cancerous cells without affecting any normal cell and they can bind tightly to a variety of molecules and deliver them right into a tumor. So in future, Nanodiamonds can be used as safe and non toxic target drug delivery system and cure many diseases including cancer etc. As nanodiamond drug delivery is an emerging and growing concept, it is gaining more attraction by industries and many research scientists due to its wide potential and acceptance.

**REFERENCES**