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# An Overview of Nano diamond Formulation in Cancer Treatment

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**Mini Review**

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## ABSTRACT

The major challenge of cancer chemotherapy is the improvement of systemic bioavailability, targeted drug delivery, reduced off-target activity, Enhanced Permeation and Retention Effect (EPR), sustained, and controlled release profiles. Most current conventional drug delivery systems cannot optimize the above mentioned problems, leading to chemotherapeutic resistance. More studies are being conducted on novel delivery systems to overcome these problems. One such system is the nano diamond formulation. Nano diamonds not only overcome these problems but also increase cytotoxicity, stimulate the immune system, prevent metastasis, decrease resistance, and optimize the formulation's pharmacodynamic properties. The unique surface chemistry of the particle allows easy modification of the outer layer with different functional groups to enhance the receptor-ligand interaction. The property of self-assembling into aggregates of a suitable size range makes it ideal for controlled and sustained drug delivery. However, much clinical investigation is required on the safety profile of the formulation for chronic use.

## INTRODUCTION

Malignancy, or cancer, is a condition in which uncontrolled cell division exists in any body part. The global incidence rate of cancer is increasing daily, thus producing a need for newer therapeutic approaches to target cancer cells effectively. But, the recent therapeutic approaches have shown lower bioavailability and poor patient compliance, ultimately causing chemotherapeutic resistance. Thus, there are much higher failure rates of the therapeutic strategies. The current research focuses on Novel Drug Delivery Systems (NDDS). This includes the nanoformulations, which have improved the bioavailability, reduced adverse effects, and sustained and controlled

release patterns. Thus, the frequency of administration is also decreased, providing good patient compliance [1]. Nano diamond is now one of the most researched NDDS for the detection and treatment of cancer. They are diamonds of size in nano-range. Nano diamonds found their application in the manufacture of resistant coat materials in the late 1980s. But in the late 1990s, they were researched for their application in cancer detection [2]. They are used to deliver chemotherapeutic agents such as small molecules, nucleic acid, protein, and cytotoxic drugs with greater precision [3]. The success of the nano diamond in targeting cancer cells is by controlling the surface chemistry and the electronic and magnetic properties.

## LITERATURE REVIEW

### Nano diamonds and their properties

They are diamonds in the nano-scale range, i.e., 1-100nm. They are octahedral, ultra-crystalline, ultra-dispersed nanoparticles mostly made of carbon (70%-90%). Another material used to manufacture nano diamonds is copper, which is eco-friendly. Commercially, they are synthesized by detonation, chemical vapor deposition, High-Pressure High-Temperature (HPHT) method, Light Hydro-Dynamic Pulse (LHDP) method, and irradiation with a pulsed laser. The size of the nano diamond produced by detonation is 4-5 nm [4]. The surface can be easily modified with good surface properties, greater surface area, fluorescent surface (used for imaging), improved biocompatibility, and better scalability at a low production cost. The cover can be modified by functional groups such as aldehydes, ketones, carbonate esters, nitroso, hydroperoxides, amides, hydroxides, and carboxylic groups [3]. These functional groups help to improve the aqueous solubility and target the ligand. However, in suspension form, these particles tend to form larger aggregates in size range of 100-200 nm, which can get trapped within the systemic circulation and block the blood vessels [5]. The other disadvantage of the formulation includes clearance by the immune system.

The aggregation of the particle is due to capillary pressure, hydrogen bonding, and Van der Waals forces [6]. However, aggregation (of size 80 nm) can be favorable in case of orderly arrangement, which has improved efficacy and half-life in drug-resistant tumors. The process of de-aggregation includes centrifugation, ball milling, Bead-Assisted Sonic Disintegration (BASD), and ultrasound-assisted disintegration [7].

The complex nano diamond consists of three layers: A core consisting of $sp^3$ hybridized carbon, a middle layer of non-homogenous carbon, and an elastic outer layer. The outer layer mainly consists of $sp^2$ hybridized carbon or $sp^2$ hybridized graphene with additional oxygen, hydrogen, or nitrogen atoms [8]. The surface should be hydrogenated for more excellent stability. However, polymer coating on the surface improves the interaction with ligand. The outer layer can be modified with glutamic acid, folic acid, epidermal growth factors, sodium alginate, polyethylene glycol, perfluorooctanoic acid, supraparticles, thenoyltrifluoroacetone, and rare earth [9]. The nano diamond can consist of impurities based on their functions. Nitrogen impurity is required to produce fluorescence when the formulation is used for imaging. 3H doping provides radiolabelling for diagnosis. Improved electro-conductivity is provided by boron doping [10].

## DISCUSSION

### Mechanism of action in cancer chemotherapy

The mechanism of action of nano diamonds in cancer treatment is as follows:

**Enhanced pharmacodynamics:** The nano diamond formulation showed good systemic acceptability and tolerability due to its precise and passive tumor targeting. It exhibits reduced action and accumulation in healthy cells [11]. This can be understood by nano diamond-doxorubicin formulation coated with polyglycerol. *In vivo* doxorubicin treatment showed systemic myelosuppression, neutropenia, and increased hepatic aminotransferases. While, nanodiamond-doxorubicin in the TNBC mouse model showed no such systemic toxicity and decreased off-target activity [12].

**Decreased chemotherapeutic resistance:** This is a significant challenge for can treatment. The efficacy of the anticancer drug is lost due to resistant malignant cells. This occurs due to enhanced expression of transporters and efflux pumps due to prolonged drug therapy. Transporters include Multi-Drug Resistance-Associated Protein (MDR ABCC1) and P-glycoprotein (P-GP). ATP-binding cassette (ABC) proteins are efflux pumps. These transporters, along with efflux pumps, remove the drugs from the cytoplasm of the malignant cells, thus reducing the concentration required for action [13]. But nano diamond conjugated drug delivery showed good activity against multi-drug resistant cancer cells. The mitoxantrone-nano diamond formulation showed enhanced activity against MDA-MB-231 cell lines, which are resistant [14].

**Enhanced cytotoxicity:** Nano diamond-drug conjugate showed enhanced cytotoxicity in both *in vivo* and *in vitro*. This mechanism can be understood by its prolonged circulation and retention time due to its self-aggregation into a suitable size range [15]. This can be understood by comparing Paclitaxel-nano diamond (hydroxylated) conjugation and free crystalline nano diamond in MCF7 cell lines. The conjugate showed sustained and controlled release for more than 70 hours, while free paclitaxel showed less than half drug delivery in the same period.

**Reversed immunogenicity:** Malignant cell-induced immunosuppression is a common complication due to the overproduction of Myeloid-Derived Suppressor Cells (MDSC), which promotes the survival and proliferation of malignant cells. Nano diamond-doxorubicin conjugate reduced Granulocyte-Colony-Stimulating Factor (G-CSF) concentration in animal models, converted M2 macrophage into M1 macrophage in 4T1 *in vitro* cell lines, and released Damage-Associated Molecular Patterns (DAMP) within the tumor cells to stimulate the immune system [16].

**Metastasis prevention:** The diagnosis, treatment, and prevention of metastasis are one of the complicated tasks in the management of malignancy. Methods to control metastasis include RNA interference induced by decreasing the expression of metastasis-associated genes, reducing angiogenesis by anti-vascular endothelial growth factor, and destroying the existent tumor cells. Nano diamonds help eliminate the primary tumor by prolonged circulation time due to surface modification with 1, 2-distearoyl-sn-glycero 3-phosphoethanolamine-N-[methoxy (polyethylene glycol)-2000] [17] .

## Challenges

The major challenge of nano diamond-mediated drug delivery is its tendency to self-aggregate during the production and delivery of the formulation. The particles can aggregate within the size range of 200nm, which can block the blood vessels and increase systemic toxicity [18]. Due to its tight arrangement, the aggregation is complex to re-disperse even through processes such as ultra-sonication [7]. Despite its good *in vitro* and *in vivo* activity, no proper testing of the formulation on humans has been conducted to confirm its safety and efficacy. Nano diamonds synthesized by the HPHT method showed the most negligible cytotoxicity and did not stimulate the inflammatory mediators. Carbon-based nano diamonds do not have short-term activity; they require prolonged administration for their cytotoxic effect. However, their efficacy is later found primarily concentration-dependent and not time-

dependent [19-21]. Most formulations showed more significant accumulation in the liver (>60%). Accumulation was also found consistently in the lungs and spleen even after 30 days, and a minor distribution was located in bone and heart [22-24]. Despite its accumulation, it showed significantly less activity. To date, no clinical investigation has been conducted on the pharmacokinetic profile of chronic administration of the nano diamond-based delivery system (Table 1).

**Table 1.** Table showing various formulations, their target and outcomes which are currently being researched.

| Sl. No. | Formulation | Target | Outcome | Reference |
|---|---|---|---|---|
| 1 | Nano diamond-doxorubicin complex | Breast cancer | Prevention of lung metastasis | [19] |
| 2 | Epirubicin-absorbed nano diamond complex | Liver cancer | Kills chemotherapeutic resistant hepatic cancer cells | [17] |
| 3 | Fructose-coated doxorubicin-nano diamond complex | Breast cancer | Target breast cancer cells with greater precision | [23] |
| 4 | Polyelectrolytes, polyethyleneimine, polyacrylic acid, and polyethylene glycol coated nano diamond-gemcitabine prodrug complex | Pancreatic cancer | Enhanced enzyme sensitivity | [20] |
| 5 | Nano diamond-paclitaxel conjugate | Lung cancer | Reduced cell viability, increased mitotic arrest, and apoptosis in A549 cell lines | [8] |
| 6 | Nano diamond-mitoxantrone conjugate | Breast cancer | Increased drug retention | [14] |
| 7 | Melittin and polypeptide grafted nano diamond conjugate | Breast cancer | Controlled release and increased cytotoxicity against MCF7 cell lines | [4] |
| 8 | Sorafenib and lipid-coated nano diamond conjugate | Gastric cancer | Prevent metastasis and increase the bioavailability | [22] |
| 9 | Cetuximab, paclitaxel, and nano diamond conjugate | Breast cancer | Target epidermal growth factor receptor of breast cancer cells (of triple-negative type) | [6] |
| 10 | Doxorubicin and DGEA peptide-nano diamond conjugate | Prostate cancer | Improved delivery and increased malignant cell death | [11] |

## CONCLUSION

Different nano diamond formulations' activity and efficacy mainly depend on their manufacturing procedure. This influences the physicochemical properties (such as surface characteristics, charges, size, and presence of impurities) and other formulation attributes for optimized drug delivery. Thus a universal standardized procedure is required to produce consistent formulation is needed. Further long-term clinical investigation is necessary to confirm the safety profile of the formulation. More research is needed to overcome the targeted area's physiological barriers to drug delivery by developing a "stealth" formulation. Currently, studies are focused on developing non-spherical forms of nano diamonds for Enhanced Permeability and Retention Effect (EPR) within the tumor micro-environment. Incorporating antibodies within the nano diamond-drug conjugate to target with more precision is also being studied.

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