International Journal of Research in Engineering, Science and Management
Volume 5, Issue 4, April 2022
https://www.ijresm.com | ISSN (Online): 2581-5792

How Nanoparticles can be Used to Deliver Avastin to Cervical Cancer Cells

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***Abstract*: This paper is intended as a review of current research and understanding the application of nanotechnology for medical treatments, with special reference to Cervical Cancer. It also uses pharmacokinetic (PBPK) modeling, which integrates system data with drug/nanoparticle in-vitro data and based on this simulation tries to identify the effective material for nanoparticles to be involved in the targeted delivery of Avastin to cervical cancer cells. The author is a higher secondary school student and this research was carried out as part of the academic project work.**

***Keywords*: Nanoparticles, Cancer cells.**

1. Introduction

A. Nanotechnology in Medicine

Nanotechnology or nanoscience is in essence, the manipulation of matter on an atomic, molecular and supramolecular scale [1]. A more precise description of nanotechnology was established by the national nanotechnology initiative, which defines nanotechnology as "the manipulation of matter with at least one dimension sized from 1 to 100 nanometers". However, since the field of nanoscience is still in the genesis of its evolution, researchers and scientists consider the scientific concepts underlying the field more important than the semantics concerning a universally accepted definition.

Nanomedicine is the medical application of nanotechnology. It ranges from the medical applications of nanomaterials and biological devices, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology as biological machines [2]. Nanomedicine treatments include nanoparticles, defined as solid submicron particles consisting of polymers or inorganic material and liquid-based drug nanocarriers such as nanoemulsions (NEs). Nanoformulations can be produced to contain a drug (or drugs), antibody, detection probe as well as several other substances [3].

B. Targeted Drug Delivery

In targeted drug delivery, medication ensures concentrated delivery of medicines to some parts of the body as warranted. This is also called smart drug delivery and is largely based on nanomedicine, which plans to make use of nanoparticles for drug delivery. To avoid healthy tissue, the nanoparticle loaded with the drug is introduced to a place with exclusively diseased cells. The advantages to the targeted release system are the reduction in the frequency of the drug dosages taken by the patient, having a more uniform effect of the drug, reduction of drug side-effects, and increased bioavailability [4].

However, the high cost of such treatments and the increased risk of nanotoxicity and toxic accumulation near the tissue discourages widespread use. Targeted drug delivery can be used to treat cardiovascular diseases and diabetes but its most important application is to treat tumors. It blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with rapidly dividing cells, like in the case of chemotherapy.

C. Nano Treatments Specific to Cancer

Nanotechnology cancer treatments are expected to destroy cancerous tumors with minimal damage to healthy tissue and organs and facilitate early detection and elimination of cancer cells before they form tumors. The high surface area to volume ratio of nanoparticles allows for a plethora of functional groups to be attached to a nanoparticle, which can then seek out and bind to certain tumor cells [9]. Particles are engineered in a way that they are attracted to the antigens of the diseased cells, which allows for direct treatment of those cells, thereby reducing damage to healthy cells in the body. Biocompatible nano-vesicles, called liposomes are spherical vesicles enveloped by a phospholipid bilayer; a variety of phospholipids can be utilized for targeted drug delivery, allowing for degradation control in cells [5].

The uniqueness of targeted drug delivery systems is that it optimizes regenerative processes in the body. The delivery of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body helps to maintain the required plasma and tissue drug levels in the body and this prevents any damage to the healthy tissue via the drug [6]. The potential value of metal-based nanomaterials as radio sensitizers in cancer treatment is also in the pre-clinical stage of in vivo and in vitro treatments [7]. Various studies have indicated that radio sensitizing ability could be influenced by nanomaterial size, concentration, surface coating, and the radiation energy [7].

D. Hollow Nanoparticle for use in Targeted Treatment

Hollow nanoparticles from corn storage protein Zein, with average diameters as small as 65 nm and capable of loading a

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large amount of drug and penetrating into the cell cytoplasm, have been developed for potential drug delivery applications. As an important protein co-product of corn-based ethanol, Zein is biocompatible and has been proved to be useful for medical applications through in vitro and in vivo evaluations [8]. Refer Figure 1. Zein can overcome the limitations of inorganic or metal nanoparticles that tend to accumulate in the organs and tissues and is therefore preferable for drug delivery applications. However, it has been observed that only small proteins and peptides are able to penetrate into cells and Zein with a molecular weight of 14–44 kDa may not be able to enter into the cells [8]. Structures of most drugs used in cancer treatments however have larger molecular structures, thus the use of Zein particles is nullified. Nanoparticles made of biocompatible metallic compounds are thus more suited to drug delivery in spite of a high risk of accumulation at target tumor.

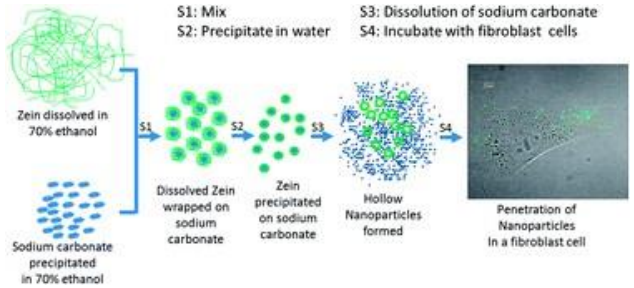

Fig. 1. Hollow nanoparticles from zein for potential medical applications
Source: Helen Xu et al [8]

Liposomes or hollow nanoparticles have uses as drug delivery vehicles in medicine, adjuvants in vaccination, signal enhancers/carriers in medical diagnostics and analytical biochemistry, solubilizers for various ingredients as well as support matrices for various ingredients. In vitro and in vivo studies of their interactions with cells have shown that the predominant interaction of liposomes with cells is either simple adsorption or subsequent endocytosis. Sterically stabilized liposomes may also act as a sustained drug release system either as a long circulating micro reservoir or localized drug depot. The drug remained encapsulated in circulating liposomes for up to one week after injection, while drug metabolites were found at tumor sites, indicating that they had been released by the liposomes. The absorption of the drug in tumors was 4–10 times superior to that in the control group which was treated with the free drug. The high efficacy was due to the approximately 10-fold higher drug concentration in lesions as compared to the administration of free drugs [9].

E. Avastin as a Drug against Cervical Cancer

Bevacizumab, marketed as Avastin, is the drug primarily used to treat cervical cancer that has not gotten better with other treatments, has metastasized, or has recurred. It is a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. These cytokines and chemo attractants are secreted by immune regulatory cells, but also by tumor cells, tumor-associated macrophages, and stromal cells. Avastin binds to VEGF and inhibits VEGF receptor binding, thereby preventing the growth and maintenance of tumor blood vessels [10].

The use of Avastin has been approved for usage in combination with chemotherapy for stage III or IV of ovarian cancerpost-surgical operation. The approval was based on a study of the addition of Avastin to Carboplatinand Paclitaxel, drugs that are commonly used in chemotherapy of primarily Ovarian Cancer, Colorectal Cancer and now being introduced in clinical trials to

Cervical Cancer. Progression-free survival was increased to 18 months from 13 months [11]. Avastin is administered as an intramuscular injection and as a pill in less severe cases. However, during the FDA approved clinical trials, adverse reactions occurred at a higher incidence (at least 5%) of patients receiving the drug: diarrhea, nausea, stomatitis, fatigue, arthralgia, muscular weakness, pain in extremities, dysarthria, headache, dyspnea, epistaxis, nasal mucosal disorder and hypertension. At a higher incidence (≥2%) the reactions included: fatigue, hypertension, platelet count decrease and white blood cell count decrease [11].

2. Variables

A. The "Perfect" Material

An ideal drug delivery mechanism should be non-toxic, biocompatible, non-immunogenic, biodegradable, and avoid recognition by the host's defense mechanisms. Biocompatible materials that do not affect the body's working or buildup like Zein are preferred in treatments, however its diameter renders it essentially useless in delivering drugs to tumor cells. Size is a major determinant in nanoparticle disposition allowing them to preferentially accumulate in solid tumor sites. Therefore, despite a higher risk of accumulation in target sites, biocompatible metals are preferred.

Metals are also more likely to be receptive to hydrophobic or hydrophilic layering to give the delivery system an edge in permeating the body's natural defences. Utilization of cell-specific ligands that allows the nanoparticle to bind specifically to the cell that has the complementary receptor, reduces chances of off-site buildup.

The major factors affecting the delivery of a targeted drug delivery system using liposomes are the permeability into the human tumor cells, how metal buildup affects the body's systems, and the reaction of said metals to the medicine payload, in this case, Avastin.

Iron oxide nanoparticles (IONPs) are one of the major players in the burgeoning nanomedicine field in part due to their super paramagnetism; a property generally exploited in imaging, size; about 10–20 nm and most importantly, the possibility of receiving a more biocompatible coating. IONPs constitute robust nanoplatforms as they achieve high drug loading as well as targeting abilities stemming from their magnetic and biological properties [12]. Their magnetic properties, low cost, and excellent biocompatibility make them the seemingly ideal candidate for targeted drug delivery systems.

Copper nanoparticles are one of the most interesting nanomaterials due to their antibacterial, antifungal, anti-inflammatory and anti-proliferative properties. Copper nanoparticles and copper-gold core/shell nanoalloys can easily be loaded by cytostatic and applied as drug nanocarriers. The introduction and release of chemotherapeutic agents show potential for kinetic and thermodynamic studies of drug adsorption. Copper nanoparticles have potential to be used in targeted cancer therapy, mainly in part due to their unique properties and cytotoxic effect in cancer cells [13].

Gold nanoparticles can be synthesized in a wide range of sizes and surface functionalities to be excellent carrier molecules for cancer drug delivery. They have been widely used in the field of radiation medicine as radiation enhancer and also to provide therapeutic enhancement in radiation therapy due to the efficient and targeted drug delivery to the tumor site. Gold nanoparticles have a multitude of applications as platform nanomaterials for biomolecular ultrasensitive detection, killing cancer cells by hyperthermal treatment, labeling for cells and proteins and delivering therapeutic agents within cells. They have large surface areas so their surfaces are readily available for modification with targeting molecules or specific biomarkers to target tumour cells easily [14].

Silver nanoparticles (AgNPs) are of special interest, especially in biomedicine. AgNPs are known for their broad-spectrum and highly efficient antimicrobial and anticancer activities. Small silver nanoparticles offer a lot of advantages as timed/controlled intracellular drug carriers; including adjustable size and shape, enhanced stability of surface-bound nucleic acids, high-density surface ligand attachment, transmembrane delivery without harsh transfection agents and protection of the attached therapeutics from degradation. Conventional cancer treatment such as chemotherapy, radiotherapy, or surgery has its limitations associated with drug toxicity, unprecedented side effects, drug resistance, and lack of specificity. AgNPs overcome these by reducing side effects and enhancing the efficiency of cancer therapy due to their ability to cross various biological barriers and to provide targeted delivery of drugs.

Zinc Oxide nanoparticles have multiple properties that are useful for biomedical applications including favorable band gap, electrostatic charge, and surface chemistry. Notably, ZnO nanoparticles appear to have inherent anti-cancer cytotoxicity actions [20]. Their low-cost, low toxicity and high biocompatibility make them a strong competitor.

3. Review of Risk and Error Assessment

The pharmacokinetics and pharmacodynamics of nanomedicine differ among different patients. Nanoparticles have beneficial properties that can be used to improve drug delivery while overcoming biological barriers and the body's natural defence mechanisms. Complex drug delivery mechanisms that include the ability to get drugs through cell membranes and into cell cytoplasm are under development. Triggered release of drugs in response to a stimulus on entry into the diseased tissue is one way for drug molecules to be used more efficiently. It is possible to prevent tissue damage through regulated drug release; reduce drug clearance rates; or by lowering the volume of distribution and reducing the effect on non-target tissue. A lot of work is still ongoing to optimize and better understand the potential and limitations of nanoparticulate systems [17].

Although research proves that targeting and distribution can be augmented by nanoparticles, the study of the dangers of nanotoxicity is of paramount importance. The toxicity of nanoparticles depends on their size, shape, and material. These factors also affect the build-up of the nanoparticles and the organ damage that may occur. Nanoparticles are made to last long, but this causes them to be trapped within organs, specifically the liver and spleen, as they cannot be broken down or excreted. Research has shown that this build-up of non-biodegradable material has been observed to cause organ damage and inflammation in mice.

The size of nanoparticles for clinical application spans from five to two hundred nanometers. Size is a major determinant in nanoparticle disposition that permits them to preferentially accumulate in solid tumor sites, characterised by increased blood capillary permeability and reduced lymphatic draining. However, particles targeting the tumors result in an average of less than 2% of the dose, as per research on targeted delivery approaches for cancer. The only drawback to the exploitation of liposomes in vivo is their immediate uptake and clearance by the Eeticuloendothelial System (RES) system and their comparatively low stability in vitro. To combat this, Polyethylene Glycol (PEG) is added to the surface of the liposomes. Increasing the mole percentage of PEG on the surface of the liposomes by 4-10% considerably multiplied circulation time in vivo from two hundred to a thousand minutes [18].

4. Simulation Tool and Rationale

Drug delivery systems can be designed to improve the pharmacokinetics and biodistribution of the drug. The pharmacokinetics and pharmacodynamics of nanomedicine is highly variable among different patients. When nanoparticles are designed to avoid the body's defence mechanisms, they have beneficial properties that can be used to improve drug delivery. Drug delivery systems may also be able to prevent tissue damage through regulated drug release; reduce drug clearance rates; or lower the volume of distribution and reduce the effect on non-target tissue [19]. Notwithstanding this, the biodistribution of these nanoparticles is still not perfect due to the complex host's reactions to nano- and microsized materials and the difficulty in targeting specific organs in the body.

The experimental procedure for determining the best way to deliver drugs to cervical cancer cells would involve a large group of people with relatively the same body composition and in similar treatment stages. Each metal or oxide will first be reacted with the tumor to observe any visible side effects before being brought to the presence of Avastin. If there does happen to be a reaction, a suitable hydrophilic or hydrophobic layer can be added to prevent reaction once inside the body. The next and final step of the first stage would be to find suitable biomarkers or ligands to target the tumor.

Table 1
Results of simulation study

Material	Tissue Permeability (at 25°C)	Buildup	Reaction with Avastin [16]	Predicted Effectiveness of Delivery System
Iron Oxide	Average permeability	Minimal Amounts; body excretes	Highly probable	Decent effectiveness
Copper	Highly permeable	Buildup around membranes, severe side effects probable	Might enhance drug's side effects	Effective but with a lot of side effects
Gold	Efficient permeability	Minimal Buildup	Not enough information; noble metal – chance of no to mild reaction	Decent Effectiveness
Silver	Efficient permeability	Buildup present in small amounts	Not enough information; noble metal – chance of no to mild reaction	Decent Effectiveness
Zinc Oxide	Good Permeability	Buildup present, body does not react well	Highly probable	Good for delivery, with probable presence of large side effects

The second stage would involve in vitro experimentation. A control group wherein the subjects are given conventional therapies would be established to compare and contrast with the effectiveness of the various materials being used in nanotherapy.

As human trials would at this stage be unethical, as well as the stifling cost of materials required for it, experimentation may be done through a pharmacokinetic simulation. A helpful pharmacological tool to simulate the distribution of nanoformulations is represented by physiologically based pharmacokinetics (PBPK) modeling [3], which integrates system data describing a population of interest with drug/nanoparticle in vitro data through a mathematical description of ADME (absorption, distribution, metabolism and elimination).

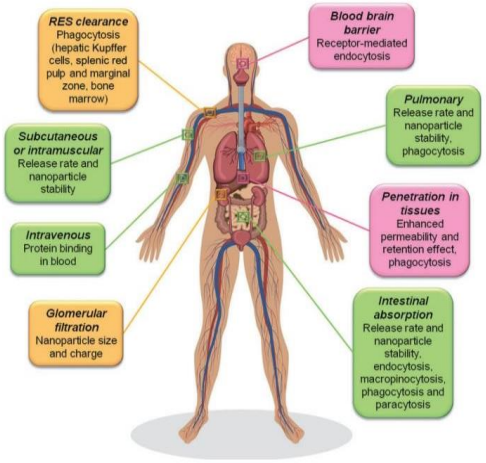

Fig. 2. Simulation screen relating to the administration, distribution and elimination of nanomedicines
Simulated using Nanohub.org

The simulation used, Polyvalent Nanoparticle Binding Simulator [15] assumes no reaction with the medicine payload takes place and hence, all data about reaction with medicine is based on previous drug databases and hypothetical. The simulation does however, offer insight into permeability of nanoparticles through tissues by using the material as a ligand to pass through a cell wall; presence of buildup of metal or oxides in the body, but not the effect of it; and the percentage of medicine reaching the target site. The Simulation also provides one single subject, diversity is nullified.

This application simulates ligand-receptor binding of metal compound ligand-decorated virus particles interacting with a cell wall (Fig 3). The viruses are modeled after P22 virus-like particles (VLPs) of diameter 60 nanometers. [15]

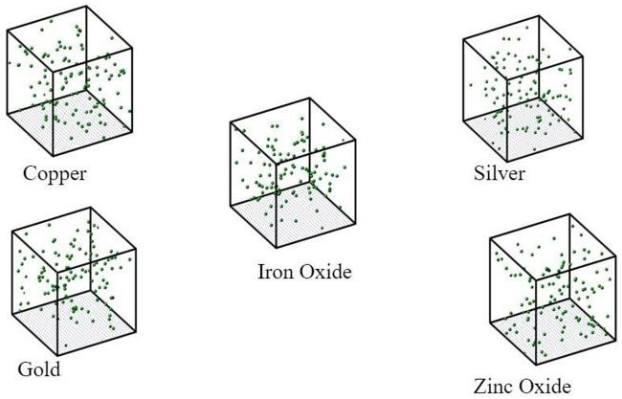

Fig. 3. A screenshot from the simulation showing permeability of Copper, Silver, Iron Oxide, Gold and Zinc Oxide nanoparticles

Nano formulations may undergo degradation in penetrated tissues or circulating blood, gradually releasing their content. Degradation kinetics is an important variable that controls drug release and complicates the design of optimal drug delivery systems with predictable drug release properties [3]. This is not reflected in the simulation.

5. Conclusion

According to the data simulated and collected, gold is the most effective material for nanoparticles to be involved in the targeted delivery of Avastin to cervical cancer cells, by virtue of its permeability, minimal buildup and effective delivery system. It stands to reason that a noble metal would have less to no reaction with a drug and that its surface area would make it a more likely contestant for efficiency. Gold nanoparticles have many benefits such as administration into the local tumor area while minimizing non-specific distribution and activation via near-infrared (NIR) laser light, creating the ability to penetrate deep into biological tissues [21]. However, gold nanoparticles are some of the most expensive nanomaterials available on the market which reduces how practical it can be.

Drugs like Tamoxifen for breast cancer already employ iron oxide nanoparticles, so it might be a possibility despite its propensity to react with the drug. Research done on copper and zinc oxide nanoparticles show that while it easily permeates lipid membranes, it destroys them. Added to the general side

effects of Avastin like blockage of arteries, it might not be the best option to deliver drugs, so as to not prolong the patient's suffering. These downfalls can however be lessened by factoring in hyperthermal therapy or radio sensitizing.

The next best option after gold would be silver nanoparticles, however most of the research done on AgNPs is in the field of imaging and not enough research has been done on using it in targeted therapies. However, the simulations show that silver nanoparticles are an interesting option based on permeability and buildup. Silver does have an advantage over gold, as it has been previously used to deliver Avastin to Glioblastoma multiforme tumors, a malignant and deadly brain tumor with good results [22]. In terms of raw material, discounting costs for producing nanoparticles, silver is also more affordable than gold, being almost 1/79th of its price, based on current world rates as seen on 22 April 2022.

In conclusion, silver nanoparticles can be a feasible mechanism for drug delivery due to their permeability, cytotoxic nature toward cancer cells, presumed lack of reaction with the drug Avastin and its affordability. Copper and zinc oxide nanoparticles also hold promise as viable alternatives; though only while factoring in treatments to help assuage the more severe side effects.

Ethics

The conclusions are based on simulation studies commensurate with the educational standard of the author. It is implied and now explicitly stated that additional studies on each of the above conclusions must be conducted as per standard clinical tests.

Acknowledgement

To all my teachers and parents for expert advice, constant support and encouragement and the online sources. The author is a higher secondary school student and this research was carried out as part of the academic project work.

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