

# THE USES OF NANOTECHNOLOGY IN IMPROVING DRUG DELIVERY SYSTEMS IN MEDICINE



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## **ABSTRACT**

Nanotechnology is a relatively new concept which involves manipulating matter at an atomic scale. It enables us to make new structures, devices and systems which will allow us to advance the technologies that already exist, as well as developing brand new ideas. One area in which research is already well underway is medicine. Nanotechnology has the potential to revolutionise medicine, particularly by improving the way drugs are administered and the way they operate once inside the body, possibly saving a great number of lives.

## **INTRODUCTION**

Miniaturisation, a simple word used to describe a complex process. For years we have watched as things around us have slowly become smaller, for example computers have gone from filling a large room to being able to fit in your palm. As our scientific knowledge of technology has developed we have been able to make products which have become increasingly accessible to the population.

We have now reached the stage where we can work at a nano-scale, dealing with matter that is one billionth of a metre in size, an incomprehensible notion to most people. By mimicking the way nature works, scientists are now working on the concept "from the bottom-up", and by altering the way atoms are structured together, are able to construct what are the vital building blocks to improving drug delivery; nanoparticles, a particle with dimensions less than 100nm

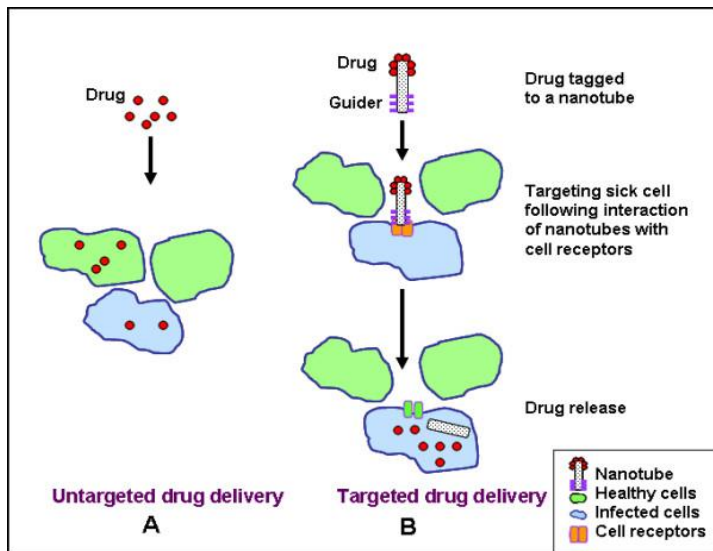
Before we can understand why nanoparticles are set to transform drug delivery, firstly we need to understand what makes a good drug. Source 2 states that "the basic point to drug delivery is based upon three facts:

- a) Efficient encapsulation of the drugs,
- b) Successful delivery of said drugs to the targeted region of the body
- c) Successful release of that drug there"

Source 2 also refers to the term bioavailability; it defines it as "the presence of drug molecules where they are needed in the body and where they will do the most good". Researchers in drug delivery are constantly attempting to improve drug delivery by maximizing bioavailability both at specific places over the body and over a period of time. It is said that \$65 billion is wasted each year due to poor bioavailability.

Nanoparticles are able to greatly improve drug bioavailability because of their targeting properties. Nanotechnology in medicine will allow us to create drugs which are targeted to the diseased region only; this will therefore reduce damage to surrounding healthy cells. This will both reduce costs as the drug doses will be able to be significantly reduced as they are cell specific, and it will also alleviate human suffering.

Figure 1, gives a brief overview of how specific targeting works with these nanoparticles; in this case a carbon based nanotube was used to encapsulate the drugs.



**Figure 1**

As you can see the untargeted drug delivery results in healthy cells being damaged due to toxicity from the drugs. In the targeted drug delivery, small molecules such as proteins on the surface of the nanotube bind to the receptors located on the plasma membrane of the diseased cell and the drugs are efficiently delivered to the targeted cell with little or no damage to surrounding healthy cells.

The small size of the nanoparticle enabled it to enter into the cells cytoplasm through the cell membrane, whereas larger particles would not have been able to. This is an extremely important development because many diseases depend upon processes within the cell and can therefore only be impeded by drugs that make their way into the cell.

Cancer affects about seven million people worldwide, and that number is projected to grow to 15 million by 2020. If we look at current cancer treatments such as chemotherapy, a cytotoxic untargeted method of delivering cancer drugs. This often means the patient experiences worse side effects from the treatment than the symptoms of the disease itself causes. Furthermore, according to Source 17, with chemotherapy treatment, 99% of drugs administered, typically don't reach the tumour. Therefore it is vital that new, targeted cancer drugs can be developed using nanoparticles.

Source 13 is The Frank Gu Research Group at the Waterloo Institute for Nanotechnology. One of their primary research focuses is targeted nanomedicine for cancer therapy. Their objective is "to deliver chemotherapeutics directly to the cancer tissues while minimizing undesirable toxicity to the rest of the body." I am going to look at how this is achieved.

Efficient Encapsulation of Drugs:

Nanoparticle formulation begins with a solution of drug (e.g. an anti-cancer chemotherapeutic agent) and diblock copolymer molecules in an organic solvent. The diblock copolymers composed of two adjoining polymer chains; one which is hydrophilic and one which is hydrophobic. The formulation of the nanoparticles occurs when the organic solution is added drop wise to rapidly stirred water. The copolymers quickly assemble around the anticancer drugs so that they form a micelle structure, with their hydrophobic blocks are surrounded and stabilized by the hydrophilic blocks, protected from the water. This outer surface of the polymer

micelle can then be modified by adding cancer targeting ligands such as antibodies to its surface

Successful delivery of said drugs to the targeted region of the body:

The nanoparticle solution is then modified so that it can be administered intravenously. The nanoparticles are quickly distributed around the body via the circulatory system where they are delivered to the site of the tumour. They are 100 times smaller than erythrocytes and can therefore pass through the fenestrations in the capillary walls in the tumours own blood system, a number of the anticancer drugs currently used are not currently small enough to enter the tumour tissue in this passive manner. Through this targeting technique the nanoparticles can become concentrated in the tumour tissue. On the cancer cells surface membrane the nanoparticles encounter surface receptor molecules. These are microscopic markers only found on cancer cells and not normal cells. Therefore this enables the nanoparticles to differentiate between the two.

Successful release of that drug there:

The targeted ligand molecules on the nanoparticles surface bind specifically to the receptors found on the cancer cell this draws the nanoparticles inside the cancer cell. This is a process referred to as receptor mediated endocytosis, and it allows thousands of nanoparticles to enter the targeted cancer cells. The nanoparticles develop inside the vesicles in which they enter the cell, and these vesicles will then join together. Inside the vesicle the anticancer drugs can be released in a controlled manner by the degradation of the polymer nanoparticle shell. The anticancer drugs will cause the cancer cells to undergo apoptosis or "programmed cell death"; this will eventually lead to the eradication of the tumour.

The highly toxic chemotherapeutic agent can therefore be delivered directly to the targeted tumour cells without affecting other body systems.

However, nanotubes and copolymers are not the only molecules that can be used in drug delivery. Figure 2, from Source 9 shows the different classes of nanoparticles and their applications in Life Sciences. This shows that many different substances can be used for efficient encapsulation of the drugs this gives the scientists a lot of options, however this also means that a lot of research will have to be undertaken to determine which type of particles will be the most effective at treating certain different diseases. Most of the substances in the table are

Overview of nanoparticles and their applications in Life Sciences		
Particle class	Materials	Application
Natural materials or derivatives	Chitosan Dextrane Gelatine Alginates Liposomes Starch	Drug/Gene delivery
Dendrimers	Branched polymers	Drug delivery
Fullerenes	Carbon based carriers	Photodynamics Drug delivery
Polymer carriers	Poly(lactic acid) Poly(cyano)acrylates Poly(ethyleneimine) Block copolymers Polycaprolactone	Drug/gene delivery
Ferrofluids	SPIONS USPIONS	Imaging (MRI)
Quantum dots	Cd/Zn-selenides	Imaging In vitro diagnostics
Various	Silica-nanoparticles Mixtures of above	Gene delivery

**Figure 2**

biodegradable and will therefore act in a similar way to the copolymers and will have effective drug release after degradation. Source 9 also states that apart from natural degradation physical means such as heat and light could be used to cause the degradation. For example nanoparticles could be made either light or heat sensitive, and therefore when they have reached the targeted area, a source of heat or light from outside the body could be used in almost a catalytic manner to provoke

nanoparticle degradation. This will therefore have the potential to reduce the time taken for the drug to begin working.

## **DISCUSSION**

We now know the basics to how nanoparticles operate to deliver drugs in the body. However, there are certain areas of medicine that nanoparticles specifically can transform. I am going to look at some of these in greater detail to try and determine what it is about nanoparticles which makes them able to function in these certain areas of the body to treat these certain diseases.

A highly promising area that is currently being explored in nanotechnology is the ability of nanoparticles to be able to cross the blood brain barrier.

**Blood Brain Barrier:** a layer of tightly packed cells that make up the walls of brain capillaries and prevent substances in the blood from diffusing freely into the brain. Passage across the cell membranes is determined by solubility in the lipid bilayer or recognition by a transport molecule.

This presently prevents many drugs from crossing from the blood into the brain and consequently prevents a major challenge in treating most brain disorders. "In its neuro protective role, the blood-brain barrier functions to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain."

Source 16 states "The global market for drugs for the central nervous system (CNS) is greatly underpenetrated and would have to grow by over 500% just to be comparable to the global market for cardiovascular drugs." Even though brain disorders are a lot less common than cardiovascular ones, this clearly shows that there is a lack of drugs in this area of medicine and that it needs to be rectified.

Recently researchers in nanotechnology have been looking into creating liposome's which are artificially prepared vesicles made of lipid bilayer, loaded with nanoparticles to gain access through the blood-brain barrier. Small lipids are able to pass through the cells that make up the blood brain barrier because they are non-polar. This will cause a major breakthrough in the treatment of patients with brain disorders, particularly brain tumours. More research is needed to understand which methods will be the most effective and how they can be improved for patients specifically with brain tumours. However, it should be noted that the blood brain barrier is not always intact if a patient is suffering with a brain tumour, this can alter the type of drug delivery system required.

There are several issues which have arisen with the interaction of nanoparticles and the CNS. One concern is that nanoparticles will result in toxicity and functionality problems on human neural cells due to their ability to enter into the cells through the plasma membrane. For example, Ag nanoparticles can pass through the blood brain barrier and have been shown to accumulate in different regions of the brain; this could be beneficial for drug delivery i.e. if they were to accumulate at the site of a brain tumour however it could also pose a serious threat to the patient if they were to accumulate in an area of healthy tissue.

Source 18 states, "The voltage-gated sodium current is responsible for modifying the excitability of neuronal cells and neuronal activity". It is expected however that metal nanoparticles could change the current which would result in a change in the functionality of the current. Some reports have even shown that nanoparticles can impair healthy cell function and further induce cell death.

The research above shows that development of nanoparticles to cross the blood brain barrier will benefit many patients, however the nanoparticles will have to be modified so that they can be targeted to the area they need to reach, for example a brain tumour, rather than an area of healthy tissue. The main issue here is creating nanoparticles which are targeted without compromising their ability to cross the blood-brain barrier. Furthermore, many nanoparticles do consist of metal elements therefore it is very important that the relationship between these metals and the electric impulses in the brain do not cause harm or functionality issues to the patient.

Above I looked at how nanoparticles can be used to treat cancerous tumours by the degradation of nanoparticles at the site of the tumour and the controlled release of anti-cancer drugs there. However, there are other methods of treating cancer using nanoparticles, without the use of anti-cancer drugs.

Source 17, is a version of an article which appeared in MIT Tech Talk in May 2009, it focuses on a study conducted by Geoffrey von Maltzahn and Sangeeta Bhatia. MIT researchers have developed gold nanoparticles which can target tumours and then by absorbing energy from a near infrared light source and emitting it as heat are able to destroy tumours with minimal side effects to the surrounding healthy tissue. Gold particles can absorb different frequencies of light depending upon their shape; in this case rod shaped ones were used. The infrared light absorbed by these nanoparticles heats the rods but can pass through human tissue without causing any harm. One of the experiments conducted by the MIT researchers was the following "tumours in mice that received an intravenous injection of nanorods plus near-infrared laser treatment disappeared within 15 days. Those mice survived for three months with no evidence of reoccurrence, until the end of the study, while mice that received no treatment or only the nanorods or laser, did not." This shows that together the nanorods and an infrared light source are effective at eliminating tumours, but if used separately are not. This is most likely because the infrared light needs a medium to convert it into heat energy in order for it to be effective and the nanoparticles need to get the energy from another source in order for them to be able to emit thermal energy.

I am going to look a little closer into how the gold nanorods work: Once they are injected they disperse throughout the blood stream. The team at MIT developed a polymer coating which allows the nanorods to survive in the bloodstream longer than any other gold particles (the half life is greater than 17 hours). Similarly to the methods above, the nanorods are small enough to be able to pass through pores in blood vessels near the tumour and accumulate within the tumour. Another advantage of these nanorods is that after three days they are removed from the blood stream by the liver and spleen if they do not manage to reach the tumour, and so cannot harm any healthy tissue. During one exposure to a near-infrared laser, the nanorods are able to heat up to 70°C, a temperature which is high enough to kill tumour cells.

Another option for the use of these nanorods is that heating them to a lower temperature weakens the tumour cells; this has the potential to advance the effectiveness of existing chemotherapy treatment. So there is the possibility to use both new and old technology side by side to produce a better result.

Researchers have also suggested that the nanorods could be used to kill tumour cells left behind after surgery. They claim the nanorods can be 1000 times more precise than surgeon's scalpel, and so could potentially remove residual cells that the surgeon has not been able to get to. This can reduce the chance of secondary tumours and therefore better the future prognosis of the patient. The nanorods also have the potential to be used as a diagnostic device, which would mean that tumours would be spotted before they became a serious threat to the patient, again improving future prognosis. However, before they can be used they must undergo several clinical trials and be approved by the FDA (US Food and Drug Administration).

The advantage with nanoparticles is that a large number of them can be used as an early diagnostic tool, particularly for cancer. Therefore which is more beneficial, do we mainly focus on developing drug delivery systems using nanoparticles to transform the treatment of these diseases, or do we focus upon the diagnostic element of the nanoparticles and attempt to remove the tumour before it becomes a serious threat to the patient. In my opinion it is important to develop both areas, because although in an ideal world it would be both beneficial for the patient and the NHS to diagnose and remove the cancer before it develops, currently we simply do not have the capacity to regularly check for tumours in patients. Often it is the first symptoms of the disease which causes the patient to visit their GP, by which time the tumour has already grown to considerable size and therefore it is the drug delivery systems which are going to be most beneficial to the patient. So, this early diagnostic device would only be really valuable to patients who were just scanned by chance, for example if they were in the hospital because they were ill from another source. Using nanoparticles to scan for cancer would mean the tumour would be easily and quickly removed through surgery or through the use of nanoparticle drug delivery systems, this would mean human suffering would be significantly reduced, the prognosis for the patient would be exponentially better and the cost to the NHS would be lower. As a result, I believe using both techniques side by side is the best way to tackle the issue, but ultimately you cannot prevent everybody becoming ill and therefore you need the best treatments in place.

Another area, away from cancer therapy, that nanotechnology shows promise is the use of "Buckyballs" to prevent an allergic reaction. Buckyballs are an allotrope of the element carbon; they consist of 60 carbon atoms bonded together in a spherical structure. They have a unique structure and are very stable due to their inertness.

According to Source 19, allergic disease is the sixth leading cause of chronic disease in the United States, and although there are various treatments involved in the control of allergies no cure has yet been found. This has sped up the development of the emerging "nanoimmunology".

Mast cells are present in nearly all tissues except the blood; they are cells which contain high levels of histamine. They are responsible for causing an allergic response because when they activated they release histamine and other cytokines into the blood and other tissues which rapidly leads to an allergic reaction.

According to Kepley, main author of the paper, "the buckyballs are able to 'interrupt' the allergy/immune response by inhibiting a basic process in the cell that leads to the release of an allergic mediator. Essentially, the buckyballs are able to prevent mast cells from releasing histamine."

He conducted an experiment which involved placing samples of human mast cells in separate dishes, and added buckyballs to one of the dishes. He then triggered an allergic response from the mast cells by exposing them to a common cause substance e.g. pollen. Source 20 states "Those with buckyballs released 50 times less histamine, and inhibited 30-40 other mediators involved in the allergic response." The test was then conducted on mice and it showed that mice treated with buckyballs intravenously, produced far less histamine and those that weren't were more susceptible to a drop in body temperature associated with anaphylaxis.

Source 20 says that how the buckyballs prevent the release of histamine is unclear; however there is a clear relationship between high levels of reactive oxygen species and the release of histamine. It is known that buckyballs have a very high electron affinity and can therefore remove reactive oxygen species, a form of free radical, by "grabbing" their unpaired electron and acting to neutralise them. Therefore this suggests that by reducing the amount of oxygen free radicals you can reduce the release of histamine from mast cells and therefore inhibit the effects of an allergic response. It is known that anti-oxidants such as Vitamin E reduce the amount of reactive oxygen species; however the buckyballs are much more effective at doing so. Furthermore, research has shown that high amounts of free radicals can be cause of cancer; therefore patients who were taking buckyballs as allergy preventing drug could significantly reduce their risk of cancer.

Researchers with Kepley at Virginia Commonwealth University claim that they have not experienced any adverse effects of using the buckyballs and that the mice did not experience any serious side effects. They are now awaiting permission to conduct human clinical trials.

Using buckyballs is a much more efficient and effective way of treating an allergic response than the current anti-histamine drugs. Anti-histamine operates by coating the receptors in your body which the histamine bonds to, and this can therefore prevent the symptoms of an allergic response. The negative aspects of the anti-histamine drugs are that once the histamine is released it operates very quickly and so by the time your symptoms appear the allergic reaction is in the middle of the process. Therefore, you need to take anti-histamines 2 to 5 hours before you are exposed to allergens or regularly take them. This is fine if you know you are going to come into contact with the allergen, however this cannot always be anticipated; therefore the allergic response cannot always be stopped. Buckyballs however, work by physically reducing the amount of histamine released by the mast cells therefore if no histamine is released no response can take place and no symptoms will occur. However, the buckyballs will still need to be taken regularly to keep the level of reactive oxygen in the body low. Perhaps in the future an immediate response could be developed working with the targeting and fast acting properties of the nanoparticles.

## **CONCLUSION**

The use of nanoparticles as drug delivery systems and methods of treatment referenced above quite clearly show the potential to revolutionize medicine. The main advantages they hold over current treatments is their size and their targeting properties, both of which help to maximize the bioavailability of the drug.

Due to the specificity of them they show promise to both reduce human suffering because they are able to target the diseased cells without causing harm to healthy tissues, this will mean very few side effects for the patient. It will cut costs to the NHS because the doses of drugs given to patients will be a lot smaller because of the increase in accuracy. This will also mean, particularly for cancer, that the chance of relapse will be reduced because of the efficiency and precision of the nanoparticles in the removal of tumours therefore prognosis for the patient for will be improved.

The potential of nanotechnology in medicine is well-known and the research is encouraged in medical organizations because the positive impacts this technology can bring are recognised and valued, so conducting this further research should not be stopped by any intervening obstacles such as funding.

The specific areas looked at in this paper, e.g. the blood brain barrier and the allergic response show a lot of promise, although may still need further research. It could take 10-15 years or longer for a drug to complete all the stages in a clinical trial and this can vary largely on several factors. Therefore this means that these drugs are still a long way off from being available on the market, and I believe the true "miracle" of these drugs cannot be fully appreciated until real patients are taking and benefitting from them.

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