

INVESTIGATING THE POTENTIAL DEVELOPMENTS THAT CAN  
BE MADE IN MEDICAL DRUG DELIVERY SYSTEMS USING  
NANOTECHNOLOGY

BY

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**PASS WITH MERIT**

RESEARCH PAPER  
BASED ON  
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AT MEDISIX 2011

## ABSTRACT

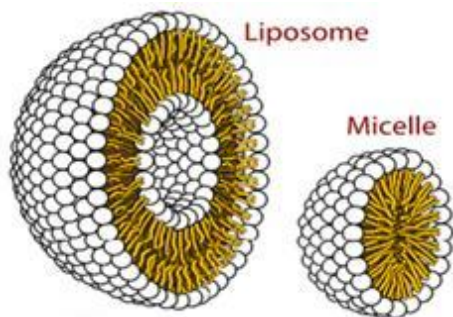
Although extensive research into the uses of nanotechnology in medicine has only really begun in relatively recent years, drug delivery systems have been using the nanometer scale for several decades, and our new understanding of nanotechnology means that further advances in the techniques used to deliver drugs to human cells can now be made. In this paper, I will examine the research into developments in drug delivery using nanotechnology that is currently in progress. I will also include some of my own ideas on how nanotechnology could be used to improve drug delivery systems in the future, by making them more efficient and more likely to directly arrive at the diseased cells which need to be treated.

## INTRODUCTION

Nanotechnology is defined as being the manipulation of matter at the nanometer scale. A nanometer is  $1 \times 10^{-9}$  metres, which is roughly the width of three atoms, so when working in nanometers scientists are effectively working at the atomic and molecular level. This relatively new scientific field has already begun to offer us some very exciting potential medical applications, and there is no doubt that nanotechnology will prove to be revolutionary in the way that we diagnose and treat medical conditions in the future.

One of the current medical fields which could benefit from the use of nanotechnology is that of medical drug delivery. The tiny size of nanomolecules means that the delivery of drugs could be made very specific, with the drugs carried directly to individual diseased cells. This increased specificity would mean that drug delivery would be more efficient, and so the costs of drugs would be lowered, as none of the drug would be wasted on healthy cells. This specificity would also be directly beneficial to the patients taking the drugs, as the medication would only target the cells that they were supposed to be treating rather than also affecting other, healthy cells and so the patients would suffer from fewer unpleasant side-effects. Another benefit of using nanotechnology rather than using conventional drug delivery systems is that nanoparticles have a very large surface area to volume ratio due to their extremely small size. This means that they have a larger surface area, and so have more space to carry drugs, making them more efficient than the larger conventional drug carrier molecules.

Although we tend to think of nanotechnology as a relatively new field of science, there are in fact a few drug delivery systems already in existence which use the nanometer scale, and the aforementioned increased efficiency and decreased discomfort for patients can be seen in these systems. The nanometer scale has, in fact, been used in drug delivery systems for several decades now. However, since extensive research into the potential applications of nanotechnology only really began in the past few years, many of the systems that use this technology to deliver drugs are still in the development stages. The few nanotechnology systems that are currently in use include liposomes, polymeric micelles and dendrimers.

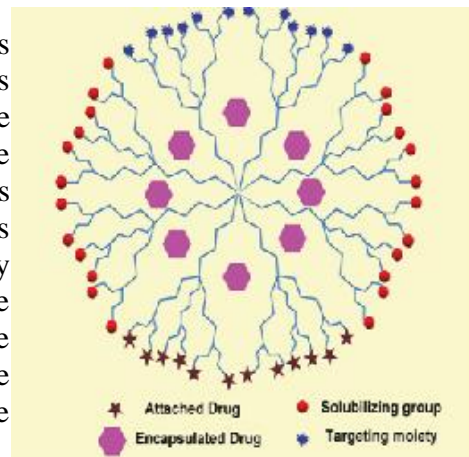


*Figure 1*

liposomes, polymeric micelles and dendrimers. Liposomes are nanometer-scale spherical vesicles which are artificially prepared from phospholipids and cholesterol. The phospholipids form a bilayer, giving the vesicle both hydrophobic and hydrophilic areas, as shown in Figure 1 (left). The presence of these two different areas means that the liposomes can carry both water-soluble and water-insoluble drugs, as the hydrophobic drugs will pass through the phospholipid layer and be carried in the centre of the vesicle, whereas the hydrophilic drugs will be trapped inside the liposomal cavity. As the liposomes are made up of phospholipids, they are able to fuse with the phospholipid bilayer of cells and deliver the drugs that they contain, thus meaning that the drugs can be delivered directly to individual cells.

Micelles are similar to liposomes, but the sphere is made up of only a single layer of phospholipids rather than two layers, so that the centre of the molecule is hydrophobic and the outside of the molecule is hydrophilic. The structure of liposomes and micelles, and the difference between the two, can be seen in Figure 1 (previous page). Polymeric micelles, which are long chains of micelles, can be formed spontaneously when micelles are placed in aqueous solution. The polymeric micelles typically only measure roughly ten nanometers in size, and so are still small enough to deliver drugs at a cellular level. In polymeric micelles, there is a large solubility difference between the hydrophilic and hydrophobic parts of the molecule, meaning that the drugs will easily diffuse out of the drug delivery molecules and into the cell where they are needed. Polymeric micelles are also more stable than their monomeric counterparts, and so can hold drugs for a longer period of time.

Dendrimers are branched, roughly sphere-shaped molecules, as they have several branches coming off a central core. The drugs attach to the ends of these branches, and there is also the possibility that some drugs could be encapsulated near the centre of these molecules. The structure of a dendrimer is shown in Figure 2 (right). This molecule also features solubilising groups so that the dendrimer can be easily transported throughout the body to reach the cells where the drugs are needed, and targeting moieties which target the surface antigen on a specific type of cell and therefore enable the drug to be delivered directly to the cells where they are needed rather than also targeting healthy cells.



*Figure 2*

However, these systems do not necessarily demonstrate the potential benefits that nanotechnology could have if it was incorporated into drug delivery systems, as according to Kinam Park's article on the potential benefits of using nanotechnology for drug delivery (2007), conventional drug delivery systems would have eventually begun to use the nanometer scale and been developed into their current form even if the "nanotechnology revolution" had not occurred. In order to explore what benefits nanotechnology could truly have for drug delivery techniques in modern medicine, we must investigate the applications of nanotechnology to drug delivery systems which are currently still in the process of being developed or researched. In the main discussion of this paper I will examine some of the systems that are currently in development, and will speculate on some possible future developments in the way that nanotechnology can be utilised to improve drug delivery systems.

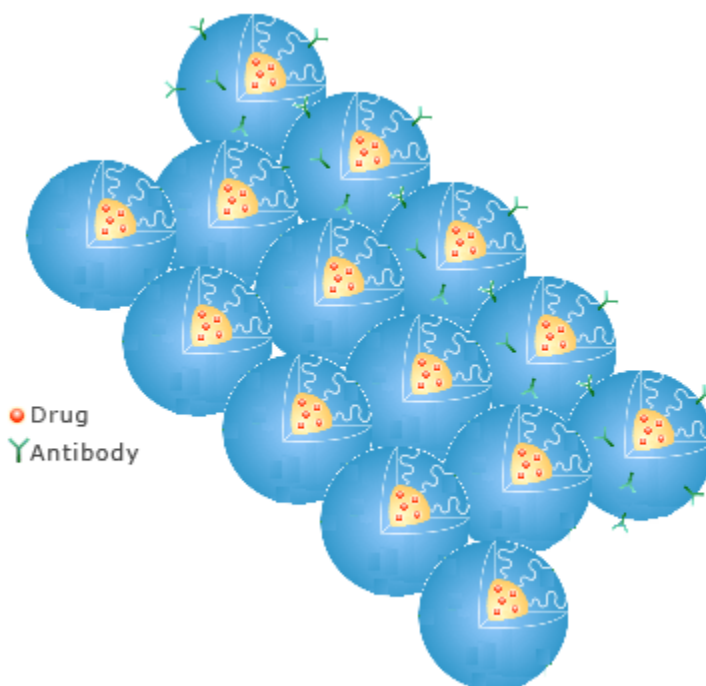
## **DISCUSSION**

It is likely that the first new advances to be made in drug delivery systems using nanotechnology will be focused on the development and improvement of the systems which already exist, namely the liposomes, polymeric micelles and dendrimers described in my introduction. These systems could be improved by being engineered to be able to recognise diseased cells and deliver drugs directly to these cells, therefore meaning that the healthy cells are unharmed. This has already been achieved in dendrimers, which have targeting moieties attached to the ends of some of their "branches" to enable them to recognise and target a particular surface antigen on a diseased cell.

In the future, this technology could also be extended to liposomes and polymeric micelles, by incorporating selectin proteins or antibodies into the phospholipid bilayer of liposomes and phospholipid layer of polymeric micelles. Both of these molecules can target and bind to diseased cells, and both are made of protein. It should therefore be fairly straightforward to incorporate them into the phospholipid layer of liposomes and micelles, since the phospholipid bilayer found in cells contains protein channels and so the two molecules must naturally be able to bond together. The antibodies would enable the drug delivery nanoparticles to directly target the diseased cells, as these cells would display an antigen on their surface as a form of cell signalling, to indicate to other cells that they are diseased. By "tuning in" to this cell signalling, the liposomes and micelles could be

engineered to only recognise and fuse with the diseased cells, allowing very specific drug delivery to take place.

Another improvement which could be made to the existing nanoparticle-based drug delivery systems at some stage in the near future would be to engineer them to be able to carry several different types of drug simultaneously. The existing polymeric micelles are a long chain of several micelles, and if a large enough polymer could be synthesised then there would be the possibility of containing several drugs within different sections of the drug carrier molecule. An example of how this molecule could look is shown in Figure 3 (right). If this carrier system was feasible, it would mean that in cases where a combination of drugs are needed to treat a disease, these drugs could all be taken in one go rather than having to take several different tablets or capsules. Perhaps each row of nanoparticles shown in Figure 3 could contain a different drug.



*Figure 3*

If a certain time period needed to elapse between the different drugs being taken in order for them to work properly, the nanoparticles could potentially be engineered so that the sections containing different drugs released their contents into the diseased cell at different times. Perhaps this could be done by making some of the carriers more stable than others, by the addition of cholesterol or another suitable substance which stabilises phospholipid membranes, so that the membranes of the micelles broke down at different rates. Alternatively, the same effect could be achieved by making some of the carrier molecules more lipid-soluble than others, so that they would fuse with the phospholipid bilayer and allow the drugs to pass into the cell more readily. One final alternative solution would involve binding the micelles together in such a way that the micelles carrying one type of drug could only fuse with the cell membrane after the micelles carrying another type of drug have already done so. Perhaps this could be achieved by arranging the micelles in several rows, with the antibodies attached to the first row of micelles so that these micelles are the first to fuse with the cell, followed by the row behind them, and so on. Figure 3 (above right) gives an indication of how this system might look, as the antibodies are only attached to the first row of micelles. As different drugs are needed in different doses, there are fewer micelles in the second row, as the drug contained in this row might only be needed in a small dose. Of course, in a real drug delivery system many more micelles would be needed than are shown in Figure 3, as each micelle can only carry a tiny amount of the required substance.

Another way in which nanotechnology could revolutionise drug delivery in the future is through oral drug administration. In this case, a nanocapsule would be used to contain the drug. In these transport devices, the drug is entrapped inside a cavity surrounded by the nanocapsule's polymer membrane, meaning that it can safely be ingested. Due to its tiny size, it would be easier for the nanocapsule to pass through the lining of the stomach and into the bloodstream than it would for a normal molecule to do so. The oral administration of drugs has several advantages over the injection method, as it is far more pleasant and comfortable for the patient, less likely for the patient to unintentionally overdose on the drug or harm themselves with the needle, more flexible as the drug can be administered at any time and in any location of the patient's choosing, and according to Michael

Fischer's research (2003) drugs taken orally are also usually cheaper overall than intravenously administered drugs.

However, if more drugs are to be administered orally, nanocapsules that are resistant to the extremely acidic conditions in the stomach will need to be developed. At present, the body's natural defences destroy a substantial portion of drugs that are taken orally before they can reach the area where they are needed to treat the disease. This occurs because the medication is recognised as a foreign body and can be destroyed by the low pH of stomach acid, or metabolised by the liver, a process which usually causes the drug to become inactive, and then excreted in urine or bile. One potential solution to this problem would be for the nanocapsules to be coated with a nanomaterial engineered to be resistant to damage by low pHs, so that they would be able to carry the drug through the stomach undamaged.

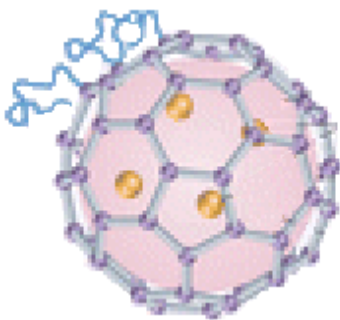
To overcome the problems presented by the process of metabolism, the drugs would need to be developed to have a resistance to conversion into water-soluble metabolites. They could achieve this by being made resistant to breakdown by the enzymes which control the metabolism process, by not being complementary to the enzymes and therefore unable to fit into their active site. For this to work, research would need to be done into how the nanoparticles could be adapted so that they were a different shape to the enzymes' active site but could still contain the drug and function correctly. The researchers would also need to ensure that the nanocapsule remained in the sort of shape needed to deliver the drug to the cell efficiently, as a team of researchers at the University of North Carolina at Chapel Hill recently discovered that shape has a great effect on how easy it is for the nanoparticle to enter the diseased cell, with rod-shaped particles found to be far better at entering human cells than rounder particles.

If it were not possible to engineer the drug carrier molecule to have a resistance to harm from the body's natural defences, an alternative way of ensuring that the drug reached the cells where it was needed would be to incorporate "stealth" characteristics into its design. New research at the University of Warwick (2011) has shown that plankton have naturally developed a nanoparticle-like protection layer, and that a similar layer could potentially be applied to drug carriers so that they could avoid detection by the body as they pass through it to reach the cells where the drug is needed.

One final method by which the destruction of drugs and their carriers by the body could be avoided would involve fitting the carrier molecule with a microscopic tracking device, made of materials which would not cause any harm the human body, which would monitor the carrier's progress through the body to the cells where the drug was required. An example of a potential tracker device would be the nano-gyroscopes that are currently being developed. These devices are minute gyroscopes which are being investigated for use in tracking the miniature cameras which are used in medical diagnostic procedures, but they could also be developed further in the future so that they were also small enough for attachment to nanocapsules and use in tracking the capsule's progress through the body.

This tracking of the nanoparticle would enable researchers to discover the locations in the body where different drugs and different carrier molecules are most likely to be attacked by the body, and therefore engineer particles to be resistant to particular conditions, for example to be resistant to damage by low pHs if it was discovered that most drug delivery molecules which did not reach the diseased cells were destroyed in the stomach. However, even after adapting the drugs there would still be a small probability that the carrier could be destroyed on its way to the diseased cells. The tracking device would also provide a solution to this problem, as it would enable medical staff to observe each individual patient to see if the drug reached the cells where it was needed, and to administer further medication if the carrier was unsuccessful in transporting the drug to its target.

In addition, there is the potential that one of the very first nanotechnology innovations, the buckyball, could be used to prevent an allergic response from occurring. The structure of a buckyball enables it to bind to free radicals extremely effectively, and therefore means that it can block mast cells, the cells which instigate an allergic reaction, from releasing histamine into the blood. According to the research of a team from Virginia Commonwealth University and Luna Innovations Inc. (2007), buckyballs are far better at blocking the allergic response than any natural antioxidant. Therefore, nano-molecules have the potential not only to be used as the transport vessels in drug delivery systems, but also to be used as a more effective replacement for the drugs themselves, in this case antihistamines. This application would be of great benefit to the medical industry, as it would mean that not so much money would need to be spent on antihistamines and other drugs used to counteract allergic reactions, as these reactions would have been prevented by the action of the buckyball. In the future, the buckyball could be used to create a drug which people with allergies could take before eating the foodstuff they are allergic to, meaning that they would not suffer an allergic reaction as the buckyball would have blocked this response, and allowing them to consume foodstuffs that they would previously have been unable to eat without having a reaction.



*Figure 4*

The buckyball could also be used as a drug carrier molecule, due to its “cagelike” structure. A minute doses of the drug would be carried in the hollow centre of each individual buckyball, which would be attached to an antibody in order to enable it to target diseased cells, as shown in Figure 4 (left). One major advantage that the buckyball has over other drug delivering nano-molecules is that it is highly resistant to being broken down by the body. This means that the buckyball could potentially be suitable for use in carrying orally administered drugs, as this stability would provide another method of overcoming the problems with oral drug administration described earlier in this essay.

## CONCLUSION

In conclusion, the first advances which are likely to be made in the field of drug delivery using nanotechnology will involve the improvement of the delivery systems which are already in existence. These systems could be improved by making them more efficient at delivering drugs directly to the diseased cells which need treatment, and engineering them so that they are able to deliver several different drugs at once.

As oral drug delivery systems become increasingly important, due to their lower costs and increased level of ease for the patients taking them, nanotechnology can also provide improvements to orally administered drugs. It could first enable the nanocapsules transporting the drugs to be tracked as they make their progress through the body, so that researchers could determine the areas in the body where drugs are most likely to be destroyed. Nanotechnology could then be used to adapt the nanocapsules so that they were resistant to being destroyed by the body’s natural defences, for example by engineering the capsules to have a coating resistant to low pHs if it was discovered that the particles were most commonly destroyed upon entering the stomach.

Lastly, there would also be the potential to use the buckminsterfullerene as both a potential carrier of orally administered drugs and an allergy treatment drug in its own right. It would be a suitable drug delivery molecule due to the fact that it is immune to attack from the body’s natural defence system, and so would be able to carry drugs to the diseased cells where they were needed without being destroyed. Additionally, the buckyball has the ability to bind to free radicals and, by doing so, can block the start of an allergic reaction, meaning that it has the potential to revolutionise the way in which allergies are treated in the future. These are the main ways in which I believe nanotechnology will be used to develop drug delivery systems in the years to come, but with the advent of new scientific techniques and discoveries we may soon discover alternative ways of delivering drugs, which could provide greater efficiency than the suggested systems using nanotechnology.

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