# Nanotechnology
# Nanoshells for Intravenous Drugs

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PASS

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# Abstract

This is a paper on nanotechnology and its applications and relevance in medicine. In it, I will be focusing on the redevelopment of intravenous drugs for oral use, by the creation of molecular shells.

Based on current research into developing chemotherapy drugs for oral use, I will examine the reasons why I hypothesise that it will soon be possible to administer drugs by mouth that are currently only useable as intravenous drugs. I will also examine the difficulties and benefits of this technique, as well as future advancements that I think it may lead to.


# Introduction

Nanotechnology is manipulating matter at the atomic scale. What makes this technology important is the scale at which it is applied. Nanotechnology is capable of manipulating individual atoms, as shown by the research of Eigler and Schweiser. Firstly, we must examine the scales involved with this.

Nanotechnology is typically defined as working on the scale of 1 nanometre – 100 nanometres.

In terms of scale, one sucrose molecule is approximately 1 nanometre (nm) long, and is already a few atoms wide. The structure of this molecule is displayed here for reference (figure 1).

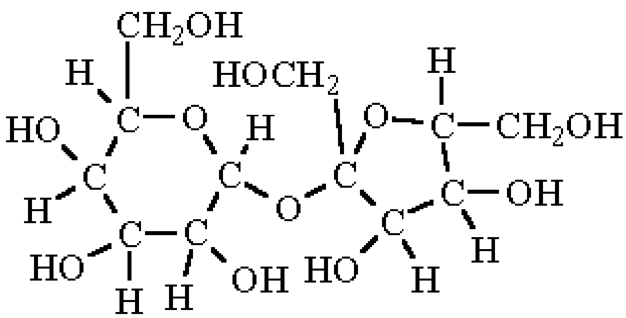


Figure 1

Working backwards, an adult human would typically range from 1.5 -2 metres tall. An adult mouse is only around 10cm long. A human fingernail is one tenth of this size again, at 1cm wide. Fast approaching the limits of conventional technology, a pinhead is 1 millimetre in diameter, while the smallest hypodermic needles in medicine have a diameter of 180 micrometres, or 0.18 millimetres. These are among the smallest equipment in medical use today, and are still far too large to interact with individual cells.

At 90 micrometres, we have the thickness of a typical sheet of paper – one tenth of the diameter of a pinhead. A human liver cell is 50 micrometres long. This means that three liver cells can fit across the diameter of the smallest medical equipment available. Bacteria are between 1 and 10 micrometres in size, or 1000-10000 nanometres. Even smaller, the HIV virus is 100 nm in diameter.

Finally, cell membranes are 10nm wide, which is ten times the size of a sucrose molecule of 1nm.There are 1,000,000,000 nanometres in a metre.

Consider a human and a scalpel. A scalpel blade would typically be around 1/20 of the size of the person; a larger blade will only cause damage. Similarly, though more difficult, it is not enough to create a machine small enough to interact with a cell, it must also be able to do so without causing serious damage to the cell. Therefore, a different approach is required. In normal mechanics, a tool can be used to build a smaller tool, which can build a smaller tool, and so on. However, nanotechnology goes the other way. Starting with individual atoms or molecules, it builds upwards into useable tools. The scales involved in this make nanotechnology of huge relevance to medicine.

Returning to Eigler and Schweiser, they first demonstrated that it is possible to manipulate individual atoms by using a scanning tunnelling microscope to move individual xenon atoms on a nickel surface in September 1989. This was a landmark in nanotechnology, and since then, other methods of manipulating atoms have been discovered.

Iron, Silicon, and Sulfur atoms have all been manipulated since, suggesting that it will be possible to manipulate all or most atoms, rather than just a few elements. In time, it may even be possible to construct molecules from individual atoms, based on this principle.

These techniques, however, fall into yet another problem with the scale: Not only must the technology be small enough to interact with individual cells; it must be produced in a large enough quantity to actually have an effect on the organism as a whole. Therefore, these techniques are currently impractical for use in medicine, as they are too difficult to mass-produce.

On a larger scale, and one more currently relevant, is the manipulation of molecules to produce molecular machines and structures. This area of nanotechnology uses an approach based on those found in nature. Simple building blocks are used as the basis for construction of more complex entities. These are designed to attract one another and fall into place naturally, so as to be more easily produced than a substance which requires extensive manipulation to create.

An easily-observable example of this aspect of nature is antibodies and antigens. Each antibody has one specific antigen that it will bind to, otherwise no change will occur. For example, a medical antibody test starts off with the antigen of the pathogen in question attached to a beaker. The solution to be tested is passed over the antigens, and the antibody if present will automatically bind to the antigen. This is washed and then a second solution is passed over, this time with a protein that contains a marker, and that will bind to the antibody if present. This system uses the natural binding properties of its building blocks to mass-produce a complex structure through far larger-scale actions than the final product. A similar approach to nanotechnology allows for easy, cost-effective production, as well as a more stable final product.

One of the first discovered nanoparticles was buckminsterfullerene, which was found to form naturally when condensing carbon at high temperatures. This discovery was made by Smalley and his co-workers in 1985. Buckminsterfullerene is a form of carbon in which 60 carbon atoms are arranged in truncated icosahedrons, or more simply put, a roughly football-like shape, with 20 hexagons and 12 pentagons. This was an important step forward in nanotechnology, as it led to the discovery of a new group of hollow molecules, the fullerenes. It also showed that molecular structures were possible, stable, and comparatively easy to form. Buckminsterfullerene’s properties are extremely useful. It has been shown to have enormous resistance to damage, high chemical stability and to react with only a few free radicals – the most reactive chemicals in existence. It is also said to be capable of having insulating, conducting, semiconducting, or superconducting forms.

Carbon nanotubes were first created at around 1952, though there is some confusion as to their discoverer, and they first became widely known in 1991, following the work of Sumio Luijima. Nanotubes are extremely important to the field of nanotechnology, being proof that not only can structures be produced readily, but that materials produced through nanotechnological means can have extraordinary properties with many practical applications.

For example, nanotubes have a hardness greater than diamond, almost no friction between separate layers of a multi-walled tube, high thermal and electrical conductivity, and the highest tensile strength of any known material. This enables them to be used for a whole host of purposes. These include wiring in nanoelectrical circuits, cooling systems for computers, body armour, or research into catalysts.

A key feature of nanotechnology is that, at the scales involved, atoms and molecules behave differently to how they would at larger scales. Quantum effects come into play at these scales, and the entities' surface area to volume ratios become much larger. These larger surface areas make catalysts more effective, so nanotechnology can be used to develop more effective catalysts. Quantum effects are less well understood, but can potentially be used, as electrons will end up where they have the lowest energy level. At this low scale, it may be possible to construct a structure where the addition of electrons can lead to a predictable outcome.

# Discussion

Many drugs are only suitable for intravenous use at the moment. However, in many cases, the mouth would be the preferred route of administration for drugs. This is because many of the drawbacks of intravenous administration do not apply to this method. Taking drugs orally is the least invasive of all the methods, as well as the least difficult: Patients are able to take oral drugs by themselves, but require medical assistance to take them intravenously. This can be a big problem for patients requiring regular doses, or those who find it difficult to travel due to their illness or for other reasons. It is therefore in these people's best interests that they have access to the drugs they need in a form they can use.

However, to accomplish this, certain difficulties must be overcome. The stomach, or other areas of the gastrointestinal tract, can break down drugs before they can be absorbed. Most proteins and peptides are broken down by enzymes in the gastrointestinal tract before they are can be absorbed, thus drugs based on these will have little effect on the patient's condition. Also, some drugs are simply too large to be absorbed normally by the intestinal lining.

Other drawbacks of the oral route include increased delay between administration and effect, when compared to intravenous drugs. They also require that the patient's gastrointestinal tract be functioning properly, in order to absorb the drug at all.

The principles of nanotechnology outlined previously can be used to overcome some of these difficulties.

Research is currently underway into the possibility of constructing nanoshells around drugs to keep them from being digested in the gastrointestinal tract. Researchers at the John Hopkins University school of Medicine have successfully constructed a nanoshell, composed of six parts N-isopropylacrylamide, two parts methylmethacrylate, and two parts acrylic acid, for cancer drugs. This shell can contain several water-insoluble drugs, and protects them from digestion in the stomach. Not only that, but the shell's composition sticks to the mucus on the gastrointestinal wall, allowing increased time for the absorption of the drug into the bloodstream.

The shell has been shown to deliver the cancer drug rapamycin to human pancreatic tumours in rats, and to have no toxic side-effects.

This research clearly shows that the development of nanoshells for the oral administration of drugs is possible, and there should be drugs available in this form within a few years.

However, there are still problems with this form of treatment; this method of delivery will be highly expensive, due to the original cost of the drug to be administered, plus the research costs of this technique, plus the costs of producing the nanoshells. This cost will be offset by the reduced costs of oral treatment: Patients do not require beds or a healthcare specialist's help in order to use this form of treatment. However this saving is likely to be small in comparison to the additional cost of treatment, so it would not be economically viable to put this treatment into widespread use.

Also, there are inherent difficulties with using oral drugs:

The time between the drugs being administered and them taking effect is increased, due to the added delay of absorption into the bloodstream. This can cause problems when drugs are needed urgently.

Also problematic is the drug's reliance on the functioning of the gastrointestinal tract, which could lead to patients not absorbing a vital drug, despite it being administered. This also makes this method of delivery unsuitable for some patients with gastrointestinal disease.

Finally, if a high dose of the drug is required, then intravenous may be the better method, as when giving drugs orally, higher doses are less likely to be completely absorbed.

These potential drawbacks ensure that this technique will not replace intravenous drugs entirely, as there are some cases where intravenous is the preferred method of treatment.

Although the goal of this research is to allow patients to take chemotherapy and other drugs without needing to see a health specialist, this is not always advisable, as chemotherapy drugs are highly dangerous, so care must be taken to ensure that only responsible adults are given control over this method of treatment.

Due mainly to the increased cost for no additional therapeutic effect, coupled with the reduced reliability of oral administration, I predict that this technique will not be widely used, but will likely be limited to private practice.

However, the applications of this technique are quite far-reaching. This experiment shows that molecular shells can be built to hold multiple types of molecule. This means that the technique will be easier to develop, as multiple drugs can be developed for at once.

Possibly most importantly, this shell was able to target the digestive membranes in the small intestine, to increase absorption. This suggests that similar shells can be developed to target other areas of the body, such as the sites of tumours. This would mean reduced damage to other areas of the body, and a greater proportion of the drug reaching the intended target. This would both increase the effectiveness of current doses, and allow higher doses with regards to side-effects.

Also notable, though easily overlooked, is the fact that the shell successfully prevented reaction with the enzymes present in the stomach. This is an important step, as it shows that shells can be developed that prevent the held drug from reacting with the body until the shell is removed. This further helps reduce side effects of targeted drugs to other areas of the body, as it prevents them from reacting with the healthy tissue on their way to their target. This also suggests a different possibility, of creating shells to bind with harmful chemicals inside the body and neutralise them, in a manner similar to antibodies.

During testing, extreme doses of the shell were given to rats, and no toxic side-effects were found to occur. This is vital to the success of the technique, as it shows that shells are capable of being usefully constructed without having toxic effects. This means that shells can be used to increase a drug's effectiveness with few to no additional side effects – this would be a huge leap forward in medicine, as most drugs and techniques are used as a "balancing act" weighing the risks against the benefits. Something that is significantly better for very few additional drawbacks is very rare in medicine, and highly valuable.

## Conclusion

Although I expect it to work as intended, I do not think that the current intended use for the technology, namely redeveloping intravenous drugs for oral use, will come into widespread use in the foreseeable future, due to the difficulties discussed earlier: The increased cost of treatment for no additional therapeutic effect, the delay in administration and effect, difficulties with higher doses, and reliance on patient's gastrointestinal system will all work to prevent the technology from going into widespread use when competing with the more reliable, cheaper, intravenous drugs.

However, I do believe that this technology will be successfully be developed for other purposes, specifically for reducing side effects and for the targeting of drugs.  I think this because of the properties of the shells already in development, namely their targeting of membranes, prevention of reactions, lack of toxicity, and multiple drug compatibility.

## References

Quatum-effect nanoscale devices http://science.jrank.org/pages/4554/Nanotechnology-Quantum-effect-nanoscale-devices.html

Scanning tunnelling microscopy and its applications
http://books.google.com/books?id=3Q08jRmmtrkC&pg=PA345&hl=en#v=onepage&q&f=false

Buckminsterfullerene - Production Of Fullerenes, Uses
http://science.jrank.org/pages/1060/Buckminsterfullerene.html

Initial Results of Phase 1 Clinical Study of Bioral Amphotericin B
http://www.understandingnano.com/clinical-study-bioral-Amphotericin-B.html

Polymer Nanoparticle for Oral Anticancer Drug Delivery
http://www.understandingnano.com/nanoparticle-oral-drug-delivery.html