

THE USE OF NANOCAPSULES IN DRUG DELIVERY  
SPECIFICALLY TO TARGET INFECTION

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**PASS WITH DISTINCTION**

RESEARCH PAPER  
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## ABSTRACT

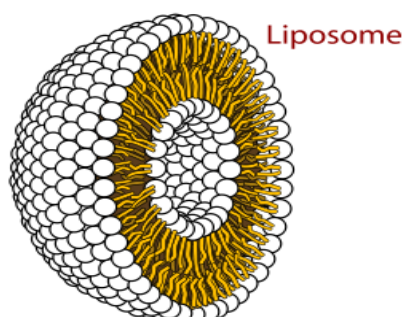
In this paper we will be discussing the current research and possible future developments of using liposomes for drug delivery. From targeting specific tissues to reducing the risk of infection for burn victims, this technology has many potential applications. We have developed our own idea using vesicles containing antibiotics and dye based on research currently being carried out. We aim to provide a possible solution to the problem of postoperative infection in particular types of surgery in a way that the risks of new antibiotic resistant pathogens developing are reduced. We will explore some of the practical, ethical and economic issues surrounding our possible future development.

## INTRODUCTION

Nanotechnology is known as the study of manipulating matter on an atomic and molecular scale. Generally nanotechnology deals with different structures sized between 1 to 100 nanometre in one or more dimension, and involves developing materials or devices within that size. Nanotechnology, in its advanced form is having a significant impact on almost all industries and all areas of society. It will eventually offer better structured, longer lasting, safer, and more intelligent products for use in the home, for aiding communications, for advancements in medicine, and for entire industry as a whole.

Previously most medical treatments have been the result of adopting the techniques found that worked with a good result and discarding the use of techniques that didn't work. Now, the much improved knowledge of how the body functions at the very small cellular and molecular level is leading to many new and better medical techniques being found. The study of nanotechnology is also helping towards finding a far faster diagnosis. Many diagnosis' can be a very lengthy task, usually with a test sample having to be sent away for some form of analysis. These results can usually take several days or a number of weeks to arrive. So, with the new development of nanotechnology this is starting to enable a much faster and more precise diagnosis. This enables the samples that are taken to be processed and analyzed quickly and accurately, resulting in test results being able to be read out near enough instantaneously.

In this paper we will be focusing on the use of nanocapsules and more specifically nanosomes in drug delivery. The term 'nanosome' refers to an artificially prepared vesicle, in the low nanometre size range, made up of a spherical lipid bilayer that can hold a substance inside of it. (Also referred to as liposomes although liposomes aren't necessarily nanosomes as they don't specify a size)



We chose to focus on liposomal drug delivery research because, although it is not the most 'technologically advanced' type of nanotechnology and is not really the 'molecular machine' people think of when referring to nanotechnology, it is more the nanotechnology of the immanent and foreseeable future rather than the distant future. The developing ideas that we will be focusing on in this paper are things that could come onto the market in our lifetime and potentially benefit us makes them particularly exciting.

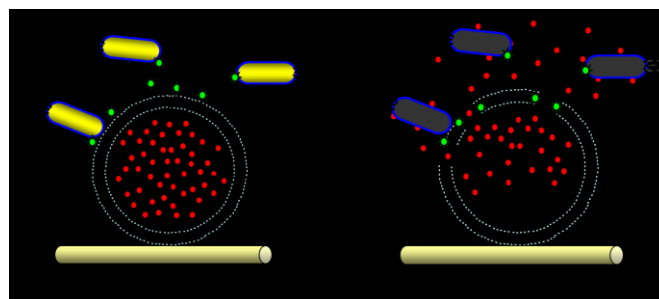
Liposomes have advantages in drug delivery. Because of their similar structure to cell surface membranes, drugs can be passed to cells by diffusion between the capsule and the cell or by the vesicle fusing with the cell membrane in a similar way to endocytosis. Drugs encapsulated in liposomes can target cells more specifically and can be released inside the body over a longer period of time after injection.

Several drug companies have developed drugs using liposomes. FDA approved liposomal drugs include:

- AmBisome<sup>®</sup> - an antifungal agent
- DaunoXome<sup>®</sup> - an anti-cancer chemotherapy drug for a particular type of cancer (Kaposi's sarcoma) that patients with HIV may develop
- DepoDur<sup>®</sup> - sustained release post surgical pain relief

Several other liposomal drugs are in clinical trials or awaiting FDA approval. Many of these are cancer drugs. The advantages of using liposomes to deliver chemotherapy drugs are that due to blood vessels having 'leaky walls' in tumours. The capsules (if made to a certain size) accumulate more inside them; meaning that the cancer is targeted directly with the drugs, resulting in fewer side effects due to healthy cells being damaged. Another developing idea for using vesicles in cancer drug delivery is to construct a liposome that binds to the cell surface receptors of the tumour's blood vessel epithelial cells or to the tumour cells using peptides attached to the vesicle. This will target the tumour so that there are fewer side effects from the chemotherapy drugs.

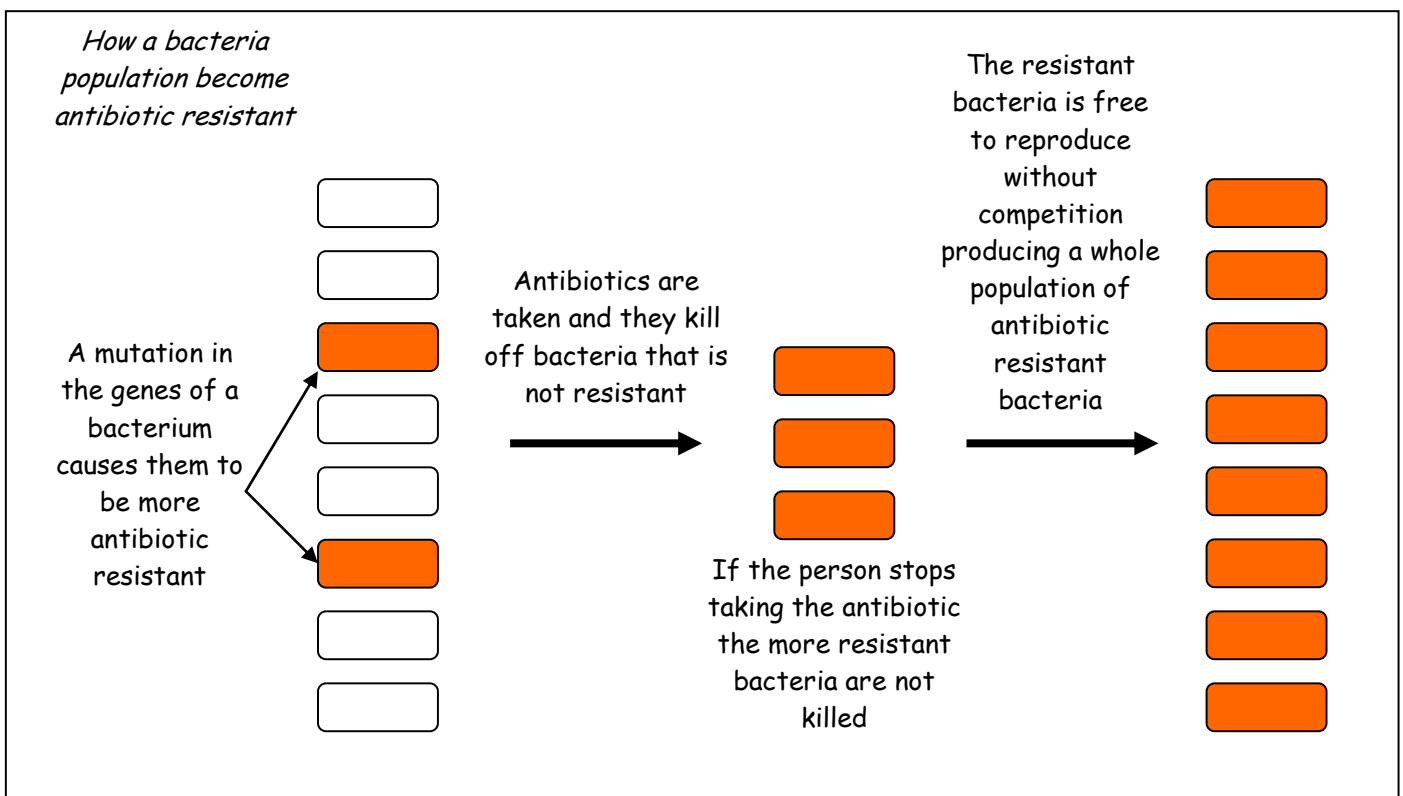
Researchers at Bath University, led by Dr Toby Jenkins, are using nanosomes for drug delivery in a different way. Instead of using them to carry drugs directly into cells they are using them on a dressing for paediatric burns. Vesicles containing antibiotics and a fluorescent dye will be attached to a dressing. The vesicles are broken down by harmful chemicals produced by the pathogenic bacteria designed to damage cells. When the membrane is broken down the antibiotics or dye that is in that vesicle will leak out. This means that the antibiotics and dye will only be released if harmful bacteria are present and the burn is infected. The antibiotics will treat the infection as soon as it appears and the dye will notify the doctors that the burn is infected.



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## DISCUSSION

Presently, in the NHS, antibiotic resistance is becoming an increasingly serious problem. Antibiotics are used to treat bacterial infection but new strains of bacteria are emerging that do not respond to normal treatment with some antibiotics. Antibiotic resistance doesn't mean the bacteria are necessarily untreatable with antibiotics but it may mean they need a far higher dose over a longer time period. For example MRSA (meticillin-resistant *Staphylococcus aureus*); an infection caused by a commonly found bacteria that can occasionally get through the skin and cause serious infection such as septicaemia, pneumonia and endocarditis. MRSA is no more aggressive than other infections, simply more resistant to treatment. Antibiotic resistance is caused by a mutation in the genes of the bacteria. For example, when a person falls ill due to a bacterial infection and are given antibiotics, the bacterial population; if they are not resistant to it, will be killed. If one or two bacterium in a population mutate and become resistant, when the population is exposed to an antibiotic all but those mutated bacteria would be killed. At this point, the patient may start to feel better even if they are only half way through their course of antibiotics and forget or decide to stop taking them despite being told to take them for the full course. This leaves the antibiotic resistant bacteria space without competition to replicate creating a whole population of antibiotic resistant bacteria. One of the main ways of trying to prevent against antibiotic resistant bacteria is to prescribe antibiotics less; only when they are strictly necessary.



Antibiotics that fight bacterial infections by killing the bacteria can cause some side effects as they can kill some good bacteria too. Everyone has millions of harmless bacteria living in places such as their mouth, gut, skin and reproductive passages. A course of antibiotics can kill some of these harmless bacteria too, leaving fungal pathogens with less competition for space and nutrients allowing them to develop into an infection. This means that taking antibiotics can leave the patient at an increased risk of developing fungal infections such as thrush.

Prophylaxis is a common method of preventing disease in patients having surgery. Prophylaxis means giving the patient antibiotics before or during surgery to decrease their chances of getting ill from an infection. The problems with this method are that antibiotics are being administered even if there is no infection, increasing the chances of antibiotic resistant bacteria developing. Bacteria already found on the body, which are not a problem in predominately healthy people, can become a problem for people with a lowered immune system for example the bacteria that cause MRSA. Giving this bacteria unnecessary exposure to antibiotics could help the population to build up resistance to it. When this bacterium infects someone who is not able to fight it off, they will be given antibiotics to help them. However, it may not work if the bacteria have built up a resistance to the antibiotic making this disease more serious as it is harder to treat.

It is important that infection after surgery is prevented even in minor operations. Stitches getting infected can slow down the healing process and increase the risk of developing bad scars. The infection can also spread into the blood and to other organs causing very serious and life threatening illness. For people with existing health problems, such as cardiovascular conditions, are at increased risk from infections. Even in procedures such as removing a mole from your skin, if the stitches get infected it can spread and cause endocarditis; an infection of the heart valves, which can be very serious.

We have developed a new idea based on the work of Dr Toby Jenkins, who is trying to incorporate vesicles with antibiotics and a fluorescent dye inside into plasters for burns patients. The vesicles would be broken down if a toxin was produced by an infection. Dye would also be released so the medics would know if there was a bacterial infection in the wound. A development of this technology could be used in stitches to reduce the amount of postoperative infections, this would reduce the risk of operations for people who are more vulnerable, or have a weaker immune system. By treating infection as soon as it appears, the wound would heal more quickly and easily, meaning there would be less risk of scarring.

However, these stitches would not be dissolvable, because, if the vesicles broke down, the antibiotics would be delivered regardless of if there was an infection or not - which defeats the object of the stitches. This means that these stitches could only be used on the skin, deeming them inappropriate for certain operations. It would be inappropriate if they were relied on for operations which involved inserting transplant organs or metal pins and plates, also lengthy operations. When something is permanently inserted into the patient, such as metal plates or an organ in a

transplant, there is an increased risk of internal infection because the foreign bodies left in the patient may be carrying some bacteria, therefore in these cases, the patient would have to be given a course of antibiotic to prevent serious internal infection, as the stitches would not be adequate protection against disease, being external. In addition, operations where the patient's internal organs are exposed to the air for a lengthy period of time, pathogens in the air are more likely to infect the patient, than if they were only in the operation for a short time.

In some cases (including the operations mentioned previously) there is still a need for prophylaxis, however, using these stitches laced with antibiotics that are only released when necessary, would reduce the need for prophylaxis. For certain types of surgery, especially cutaneous, in otherwise healthy patients this thread would be very suitable. Stopping the infection developing on the outside of the body greatly reduces the risk of the infection spreading on the inside of the body. If the wound does get infected the stitches will be a different colour under UV-light due to the dye being released and the doctor will be able to prescribe a course of antibiotics to make sure the infection is killed off but due to early intervention of the antibiotics there is a much smaller chance of the infection becoming a problem.

Side effects of some antibiotics include diarrhoea. This is due to the antibiotics decreasing the numbers of gut flora which aid digestion. Babies are not born with this gut flora, during birth and rapidly thereafter, bacteria from the mother and the surrounding environment colonize the infant's gut. If giving a newborn baby a course of antibiotics can be avoided it would be beneficial as they already have a lot less gut flora than adults so the chance of antibiotic-associated diarrhoea is increased. Therefore using these sutures instead of normal thread and a course of antibiotics in a new born would be beneficial.

The advantages of these stitches over prophylaxis or no antibiotic treatment are that the antibiotic is only released if and when there is an infection. If no antibiotics were given and the wound did get infected it could cause more serious internal infection if it spreads and also slow down the healing of the wound possibly leading to worse scarring. If antibiotics were given but the wound did not get infected, it could leave the patient more susceptible to fungal infection and diarrhoea unnecessarily, and it slightly increases the risks of an antibiotic resistant bacteria developing. By releasing antibiotics only when needed, these sutures could play an important role in the prevention of developing superbugs.

This technology could be used not only for surgical stitches but for closing wounds after injury and in any cases removable stitches are used externally. If this thread was developed it could replace any used in incidences where antibiotics are only given as a precaution to stop infections occurring around them and not for any other internal infection. However, we feel they would be most appropriate as surgical sutures because you know exactly how long the wound has been open for, exactly what objects it has been in contact with, and that everything it has been in contact with has been thoroughly sanitised so you are aware of the risks of infection.

## CONCLUSION

Based on the research overseen by Dr Jenkins at University of Bath, we have developed an idea for a new medical advancement to target the problem of bacterial infections after mainly cutaneous surgery. This technology would, hopefully, reduce the necessity for prophylaxis and therefore unnecessary exposure to antibiotics, in the hope that this would reduce the chance of antibiotic resistant bacteria developing. Another problem that it could eradicate is stitches getting infected. This is important because infected stitches can cause scarring, delayed healing and, if it spreads, more serious internal infection.

The basic concept of our possible future development is that vesicles containing antibiotics and dye would be incorporated into the thread. When the site is infected, the bacteria release toxins. These toxins would break down the vesicles releasing the antibiotics and dye into the surrounding area. This means that antibiotics are only given when necessary and the medical professionals would be alerted to an infection.

Having spoken to Dr Jenkins about the technology he's developing, certain issues that he and his team had encountered during their research were highlighted, including problems relating to preventing the vesicles from disintegrating and fixing the vesicles to the fabric. It is vital that the vesicles don't break down because the main objective of this technology is that the antibiotics are only administered when the toxin is produced by the bacteria. If the vesicles were to break down without this trigger they would be pointless and a full course of antibiotics could be given in their place. The other main issue they encountered was fixing the vesicles to the plaster which is obviously vital for the technology to function. If the vesicles separated themselves from the plaster and were released into the blood stream they could not be removed again so would eventually release the antibiotic and dye. For our product to work we would have to overcome the same practical issues; making the vesicles stable enough yet still able to be broken down by the toxins, and fixing them to the thread. If Dr Jenkins and his team manage to, in their research, overcome this problem, the development of our specialised sutures would also be possible.

Before any new drug is available on the market it has to go through vigorous safety tests and trials. One benefit our product would have over many other drugs in clinical trials would be that it would be using pre-tested and approved antibiotics meaning that the possible risks of adverse reaction are known and deemed acceptable. A small percentage of people may react to the antibiotics or dye however this risk is the same with the majority of drugs. The dye would have been specifically chosen so that it would not cause any objectionable side-effects.

One problem with carrying out clinical trials would be that it would not be possible to test the product first on healthy volunteers; they must be undergoing the right type of surgery. When undergoing clinical trials a control group is given the current best treatment to compare the new treatment to. For particular procedures, for example removing moles, in general no antibiotics are administered. When comparing our new treatment to these cases, it would demonstrate if there was a

significant reduction in the cases of infection and therefore if it provided sufficient benefits. When the control group would take antibiotics as a precaution it could be unfair to give the trial group our sutures and no additional antibiotics as we are as yet unsure about the effectiveness of the sutures. Therefore the trial group could be putting themselves at an unknown level of risk although they would have the benefits of no unnecessary side-effects from the antibiotics. For this reason it would be sensible to first undertake clinical trials in patients who would not normally receive any treatment to prevent infection.

Conducting a double-blind trial could be problematic due to the fact that healthcare professionals would need to check for dye around the operated area. If it is revealed that the dye is present, it will become quite obvious which group the patient is in, therefore the results could be slightly influenced and be inaccurate. One of the main aims with this new product is that it would help to combat the development of antibiotic resistant bacteria. In clinical trial or otherwise this principle is very difficult to measure in a clinical setting. Although theoretically it should help, the effectiveness will be near impossible to quantify.

The research, development and manufacture of new a drug is very expensive and therefore at times it can be hard to justify the cost of the drugs by their benefits. Many people would argue that the money used to develop new products like our idea could be better used to develop life saving treatments rather than treatment that may improve quality of life for a short time. US scientists have developed antibodies against a protein belonging to MRSA bacteria and on their way to finding a vaccine for MRSA. There is arguably more need for funding for products like this than products like ours that try to stop more antibiotic resistant bacteria developing seeing as superbugs like MRSA have already developed.

There is no healthcare system in the world that has sufficient money to provide the best possible treatment for all patients in all situations. The implications of this are that the NHS may not be able to provide this treatment for patients if it was developed. They would have to weigh up whether or not they would rather spend the limited money that they have on this intervention which would statistically prevent infection though they won't know who it will benefit. Some people who do receive the treatment may not get an infection so it will have been of no use in their case however it is not possible to tell who will get an infection so will benefit and also the advantage of preventing the development of antibiotic resistant superbugs is not measurable. The option would be to spend it on an intervention which would definitely help every person who received it (for example kidney dialysis which will extend life for that person). Another decision they would have to make is whether the cost of providing this treatment for a large number of people is cheaper than the cost of the alternative treatments.

For the drug company, possible future developments to their technology could make the manufacture of the drug cheaper and therefore increasing the profit so that they will have enough money for research and development of new drugs. The NHS will probably never be able to overcome the issue of resource allocation and will

always face these issues due to lack of money.

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