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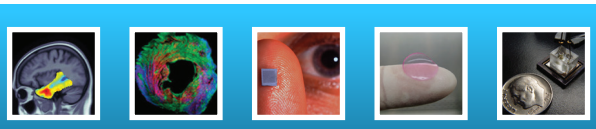


Drug Delivery Systems: Getting Drugs to Their Targets in a Controlled Manner

National Institutes of Health

What are drug delivery systems?

Drug delivery systems are engineered technologies for the targeted delivery and/or controlled release of therapeutic agents.

Drugs have long been used to improve health and extend lives. The practice of drug delivery has changed dramatically in the past few decades and even greater changes are anticipated in the near future. Biomedical engineers have contributed substantially to our understanding of the physiological barriers to efficient drug delivery, such as transport in the circulatory system and drug movement through cells and tissues; they have also contributed to the development of several new modes of drug delivery that have entered clinical practice.

Yet, with all of this progress, many drugs, even those discovered using the most advanced molecular biology strategies, have unacceptable side effects due to the drug interacting with parts of the body that are not the target of the it. Side effects limit our ability to design optimal medications for many diseases such as cancer, neurodegenerative diseases, and infectious diseases.

Drug delivery systems control the rate at which a drug is released and the location in the body where it is released. Some systems can control both.

How are drug delivery systems used in current medical practice?

Clinicians historically have attempted to direct their interventions to areas of the body at risk or affected by a disease. Depending on the medication, the way it is delivered, and how our bodies respond, side effects sometimes occur. These side effects can vary greatly from person to person in type and severity. For example, an oral drug for seasonal allergies may cause unwanted drowsiness or an upset stomach.

Administering drugs locally rather than systemically (affecting the whole body) is a common way to decrease side effects and drug toxicity while maximizing a treatment's impact. A topical (used on the skin) antibacterial ointment for a localized infection or a cortisone injection of a painful joint can avoid some of the systemic side effects of these medications.

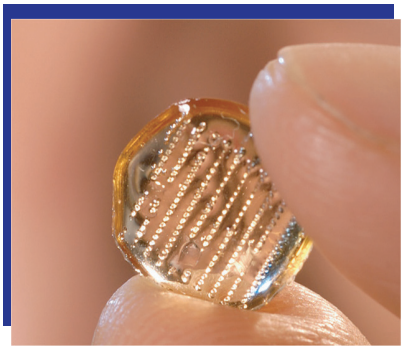


Image of microneedle patch the size of a fingertip used to deliver influenza vaccines.
Photo Credit: Dr. Mark Prausnitz, Georgia Institute of Technology.

There are other ways to achieve targeted drug delivery, but some medications can only be given systemically.

What technologies are NIBIB-funded researchers developing for drug delivery?

Current research on drug delivery systems can be described in four broad categories: routes of delivery, delivery vehicles, cargo, and targeting strategies.

Routes of delivery. Medications can be taken in a variety of ways—by swallowing, by inhalation, by absorption through the skin, or by intravenous injection. Each method has advantages and disadvantages, and not all methods can be used for every medication. Improving current delivery methods or designing new ones can enhance the use of existing medications.

Microneedle arrays are one example of a new method to deliver medications through the skin. In these arrays, dozens of microscopic needles, each far thinner than a strand of hair, can be fabricated to contain a medicine. The needles are so small that, although they penetrate the skin, they don't reach nerves in the skin, thus delivering medications painlessly. These patches are easy to use and do not require refrigeration or special disposal methods, so they could be used by patients themselves at home. This technology could be especially helpful in low-resource communities that may not have many health care providers or adequate storage facilities for traditional, refrigerated medicines.

Delivery vehicles. Biotechnology advances are leading to improved medications that can target diseases more effectively and precisely. Researchers have begun to reformulate drugs so they may be more safely used in specific conditions. The more targeted a drug is, the lower its chance of triggering drug resistance, a cautionary concern surrounding the use of broad-spectrum antibiotics.

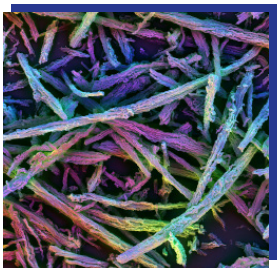
Nanotechnology is opening up new avenues for drug delivery vehicles. NIBIB-funded researchers have reported promising results in developing a treatment for glioblastoma, a devastating brain cancer. In rat models of the disease, they have shown that tumors can be penetrated and shrunken when injected with nanoparticles. The nanoparticles target the tumor by delivering an altered gene, or suicide gene, that is programmed for cell death. The nanoparticle method replaces a type of gene therapy using viruses, which can have unpredictable outcomes.

Other NIBIB-funded researchers are developing a system of drug delivery using a type of bacteria that has a two-part navigation system—magnetic and oxygen sensing. They have tested the delivery system in mice, achieving a remarkable success delivering drugs to tumors. The bacteria seek out oxygen-poor zones, which are a feature of tumors. Using a computer-programmed magnetic field to direct the bacteria to tumors, the researchers found that the bacteria were drawn deep into the oxygen starved tumors, away from healthy cells. This

process could open the door for directing drug-laden bacteria to tumors deep in the body.process could open the door for directing drug-laden bacteria to tumors deep in the body.

Cargo. Perhaps the most obvious route to improving disease treatment would be to focus on the medications themselves. In addition to drugs and novel vaccines, researchers are also exploring the use of genes, proteins, and stem cells as treatments.

NIBIB-funded researchers are pursuing ways to improve the immune response against cancer and infection using nanovaccines that have unique structures and incorporate inorganic materials. In one study, they injected mice with a vaccine formulated with silica rods that assemble like a stack of match sticks. The scaffold of rods is capable of recruiting, housing, and manipulating immune cells to generate a powerful immune response. Researchers found that the nanovaccine could delay tumor growth in mice with lymphoma, a cancer affecting the infection-fighting cells of the immune system.



Polychromatic scanning electron microscopy of 3-D vaccine consisting of microsized, porous silica rods.
Source: James C Weaver, Wyss Institute.

In another study, researchers prolonged survival for mice with melanoma by treating them with a nanovaccine that combines a bacterial DNA—programmed to trigger an immune response—and a nano-sized inorganic substance that helps the nanovaccine remain longer in the tumor environment. Once inside, the nanovacine instructs the immune cells to recognize cancer cells as foreign and attack them.

Targeting Strategies. Working backwards is sometimes an effective way to solve a problem. In drug delivery research, this means starting with a delivery method. The target may be whole organs (heart, lung, brain), tissue types (muscle, nerve), disease-specific structures (tumor cells), or structures inside of cells. Using this reverse-engineering approach, NIBIB-funded researchers developed a plant virus nanoparticle that can target and attach itself to prostate cancer cells. When labeled with fluorescent dyes, the viral nanoparticles can show researchers whether cancer cells have spread into bone at earlier stages of the disease than with traditional bone scans.

Made from modified viruses, viral nanoparticles take advantage of the natural ways that viruses have developed to slip past immune defenses and enter cells. This means they do not need to be modified as much as other types of nanoparticles to behave in desired ways, and their actions within the human body are well understood. Plant-based viral nanoparticles are also biodegradable, harmless to humans, easy to use, and cheap to produce. Further research aims to develop viral nanoparticles that can deliver chemotherapy drugs directly to tumors. Such an advance would reduce the severe side effects usually associated with cancer treatment.

What are some important areas for future research in drug delivery systems?

As scientists study how diseases develop and progress, they are also learning more about the different ways our bodies respond to illness and the influence of specific environmental or genetic cues. Coupled with advances in technology, this increased understanding suggests new approaches for drug delivery research. Key areas for future research include:

Crossing the blood-brain barrier (BBB). The BBB works constantly to allow essential substances from the bloodstream into the central nervous system and keep out harmful substances. Delivering drugs into the brain is critical to the successful treatment of certain diseases such as brain tumors, Alzheimer's disease, and Parkinson's disease, but better methods are needed to cross or bypass the BBB. One method currently under study uses advanced ultrasound techniques that disrupt the BBB briefly and safely so medications can target brain tumors directly, with no surgery required.

Enhancing targeted intracellular delivery. Just as the immune system defends the body against disease, each cell also has internal processes to recognize and get rid of potentially harmful substances and foreign objects. These foreign agents may include drugs enclosed in targeted delivery vehicles. So as researchers work to develop reliable methods of delivering treatments to targeted cells, further engineering is still needed to ensure the treatments reach the correct structures inside cells. Ideally, future health care will incorporate smart delivery systems that can bypass cellular defenses, transport drugs to targeted intracellular sites, and release the drugs in response to specific molecular signals.

Combining diagnosis and treatment. The full potential of drug delivery systems extends beyond treatment. By using advanced imaging technologies with targeted delivery, doctors may someday be able to diagnose and treat diseases in one step, a new strategy called theranostics.

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