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Slow and steady wins the race: an exciting new material for long-acting medicines

Olga Matsarskaia

Researchers have developed a molecular delivery system for continuous release of an anti-HIV medicine.

The following was adapted from an [ILL News](#) article.

Do you remember the last time you took a medicine? It was very likely in the form of a pill. But what actually happens to the medicine in your body after you swallow it? Once the pill arrives in your stomach, it is broken down to release the

medically active molecules that will treat your illness. These molecules travel through the walls of the stomach into your bloodstream. The blood then transports it within your body so that the medicine can reach the organ(s) where it is needed.

At first, the level of the medication in your blood will increase. Over time, the medication will be broken down by your body and eventually excreted, meaning that its levels will decrease again. You can see this increase and decrease in figure 1.

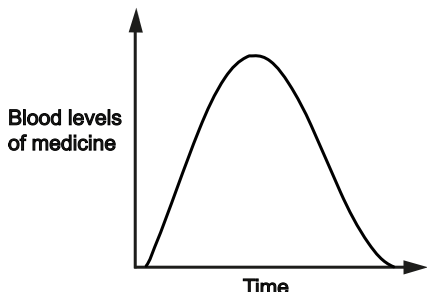


Figure 1: Blood levels of medicine as a function of time. Initially, the levels increase and subsequently decrease as the medicine is broken down and excreted.

Image courtesy of the author

Once the amount in the blood falls below a certain level, the medication is no longer effective. However, high levels need to be avoided because medication can also have harmful side effects. For example, paracetamol, which is used to treat pain and fever, can damage your liver at high doses. Therefore, it is very important that we carefully control the level of medicine in the blood.

In fact, there is a specific dose range corresponding to an amount of medicine which is sufficiently high to treat your disease, but not high enough to harm your body. This range is known as the ‘therapeutic window’ (see figure 2). If we remember that the levels of the medicine rise and fall after you take a pill, as we described above, we see that the blood levels of the medication are only within the therapeutic window for a rather short time.

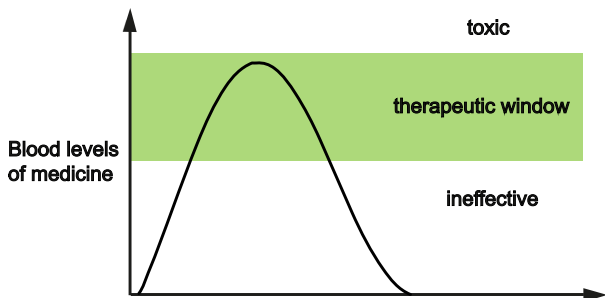


Figure 2: Increase and decrease of the blood levels of a medicine. The green area illustrates the therapeutic window.

Image courtesy of the author

A very important question is: how can we increase the time span during which the medication level is within the therapeutic window so that the target disease can be treated over a longer time?

There are two options: you can take a higher dose of the medicine or you can take it frequently. This will give rise to medicine blood levels like the ones shown in figure 3. However, a large single dose can increase the medicine blood levels into the toxic range, whereas having to take repeated doses can easily lead to doses being forgotten.

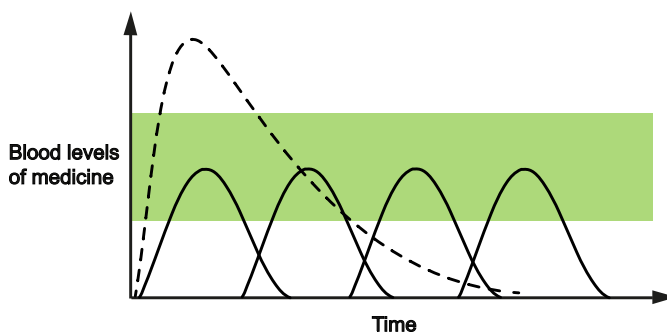


Figure 3: Blood levels of a medicine after taking a large dose (---) or multiple smaller doses (—)

Image courtesy of the author

For people infected with the human immunodeficiency virus (HIV), which can cause autoimmune deficiency syndrome (AIDS), this is a particular challenge: to keep the virus under control, it is very important to maintain the medicine level within the therapeutic window at all times. This implies that HIV patients need to take pills every day. Not everybody is able to follow such a strict treatment plan, which can lead to the treatment being inefficient, with serious health consequences.

A very good solution to this problem would be a delivery system that releases an anti-HIV treatment into the bloodstream slowly and continuously (figure 4).

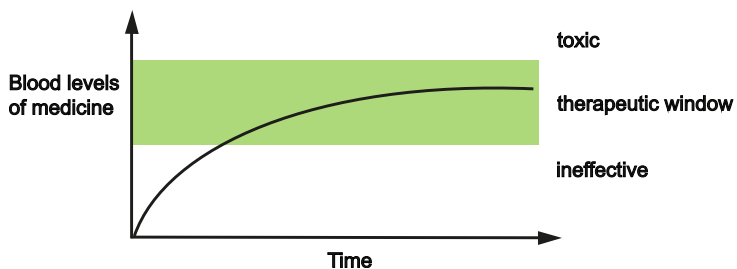


Figure 4: An optimized profile of continuous medicine release into the bloodstream

Image courtesy of the author

In the past, scientists developed such delivery systems based on peptides (short chains made up of amino acids). The peptides containing the medicine are injected under the skin, where enzymes arrange them into a molecular ‘store’ in the form of a hydrogel, which is a peptide mesh containing water. The medicine is then released slowly from the hydrogel. Unfortunately, peptides are broken down rather quickly by enzymes in the body (figure 5, yellow shapes). To improve these delivery systems, researchers have designed a new type of hydrogel that is made of a mixture of peptides and peptoids (synthetic molecules that resemble peptides but have a different chemical group in the place of the proton on the nitrogen atom in the peptide bond). One of the advantages of peptoids is that they are less well recognized by enzymes that break down peptides, meaning that peptoids are more stable in the body (figure 5, right).

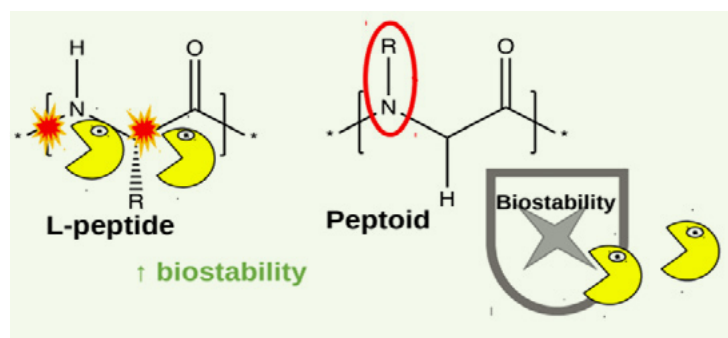


Figure 5: Illustration of a conventional peptide (left) and a peptoid (right). Compared with peptides, peptoids are much more resistant to degradation enzymes (represented by the yellow shapes) and, therefore, feature higher biostability in the body.

Image adapted from Ref. [1]

The newly developed peptoid–peptide structures are attached to an anti-HIV medicine (zidovudine, AZT for short)

and chemically modified to contain a phosphate group. This group prevents the formation of a gel network until the peptoid–peptide system is injected into the skin, where phosphatase enzymes remove the diphosphate group, which leads to rapid gel formation. The gel network is then hydrolyzed over time, releasing the medicine slowly and continuously into the bloodstream (figure 6).

To optimize their ability to release AZT and get the right dosage, understanding the microscopic structure of the hydrogels is important. First, detailed images of the hydrogels were obtained by using high-resolution microscopy techniques (figure 7). The images show that the hydrogels consist of a three-dimensional sponge-like network of peptoid fibres.

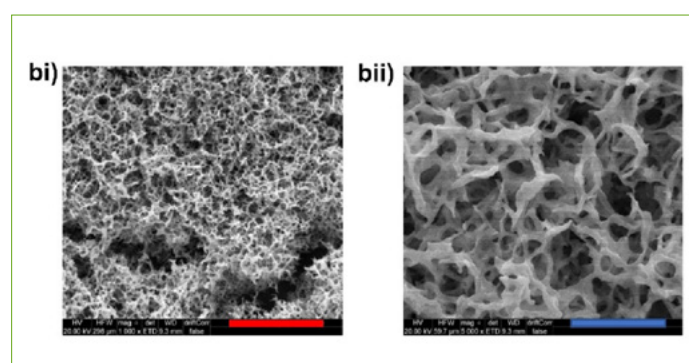


Figure 7: Scanning electron microscopy images showing the fibrous architecture of the hydrogels at (a) 1000× magnification and (b) 5000× magnification; red scale bar = 100 μm , blue scale bar = 20 μm . Image adapted from Ref. [1]

While microscopy shows a snapshot of one specific length scale of the hydrogels, other techniques can provide detailed information over several length scales at the same time. One such technique is small-angle neutron scattering (SANS).

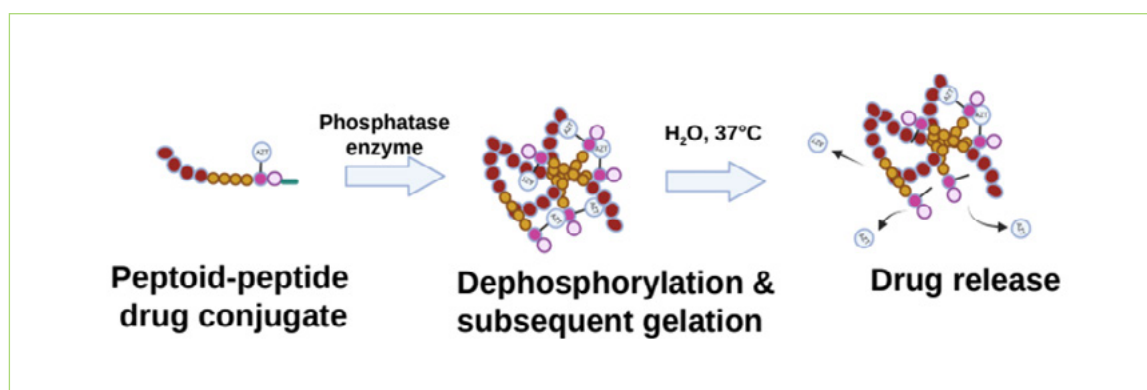


Figure 6: After injection, gelation of the peptoid–peptide which is conjugated to an anti-HIV medicine (AZT) is triggered by phosphatase-catalyzed dephosphorylation. AZT is then released continuously from the hydrogel.

Image adapted from Ref. [1]

Neutrons in research

Neutrons are particles that are usually found within atomic nuclei. Free neutrons for experiments (like SANS) need to be produced at specialized spallation sources or at neutron reactors. One such reactor is located at the Institut Laue-Langevin (ILL) in Grenoble, France.



The SANS instrument D11 (long yellow tube) at ILL.
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Neutrons produced by the ILL nuclear reactor are a powerful probe to study small samples of materials. They have specific properties that enable them to yield information that is often impossible to obtain using other techniques. Neutrons interact with the nuclei of matter, and observing how they are deflected and change speed gives precise information about the position and motion of the nuclei. Using dedicated instruments, neutrons beams are directed at samples such as the hydrogels described here. The samples scatter some of the neutrons, which are recorded on a special detector. By analyzing how many neutrons are scattered at different angles, researchers can understand the molecular structure and properties of the samples. Importantly, neutrons interact strongly with hydrogen and less so with its isotope deuterium ('heavy hydrogen'), so if some of the hydrogen in the sample is replaced with deuterium, selected parts of the sample can be highlighted for even more detailed studies.

SANS showed that the molecular structure of the peptoid hydrogels remains the same whether or not they contain AZT. This means that in terms of contributing to the overall structure of the network, the properties of the fibres themselves are more important than the addition of the medicine. It also implies that the network structure is not perturbed by the medicine.

The novel peptoid hydrogels were shown to release AZT over a period of 28 days in test tubes. Further experiments showed that it was absorbed in clinically relevant amounts in an animal model over 35 days. These data mean that the hydrogels are a very good template for the development of long-acting drug delivery systems. Importantly, this technique is expected to be equally efficient in treating a variety of other diseases, such as cancer, malaria, or tuberculosis. Another advantage of these delivery systems is that they can target body parts that are usually hard to access, such as the eyes or the central nervous system. <<

Acknowledgements

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References

- [1] Coutler SM et al. (2024) [In Situ Forming, Enzyme-Responsive Peptoid-Peptide Hydrogels: An Advanced Long-Acting Injectable Drug Delivery System](#). *Journal of the American Chemical Society* **146**: 401–21 416. doi: 10.1021/jacs.4c03751

Resources

- Find out more about the [Institut Laue-Langevin](#)
- Inspiring teaching resources for particle physics can be found through Accelerate Your Teaching: Lewis J (2024) [Accelerate your teaching with links to cutting-edge science](#). *Science in School* **67**.
- Build a Gauss cannon to model linear acceleration and spallation: Lewis J, Michalak L (2024) [Build a linear accelerator model](#). *Science in School* **67**.

- Try some activities to find and learn about particle accelerators near you: Lewis J, Darve C (2024) [Accelerators are everywhere, perhaps closer than you think...](#) *Science in School* **69**.
- Try this role-playing activity to teach your students about synaptic transmission: Andersen-Gassner M, Möller A (2023) [Hold your nerve: acting out chemical synaptic transmission](#). *Science in School* **63**.
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- Read about magnetic bacteria and their potential for medical applications: ILL (2020) [Insights into magnetic bacteria may guide research into medical nanorobots](#). *Science in School* **51**.
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AUTHOR BIOGRAPHY

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