TRANSPORT WITHOUT SIDE EFFECTS

Researchers have been working for 120 years to provide drugs with good chemical packaging so that they can reach their targets in the human body. In the past, the active ingredients were protected by a layer of sugar in dragées. Today nanotechnology is opening up entirely new opportunities

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Packaging counts. This basic principle applies not only to perfumes and filled chocolates in elegant flasks or decorative boxes but also to medical active ingredients if they are to optimally develop their healing effects inside the human body. For example, the active pharmaceutical ingredient in a tablet must be bound and safely packed in such a way that it can penetrate all of the body's physiological barriers against foreign substances. That's the only way it can reach the diseased organ and precisely deliver its desired effect. The art of finding the right packaging or formulation for drugs is professionally known as galenics, after a renowned physician of antiquity, Galen of Pergamon.

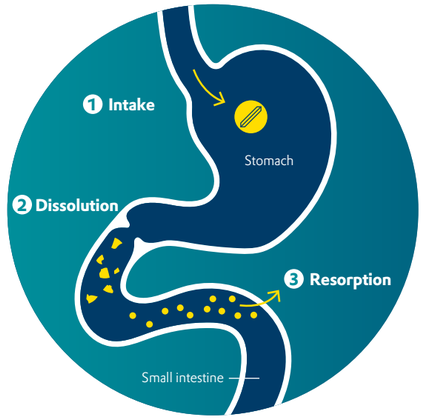
Whereas the science of curative substances, which originally came from plant parts such as leaves and roots, developed over the whole course of human history, pharmaceutical research in the area of formulations is less than 120 years old. During this time, chemists and apothecaries have repeatedly found new ways to deliver active ingredients to their targets.

PAINKILLERS UPSET THE STOMACH

As long as this knowledge was missing, drugs were prescribed fairly nonspecifically. As a result, on their journey through the body they often lost much of their effectiveness and in many cases caused unwanted side effects. Some 2,400 years ago, the ancient Greek physician Hippocrates advised pregnant women to chew willow bark in order to mitigate their labor pains before giving birth. He didn't know that the cause of the analgesic effect was the salicylic acid salts contained in the bark. Nor did he know about the side effects of these salts. Even in 1874, when salicylic acid was first produced on an industrial scale, it was a double-edged sword for the patients who used it. Their original symptoms disappeared—but the patients then complained of stomachaches.

Jakob Hoffmann, a merchant in Ludwigsburg, was not satisfied with this outcome. He challenged his son Felix, an up-and-coming chemist, to find out the cause of the problem. At the time, Felix was working in the scientific laboratory of the pharmaceutical company Farbenfabriken vorm. Friedr. Bayer & Co. in Wuppertal-Elberfeld. He went to work immediately. The experiment in which he reacted salicylic acid with acetic acid finally yielded the desired result: acetylsalicylic acid. Hoffmann produced this substance synthetically for the first time on August 10, 1897. Under the brand name Aspirin, acetylsalicylic acid became one of the best-known medications of the modern era. Aspirin was initially sold in bags in powder form, but in 1900 Bayer launched this active ingredient on the market in the form of tablets containing 500 mg of acetylsalicylic acid.

Orally administered active ingredients were initially simply pressed into tablets, but the producers soon realized that the tablets would be more durable and effective if they had a protective coating. Apothecaries would traditionally coat the tablets with a thick coating of sugar. These dragées often also contained pigments such as titanium dioxide that would block the ultraviolet radiation of sunlight. As a result, the active ingredients would not disintegrate into undesirable decomposition products, even if they were stored for a long period of time.



RESORPTION AFTER ORAL ADMINISTRATION

Orally administered medications pass via the stomach to the small intestine. Thin coatings protect them from the acidic gastric juices, so that they reach the small intestine before they dissolve and pass through the intestinal tissue into the bloodstream.

PLASTIC COATINGS FOR MEDICATIONS

On a drug's journey through the body, the gastrointestinal tract is the first major barrier. From here, the active ingredient must find its way into the bloodstream so that it can be transported into the diseased tissue. "Resorption" is the term used by pharmacists for the passage of the active pharmaceutical ingredient through the cells of the intestinal wall. But before the substance reaches the small intestine, it must first pass through the very acidic environment within the stomach. It can do this successfully if it is covered with a film of polymethacrylate. A layer that is only 50 micrometers thick is sufficient to resist the gastric fluids.

The chemist Otto Röhm Jr. was the first one to recognize the pharmaceutical significance of this plastic. Röhm's father is still well-known as the inventor of Plexiglas. He applied for a trademark for it in 1933. Two decades later, his son launched pharmaceutical film coatings under the brand name EUDRAGIT on the market. Incidentally, the company he worked for is now part of Evonik. EUDRAGIT has a crucial advantage over traditional sugar coatings: Whereas sugar coatings can double the weight of a tablet, a film coating of EUDRAGIT only increases the weight by about three percent.

Ever since then, this material has developed into a versatile technology platform. Today it can be used to combine the different attributes of medications by means of a modular system. For example, active ingredients can be precisely released in a certain section of the small intestine. This is made possible by the fact that the polymethacrylates used for this purpose do not dissolve in acidic environments, but rather in the neutral environment of the intestine.

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How Medications Enter the Body

In the past 200 years, pharmacology and medicine have considerably expanded the methods by which medical active ingredients can be transported into the body. All four methods were basically already known in antiquity

Intranasal formulations
Medications are administered via the nose and the respiratory tract

Nasal spray

Oral formulations
Medications are transferred via the mouth to the gastrointestinal tract

Inhaler
Syrup/drops
Tablet
Capsule

Percutaneous formulations
Medications are absorbed by the skin

Active ingredient patch
Ointment

Parenteral formulations
Medications are injected directly into the bloodstream

Infusion
Injection

HIPPOCRATES OF KOS
The father of (modern) medicine

Thanks to increasing knowledge about the biochemistry of the body, formulations of active ingredients have become high-tech processes.

Active ingredient · Excipient · Coating

1870s
Capsule

Two-piece telescoping capsules enable better administration of unpleasant-tasting active ingredients in powder form.

1930s
Dragée—A tablet with a sugar coating

Dragées have a thick sugar coating to protect them against light and moisture, which is modeled on those used by confectioners.

1850s
Tablet

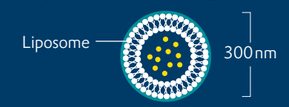
Early tablets were pressed from a mixture of the active ingredient, fillers such as starch, and binders such as gelatin.

1950s
Modern tablet

Thanks to extremely thin polymer coatings, tablets can work after a time delay or only when they reach specific parts of the intestine.

1990s
Passive drug delivery—Liposomes

The lipid bilayer, sometimes enhanced with a layer of polyethylene glycol, protects the active ingredient until it reaches its target tissue.

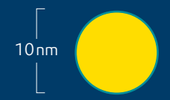


The future
Active drug delivery—Liposomes

Formulations such as liposomes will use special ligand molecules to dock precisely onto receptors on tumor cells.

2000s
Passive drug delivery—Metal particles

Sugar-coated particles of gold or iron oxide are physically excited to cause cell death in tumor tissue.



Size comparison:

The pH of an aqueous medium indicates how acidic it is. In an empty stomach with high acidity, the pH value is between 1 and 2. By contrast, in the small intestine the pH value is initially 5.5 and gradually increases to as much as 7. If the solubility of the polymethacrylate film is set at a pH value of 7, the active ingredient is not released until the passage between the small and large intestines. This is medically useful in cases such as the local treatment of inflammatory intestinal diseases.

OPTIMAL TIMING FOR HEART PATIENTS

Polymethacrylates also have another important use, in addition to the guaranteed targeted release of active ingredients at the right location. With their help, poorly water-soluble active ingredients can be made more easily available in the body. The molecules of the active ingredient are individually embedded in a matrix made of polymethacrylates—quite like the way they would be embedded between water molecules in an aqueous solution. That's why this is called "solid-solution" drug delivery. The molecules of the active ingredient are gradually released into the aqueous environment of the small intestine. If these molecules were to be quickly released in large amounts, they would form crystals and so be unable to pass through the intestinal wall—thus delivering no medicinal effect.

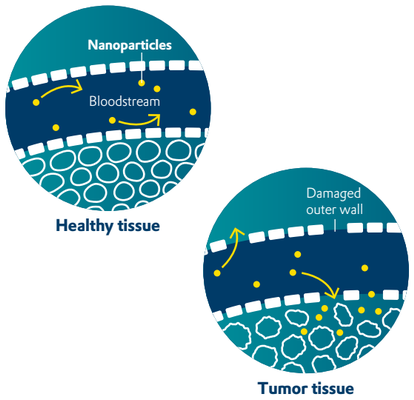
If active ingredients need to be released with a long delay, polymethacrylates can also be used to create formulations with pulsed release. These ensure that the active ingredient is released after a predefined period of time. They can be used to treat diseases that are especially dangerous in the early morning hours. For example, in cases of coronary heart disease the risk of a heart attack is greatest in the early morning. The patient can take a medication with pulsed release in the evening before going to bed. The film coating dissolves only between six and eight hours later, so that the blood level of the active ingredient increases exactly when the risk of a heart attack is greatest—and this happens unnoticeably, while the patient is sleeping.

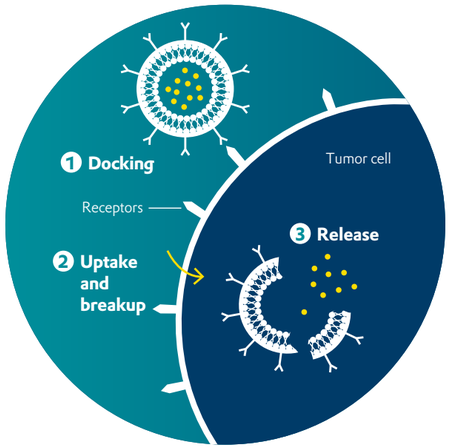
But tablets and capsules are not always the best choice. In some therapies, it's more effective to bypass the intestines altogether and inject the medication directly into the bloodstream. Alternatively, the active ingredient can be released into the body over a longer period of time from a depot that is located under the skin, for example. In these cases, parenteral drug formulations are used. A polymer such as polylactic acid or polyglycolic acid serves as the embedding matrix and breaks down over time within the body. The speed of this decomposition process can be precisely controlled. Meanwhile, the active pharmaceutical ingredient is released over a period of weeks or even months. This kind of delivery is used for implants against prostate cancer.

In the struggle against cancer cells, nanomedicine has an even broader vision: It aims to fight cancer with minimally invasive, personalized therapies. With the help of tiny particles, researchers are aiming to specifically deactivate cancer cells with molecular precision. That's because in spite of all the refinements of new cancer medications, it's still possible for the released active ingredients to attack healthy tissue as well. The resulting side effects can make ingestion of the drugs a form of torture for the patient.

PASSIVE DRUG DELIVERY

In cancer tissue (below) the blood vessels are porous, unlike those in healthy tissue (above). The active ingredient carrier can pass through the openings and into the tumor tissue. This is known as the enhanced permeability and retention or EPR effect.





ACTIVE DRUG DELIVERY

Special molecules known as ligands on the outside of the active ingredient carrier dock onto receptors on the tumor cell. The active ingredient carrier passes through transport channels in the cell membrane into the cell interior, where it releases the active ingredient.

This situation is set to change by means of "drug targeting," a process in which the drug is concentrated in a targeted manner exclusively in the diseased tissue, where it penetrates the cell membranes. In passive drug targeting, the tiny particles are injected directly into the tumor tissue. Alternatively, the enhanced permeability and retention, or EPR, effect is used: Because the blood vessels in tumors are not developed to the fully functional stage, particles loaded with the active ingredient can reach the tumor from the bloodstream through these gaps. The extent of this effect depends greatly on the nature of the tumor and on the formulation of the active ingredient.

Such transport systems of active ingredients made of lipids have already been used successfully since the 1990s. In the near future they are expected to also make RNA therapies possible (see the article on p. 30). The first liposomal RNA medication was recently approved by the FDA. Onpattro® will in the future be used for the treatment of familial amyloid polyneuropathy, a hereditary disease that leads to symptoms including signs of paralysis and muscle wasting in the extremities. The therapy promises to substantially improve the patients' quality of life in the future.

The particles for "passive drug targeting" consist of lipids, polymers or proteins. Some formulations also contain substances such as iron oxide or gold, which differ from traditional liposomes and other organic particles in that they do not transport any active ingredients. Instead, they themselves become active ingredients within the cell. The best-known example of this therapy is hyperthermia, in which the particles are injected into the diseased tissue and there energized through electromagnetic radiation from infrared light or through magnetic fields. This drastically heats up the cancer cells and thus kills them. A number of preparations that use this process have received official approval in recent years and are already being used in the first clinics.

"Active drug targeting" is even more ambitious: The carriers of the active ingredient are coated with special molecules that are supposed to dock onto receptors on the cells of the diseased tissue. Unlike passive drug targeting, these transport systems are provided with a targeting mechanism that enables their controlled uptake by special cells. In this case, success depends on whether the researchers can find the right molecules with the desired attributes. So far, the research results have admittedly been modest. In the past decade, 40,000 studies of this topic have been published, but almost none of the approaches they describe have so far been put into routine medical use.

DESTROYING TUMORS ON TARGET

In recent years, the progress made in the diagnostics of diseases has also made it possible to develop personalized therapies. This approach aims to use the perfect drug for treating each individual patient on the basis of his or her genetic, molecular, and cellular characteristics. That will make treatment better, safer, and more effective.

In any case, our understanding of the interactions between active ingredient carriers and cells is constantly improving. As a result, researchers are holding fast to their grand vision: that in the struggle against cancer, one day they will actually be able to offer medications that can use active drug targeting to eliminate even a tiny tumor right on target without any side effects before the tumor grows into a life-threatening case of cancer.