Complications of drug delivery discussed with an expert

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Drug delivery plays an important role in the treatment of diseases. Matching a specific drug molecule with the right delivery route optimizes therapeutic performance and minimizes side effects. Associate Professor Matthias Wacker from NUS Pharmacy breaks down the different drug administration methods and sheds light on the current

trends and future of drug delivery.

Q: What are the main ways currently available to administer a drug into the body?

A: Looking at the overall market size, oral and topical drug products are leading the field. However, that is also where it becomes more difficult for pharmaceutical companies to make significant money these days. So, for almost a decade, there has been much focus on "niche buster" rather than "blockbuster" products. Also, we have to consider that the trend towards biopharmaceuticals caused a shift in the market. Most proteins or peptides such as antibodies or insulin cannot be administered orally. This slowly leads to more diversity in the ways drugs are being administered.

Q: How can the differences in patients be accounted for different drug delivery routes?

A: The delivery strategy is closely related to the medical condition. Some diseases do not justify an injection or cannot be treated with a cream. The need to personalize therapies for the individual arises only when it leads to much better treatment. The development of individual medicines for each patient has an impact on the market size and the price of medicines as well, so you have to know when to develop a personalized therapy.

Nevertheless, personalized therapies are playing a more pronounced role today because there is stronger specialization in the pharmaceutical sciences as compared to several years ago. In fact, NUS Pharmacy launched a Bachelor of Science (Pharmaceutical Science) in 2018 to equip students with drug discovery and development knowledge, as well as a mastery of the regulatory and commercial environment in the

pharmaceutical industry.

Q: What are the factors to be considered when designing a drug delivery system?

A: This very much depends on the administration route. In short, there are three aspects to look at. Quality, safety, efficacy. Whenever the drug is delivered through the skin, texture, and viscosity must be taken into consideration. This will affect efficacy. For injectables, there must be a stronger focus on sterility to make sure the drug product is safe. Sophisticated delivery strategies will involve problem-solving for those compounds that cannot be administered easily, for instance when there is an injectable, but the drug is not going in solution. In these cases, there is a need to find a drug formulation that enables therapy, first in drug development and later in the patient. Depending on the research area the company is focusing on, 30 to 70 percent of the drug candidates discovered today have such unfavorable properties. That raises a very fundamental question: how can you investigate the efficacy and safety of a drug if it is not able to enter the body?

Q: How do we choose one drug delivery system over another?

A: This is a huge decision. First, we define a target product profile, outlining the characteristics of the new medicine. It includes a description of the exact medical condition and patient population, but also some technical and regulatory considerations relevant for the desired product. After all, who will use an injectable to treat a simple headache? Such misalignments between the delivery strategy and the needs of the patient must be sorted out early in drug development. However, being able to manufacture the drug product at reasonable cost is equally important.

Q: How do we test the effectiveness of drug delivery systems?

A: At the early discovery stage, testing often begins with isolated cells or tissues to provide evidence for the interactions of the delivery system with a particular area in the human body. Very often, these assays provide qualitative information and will have limited sensitivity for small differences between drug delivery systems. We can show that the interaction happens, but we not sure whether this interaction will be strong enough in a living organism. These studies have high relevance in the early stages of drug development, they look at every interactions at high resolution.

When it is closer to the market, there will be known characteristics that must be optimized to make the drug delivery system safe and effective. We now have many very similar drug delivery systems that slightly differ in their performances. This is where in vitro performance testing comes in: it is one of the most common tools in the development—not discovery—of drug delivery systems, and will, in a simplified form, be used to test every single batch of the drug product that leaves the factory.

Q: What is the future of drug delivery systems?

A: In the future, we will see more biotechnological products and individualized treatments. This is due to changes in the business model of the pharmaceutical industry, as well as the existing knowledge base. Today, conventional manufacturing processes and methods come with competition while more complex drug products are not only protected by patents, they also require a very specific know-how and supply chain to be manufactured.

Take COVID-19 vaccines for instance. There is very high demand

globally, but the vaccines cannot be manufactured fast enough due to a shortage of high-purity lipids. As such, manufacturers with the best supply chain can produce the vaccine quicker than their competitors and get a foot into the market.

In areas where you need this specific know-how or network, the competition is limited to a few companies. Biotechnological drug products often involve a sophisticated delivery technology and that is what we will see more in the future. Today, most innovations are made by highly specialized start-up companies. "Big Pharma" comes in later, once the success is close, and buys the license or the company.

Q: What direction is your research heading?

A: For many decades, drug delivery systems have changed continuously, but the existing performance assays do not address the new features of advanced therapeutics. We are filling libraries with more knowledge on the interactions of delivery systems with the human body on the cellular level, but often fail to go through the last few steps and develop clinically successful medicines. This is where my research comes in. We benchmark every new strategy against the clinical performance of previous formulations. Commonly, every product is the one successor following a huge number of failures. Learning from these failures and using the information we have in the best possible way is one of our signatures. Here we use not only lab experiments, but also computational models and establish so-called in vitro-in vivo correlations.

A common measure for the performance of small-molecular drugs of the last century was their solubility and dissolution behavior. This property can be measured in the lab and enables an accurate prediction of the amount of the drug that becomes available to the human body. In clinical trials, this leads to improved efficacy and more predictable safety characteristics. Today, drug delivery has become more sophisticated.

Many drug products are at least partially manufactured in biological systems and undergo a very complex production process. Nanomedicines are only one example, where several molecules assemble into tiny structures to facilitate drug delivery. Once this assembly enters the body, it is exposed to various cells, tissues, fluids, and enzymes before it reaches the target site.

To cover this whole complexity in our assay systems without compromising on practicality is one of the big challenges we are facing today. My group is doing this "top-down." Once we have identified a certain effect that has been observed in patients, for example, a reduction of side effects or prolonged exposure to the drug, we identify the source and ask why this one formulation was better than others. Many clinical trials are sponsored by private companies and we have many interactions with the pharmaceutical industry. This makes it even more interesting. Many drug delivery strategies we see during our daily work will reach the market within few years.

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