It's all in the mixture

The first pharmaceutical development for a capsule-based inhaler was a real challenge for Harro Höfliger's Pharma Services team. But the new options in the analytical laboratory paved the way for the perfect powder.

Suddenly there is no air to breathe, the chest feels tight and aches, agonizing coughs shake the body – asthma sprays help to prevent such episodes. Soon, patients shall be able to benefit from a new drug: An inhaler that treats symptoms with a combination of two active pharmaceutical substances (APIs). The generic drug is currently being developed by a pharmaceutical company together with Harro Höfliger. "The original product is a blister inhaler in which the two APIs are stored separately," says Dr. Elke Sternberger-Rützel, Division Leader of Pharma Services at Harro Höfliger. "For the generic drug, the customer had a special request: a capsule-based inhaler in which both APIs are combined in one powder."

Protect the active substance

Not an easy task for the team, which now has to implement the first project in the field of inhalation powder development. Under no circumstances must the two APIs react with each other. „We had to protect one substance from the other, to prevent them from degradation," explains Dr. Sternberger-Rützel. How exactly this works was explored by the experts from Pharma Services in the new, state-of-the-art laboratory.

Mixing, filling, analysing

First, they selected the right lactose qualities for the powder mixture. This is important in order to enable dilution of the APIs in small dosages so that filling is possible, and to ensure that the patient feels an effect during inhalation. Since one of the APIs is degradated when getting into direct contact with lactose, the lubricant magnesium stearate was added to the blend. Mixing experiments then followed. This resulted in eight mixtures per API, which the experts filled and tested in the laboratory. In order to assess the quality of the powders, laboratory manager Karin Marek developed a six-step analysis.

Six steps for a perfect result

1

Flowability: Can this powder be used in the filling process?
First of all, the lab co-workers examine the powder's behaviour. Does it flow well or poorly? Can it be easily filled into capsules?

2

Water contact angle: Is the lactose coated with magnesium stearate?
Then they test whether the amount of magnesium stearate added to the lactose and the blending quality is correct. For this purpose, Harro Höfliger developed an in-house method: The researchers put a drop of water on the surface of the lactose. If it remains on the surface, the blend is correct.

3

Blend uniformity: Is the API uniformly distributed in the total mixture?
In order to check whether the two APIs are uniformly distributed throughout the mixture, the experts take samples and measure the concentration of the active ingredient. If the blend is not homogeneous, the blending parameters must be adapted in the next test.

4

Content uniformity: Does the capsule contain the correct amount of active ingredient?
If the blend in the total quantity is correct, the concentration in the individual capsules has to be verified. 25 micrograms of API 1 and 200 micrograms of API 2 should be contained in each of the examined capsules. By determining the concentration, it is possible to assess the quality of the filling process.

5

Emitted dose: How much API is released from the inhaler?
The next step is to check whether enough API is supplied to the patient. For this purpose the Harro Höfliger team uses a so-called "Dosage Unit Sampling Apparatus" (DUSA). The device generates negative pressure, thus simulating a patient's inhalation. What DUSA "breathes in", is flushed into a solution. A high-pressure liquid chromatograph (HPLC) determines the API level contained in the solution. "Some of the API always sticks to the capsule," explains Karin Marek. If the emitted quantity is not sufficient, either more API must be added to the capsule or the formulation needs to adapted.

6

Determination of aerodynamic particle size: Does the correct amount reach the alveoli?
Now the experts are measuring whether enough of the API is delivered to the alveoli. To this purpose, the Next Generation Impactor (NGI) is used – a kind of aerodynamic flow model of the lungs through which the particles are sucked with the help of negative pressure. Depending on their size, they come to rest in different sections of the model, corresponding to the bronchial tubes and alveoli. The lab technicians analyze how much of the API has settled, in which section. A correct distribution is prerequisite for a successful powder development.

Testing and adapting, again and again

Of course, the perfect blend is not achieved in the first trial. Adjustments to the process are always necessary. Despite all challenges, the team has made good progress within few months and the project is close to completion. "This is one of the major advantages when machine manufacturers are involved in powder development right from the start," says Karin Marek. "Project time is vastly reduced when all parties involved are located under one roof. Together with our colleagues from equipment development, the steps required for optimization can be initiated a lot faster." Dr. Sternberger-Rützel agrees: "We focus on the interaction between formulation, filling technology and device from the very beginning. This is the key to success for our Pharma Services."