It takes more than an active ingredient to make a medicine
BASF supports pharmaceutical manufacturers worldwide with a full range of excipients

Just press the tablet out of the pack and wash it down with a drink of water – medicines are part of everyday life, whether taken to dispel headaches, lower blood pressure or combat infections. But not only the development of a new active ingredient requires intensive research activities. About 15 per cent of the price of a medicine is due to the tricks and techniques employed to ensure it reaches its intended destination in the body. Tablets, capsules, emulsions, infusion solutions, ointments, drug patches and all the other administration forms of modern medicines are the ingenious products of a special research area: pharmaceutical technology, also known as galenics after the Greek physician Galen.

The challenges faced by Galen’s heirs are numerous and different for every active agent – masking a bitter taste is one of the easier exercises. Things become more difficult with drugs that refuse to dissolve in the body’s aqueous environment. Some tablets are only allowed to release their active ingredient on reaching the intestine, while sustained-release tablets are designed to permit only gradual drug dissolution to maintain a consistent dose level in the blood – without which patients would have to remember every few hours to take their medication.

"BASF offers pharmaceutical manufacturers a full range of excipients to help turn promising active agents into successful medications", explains Dr. Jan-Peter Mittwollen of Strategic Marketing for Pharmaceutical Excipients at BASF. "Polymers, i.e. chains of molecules consisting of identical building blocks are particularly relevant in this respect. Our Kollidon® products, for example, are based on the particularly stable polyvinylpyrrolidones*. Even a simple headache tablet can contain several BASF products, continues Mittwollen. For instance the directly compressible tableting excipient Ludipress® consisting of lactose, a binder (Kollidon® 30) and a highly swelling disintegrant (Kollidon® CL). The disintegrant ensures that the tablet breaks down quickly allowing the active ingredient to be rapidly released. Another polymer, Kollicoat® IR, is applied as a smooth coat to protect the tablet and make it easier to take.
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Each active ingredient places different demands on pharmaceutical technology: acid-sensitive drugs, for example, have to be protected against the aggressive gastric fluids – a task for the protective coat made of Kollicoat® MAE, which encloses either a complete tablet or the individual pellets inside a gelatin capsule. These capsules can also be filled with combinations of differently prepared pellets which release part of the active ingredient while still in the stomach and the other part only later on reaching the intestine.

Mittwollen is particularly proud of Kollicoat® SR 30 D. "Matrix tablets made from this novel mixture of polymers do away with the need for frequent repeat dosing". The sustained-release tablet takes about 24 hours to release its content of active ingredient completely and at a steady rate, a particularly important requirement for antihypertensive drugs or hormone preparations.

BASF’s range of products also includes a large number of other substances such as solubilizers which create a bond between lipophilic (fat-loving) drugs and water – a function becoming increasingly important in pharmacy. Besides all the medical and chemical requirements placed on active agents and excipients, however, it is always important not to neglect one other aspect: active agents and excipients must be easy to process (see info box).

The pharmaceutical industry posts annual sales of around 3.6 billion Euros with excipients – with BASF among the world’s top five excipient manufacturers. The highest selling products: the polyvinylpyrrolidone based Kollidon® brands used as binders and granulating agents. The most important sales regions besides Europe are the USA and Asia where the excipient market is currently experiencing rapid growth. China, for example, looks set to be among the three biggest net exporters of pharmaceutical products in the next three to five years with licensed production of a range of standard products.

"The high rate of innovation in drug research means that BASF is also engaged in a constant search for new solutions in the pharmaceutical excipients field", comments Dr. Karl Kolter, who is in charge of developing new excipients at BASF. "Modern, computer-designed active agents are often highly hydrophobic i.e. difficult to dissolve. But
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in water. Finding suitable excipients which facilitate optimal drug absorption is one of the major challenges facing us in the future”.

New developments are also coming onstream in cooperation with leading international universities, such as the University of Sunderland in the UK. The head of the university’s Department of Pharmaceutical Technology, Prof. Fridrun Podczeck, describes the joint project: “We are currently working closely with BASF on developing improved sustained-release preparations. Our aim is to compress coated pellet granules directly into tablet form, a process which one day could make the use of expensive and sensitive gelatin capsules superfluous. The coating polymer Kollicoat® SR 30 D shows promising characteristics in this respect”.

Matrix sustained-release tablets distribute the dose of medication throughout the day

- On the way through the gastrointestinal tract, minimal quantities of water penetrate the pores of the insoluble polymer matrix (Kollidon® SR or Kollicoat® SR 30 D) into the interior of the tablet.
- The moisture gradually dissolves the active ingredient from out of the insoluble polymer carrier.
- The sustained release mechanism of the film coating means that a very much slower and constant release of the active ingredient is ensured.
- The empty matrix is finally excreted as visible sheath.
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The technology of today’s pill makers

Active ingredients and excipients have to fulfill not only medical but also practical requirements: they must have favorable processing characteristics. On the one hand, the tablet substrate must be sufficiently cohesive, but on the other hand must not stick to the tablet press. Good flow properties are equally important to achieve homogeneous mixing of constituents, especially because of the often minimal dose of active agent per tablet used in modern medications. Binders and granulating aids from the Kollidon® family, which transform difficult to process drug substances into easily miscible and compressible granules, are valuable auxiliaries. Depending on the technical and medical requirements, several production techniques are used:

Direct tableting: This is the compression of powder or powder mixtures with or without adding excipients and without further pretreatment. Advantage: undemanding, cost effective. Disadvantage: only possible with a small number of active ingredients.

Granulation (wet/dry): In wet granulation, the active ingredient is mixed with the granulating fluid to form a doughy paste which is then chopped up into the required granule size. Some granules can also be produced by dry compression of powders into briquettes followed by milling. Instead of being compressed into tablets, granules can also be filled directly into gelatin capsules.

Film coating: Coating the tablet itself can fulfill a variety of purposes, such as masking taste, delaying active ingredient release, enhancing use characteristics or modifying color. In the past, tablets were usually coated with sugar solutions, while today mainly polymers, for example from BASF’s Kollicoat® family, are preferred. Besides offering the possibility of creating special functions by making modifications, these molecule chains have one decisive advantage: while sugar coating was a procedure that almost always took several days, coating with Kollicoat® in modern drum coaters now requires only a few hours.

Further information can be found at:

http://en.wikipedia.org/wiki/Excipient
http://www.ipecamericas.org/public/faqs.html
http://www.pharma-solutions.basf.com

Text, photography and illustration are available at:
www.basf.de/science_around_us

The Info Box

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