

New intrauterine system thanks to innovative materials

# It all depends on the right mix



*To most people, medicines mean primarily pills, drops or injections. But drugs can also be delivered selectively and effectively to the target site by other means. Bayer HealthCare researchers are developing tiny intrauterine systems which release active substances in the precise spot where they are needed – for example for contraception.*

Millions of women live stressful lives. Whether it's because she's on a long-haul journey or suffering from a stomach upset, going through hassle in the family or a hectic phase at work – there are all sorts of reasons why a woman might forget to take the Pill. Vomiting and diarrhea also represent a risk to reliable contraception. Anyone who has to take a certain daily dose of active substances either needs to be totally disciplined or to have innovative systems available which deliver the drugs themselves – for years, just like those for patients with diabetes, high blood pressure or other chronic illnesses.

Bayer researchers developed methods such as the intrauterine system, or IUS for short, about 20 years ago. The intrauterine system is a T-shaped, flexible polymer structure with a cylinder which regularly releases tiny amounts of the hormone levonorgestrel. It is fitted directly inside the womb by a doctor.

The intrauterine system provides protection against pregnancy in several ways at the same time: firstly the substance stops the lining of the womb from thickening. Secondly, the hormone makes the plug of mucus in the cervix thicker and hence more impermeable for sperm, the function and motility of which are impaired. It can also prevent ovulation in some women.

Bayer researchers at Turku, Finland, now want to build on their good experiences with the intrauterine system. "We are currently working on the development of a new, smaller, lower-dosed contraceptive intrauterine system and we also want to use this principle of long-term administration of medicinally active substances for the treatment of chronic uterine disorders," explains Dr. Joachim Moede, Head of the Polymer Based Delivery Systems Department at Bayer HealthCare. It all depends on the right mix. "For an intrauterine system to release a specific active substance in

the human body reliably and constantly, numerous components have to be very finely co-ordinated," says Moede.

## Innovative plastics ensure the ideal hormone dose

He and his team are therefore also searching for the optimal plastic formulation in each case to act as the active substance reservoir. Pharmaceutical substances can not only be extremely finely distributed through polymers; scientists can also alter the composition of the polymer to order, so that the materials have the optimum characteristics for each requirement: for example being solid, flexible, impermeable or permeable. The top priority is always that "the polymer has to be tolerated by the human body and should not cause either inflammation or rejection reactions. And it should deliver the medicinal product at an even rate," explains Moede.

Reliable contraception: the tiny carriers for the intrauterine system (photo, left) made from an innovative mixture of Bayer materials are checked by video camera after their manufacture. This quality assurance method is just one of many measures to ensure that doctors like Ursula Schröder (left in photo, right) can recommend reliable forms of contraception such as intrauterine systems to their patients.





Intrauterine system under the microscope: in the Pharmaceutical Development lab, technical assistant Toni Rosholm assembles tiny parts for the clinical trial.

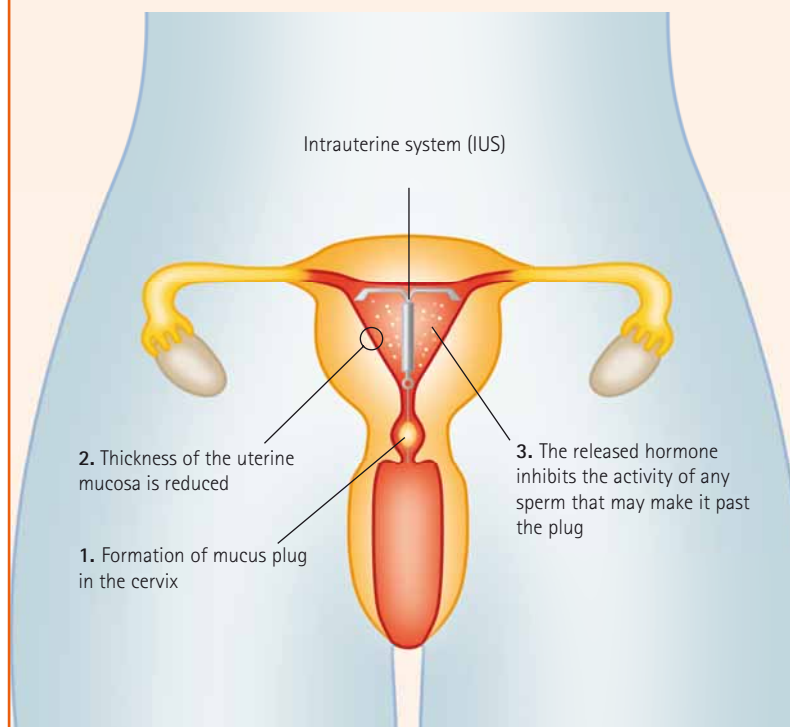
The driving force behind active substance release is the simple physical process of classic diffusion. As soon as the intrauterine system is placed in the womb – also known as the uterus – bodily fluids penetrate the carrier substance. The large quantities of active substance stored in it are gradually dissolved and migrate over many years into the surrounding tissue. Theoretically, this process only ends when the carrier substance contains virtually no more active substance and the concentration gradient has completely disappeared. But of course the gynecologist will have replaced the coil long before that.

### Silicon for intrauterine system: reliable and well tolerated

Silicons are considered to be one of the most reliable materials for these intrauterine systems. The polydimethylsiloxanes are not only very inert – which means that they do not give off their own molecules, and nor do they react chemically with substances produced in the body – but they are also hydrophobic, i.e. water-repellent, and therefore mix well with hormones such as levonorgestrel which are also hydrophobic. Provided, of course, that you know how

## Reliable contraception

*By releasing the progestogen levonorgestrel directly into the uterine cavity at a uniform rate, Bayer's intrauterine system provides triple protection against unwanted pregnancy. The hormone balance remains largely unaffected.*



to do it: "In its original form, silicon is a solid, rubber-like substance," explains Moede. But together with his team he selects special additives which make the material more flexible.

The Bayer researchers mix the viscous polymer with the active substance in powder form to a dough-like mass, known as a dispersion. This is then pressed in an extruder – using a worm shaft through a tubular nozzle – in the same way as spaghetti is made. The polymer tube is then crosslinked ("polymerized") for one or two minutes by warming it with an infrared light. In a separate process, an automatic blade cuts the rods to the desired length. Hormonal active substances such as steroids – including levonorgestrel – are not damaged by this brief warming.

The rate at which the carrier material subsequently releases the active substance depends, amongst other things, on the degree of crosslinking and elasticity of the silicon. These are very finely adjusted by the Bayer materials experts during the extrusion process. Says Moede, "We use certain additives such as fillers (silicon dioxide) to make the silicon less permeable to the active substance molecules so that the active substance will diffuse out of the carrier material more slowly."

### One 20 millionth of a gram for reliable contraception

Another trick makes a major contribution to controlling the release of the active substance: as soon as the core



Materials development: Bayer HealthCare employee Satu Raitala prepares the liquid chromatograph for a chemical analysis of the new intrauterine system.



Materials experts: Dr. Joachim Moede (center) and his colleagues Sirpa Makela (left) and Juha Ala-Sorvari together developed the materials for the new intrauterine systems in Finland.

of the rod is finished, it is coated with a membrane which is only one tenth of a millimeter thick. It too is made of silicon, but does not contain any active substance. This layer prevents the body from encapsulating the intrauterine system with tissue, but its main function is to slow down the diffusion of the hormones out of the core so that the daily dose remains virtually the same for years. No mean feat, concedes Moede: "The margin of fluctuation that we can allow ourselves with intrauterine systems is very small." The intrauterine systems currently available release just one 20 millionth of a gram of levonorgestrel into the womb each day. That is all that is needed to reliably prevent a pregnancy. And for this reason, that is all that should find its way into the body.

Moede's team has succeeded, by means of various modifications, in developing a smaller version of the tried and tested intrauterine systems. The new system is also fitted in the womb and releases an even smaller amount of levonorgestrel each day.

The new intrauterine system, which is already being tested throughout the world in Phase III clinical studies under the name LCS – Levonorgestrel Contraceptive System – will be easier for

doctors to fit and more comfortable for patients. This is not only because of its smaller size and improved shape, but because the Bayer experts have also changed the applicator which the doctor uses to fit the system so that the whole procedure takes less time and effort.

In contrast to existing intrauterine systems which are effective for up to five years, the newer, smaller version is intended to be used for a period of three years. The results to date are promising. "Despite the low dosage, the LCS provides just as effective protection as the previous intrauterine systems and is also very well tolerated by the women who are currently testing the LCS in the clinical studies," says Moede.

### New systems to help against chronic women's diseases

Moede's team has now turned to its next challenge, as it may be possible to use intrauterine systems in a similar way in the future with other active substances for the treatment of two of the most common gynecological disorders: benign uterine tumors known as fibroids and endometriosis. Bayer HealthCare researchers are develop-

ing new therapeutic approaches, and also medication in some cases, for the treatment of both conditions (see also "When pain becomes the rule," page 64). Moede and his team are already thinking about combining their materials with the new active substances. The medical technology expert is certain: "If we succeed in developing an intrauterine system which acts purely locally in the womb and needs only a fraction of the quantities of active substance, women will not only be spared severe monthly pain and many side effects, but possibly also a lot of surgery."

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