

SENSOR TECHNOLOGY

Liquid Drug Delivery Monitoring & Control

By: Mr. Ulf Kanne

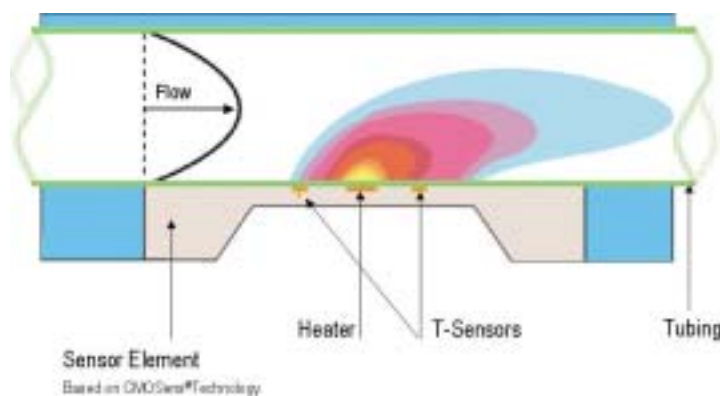
INTRODUCTION

New microchips combining sensor technology with digital signal processing on one single CMOS microchip are boosting performance levels and reducing costs in measurement technology. While a real revolution is

already taking place in the market for consumer products using integrated digital CMOS humidity and temperature sensors, disposable digital sensor solutions for liquid drug delivery are becoming available.

FIGURE 1

Principle of Thermal Flow Measurement



CURRENT SITUATION

Product and marketing managers for disposable drug delivery products see various desirable features that are not yet implemented in their products. Improved safety profiles, process monitoring functions (such as detection of clogging or bubbles) and electronic recording of delivered volumes are increasingly being discussed (Inset 1).

Furthermore, progress in pharmaceutical development is leading to increased demand for improved dosing accuracy, which can be achieved by active control of pumping and dosing processes using feedback control.

The key to technical features, such as delivery monitoring and feedback control, are flow sensors that allow flow rates to be measured accurately over the range of millilitres per minute to nanolitres per minute, depending on the application. Continuous measurement of flow over time even allows the total delivered amount of the drug to be calculated.

Sensors for these flow ranges have been commercially available for several years already. However, they have been disqualified due to factors such as high cost, size, and for battery-operated applications, high energy consumption.

Inset 1. Lack of Monitoring Functionality? An example:

X Recalls Infusion Kits

NEW YORK (2004 Reuters Health) –

Medical device maker X said on Tuesday it is recalling Y-Type infusion sets used by (...) because of problems that can interrupt (...) flow and cause serious consequences, including death. The company said patients should exchange any unused Y-Type infusion sets for replacements. X said that the problems that led to the recall have resulted in a number of serious injuries, including some hospitalizations.

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Measuring the Impact of Innovation in Discovery and Development

KEYNOTE SPEAKERS

Is Innovation Positively or Negatively Impacting Discovery and Development?

Dr. John L. LaMattina, Senior Vice President, Pfizer Inc and President, Pfizer Global Research and Development

Bridging the Industry and Academia Divide to Drive Innovation Forward

Dr. Christopher P. Austin, Director, NIH Chemical Genomics Centre, National Institutes of Health

How is Industry Responding to the FDA's Critical Path White Paper? A 2006 Update

Dr. Janet Woodcock, Deputy Commissioner for Operations and Chief Operating Officer, US Food and Drug Administration

Drug Hunting from a Drug Hunter

Dr. Roger Newton, Senior Vice President and Director, Esperion Therapeutics, a Division of Pfizer Global R&D

Sex in an Age of Mechanical Reproduction: Implications for Drug Innovation

Professor Carl Djerassi, Playwright and Emeritus Professor of Chemistry, Stanford University

Maintaining a Culture of Innovation as the Biotech Industry Evolves

Dr. Joseph Miletich, Senior Vice President, Research and Pre-Clinical Development, Amgen

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FIGURE 2

Highly Integrated, Digital Flow Sensor Chip

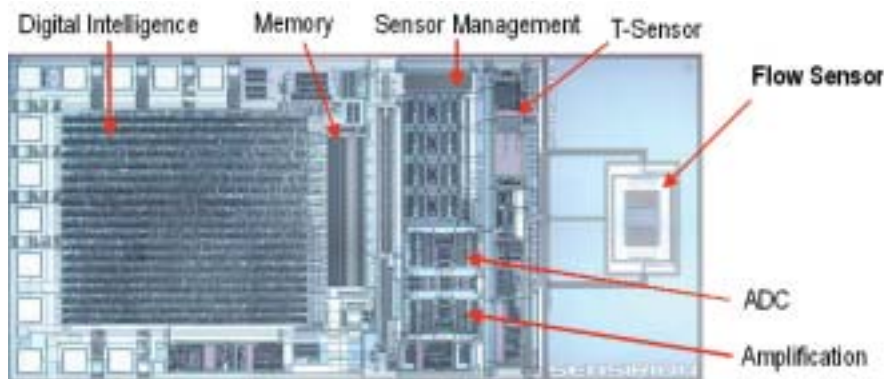
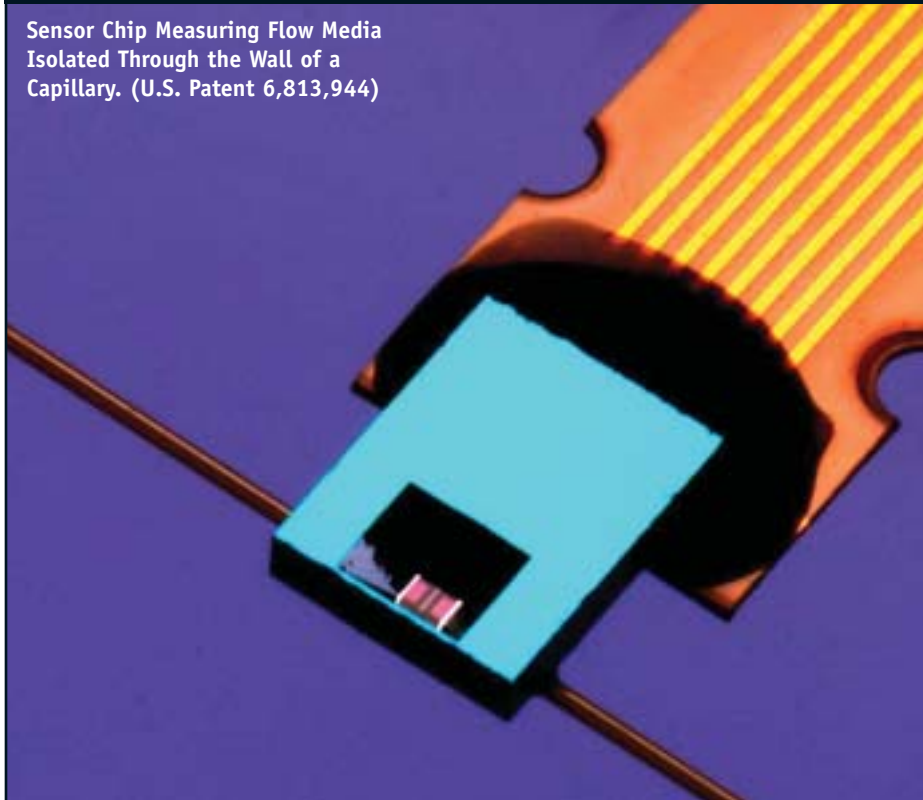


FIGURE 3

Sensor Chip Measuring Flow Media Isolated Through the Wall of a Capillary. (U.S. Patent 6,813,944)



TECHNOLOGICAL PROGRESS

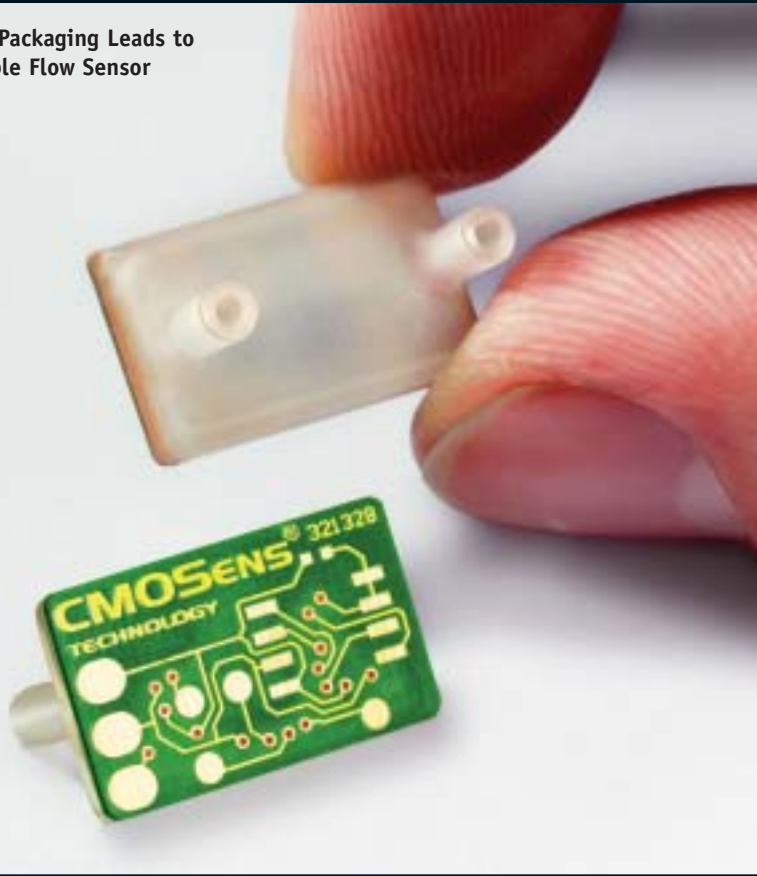
Times have changed, and new sensor generations are appearing on the scene.

What do they look like, and what do they mean for the drug delivery sector? Today, CMOSens Technology is available. It is described as the combination of microsensor technology and digital signal processing on a single CMOS microchip. CMOSens sensors based on MEMS (Micro-Electromechanical System) technology are extremely fast, small, and light, and they can be produced in large quantities. For example, digital CMOSens humidity sensors are being manufactured in quantities of millions per year for consumer applications (Sensirion Inc., Switzerland).

A CMOSens sensor chip for flow measurement obtains its measurement signals from a well-known type of structure (Figure 1). A miniature heating element on the microchip adds a minute amount of heat to the liquid medium for thermal flow measurement. The latest designs can obtain high accuracy using only 90 to 300 micro joule of energy per measurement. Concerns about introducing heat into the medium are thus unfounded in most cases. Two temperature sensors positioned symmetrically upstream and downstream of the heat source detect even the slightest temperature difference, thus providing basic information about the distribution of the caloric energy being transported by the flow. This is the fundamental information needed to subsequently calculate the actual total flow or dosed volume. Additional details of the CMOSens chips (such as a minimized thermal capacity) significantly distinguish these sensors from similar designs and guarantee low power consumption, reliability, and measurement speed (response times < 20 ms). Very high repeatability (approximately 0.6% of the measured value) is an additional benefit of CMOSens flow sensors and by the way a thermal MEMS flow sensor measuring the flow of a liquid is able to detect bubbles therein (see U.S. patent 6,763,710) because the thermal properties of the gas in the bubbles differ from those of the liquid.

FIGURE 4

Appropriate Packaging Leads to the Disposable Flow Sensor



DIGITAL INTELLIGENCE IS THE KEY

A sensor signal must be processed in an appropriate manner to maintain high signal quality and allow them to be integrated into user systems. For most sensors, the essential functions necessary to achieve the high performance required by the application are amplification, digitization, linearization, and temperature compensation. Depending on the MEMS sensor generation (Inset 2), with CMOSens, these functions may be integrated into the sensor chip to provide high resistance to electromagnetic interference (EMC) and superb signal quality at low cost. The structure of such a CMOSens chip can be seen in Figure 2.

Characteristic sensor data needed for linearization and temperature compensation during operation is generated by a calibration process during production. As freedom from user calibration before initial use is essential for single use sensor solutions, this calibration data must be stored and processed inside the sensor. That is possible in the fourth generation of MEMS sensors. In addition to the actual thermal sensor element, these chips contain the full digital intelligence and even the memory required for signal linearization, temperature compensation, and self-test algorithms.

Achieving this level of integration (a full single-chip solution) is now a reality.

At the same time, a fourth-generation, CMOSens-based MEMS sensor chip for flow measurement is only around 2 X 2 mm in

Inset 2. Progress Made in Microsensor Technology

MEMS Sensor Generations

- **1st Generation**
MEMS sensor element usually based on a silicon structure, sometimes combined with analog amplification on a microchip.
- **2nd Generation**
MEMS sensor element combined with analog amplification and an analog-to-digital converter on a single microchip.
- **3rd Generation**
Merging the sensor element with analog amplification, an analog-to-digital converter and digital intelligence for linearization and temperature compensation on a single microchip.
- **4th Generation**
The same features as third-generation MEMS sensor, plus memory for calibration data and temperature compensation data.

size. Use of standard chip technology makes it possible to produce such sensors at very low cost.

Due to the low energy consumption an interesting option is to provide such sensors with RFID-like on-chip circuitries for wireless communication and/or wireless power supply. Such circuitry can for example comprise a demodulator and rectifier for receiving power and data through a coil antenna as well as a modulator and driver to send back data through the same antenna.

SENSOR TECHNOLOGY

Inset 3. About CMOSens & CMOS

CMOSens (see-mo-sens): is a basic technology that is setting standards for high-precision sensor systems. Merging a semiconductor chip (CMOS) with sensor technology makes it possible to achieve highly integrated system solutions characterized by excellent sensor precision, digital intelligence, and reliability. The sensor component, amplifier, and A/D converter form a single unit on the same silicon chip. The digital intelligence of the CMOSens sensor facilitates output of a fully calibrated, temperature-compensated signal. The integral CMOSens “intelligence” of the chip thus allows measurement data to be output using a standard digital interface, such as SPI, for extremely straightforward processing. Thanks to their compact single-chip design, sensors based on CMOSens Technology have excellent resistance to electromagnetic interference (EMC), which is significant technical advantage of this highly modern sensor technology.

Further reading: www.sensirion.com and Medical Device Technology May 2003 - “Digital CMOS Sensor Chips for Media-Isolated Liquid Flow Sensing.”

CMOS (see-mos): is a standard fabrication technology for integrated circuits. CMOS chips are commonly referred to as “semiconductor chips,” “silicon chips” or “computer chips.” They are widely used in almost all areas of everyday life. The best example of a CMOS chip is probably the Intel Pentium processor in your PC.

ISOLATED MEDIA

Especially in medical and life-science applications, full isolation of the medium from its environment is often required. A surprising solution has been found to achieve this goal. Special packaging enables highly sensitive microchips to measure flow through (thin) walls of PEEK®, steel, or glass with full media isolation. This can be done while maintaining heating power at the same very low level, due to the high sensitivity and signal quality (signal-to-noise ratio) achieved using digital CMOSens chips.

Nowadays, a simple, straight capillary (inner diameter 20 micro meter to >1 mm) is used as a flow channel for sensors based on this patented principle, with the sensor chip bonded to the outside (Figure 3).

OUTLOOK

This technical development changes the product design ground rules for disposable drug delivery systems. Ultra-small amounts of liquid can now be monitored and dosed with much higher accuracy at low cost. Tiny, fully digital, calibrated flow sensor chips will be part of single use products in the future. As the tiny chips are based on CMOS technology, they can easily be produced in high volumes at low cost in standard semiconductor wafer fabs.

Additional technological issues on the way to single use solutions are packaging (Figure 4) and calibration during production, as well as communication and power supply.

Other issues also become important when the drug delivery system is viewed as a whole. A sensor-actuator combination is needed for most applications, and the actuator must be combined with the sensor and additional components to form a microsystem (such as a disposable dosing unit). The demand for microvalves (active and passive) and micropumps that can be produced in high

volume at very low cost will rise significantly in the future. Pumps with no moving parts at all appear to have enormous potential, but even piezopumps and MEMS-based membrane pumps offer attractive features for disposable designs.

The scope of the technical options for increasing the safety and accuracy of drug delivery systems and adding supplementary electronic monitoring and control features has been enlarged significantly. The key are fully calibrated single-chip solutions. Due to the low power consumption and short power-up times of the new sensors, battery-operated systems also benefit from CMOSens Technology, and wireless RFID-like solutions are possible.

The disposable portion of medical solutions will incorporate more functionality in future products. That will make it possible to improve safety and performance while reducing investment and maintenance costs for reusable devices.

Impressive sensor performance (high resolution and high speed at low cost) makes competitive design solutions possible.

Inset 4. Some Potential Liquid Drug Delivery Solutions Based on Thermal MEMS Flow Sensors In Particular Sensors Using CMOSens Technology

A: Combination with conventional gravity-based drug delivery

1. Monitoring the flow of drug for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling flow or dosing of drug with electronic feedback control using a disposable valve or a reusable pinch valve with a disposable tubing.

B: Combination with conventional, reusable (portable or non-portable) drug delivery pump or integration into an implantable pump

1. Monitoring the flow of drug to the human body generated by a peristaltic pump or a syringe pump to the human body for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling flow or dosing of drug with electronic feedback control using a peristaltic pump or a syringe pump as actuator.

C: Combination with a disposable (portable or non-portable) drug delivery pump

1. Monitoring the flow of drug generated by a disposable pump (e.g. membrane pump, electrokinetic pump, or electro-osmotic pump) to the human body for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling the flow or dosing of drug with electronic feedback control using a disposable pump (e.g. membrane pump, electrokinetic pump, or electro-osmotic pump) as actuator.

D: Combination with a physically or chemically pressurized disposable or non-disposable drug reservoir

1. Monitoring the flow of drug for metering and/or recording purposes or to detect leakages, interruption of flow, or bubbles.
2. Controlling flow or dosing of drug with electronic feedback control using a disposable valve or a reusable pinch valve with a disposable tubing as actuator.

E: Pre-dosing of drug into a reservoir before further processing and/or delivery to the body

1. Measuring the flow from one reservoir into another to determine the total amount of liquid moved.
2. Controlling the amount of drug moved from one reservoir into another with flow generated by a disposable pump (e.g. membrane pump, electrokinetic pump, or electro-osmotic pump), with electronic feedback control.
3. Controlling the amount of drug moved from a pressurized reservoir into another reservoir with electronic feedback control in combination with an actuator like a disposable valve or a reusable pinch valve with a disposable tubing.

D: Wireless Applications

The monitoring and control applications according to examples A-E can be extended with wireless transponder technology for the sensor to receive electric energy from and transmit measurement data to a separate control and/or communication unit via an antenna (similar to RFID solutions). This allows to increase comfort for patients and clinical staff and to reduce effort for electrical connections as no batteries and electrical connectors are necessary. Implanted devices measuring the flow of body fluids can benefit in the same way. In portable and non portable systems the wireless readout unit can be positioned in a convenient position in vicinity of the sensor.

BIOGRAPHY



Mr. Ulf Kanne is Product Manager & Sales Director for liquid flow products at Sensirion AG (Switzerland), a leading high-tech sensor company. Throughout the past 4 years. Mr. Kanne has focused on new markets and microsensor applications in the biotech and life science sector as well as in general process technology. Prior to joining Sensirion, he was actively engaged in new technology product management and R&D in the process technology and semiconductor industry for several years. Mr. Kanne studied electronics at the Technical University of Aachen (Germany) and the Federal Technical Institute of Zurich (Switzerland).