Ultrapure water

Monitoring pharmaceutical water online

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The requirements placed on the quality of water for pharmaceutical purposes by the pharmacopoeias are precisely defined. Modern process analytics offers users of water treatment and distribution systems high performance monitoring systems for quality control of pharmaceutical water, which are superior to traditional laboratory analysis not only in terms of accuracy and speed, but also making possible a 100% monitoring with significantly lower operating costs, and the ability to directly intervene in the process procedure.

Requirements of the pharmacopoeias

In addition to microbiological parameters, such as microbial count and endotoxin content, bulk water for pharmaceutical purposes is monitored in respect to inorganic and organic contaminants. Today this is usually performed by an online determination of electrolytic conductivity and TOC content (total organic carbon). The legal requirements of the European (EP) and the American Pharmacopoeia (USP) are nearly identical. Table 1 offers an overview.

Note: The exact TOC limit depends on the result of the SST (System Suitability Test); for details see below.

Thus the American Pharmacopoeia sets the same limits for conductivity for all three water qualities, while the European Pharmacopoeia for purified water, permits a higher limit. Another difference is that under European law the antiquated, wet chemical analysis for oxidisable substances is allowed as an alternative to a TOC determination in purified water. In one point, however, the European Pharmacopoeia is stricter: water for injection can only be produced by distillation. Under U.S. law alternative methods such as reverse osmosis or (C) EDI ((continuous) electronic de-ionisation) may also be used.

The online monitoring of both the conductivity measurement and the TOC determination is not required, and sampling and analysis can both be performed in the laboratory. State of the art today, however, is the online determination, which offers only advantages:

- more accurate and more reproducible measurement,
- continuous quality monitoring,
- short response times,
- possibility of direct intervention in the process,
- overall more cost-effective.

Conductivity measurement

If the conductivity is determined online, the conductivity measured at a given temperature and the measured temperature will be recorded. Temperature compensation is not allowed for. The basis for this is a limits table in which, after rounding down to the nearest 5 °C, the specified value must not be exceeded.

If the conductivity is determined in the laboratory offline then the sample, by stirring or shaking, is saturated with CO_2 from the air and heated to 25 °C. The measured conductivity may not exceed 2.1 µS / cm.

The new UniCond ™ conductivity sensors from Mettler Toledo Thornton prepare the measuring signal directly in the sensor head and transmit it unaffected, digitally and over long distances to the display device. Since all sensor data are stored in the probe, after connecting to the transmitter they are automatically detected, so that all

Tab. 1 Requirements of the EP (European Pharmacopoeia) and USP (US Pharmacopoeia)

European Pharmacopoeia			US Pharmacopoeia		
Monograph	**Eur. Ph.**	**EP 2.2.44**	**Eur. Ph.**	**USP <645>**	**USP <643>**
Water Quality	Cond. limit at 25 °C	TOC limit	Water Quality	Cond. limit at 25 °C	TOC limit
Aqua Purificata	5,1 µS/cm	~ 500 ppb C ($r_u < r_s - r_w$), alternative wetchemical test of oxidisable substances	**Purified Water**	1,3 µS/cm	~ 500 ppb C ($r_u < r_s - r_w$)
Aqua Valde Purificata	1,3 µS/cm	~ 500 ppb C ($r_u < r_s - r_w$)	**Highly Purified Water**	1,3 µS/cm	~ 500 ppb C ($r_u < r_s - r_w$)
Aqua Ad Iniectabilia	1,3 µS/cm	~ 500 ppb C ($r_u < r_s - r_w$)	**Water For Injection**	1,3 µS/cm	~ 500 ppb C ($r_u < r_s - r_w$)

relevant data, such as the cell constants, are read and the measuring system parameterises itself. Using this "Plug and Measure" functionality, error-free installation and commissioning can take place in a short period of time. A typical conductivity sensor for the monitoring of pharmaceutical water meets the following specifications:

Measurement range	0.2 to 3,000 µS/cm
Cell constant	0.1 cm^{-1}
Temperature and Pressure range	31 barg at 25 °C or 14 barg at 130 °C
Process connection	1.5″ or 2″ TriClamp

TOC determination

The 4000TOC sensor uses the principle of dynamic UV-oxidation (Fig. 1). The sample flows continuously through the oxidation chamber (quartz glass coil) at a constant rate of 20 ml / min., where it is irradiated with UV-light at the high-energy wavelength of 185 nm, and oxidised. CO_2 is produced as one of the final products of oxidation, which increases the conductivity due to its slightly acidic properties.

$$CO_2 + H_2O \rightarrow H_2CO_3$$

$$H_2CO_3 \rightarrow H^+ + HCO_3^-$$

The TOC content is calculated by the difference in conductivity before and after UV-oxidation (Fig. 3).

This measurement method offers the following advantages over conventional batch oxidation:

- shortest analysis times of < 1 minute,
- continuous monitoring of the water quality in real time
- low maintenance (no chemicals, membranes or moving parts).

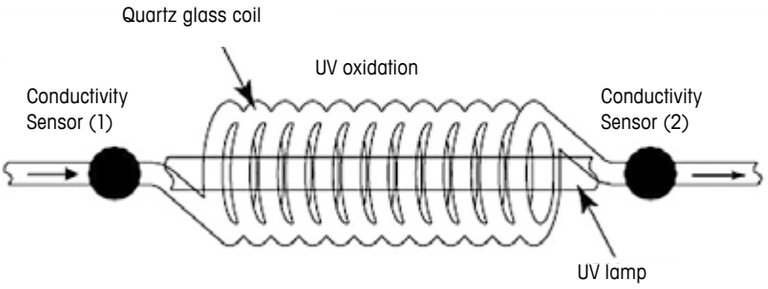

Abb. 1 Principle of differential conductivity before and after UV oxidation

The system offers following performance data:

Measurement range	0.05 to 1,000 ppb C
Detection limit	0.025 ppb C
Response time	< 60 secs.
Measurement method	continuous
Pressure range	0.3 to 13.6 barg
Water usage	20 mL/Min.
Water Quality	< 2 µS/cm at 25 °C

SST – System Suitability Test

The system suitability of a TOC analyser must be demonstrated regularly according to 2.2.44 EP and USP <643>. The system must be just as able to detect difficult as well as easily oxidisable substances. For this there are two standard solutions, each containing 500 ppb of carbon, one in the form of p-benzoquinone (Fig.2) and the other as sucrose (Fig. 3).

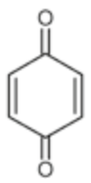

Abb. 2 p-benzoquinone

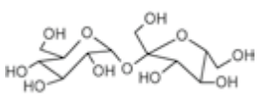

Abb. 3 sucrose

Both solutions and the reagent water used to prepare the solutions are measured. The blank (r_w) value is subtracted from the two values for p-benzoquinone (r_{ss}) and sucrose (r_s), and the ratio formed, which is then multiplied by 100%. The SST is passed when the so-called response is in the range of 100 ± 15%. The upper limit for the TOC in pharmaceutical water is obtained as $r_u < r_s - r_w$, which in practice yields a value of 500 ppb C.

$$\text{Response} = \frac{r_{ss} - r_w}{r_s - r_w} \times 100\,\%$$

$$r_u < r_s - r_w$$

Dr. Klaus-Peter Mang has been working for Mettler Toledo since 1993 and now heads Product and Market Management at Mettler Toledo, in the business area Process Analytics, for the Region Central Europe. Specialist areas are the Thornton Ultrapure Water Analysis (conductivity, TOC, ozone) and Ingold Process Analytics (pH, ORP).

Complete package for Ultrapure Water Analysis

A comprehensive solution package is available for online measurement of conductivity, TOC, pH, ORP and dissolved oxygen and ozone. Customised service packages complete the offer. Mulitparameter measurement systems offer a broad cover of a range of parameters on a common platform for all industry-standard (ultra)pure water applications. The digital measurement technology with "Plug and Measure" functionality provides a particularly high comfort and maximum process safety. The legal requirements of EP and USP are, of course, are fully met.

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Tab. 2 Conductivity Limits

Temperature [°C]	Conductivity value [µS/cm]
0	0,6
5	0,8
10	0,9
15	1,0
20	1,1
25	1,3
30	1,4
35	1,5
40	1,7
45	1,8
50	1,9
55	2,1
60	2,2
65	2,4
70	2,5
75	2,7
80	2,7
85	2,7
90	2,7
95	2,9
100	3,1