

Feature Article

A New Sanitary Conductivity Meter and the Future Management of Pharmaceutical Water

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We have developed a conductivity meter and sanitary electrodes (two types) for pharmaceutical water that meet the conductivity requirements of the United States Pharmacopeia (USP) General Chapters article 645. In particular, the flow-through type does not have any inner projections inside, which allows a full bore structure and excellent cleanability. Ideal sanitary properties corresponding to strict sanitary conditions for food, etc. are required by customers. We have concurrently developed a validation kit for performance evaluation to support the customer GMP (Good Manufacturing Practice) system. In pharmaceutical processes, analyzers are not used for process control as often as in petrochemical processes. However, the use of analyzers is actively being considered under the leadership of the Food and Drug Administration (FDA). The trend in US Pharmacopeia is toward more reliable and safer water, and the importance of water management is increasing.

Introduction

According to the Japanese Pharmacopeia (JP), pharmaceutical water is broadly classified into water, purified water (PW), sterile purified water (SPW), and water for injection (WFI). Various testing requirements are specified for each. For the United States Pharmacopeia (USP), pharmaceutical water is further classified into detailed categories based on usage.

In the 23rd amendment of the United States Pharmacopeia (USP23), 2003, the conventional off-line purity test was changed to an on-line first stage test using a conductivity meter. PW and WFI are required to pass this first stage test. If not, execution of the next stage test is made compulsory. The relationship between water temperature and conductivity is described in **Figure 1** and the first stage test is carried out in order to verify that conductivity is below this limit. Note that the off-line purity test is carried out in JP (14th amendment). Based on this background, conductivity meters have been adopted for

WFI management criteria and so conductivity meters are widely used. Also in Japan, WFI is frequently managed according to USP directives, and conductivity meters are the on-line instruments most frequently used in pharmaceutical water facilities. In this article, a newly constructed validation system^{*1} has also been introduced. The system is compatible with the sanitary electrode^{*2} specially developed for conductivity monitoring, the meter, and GMP^{*3}. Furthermore, the future direction of pharmaceutical water management is summarized.

*1: Evaluation system to verify whether the instrument satisfies requirements and document the verification.

*2: An electrode compliant with strict sanitary conditions for food, etc.

*3: Good Manufacturing Practice: Criteria specified by FDA (Food and Drug Administration) or Ministry of Health, Labor and Welfare in order to secure quality in pharmaceutical manufacturing and perform manufacturing and quality control adequately.

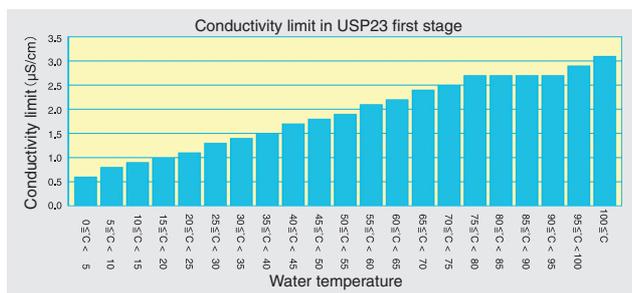


Figure 1 USP Conductivity Limit Table

Features and Applications of the Conductivity Meter

The meter is DIN-sized*4 (96 mm × 96 mm) and can be panel-mounted (Figure 2). Table 1 shows the basic specifications.

*4: Abbreviation of Deutsche Institute Norm. The size conforms to the DIN standard.



Figure 2 Appearance of the Conductivity Meter

Table 1 Basic Specifications

Number of sensor inputs	2 ch
Number of transmission outputs	2 ch (4–20 mA)
Number of contact outputs	4 ch
Contact output operation	<ul style="list-style-type: none"> Upper/lower limit operation Compatible with conductivity, rejection ratio, and difference Alarm operation Error alarm, USP limit alarm Remote range output
Contact input	2 ch (for outside range switching)
Compatible cell constant	0.01, 0.1, and 1
Measurement range	Restricted according to cell constant as follows 0.01: 0 to 2.20 µS/cm* 0.1: 0 to 20, 200 µS/cm* 1: 0 to 200, 2000 µS/cm*
Temperature compensating range	0 to 100 °C
Power source	24V DC
Compatible specification	CE Marking

* The unit µS/cm is idiomatically used in medicines.
(1 µS/cm = 0.1 mS/m, 1S (siemens) = 1/(1Ω))

Features of the Conductivity Meter

The converter has the following features:

- Temperature and conductivity (without temperature compensation) required by USP are output simultaneously via the transmitter output.
- Conductivity and temperature can be displayed at the same time on the two display units.
- The measurement range can be switched by an external signal.
- Transmitter output (4 to 20 mA) can be set for an arbitrary full scale.
- The contact output can be defined arbitrarily including upper limit alarm, lower limit alarm, error alarm, and USP alarm.
- The rejection ratio and difference before/after ion exchange can be displayed by connecting the electrode to two channels.

Applications

The conductivity meter is used mainly in the following three ways.

General Pure Water Management

In pharmaceutical water processes, running water or well water as raw water is treated with ultrafiltration (UF), reverse osmosis (RO), and ion-exchange resins to increase purity. At the same time, impurities are removed by filtering, then ultraviolet (UV) sterilization is performed. Systems for these processes are used in combination depending on the purpose.

Figure 3 shows where conductivity meters are used in representative pharmaceutical water processes.

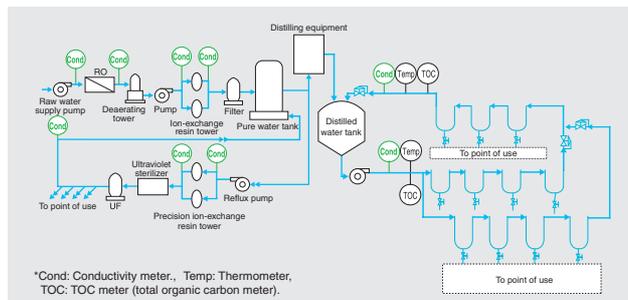


Figure 3 Flow Schematic of Typical Pharmaceutical Water Manufacturing

Especially, conductivity meters are used before and after the membrane units (UF and RO) and ion-exchange resins

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to check equipment function. Taking advantage of the 2-channel specification, this conductivity meter is used to monitor prior and subsequent conductivities and so manage the equipment by calculating the rejection ratio from the conductivity. The measurement range of this meter extends from raw water to pure water levels.

Management of Sterile Purified Water (SPW)

As shown in Figure 3, water purified by the primary side water purifying equipment is sterilized (made pyrogen-free^{*5}) by the distilling equipment and then used to manufacture water for injection (WFI). This line is required to be extremely clean.

Here, water is kept between 80 and 85 °C, supplied to the point of use, and circulated. To use it as WFI, the USP<645> conductivity meter is required to satisfy the following criteria.

- (1) Conductivity of water shall be below the prescribed value (limit value) for each temperature (Figure 1).
- (2) Temperature shall not be compensated for conductivity being measured.
- (3) The conductivity meter shall be able to continuously output conductivity and temperature at the same time.
- (4) The display resolution of the conductivity meter shall be 0.1 $\mu\text{S}/\text{cm}$.

The limit value is input to the conductivity meter to manage (1) above. If conductivity exceeds the limit value, an alarm is activated. In addition, there is a function to set up the management level arbitrarily between 0 and 100% against the standard value, i.e., the self-management level can be specified against the limit value. This conductivity meter has a USP-compatible function to set up functions (1) to (3) all together, which allows customers to easily set up measurements in conformance with USP.

*5: Removal of substances such as cell walls of bacteria which can cause fever (Pyrogen).

Cleaning Validation

The water manufacturing equipment must be periodically cleaned. Often, the membrane parts have to be chemically cleaned. For this purpose, the conductivity meter is used as a rinse monitor and the cleaning process is managed by

monitoring the conductivity after cleaning. This conductivity meter, in particular, has a function for expanding the range by using the external contact input. When conductivity has dropped in the course of cleaning, the meter is switched to the low range to verify the direction, which makes it possible to more reliably verify the cleaning effectiveness.

Features of Sensors used for Sanitary Conductivity Meter

The sensors consist of two types, a flow-through type (Figure 4) and insertion type (Figure 5).



Figure 4 Flow-through Type



Figure 5 Insertion Type

Flow-through Type

The inside of this sensor does not have any projections, and the inner diameter of the sensor is exactly the same as the diameter of the connector piping, i.e. a full bore structure.

The sensors are available in a large assortment of sizes to fit five types of piping diameters: 15 A^{*6}, 1S, 1.5S, 2S, and 2.5S^{*7}.

*6: Piping with the outside diameter of 21.7 mm based on JIS G 3459.

*7: Piping based on 3A standard (US sanitary standard). The number before S indicates the outside diameter in inches.

Because there are no projections, the flow-through type sensors have the following advantages:

- (1) The sensor section has no detention area.
- (2) The sensor section can be treated in the same manner as piping components.
- (3) Sensor holders are unnecessary.
- (4) Fluid substitution is executed immediately after cleaning.
- (5) Fluid removal from the sensor section can be executed in the same way as with the piping.
- (6) Because there are no projections or crevasses, an excellent cleaning performance is evident compared to conventional construction.

These advantages realize ideal sanitary properties. Furthermore, electrolytic polishing (EP) is applied to the electrode surface after #400^{*8} polishing in order to improve cleanability and chemical resistance. As adopted in the insertion type structure discussed next, the seal section has no crevasses.

Highly heat-resistant PTFE (Polytetrafluoroethylene) and PEEKTM plastics are used as the insulator materials and fluorocarbon rubbers (FKM) with high antigas-permeability are used as sealing materials. A double sealing structure has been adopted.

*8: #400 is a type of fine powder for precision polishing of which the average particle diameter is 30 μm (particle size of polishing agent for grindstones JIS R 6001).

Figure 6 shows the internal structure of the flow-through type sensor.

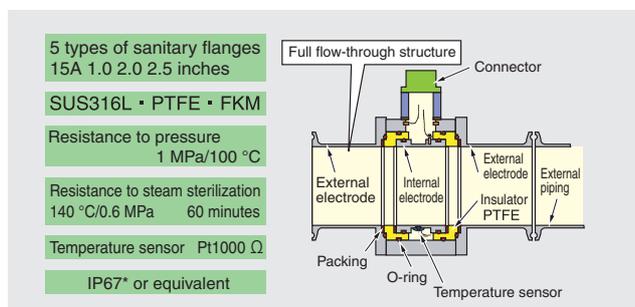


Figure 6 Internal Structure of the Flow-through Type Sensor

* IP (Ingress Protection) is the IEC standard that indicates the grade of protection against foreign substances and water intrusions. For protection grade "67," fine particles shall not intrude to the inside and water shall not intrude even if submerged 1 m below the water surface for 30 minutes.

When used in the WFI line, the sensor is constantly exposed to high temperatures around 85 °C and periodically subjected to steam sterilization (Steam in Place: SIP). It is important that such an environment does not cause change of the cell constant and seal performance problems. Normally, the SIP frequency is from once a week to once a month.

As shown in Figure 7, temperature cycle tests (200 times) are performed to verify that there is no problem in approx. 4 year cycles ((once/week) × 200 weeks). There is almost no change of the cell constant after the 100th cycle. It is considered that the cell constant has been stabilized because the oxidation on the surface state became saturated due to high temperature steam or mechanical strains had been removed.

The 200-cycle test was performed under the following temperature conditions: 1 cycle= 4 hours, temperature rise time= 1 hour, 145 °C maintaining time= 1 hour, and cooling time= 2 hours.

Because validation of the conductivity meter is usually performed annually, the actual deviation becomes lower in practical use.

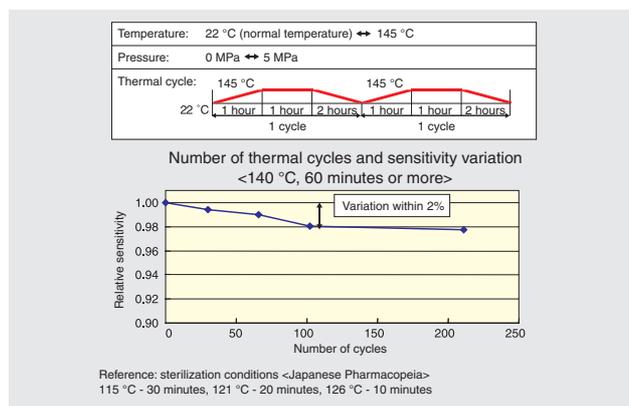


Figure 7 Thermal Cycle Test

Insertion Type

The insertion type sensor has the conventional type concentric cylindrical electrodes. It has the following advantages.

Particularly to improve resistance to increase/decrease of the internal pressure and withstand expansion/contraction of the seal components due to the temperature cycle, the

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spring structure and press-fit structure^{*9} are adopted for the inside. The seal section is structured so that the joint section adheres to each other and no crack develops between the electrode section (metal) and insulator (plastics) even if pressure fluctuation or temperature fluctuation occurs. In the pharmaceutical field, especially, cracks or fissures formed at a joint section can grow microorganisms and present a problem with cleanability. Thus, structural considerations are required.

*9: This is one of the component connection methods. The joint section is structured so as not to create crevasses by pressing a plastics component into a metal one (press-fitting). To join without any crevasses, welding is used for joining metals together. However, welding cannot be used to join metals with plastics. Also, adhesive agents cannot be used in the pharmaceutical field, because they deteriorate due to high temperatures and cause the elution.

Basic Performance (Linearity)

As shown in Figure 8, an excellent linearity has been verified.

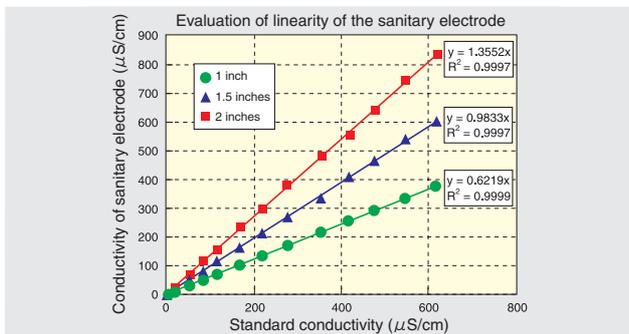


Figure 8 Linearity (Flow-through Type)

Validation

Conductivity Calibration

General testing methods for conductivity are prescribed in JIS or the Japanese Pharmacopoeia. Basically, the cell constant^{*10} is examined using a potassium chloride solution with the prescribed concentration (Table 2). The cell constant of the conductivity cell is calibrated based on a traceability system. As repeatability precision, $\pm 2\%$ is guaranteed.

*10: The cell constant is examined by measuring the degree of electrical conductivity of a standard solution using a conductivity meter and dividing the conductivity value in Table 2 by the measurement value (Electrical conductivity = Cell constant x Degree of electric conduction).

Table 2 JIS K 0101: Standard Conductivity Values indicated in the 1998 Industrial Water Testing Method (Only values under 25 °C were extracted.)

	KCl concentration	Electric conductivity under 25 °C
A	74.246 g/L	111340 $\mu\text{S/cm}$
B	7.437 g/L	12860 $\mu\text{S/cm}$
C	0.744 g/L	1409 $\mu\text{S/cm}$
D	1/10 of C	147 $\mu\text{S/cm}$

Temperature Calibration

Platinum resistance elements (Pt1000 Ω) are used in the temperature sensor. In particular, resistance of the cable which can cause errors is compensated for by the cable compensating function and the element variations are compensated for by inputting the resistance deviation of the resistor under 0°C.

Because conductivity is an extremely important parameter for pharmaceutical water, validation of its calibration is important. In relation to GMP, customers always perform validation in the field annually. Transportable calibration units (validation kits) are available so that prompt and reliable calibration can be performed. Not only a standard conductivity meter, standard sensor and distribution holder that has been examined by the intra-company traceability system but also components for connecting with the customer's processes are compactly stored in this kit (Figure 9).

Sample water collected from the sampling valve located near the sensor is supplied to the distribution holder. Then, validation is performed by comparing temperature and conductivity of the standard sensor and installed sensor. This kit was developed in order to provide prompt services for customers. By using this kit, validation can be performed by not only the customers themselves but also plant maintenance companies or calibration specialty companies.



Figure 9 Validation Kit

The connection flow in the actual process is shown below (Figure 10).

In particular, lagging is used in the sampling line to prevent temperature drop.

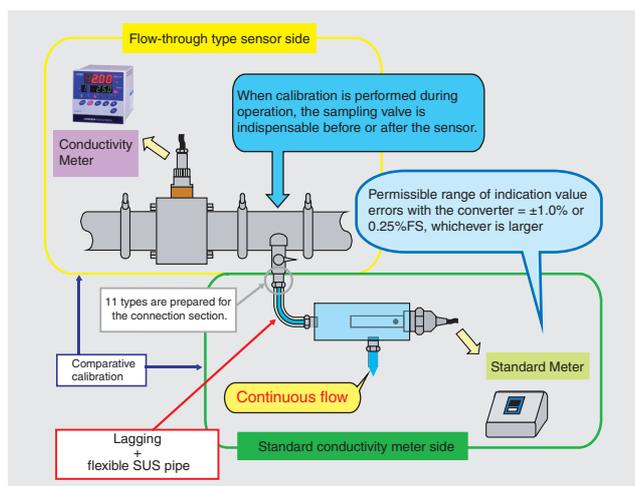


Figure 10 Process Connection Flow

Trends in Pharmaceutical Water Management

The European Pharmacopeia (EP), the United States Pharmacopeia (USP), and the Japanese Pharmacopeia have been working toward harmony with mutual differences. In fiscal 2006, some of the matters agreed up to now will come into operation as the 15th amendment of the JP. Among them, it seems to be considered that WFI management will be shifted to conductivity management of the USP and the conventional physical and chemical testing item (purity test) will be eliminated. If WFI management becomes the same as in the USP, the role of

conductivity meters will be of great importance.

Also, if TOC measurements become the same as in the USP, monitoring will be required and TOC will be added as a water measurement item.

The Food and Drug Administration (FDA) is working toward applying PAT (Process Analysis Technology) to pharmaceutical processes. Over a long history in petrochemical plants, various analyzers were introduced to the processes, which contributed to improvement of quality, yield, and safety. In Japan, introduction of analyzers to pharmaceutical processes is still at quite an early stage. Granulation related processes are dominant in pharmaceutical processes and application of PAT to liquid preparation processes is a future task. We are especially planning to consider the applied development of liquid analyzers.

Conclusion

Pharmaceutical water management continues to be an issue of increasing importance. The most pressing problem is still that of bacteria measurement and it will take considerable time to measure because a culture process is involved.

Pharmaceutical products are different from food products in that they cannot be shipped until all the inspection processes are accepted by the Pharmaceutical Affairs Law. In order to secure safety in processes, observations of water trends through bacteria measurement are also important future tasks for water management.

Furthermore, it is known that the quality of raw water slightly affects the quality of final purified water. Taking a cue from the sanitary conductivity meters, we would like to apply liquid analysis technology and reinforce our product development as a total monitoring supplier from raw water to final water in pharmaceutical water manufacturing facilities.



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