Sanitization at Micro-Sphere – Innovation in Determining Residual Ozone

With the upgrade to its disinfectant analyzer, Swan Analytische Instrumente AG has responded to an urgent need in the pharmaceutical industry for accurate and reliable ozone measurement in pure and highly purified water storage and distribution systems. This use case is the result of a collaboration with Micro-Sphere, a contract development and manufacturing organisation (CDMO) with specialist expertise in the spray drying of APIs (Active Pharmarceutical Ingredients) and HPAPIs (High-Potency Active Pharmaceutical Ingredients).

Ozone sanitization is a standard method for protecting pure and highly purified cold water storage and distribution systems against microbial contamination. However, reliable and safe implementation requires the precise determination of ozone at all relevant sampling points. Indeed, it is necessary to ensure constantly sufficient levels of ozone in the tank, effective periodic sanitization of the distribution system and complete removal of the ozone before the water is used in pharmaceutical production processes.

Swan Analytische Instrumente AG, a leader in online analytical instrumentation in the pure and highly purified water (PW and HPW) sectors, has recently made significant changes to its Monitor AMI Codes-II disinfectants analyzer to respond to an increasingly pressing need in the pharmaceutical industry: Accurate and reliable ozone measurement in PW and HPW storage and distribution systems.

Pure Water Production in the Pharmaceutical Sector

Pure water (PW), highly purified water (HPW) and water for injection (WFI) are different grades of water that are produced and stored in various phases within the pharmaceutical production. The main characteristics inherent to PW and WFI have been globally harmonized and indicated by all pharmacopoeias (USP, EP and JP). However, only the European Pharmacopoeia clearly specifies HPW, which must be manufactured to more stringent microbiological standards than WFI, although it cannot be used in parenteral applications (i.e. injections).

The production of PW/HPW from drinking water (according to local regulations) is divided into two phases:

- Pre-treatment: In which drinking water is prepared for the subsequent reverse osmosis (RO), to eliminate most suspended solids and water hardness and to remove any residual disinfectant agents, which are known to be very damaging to the RO membranes.
- The PW/HPW purification process itself: Which reduces the quantity of salts (Total Dissolved Solids, TDS) and bacterial load. This part of the system always includes a reverse osmosis (RO) step, a possible membrane degassing phase (ME) and a further purification step (electro-deionization, EDI) or a second RO step and an ultrafiltration (UF) step – only for HPW. From this year, the European Pharmacopoeia is following its American and Japanese counterparts by allowing WFI water production even at low temperatures. This process is still not very widespread but will become increasingly common in the future.

PW and HPW are normally stored at room temperature or lower, whereas WFI, which is already produced at high temperatures, is stored at between 65°C and 90°C. The primary reason for permanent sanitization is that the high temperature significantly reduces any risk of microbial contamination in the case of poor management/design of the storage and distribution system.

Cold storage and distribution systems, which are therefore not protected by high temperatures, require periodic sanitization, for which the use of ozone is becoming increasingly widespread.

Description of a Storage and Distribution System

Figure 1 shows an ozone-sanitized PW storage and distribution system, designed by Stilmas SpA, a long-established Italian company specialized in the design and construction of clean utilities production plants and installed at Micro-Sphere SA, a company in the Canton of Ticino that produces pharmaceutical powders using spray-drying technology. Various key components can be identified in the system:

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- Ozone generator with an electrolytic system
- Ozone analysis point upstream of the UV lamp, used to monitor and regulate the ozone concentration inside the tank, which remains almost constant at 50 ppb
- UV lamp to eliminate residual ozone
- Ozone analysis point downstream of the UV lamp, before the sampling points, which is required to verify the correct operation of the lamp by monitoring the total absence of ozone. It is particularly critical to determine the absence of ozone before releasing the purified water into production, with the certainty that a reading of zero is accurate and not due to a malfunction in the analysis system.
- Ozone analysis point downstream of the UV lamp, used during periodic sanitization, in which the UV lamp is switched off and the ozone concentration is increased for a specific period of time. (To ensure efficient sanitization, a concentration of 100 ppb is maintained for 30 minutes.)
- A gas analyzer, which monitors the air quality continuously at the equipment installation site to prevent any ozone leakage if detected.
- The ozone is injected through a distributor installed in the base of the storage tank, always below the water level. The ozone present in the gas phase inside the tank is sufficient to sanitize all surfaces not normally in contact with ozonated water.

In the system described, two analysis points are used simultaneously:

- During the operating phase (UV lamp on), the analysis point downstream of the UV lamp must verify the latter's efficacy (ozone concentration of zero), while the upstream point must verify the ozone concentration to ensure continuous sanitization of the storage tank.
- During the sanitization phase (UV lamp off), the analysis point downstream of the UV lamp is required to check the ozone concentration inside the distribution loop.

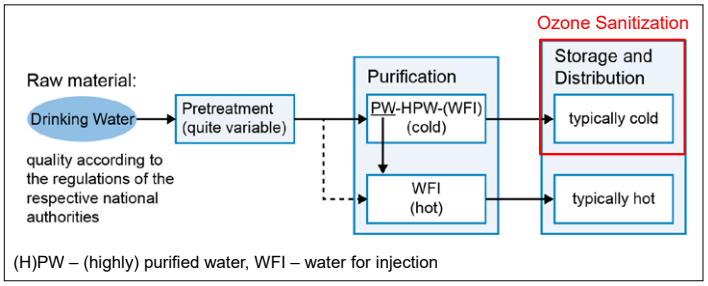

Figure 1: Overview: Production and Storage of Pharma Water

Shortcomings and Limitations of Current Measurement Systems

Ozone monitoring for pure water has almost always been based on amperometric analysis techniques with selective membrane sensors. However, most sensors on the market are not suited for pharmaceutical use, principally due to their poor accuracy at low concentrations, which makes it difficult to detect a few ppb. After the UV lamp, the most critical measuring point is therefore where the amperometric sensor can fail. If the sample has zero ozone for a long period (e.g. one week), the sensor becomes "blind" and insensitive to low ozone levels, while giving slow and fluctuating responses as ozone concentration increases during the sanitization phase. In addition, this type of probe requires significant maintenance, which must be performed periodically by an expert technician. However, the main shortcomings of the amperometric systems lie in the calibration and verification of the measurement. There are two ways to perform a calibration, neither of which is straightforward even for an expert operator:

- "In air" calibration: This uses the atmospheric concentration of O_2 as a standard, but requires a subsequent polarization phase lasting several hours and does not take into account that the calibration is actually performed under operating conditions that differ from normal, i.e. measurement of oxygen in air instead of ozone in water.
- Process calibration: This makes a comparison with a photometric instrument, a technique that is difficult to perform manually due to the instability of ozone and the need for at least 100 ppb of O_3 to be present to achieve a reliable measurement.

The use of an automatic colorimetric analysis technique therefore allows the elimination of the above-mentioned critical issues affecting amperometric measurement systems.

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An Effective Alternative: AMI Codes-II O_3

The monitor AMI Codes-II O_3, like the already established AMI Codes-II, applies the proven standard colorimetric method online according to DIN38408-3 (DPD), but is optimized to detect low ozone concentrations and designed to meet the needs of the pharmaceutical industry. The reaction is complex but, under ideal conditions and in a buffered system, it can be outlined as shown in **figure 2**.

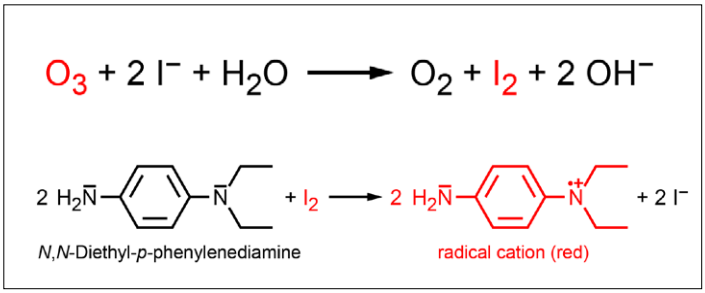

Figure 2: Specific, well defined reaction conditions assure 1:1 stoichometry (cf. iodometric ozone determination).

Ozone itself is highly reactive, so its direct reaction with DPD would lead in part to other oxidation products. To avoid unwanted side reactions, excess iodide is added first, which is oxidized to iodine; The excess iodide prevents the subsequent oxidation of iodine, for example to iodate. The iodine then reacts at a 1:2 ratio with N,N-diethyl-p-phenylenediamine (DPD), which is well known and used in various standard procedures; The radical cation formed is red in color and is quantified by measuring the absorbance of a green light.

Innovations in the AMI Codes-II O_3

AMI Codes-II O_3 has some interesting innovations:

- A measurement limit that has been lowered to 1 ppb by improving the reagent dosing system (ideal for demonstrating the absence of ozone after removal with UV rays.
- The photometer data processing algorithm has been improved to prevent abnormal values due to air bubbles present in the sample passing through the photometer.
- Traceability of the factory calibration, based on the UV absorption of ozone, measured with a high-precision spectrometer.

General Features of the AMI Codes-II O_3

- Maximum measurement limit of 500 ppb, which is more than sufficient for all sampling points in pharmaceutical water distribution and storage systems, where the ozone concentration during sanitization never exceeds 150 ppb.
- Response time = measuring interval: The minimum measuring interval that guarantees the optimal photometer flushing conditions for reaching low values is 5 minutes, which means changing the reagents every month. If a longer measuring interval is selected, the AMI Codes-II O_3 displays a warning to remind the user to change the reagents if they deteriorate.
- Detailed self-diagnosis of the main instrument parameters and the sample flow, which excludes any undetected instrument malfunctions.

Requirements for the pharmaceutical industry:

- Available with a validation package, which includes IQ/OQ/PQ protocols and a risk analysis (other contents/models: maintenance plan, user training, SOP, etc.) for easy integration of the system and smooth validation.
- Audit trail included in the AMI software.
- Traceability of reagents ensured by respective production certificates, available on request.
- Stainless-steel panel, not expressly required but common to all Swan instruments intended for high-purity water applications.

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Maintenance and Calibration

The AMI Codes-II O_3 has several maintenance advantages over conventional amperometric instruments. Operation of the analyzer is interrupted only for a few minutes, once a month, to change the reagents, and once every six months for easy changing of the peristaltic pump tubes; in addition, since it is used for HPW, no cleaning is required. Compared to amperometric sensors, maintenance is therefore much faster and cheaper and the instrument is operational again immediately.

The AMI Codes-II O_3 is calibrated at the factory under optimal operating conditions and does not vary over time as the chemical reaction is always identical; in addition, absorbance measurement is stable and precise due to auto-zeroing before each measurement. However, it is possible for users to perform a process calibration with a portable photometer and verify the accuracy and linearity in the range of application with a set of secondary standards with certified precision and known absorbance: 250 and 500 ppb O_3.

Field Application

The AMI Codes-II O_3 was tested recently by a leading pharmaceutical company in Switzerland and the results are shown in **figure 3**:

- The graph on the left shows data from a nine-day period, during which three sanitizations were performed.
- The graph on the right shows the details of a sanitization. The time when the UV lamp was turned off (07:30 am) can be clearly seen, as well as the increase in ozone production until around 08:45 am, when the UV lamp was switched on again and the ozone concentration dropped to zero immediately.

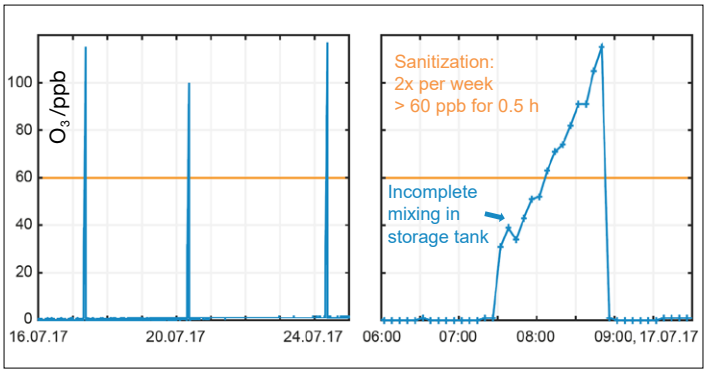

Figure 3: Field Test Codes-II O_3

Conclusions

In refining the already proven AMI Codes-II, Swan focused primarily on:

- Improving the minimum detection limit, which was lowered to 1 ppb.
- Stabilizing the measurement of low values, eliminating the risk of measurement errors due to bubbles in the sample.
- Creating a system that does not require periodic calibration and can be checked easily for accuracy and linearity at any time using a verification kit.

These research and development efforts have paid off in the AMI Codes-II O_3, which fully satisfies pharmacopoeia recommendations and end-customer expectations.

About Micro-Sphere

Micro-Sphere S.A. is a contract development and manufacturing organisation (CDMO) with specialist expertise in spray drying of aqueous and organic solutions, conventional APIs, HPAPIs, proteins, and capsule filling for dry powder inhalation.

Founded in 1998, Micro-Sphere has a long track record in overcoming complex formulation challenges and then taking products from development batches to Phase II and beyond. Micro-Sphere provides an unparalleled level of quality and has the compliance track record to prove it. Their EU GMP, FDA and SwissMedic approved facility boasts big pharma standard quality systems and infrastructure.

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