



Hydrogen peroxide: Is material compatibility a real challenge for this decontamination technology?

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ABSTRACT

One of the most important challenges of the hydrogen peroxide technology has traditionally been the material compatibility. The high oxidation potential of the compound is the main driver of the microorganism deactivation, but it is also, in some cases, the main driver of the damage that the materials could undergo when treated with this chemical. This study has demonstrated that, even though there is oxidation in materials such as copper or POM, the most common materials found in the pharmaceutical industry are not affected by a low concentrated solution. It emphasizes the importance of the type of injection technology as well as the sterilant formulation when discussing about hydrogen peroxide material compatibility.

1. Introduction

Innovation in the pharmaceutical industry is starting to be always linked to customized and low production manufacturing volumes. Biotechnology industry is solving challenges that the traditional chemical pharmaceutical industry could not. Advanced Therapeutic Medicinal Products (ATMPs) and its requirements (specified in Regulation (EC) No 1394/2007), are the main example of this type of evolution. Those new products have all something in common: Aseptic manufacturing is required.

In this type of evolution, Hydrogen Peroxide water solution has become a well-established bio-decontamination agent due to its efficacy and ability to rapidly inactivate the most resistant microorganisms. Even though there are traditional methods, such as ethylene oxide or formaldehyde, that count with more experience in the market, this technique is increasingly displacing them due to several reasons: non-toxic decomposition product, much lower risk of explosion (though not null at high concentrations), lower working temperatures or lower toxicity levels.

However, not all the aspects of this technique appear to be advantageous. The main microorganism deactivation mechanism is based in a redox reaction. There are studies that reveal that there are two modes of killing, denaturation of the DNA and/or damage to all macromolecules of the microorganism depending on the range of exposure concentration. In any case, there is an oxidative stress caused by an imbalance between the exposure to the reactive oxygen species (ROS) and the defences of the microorganism against them (Uhl, Gerstel, Chabalier, & Dukan, 2015).

This oxidation potential does not just have an impact in the subject microorganisms but also in the surrounding environment. Hydrogen

peroxide is one of the most powerful chemicals when discussing oxidizing agents.

Table 1 shows the oxidation potential of certain chemicals:

Oxidant	Oxidation Potential, V
Fluorine	3.0
Hydroxyl radical	2.8
Ozone	2.1
Hydrogen peroxide	1.8
Potassium permanganate	1.7
Chlorine dioxide	1.5
Chlorine	1.4

Table 1: Oxidation Potential

Back to the basics, a redox reaction does always imply a pair of elements with different oxidation potentials that exchange electrons depending on their ability to gain or lose electrons. So, the first point to consider when discussing about the hydrogen peroxide is that it will be an oxidizing agent (strong, weak or even become reducing agent) depending on the environment and material in contact. There are aspects such as pH of the solution, the presence of stabilizers, catalysts or temperature that will control the hydrogen peroxide reaction, and therefore the oxidizing capability (Hultman, Hill, & McDonnell, 2007).

Currently, the market proposes many techniques for delivering hydrogen peroxide into the area to be decontaminated and eventually deactivate the microorganisms. They vary not just in the way they are injected into the system but also in the way the hydrogen peroxide solution is prepared (concentration, pH, stabilizers, etc.) (Finnegan et al., 2010). Therefore, the oxidation potential of every technology might vary very much depending on the described conditions.

Popular solutions in the market rely in the gas phase of the hydrogen peroxide (Vapor Hydrogen Peroxide, so called VHP) for a proper distribution and decontamination, using a formula of 35-40% w/v of hydrogen peroxide in water. The solution is stabilized and maintained in an acidic solution (pH 2,5-4,5) that ensures a certain shelf life.

Other solutions, such as atomization of the hydrogen peroxide, due to the nature of the technology itself, are able to use lower concentrations while achieving the same decontamination level. The concentrations that are used in this type of technology can change from 4 to 12% w/v depending on the decontamination target: sterilization, disinfection or sanitization. They are also maintained in acidic solution to enhance the electron exchange. These formulas can be enhanced in their inactivation capabilities throughout the addition of a secondary active component: alcohols, metals such as silver or copper, or throughout a physical shearing effect to produce ionization.

This study intends to experimentally describe the corrosion effect of the Telstar solution ionHP+ over certain materials, commonly found in the pharmaceutical industry. This technology uses an 7,99% w/v hydrogen peroxide solution together with a 10% w/v of a short-chain alcohol. Even though there will be a mention to other systems, it is not the object of the study to compare with other manufacturers.

2. Basic concepts

In this study, the atomization technology will be studied from the material compatibility point of view. To do so, it is important to first recall some concepts of the physico-chemical aspects of the hydrogen peroxide solution as well as the technological aspects of the equipment itself.

Physico-chemical and Regulatory aspects

Hydrogen peroxide solutions, as mentioned above, can be delivered into the system in different ways. However, the physio-chemistry of the solutions is still same for every technology.

The following should be considered:

- Water vapour pressure is higher than the hydrogen peroxide one, and so is the evaporating rate (Schumb, Satterfield & Wentworth, 1956)
- The mixture hydrogen peroxide and water cannot

be considered ideal, so Raoult law cannot be directly applied. There are interactions between both molecules that should be considered (Watling, Ryle, Parks, & Christopher, 2002)

- Gas from the generated stream will always condense at a higher hydrogen peroxide concentration than the initial solution. For instance, a 35% w/v solution that is flash vaporized, then, if condenses, will deliver a 78% w/v liquid phase.
- Hydrogen peroxide is differently considered by Code of Federal Regulation in the US or ADR (European Agreement concerning the International Carriage of Dangerous Goods by Road) depending on its aqueous concentration:
 - < 8 % - Non-hazardous material
 - From 8%-28% is considered a Class I oxidizer
 - From 28,1%-52% is considered a Class II oxidizer, a corrosive and Class I unstable (reactive) substance
 - Concentrations from 52.1% to 91% are rated as Class 3 Oxidizers, Corrosive and Class 3 Unstable (reactive) substances. H₂O₂ at these concentrations are used for specialty chemical processes. At concentrations above 70%, H₂O₂ is usually designated as high-test peroxide (HTP).
 - Concentrations of H₂O₂ greater than 91% are currently used as rocket propellant. At these concentrations, H₂O₂ is rated as a Class 4 Oxidizer, Corrosive and a Class 3 Unstable (reactive) substance.

IonHP+ Technology

The atomization process is the key aspect of the technology. Atomization is defined as a process of generating droplets from a liquid jet (usually generated at an injecting nozzle). There are different types of atomization techniques depending on the disturbance: pressure disturbances, temperature differences, hydraulic forces etc (Ashgriz, 2011). Figure 1 shows two different disturbances and their differences in particle formation:

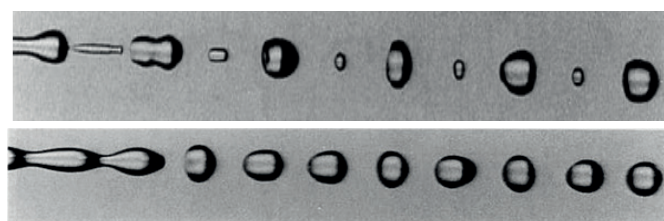


Figure 1: Liquid jet into droplets: two type of disturbances, uniform and non uniform wavelength

The atomization process in the ionHP+ ensures a proper distribution of the micro-droplets into the system as well as favouring the evaporation rate of both water and hydrogen peroxide components of the injected mixture.

Therefore, in ionHP+, micro-condensing is occurring. The deactivation of the microorganisms is achieved throughout an attack, not just in gas phase but also in liquid phase. The working vapour concentration is much lower than other techniques (<400 ppm) but, as the liquid phase is also present, the deactivation kinetics are even faster than others (Unger-Bimczok, Kottke, Hertel, & Rauschnabel, 2008).

Back to the regulatory classification, it is important to remember that solutions below 7,99% are not even considered oxidizers. However, traditionally, in the most popular decontamination methods, condensing had been totally avoided in order to minimize the oxidizing properties of a solution that is certainly considered an oxidizer, Class II and therefore corrosive.

The following study intends to understand the effect of a low hydrogen peroxide solution (7,99%) over certain materials.

3. Material and method

Methodology

The first phase implied an electrochemical study for metallic materials. The study was carried out together with the University of Barcelona in the Laboratory of Corrosion and Electrodeposition laboratory and sourced by Jose Collado S.A.

In the second phase, the study was performed inside an isolator, simulating a real bio-decontamination cycle, placing materials usually found in clean rooms, isolators or BioSAS and performing up to 1000 cycles.

Phase I: Laboratory tests

To analyse the potential corrosive impact over metallic materials, electrochemical parameters such as Open Circuit Potential, Polarisation Resistance, Spectroscopy of Impacts on OC or Corrosion Current can be measured. In this case, Corrosion current (i_{corr}) will be the main parameter to compare the materials. It is the current produced in an electrochemical cell while corrosion is occurring. The magnitude of the corrosion current in the system is proportional to

the potential difference. That is, the greater the potential difference, the greater the corrosion current generated, and therefore the more severe the rate of corrosion at the anode.

The tests were carried out using a multipotentiostat, working with 3 electrode cells inserted into a Faraday box to improve signal quality. A reference electrode of Ag/AgCl in KCl 0.1 M was used. The total test duration was 5 hours.



Figure 2: Bench for electrochemical testing

Phase II: Field tests

In phase II the tests were carried out inside an enclosure with a volume of 0.25m³. The cycle was developed simulating the conditions that the materials would be subjected to under normal bio-decontamination cycles of a 6log reduction. The test cycle included an injection phase of 5 minutes duration, dwell phase of 5 minutes duration and an aeration phase of 20 minutes duration. The sterilant injection rate was 3ml/min, giving a total sterilant volume of 15 ml per cycle.

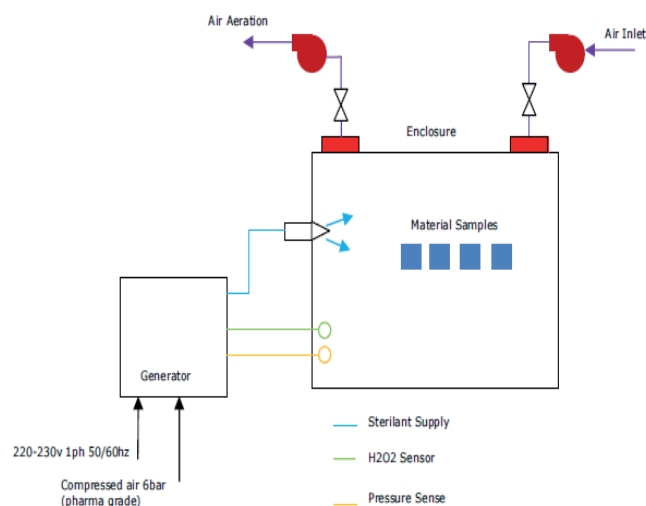


Figure 3: Bench for simulating real decontamination cycle

Sample pieces of the materials were placed inside the enclosure on wire racks or individually hung to ensure total surface contact of the sterilant on the material. Repeated cycles were carried out until a total of 1000 cycles were completed equating to 160 hours of exposure to the hydrogen peroxide

sterilant. The samples were examined for signs of degradation, discoloration or oxidation after the 1000 cycles.



4. Results

Phase I: Laboratory

	5083 ALUMINIUM	BRASS	COPPER	BRONZE	304 STAINLESS STEEL	316 STAINLESS STEEL	316 STAINLESS STEEL BAR	LACQUERED STEEL
icorr/µA	25	55	60	46	3	3	2	0.41

Table 2: Electrochemical testing results

Phase II: Field test

Material	Observations after 1000 cycles
304L Stainless Steel plate	None
Copper pipe 15mm	The pipework turned a dull colour and oxidised at an early stage. 5 cycles already showed an effect in the pipe. 
Untreated Aluminium	Found that the aluminium plate was showing signs of oxidation. This started to happen after the initial 100 cycles.
Mild Steel plate	This started to show signs of rust with the first 100 cycles
PFTE	None
Elastomeric materials: EPDM and FPM	None
Plastic materials: Polyacetal	The material changed colour after the first 100 cycles. The material started to disintegrate after 1000 cycles. 
Natural rubber	The rubber started to show slight brittle signs when it reached the end of experiment. However it still had its original material properties.
IPVC	None

The results showed clear differences between the metals when a redox reaction is forced and the electrons exchange is measured. It is very obvious that coatings will reduce the potential difference and transmission of electrons between electrodes. Also, the presence of chromium in the steel ensures that less corrosion occurs in the surface of the material.



Material	Observations after 1000 cycles
PVC plastic pipework fittings	No sign of change in shape or material properties. One fitting had a change in colour on one end which was believed to be from hydrogen peroxide build up during the gassing. 
Nickel plated brass fittings	After the first 100 cycles the coating was found to be blistering from contact with the hydrogen peroxide gas. This happened during the gassing cycles. At 400 cycles the plastic end started to lose colour and become brittle.
Silicone	None
Toughened glass	None
Laptop	After 100 cycles the laptop still powered up. No change was seen to the screen keys or housing. Corrosion was found on some of the exposed connections. After 300 cycles the battery indicator light would not come on and the power connection did not work. From 300 cycles onwards the connections and housing showed further corrosion. Towards the end of the cycle the keyboard keys started to come loose and fluid started to come out of the laptop. 
Nitrex glove	None
Yellow and Light-yellow Marigold glove	None
Piecan CE0333 white clean room glove	None

Table 3: Field testing and visual inspection

5. Conclusions and recommendations

It has been proved that an <8% w/v solution of hydrogen peroxide is gentle, even by immersion, with the most common materials found in the pharmaceutical industry. Metals such as Stainless steel (SS) 304 or SS 316 do not present any alteration in their surfaces. Attention should be paid when aluminium is used, overall, if the material is not treated.

It is remarkable the effect of the lacquer coating in the steel. It looks as though no physical wear occurs in the material surface, carbon steel can be used perfectly (it is not accepted in the pharmaceutical industry).

Non-metallic materials showed good compatibility with the atomized hydrogen peroxide. The only material that was surprisingly highly affected is the Polyacetal. Therefore attention should be paid when choosing the glove ports manufacturing material. PTFE should be the preferred material.

Thus, it is important to remember that in this case, a maximum of 8% w/v hydrogen peroxide is in contact with the materials. When choosing other sort of technique with concentrations above 28% w/v, materials should be chosen considering that in the best case, a Class II Oxidizer (corrosive) is in use and that eventually, even a >70% w/v solution might condense when a certain surface or area is not maintained within the margins of temperature and relative humidity to avoid saturation.

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About the Authors



Ignacio Cantera, R&D Pharma Manager at Telstar, holds a MEng in Chemical Engineering from the University of the Basque Country (Spain) together with a MSc from Cranfield University (UK) in Environmental diagnostics and Management. In 2015, Ignacio joined Azbil Telstar Technologies SLU as R&D Pharma & Vacuum Manager, participating in a wide variety of projects related to the Life Science industry. Recently in 2017 he started an Industrial Doctorate titled “Cold Sterilization in the Pharmaceutical Industry” together with the Universitat Autònoma de Barcelona allowing him to look further into an important trend in the Life Science industry.



Mireia Capella holds a Bachelor’s Degree in Chemical Engineering from the “Universitat Politècnica de Catalunya” as well as a Master of Engineering in Chemical Processes from the “Institut Químic Sarrià”. During the past 3 years working as an R&D Project Engineer at Telstar, Mireia has actively contributed to process related projects, with hydrogen peroxide technology development and validation being her main area of expertise. Due to her academic background and her continuous involvement she has been able to lead the launching of the ionHP+ technology at Telstar.

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