Understanding the hydrogen peroxide vapour sanitisation process and introducing the MCHP concept, a personal account

Tim Coles

Abstract

This article traces the history of hydrogen peroxide vapour as used for sanitising pharmaceutical isolators and similar volumes. From an early puzzle as to how the vapour could be so effective in deactivating resistant test organisms, the author moves forward through his own career to develop a clearer comprehension of the hydrogen peroxide vapour process. The term "micro-condensed hydrogen peroxide" (MCHP) is introduced as an aid to understanding how the process truly acts and this understanding helps to generate robust sanitisation cycles. This new knowledge can be applied to the many devices becoming commercially available for sanitising isolators.

Introduction

It is now more than 30 years since I first encountered gas phase sanitisation as applied to pharmaceutical isolators. This was in the form of the old MAN peracetic acid vaporiser produced by the French company La Calhene (now Getinge La Calhene). It immediately struck me as remarkable that the vapour generated from a 3.5% solution of peracetic acid could be so effective in killing off micro-organisms. How could a mere gas, with concentrations of just 0.1% (which is the result of warming a 3.5% solution), act so quickly to inactivate the very resistant spores of an organism like *G. stearothermophilus*?

Moving on, when I formed Cambridge Isolation Technology (CIT), I became involved in the development of a gas generator to supersede the MAN, working with a combination of 10% hydrogen peroxide and 1% peracetic acid that we named "Citanox". In theory, the new "Citomat" gas generator and Citanox should have easily out-performed the MAN in terms of time to achieve kill, but it did not always do so. On some occasions the test Biological Indicators (BIs) would be completely deactivated, while at other times, with exactly the same operating parameters, there were many survivors. I could find no obvious explanation for this unpredictable behaviour.

Amsco Steris

Time passed and I encountered the more complex hydrogen peroxide vapour generators from Amsco (now Steris), such as the "VHP 1000" unit. Many isolator users look for a short gassing cycle and so rapid gassing has essentially been the target of all vapour phase hydrogen peroxide (VPHP) generators. The VHP 1000 first dehumidified the air present in the isolator before introducing hydrogen peroxide vapour from an evaporating device. The logic here was that if the water vapour were removed, there would be "more room" for hydrogen peroxide vapour. Thus a high concentration of VPHP could be achieved, and a quick kill of the BIs would result, while keeping the hydrogen peroxide apparently in the vapour phase at all times. The VHP 1000 also carried a catalyser cartridge which broke down the VPHP to water vapour and oxygen, allowing a closed loop cycle, so that no exhaust duct to atmosphere was required.

Steris developed what became the classic vapour phase hydrogen peroxide (VPHP) cycle consisting of four phases:

1. Dehumidification: during this phase the air in the isolator is brought down to low water vapour content, perhaps less than 10% RH.
2. Raising gas concentration: in this phase the concentration of VPHP in the isolator is raised quickly, by delivering hydrogen peroxide solution to the evaporator at a high rate.
3. Gas dwell: during this phase the gas concentration is held at high level, just short of apparent, visible, condensation.
4. Aeration or purge: here the VPHP supply is cut off and the air /gas mixture in the isolator is passed across a catalyser until a low gas concentration is achieved, usually less than 1 ppm. Alternatively, the gas can be ducted away to atmosphere to accelerate the overall cycle.

All-in-all, this appeared to be a very attractive package. However, developing robust and repeatable cycles was not altogether a simple process. Indeed, the whole subject began to take on the air of a "black art", requiring long periods of time, large manuals and lengthy tables for validation.

MDH – BioQuell

At this stage MDH (now BioQuell) entered the arena and carried out some significant research on the VPHP process (Watling and Parks 2004). If the concentration of VPHP is measured throughout the classic four-phase cycle, something strange takes place when the gas dwell ends and the purge begins. At this point, the supply of vapour is cut off and one would intuitively expect that the concentration of the vapour would immediately begin to fall away. Paradoxically it does not. Instead it *increases* quite significantly for a short time.

Prior to the research, there was no clear reasoning for this phenomenon. Then the work of Watling and Parks (2004) offered a plausible explanation which may be summed up thus: under the conditions of isolator gassing, hydrogen peroxide will condense onto the surfaces of the chamber in a manner not visible to the naked eye. The condensation is in the form of droplets which are of the order of a few microns across. This has been termed "micro-condensation". Because hydrogen peroxide has a lower vapour pressure than the water vapour, which is inevitably present when an aqueous solution is used as the source, this micro-condensation has a high concentration, perhaps 60% or 70%. It is the presence of liquid hydrogen peroxide solution on the surfaces

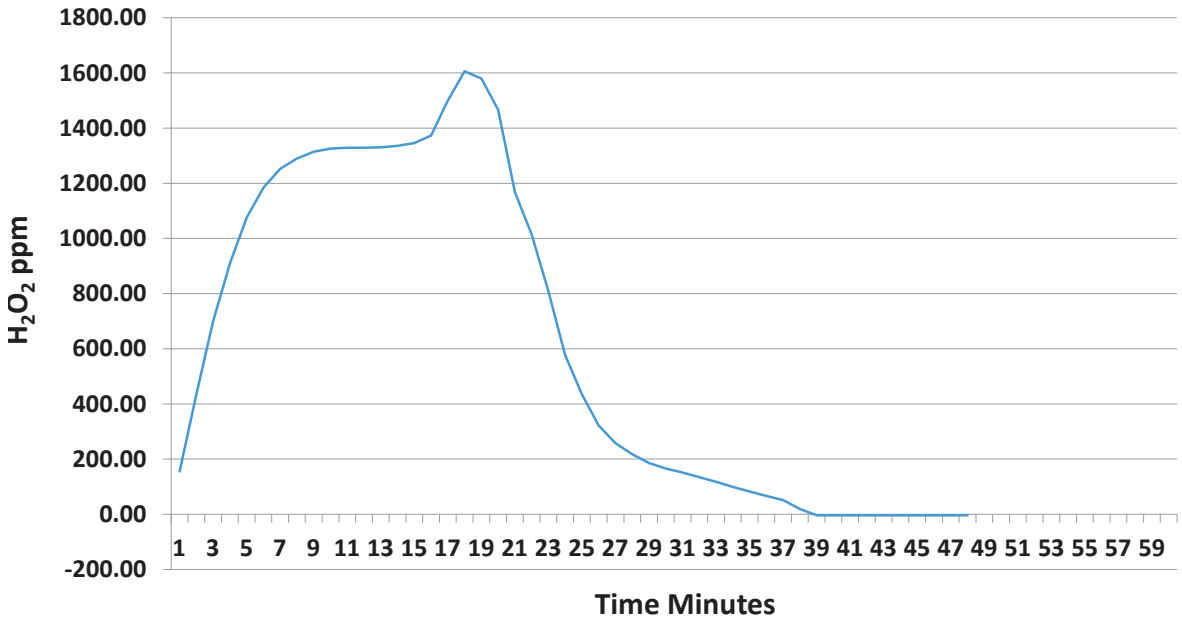

Figure 1: Phase 3 of a classic VPHP gassing cycle showing VPHP concentration against time

inside the isolator, at high concentration, that produces the very rapid kill observed. The VPHP process is, in fact, a liquid-based process, at the micron-scale level. Furthermore it is a condensation-based process, a fact which radically alters the way in which the subject should be approached, as this paper indicates.

How does this knowledge explain the rise in VPHP concentration at the end of the gassing phase? The logic runs thus: during the gassing phase, an equilibrium is set up between the in-coming VPHP and the micro-condensation on the internal surfaces. VPHP steadily enters the micro-condensation layer and, equally steadily, leaves it. When the supply of VPHP is cut off, the equilibrium shifts and the micro-condensation layer is able to evaporate fully. Since the micro-condensation has high concentration, the concentration in the vapour phase rises consequently. Hence the "blip" in the graph at the end of the gassing phase.

"Dry and high" versus "wet and low"

Thus far, users were essentially offered a VPHP process which we could term "dry and high". In other words the air in the isolator was dry at the start of gassing, and the concentration of the VPHP was high, at around 1,200 ppm, or roughly 1 mg per litre in Steris terminology. This appeared to offer the best route to the industry-standard requirement of log 6 reduction (the reduction of a population of spores in a BI by 6 orders of magnitude) of *G. stearothermophilus* spore BIs, in the minimum amount of time.

At this point a number of other manufacturers entered the arena with alternative forms of gas generator. These were simpler in concept and, somewhat boldly, left out the dehumidification phase of the gassing cycle. My new company, Pharminox Isolation Limited, was asked to carry out some cycle development using a generator that simply evaporated hydrogen peroxide solution and provided a fan to blow this into an isolator. The results were quite surprising and highly significant. Early tests showed that the concentrations of peroxide developed were low, at just a few hundred ppm, and yet log 6 reduction could be achieved, although not on every occasion.

Further investigation revealed that log 6 reduction could be achieved reliably if the room RH was below 50%. If the starting air was above 50% RH, then visible frank condensation appeared quickly, and log 6 was not achieved. The explanation was surely simple – if the starting air was below 50% RH, then conditions inside the isolator were such that micro-condensation could form, leading to full log 6 reduction. If the starting air was above 50% then the conditions favoured frank, visible, "*macro*-condensation", this having a very low peroxide concentration, incapable of significant log reduction.

Unfortunately the test programme did not extend to checking the lower RH limit of the process. Presumably, if the RH of the starting air is below a certain value, with given gas generator settings, then no condensation will form, either micro or macro.

Pharminox was also asked to review the data from another form of the VPHP process, developed by a UK isolator manufacturer. This system generated an aerosol of hydrogen peroxide solution within the isolator, using a sophisticated compressed air nozzle. During the cycle the air was static in the chamber, and once again there was no prior air dehumidification. The aerosol was introduced for one or two minutes, until a thick "fog" filled the chamber to the extent that the far wall was obscured. At this point aerosolisation was stopped and, after a further one or two minutes, the fog cleared completely as the aerosol evaporated. This cycle lead to quite reliable log 6 reduction. The suggestion here is that as the aerosol droplets with a concentration of 35% hydrogen peroxide evaporated, and micro-condensation then developed on the walls of the chamber because the hydrogen peroxide content has a significantly lower vapour pressure than water vapour.

The MCHP® concept

The evidence seems very clear. The VPHP process, which can reliably deliver log 6 reduction of BIs, results from the preferential deposition of high-concentration hydrogen peroxide solution, in the form of micro-condensation, on the surfaces inside an isolator. It is not the vapour that produces the kill. The vapour is only the vehicle which delivers liquid to the site. If visible macro-condensation

appears, the gassing cycle probably will not lead to log 6 reduction, though in some cases MCHP® may have preceded macro-condensation with enough time to establish kill.

Thus we should reconsider the title of the sanitising cycle which involves the use of hydrogen peroxide vapour and avoid using the erroneous phrase "vapour phase hydrogen peroxide". It is suggested that the correct title for the process should be "*micro-condensed hydrogen peroxide*" abbreviated to MCHP®. This would then lead to a shift in philosophy when using the process. Instead of thinking in terms of a vapour, we need to understand that it is the micro-condensation which leads to the desired effect of log 6 reduction. It does not matter what the measured hydrogen peroxide concentration is. Within limits, it does not matter what the temperature is. Within limits, it does not matter what the RH is. What matters is the development of MCHP®. If conditions are consistently set up to develop MCHP®, then reliable log 6 reduction will take place.

Conclusion

So, what light does all of this evidence shed on my unreliable gassing cycles with the Citomat gas generator and Citanox solution described earlier? At the time we had no knowledge of the MCHP process. We did not realise that the RH of the starting air had such a radical effect on the gassing process. Evidently, on some occasions the starting air was dry enough to lead to micro-condensation, whilst on other occasions the air was humid and micro-condensation could not form. This lack of understanding led to a loss of confidence in Citomat and Citanox. Now that the concept of MCHP is understood, it should now be possible to use hydrogen peroxide with confidence. A variety of gas generators and aerosol generators, simple and complex, integrated and free-standing, can be harnessed, provided that the operators understand how the process works.

Reference

Watling D, Parks M: The Relationship Between Saturated Hydrogen Peroxide, Water Vapour and Temperature. *Pharmaceutical Technology Europe*, 2004: 16:3:50

Tim Coles, BSc (Hons), M.Phil., Managing Director, Pharminox Isolation Ltd., has worked in the field of isolator technology for over twenty years. He was a founding member of the UK Pharmaceutical Isolator Working Party that produced Pharmaceutical Isolators, Pharmaceutical Press, 2004, and more recently of the PDA committee that has just produced Technical Report No 51. "Biological Indicators for Gas and Vapour Phase Decontamination Processes" [for the validation of isolator sanitisation]. His book Isolation Technology - a Practical Guide, CRC Press Inc. 2004, is now in its second edition.