SELECTION OF CLEANING AGENTS AND PARAMETERS FOR CGMP PROCESSES

by

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Abstract

Selecting suitable cleaning agents and determining justifiable cleaning process parameters are critical prerequisites for cleaning validation. Proper selection of these cleaning agents and parameters could simplify cleaning validation efforts immensely.

Process cleaners may range from a single component, such as an organic solvent, to multi-component formulations that use multiple cleaning mechanisms such as solvency, solubilization, emulsification, wetting, chelation, dispersion, hydrolysis, and oxidation. Although the most important cleaning parameters are cleaning time, impingement-level, cleaning solution concentration and temperature, other factors that influence cleaning performance may include, nature of the substrate, surface finish, soil conditions, soil levels before cleaning, level of mixing, water quality, and rinsing. Proper selection of cleaning agents and parameters can be achieved through laboratory evaluation followed by field confirmation, and requires an understanding of substrate and design constraints, residue limits, desired cleaning objectives, cleaning chemistry and the contribution of various parameters to performance.

Introduction

Cleaning processes are required to be validated according to current GMPs. As this can be a time consuming process for a multi-product facility, there is often an urgency to embark on executing the cleaning validation process. Selecting suitable cleaning agents and determining appropriate cleaning parameters are, however, critical prerequisites for cleaning validation. Proper selection of these agents and parameters could help in developing a system that is more easily validatable, thus simplifying cleaning validation efforts immensely. Also, since these cleaning agents and parameters are difficult to change once they are validated, and can have an important influence on the operating procedures and therefore on the cost of manufacture, it is important to understand and evaluate the various available options at an early stage.

This paper provides a broad perspective and an overview, based on laboratory and field experience, of the various options and factors that need to be considered in selecting cleaning agents and parameters. Various cleaning mechanisms, types of cleaning agents, cleaning parameters and factors affecting performance, laboratory screening and evaluation processes, and an overall strategy for selection of cleaning agents and parameters are presented.

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Cleaning Mechanisms

Depending on the type of cleaning agent selected, one or more of the following mechanisms are involved in the removal of the soil (product contaminant) from the surface. These mechanisms have been discussed in literature[1-4] and only a brief summary is presented here.

Solubility
The solubility of one substance in another is commonly defined and reported as the maximum amount that can be dissolved (uniformly dispersed at the molecular or ionic level) at a given temperature and pressure. Solvents are either polar (e.g., water, alcohol) or non-polar (e.g., hexane); from basic chemistry, like dissolves like. Solubility provides useful information on the capacity of the solvent for dissolving the solute, but does not address the issue of the required dynamics or time taken for that solute to be removed from a product contact surface. The dissolution process works fast when the soil is broken down into small fragments, thus increasing the interfacial surface area. Pharmaceutical product soils can, however, be attached to surfaces by a combination of van der Waal=s forces, electrostatic effects and mechanical adhesion making cleaning a more complex process.

Solubilization
This is a term used for the process of converting a normally insoluble material to a soluble one. This is usually achieved with the use of surfactants in detergent formulations, but a simple change in the pH may aid the process.

Emulsification
Emulsification, as applicable to process cleaning, is the process of suspending a water insoluble liquid material, such as an oil, in an aqueous solution and preventing its redeposition. The lipophilic or Aoil loving@ end of surfactants could attach to the soil, leaving the hydrophillic or Awater loving@ end exposed to the water, thus completely covering the surface of the soil and converting it into a Amicelle@ or an easily removable droplet. In cases where the soil is not soluble in an aqueous solution, emulsification could be an easier and faster way to remove the soil out of the system without redeposition.

Wetting
When cleaning a surface, the surface energy of both the substrate and the liquid, and the interfacial energy are important. This determines how well the cleaning solution will wet and spread into the soil and surface irregularities. This in turn will determine its ability to displace particles and penetrate the soil, providing a larger surface area which will allow for an increased rate of other mechanisms such as solubilization and diffusion. Wetting agents in formulated detergent systems lower the surface energy of the solution very significantly.

Chelation
Complexing agents, or chelants, are used in formulations to improve the cleaning effectiveness for inorganic soils. Chelants can Agrab@ onto metal ions to form strong complex bonds preventing these ions from other adverse influences. Chelants are also used for iron oxide removal in derouging and passivating agents.

Dispersion
Dispersants are used in formulated cleaning agents to prevent particulates from clumping, and thus helping to ease their transport by the cleaning solution flow. This mechanism can be useful also in preventing hard water scale from depositing on the surface while rinsing alkaline cleaning solutions.

Hydrolysis
This is the process of using acids or bases to Alyse@ or break chemical bonds, thus creating smaller molecules that are more easily solvated. When this mechanism is employed, it is important for analytical methods to be able to target and account for such breakdown products.

Oxidation
Oxidants, like sodium hypochlorite, can be used to break down proteins and other organic compounds that cannot be cleaned by other mechanisms. Since these aggressive agents can also act on the substrate, they are used for process cleaning applications only when other mechanisms are inadequate.

Physical
Mechanisms such as diffusion and convection help to transport soil molecules away from the surface while allowing Afresh@cleaning solution to interact with the soil. Unfortunately, the active components are usually relatively large molecules with low diffusivities, thus requiring convective flow to transport them.

Cleaning Agent Options

Broadly, three categories of cleaning agents are used for cGMP processes. These are organic solvents, commodity acids and alkalis, and formulated detergents.

Organic Solvents
Organic solvents are used mainly in the bulk pharmaceutical manufacturing industry. They rely primarily on solubility for residue removal. There are some advantages of using organic solvents. If the solvent is the same as the process solvent that is used in the manufacture of the next batch, there is no external contaminant introduced. The solvent being usually a single component cleaning agent, analytical methods are simplified. Unlike aqueous cleaning agents, solvents also have some, although limited, cleaning action when vaporized and refluxed. Safety, environmental and disposal

issues, and cost are the main disadvantages and reasons why manufacturers prefer aqueous cleaning agents when possible.

Commodity Alkalis and Acids
Aqueous solutions of commodity alkalis (such as sodium hydroxide or potassium hydroxide) and acids (such as phosphoric acid or citric acid) are commonly used for process cleaning. The advantages of these agents are that they are widely available, relatively inexpensive, and are simple, single component cleaning systems. They utilize cleaning mechanisms such as solvation and hydrolysis, but do not take advantage of the other mechanisms described above, particularly wetting, emulsification, and dispersion. For these reasons, sodium hydroxide alone, which is a very commonly used cleaning agent, has drawbacks such as precipitation of water hardness, limited soil suspending ability, and insufficient penetration into soil due to low wetting characteristics. The commodity alkalis are generally difficult to rinse and often require follow up with acid rinsing.

Formulated Detergents
Formulated detergents take advantage of several of the above cleaning mechanisms. Surfactants in these formulations may provide better wetting, surface action, and emulsification, depending on the chemistry and concentrations used. Multiple mechanisms could provide faster and more effective cleaning of a broader spectrum of soils. This is important because pharmaceutical product residues may be complex formulations of different chemistries that comprise the actives and the excipients. Over a period of time there could also be other contaminants from the water, such as scale, or from the substrate, such as iron oxides, that could build up. Addressing a broad spectrum of soils with a single cleaning agent can also help in using product grouping strategies, thus simplifying validation efforts. The disadvantages of using formulated detergents are that they are often proprietary formulations, there are a limited number of sources, and their selection process and mechanism of action are not always well understood.

Cleaning Parameters

For a given cleaning agent and soil, the most important parameters that determine cleaning performance are the cleaning time, the action or impingement on the surface, the concentration of the cleaning agent and the temperature of the cleaning solution. These parameters- time, action, concentration and temperature- are closely related. It is therefore possible to compensate one for the other and obtain the same cleaning performance. This will be discussed later in more detail.

Time
It is well known that the cleaning performance improves with cleaning time, provided all other parameters are at their desired level. To help design and understand a cleaning process, the total cleaning time should be divided into its components, such as effective wash time, soak time, rinse

time or other lost time. The implications of those times on the overall cleaning performance should be assessed. The following examples illustrate the point. For a half hour manual scrubbing of a tank with a brush, the time for which the brush moves across any specific surface area would be a very small fraction (typically a few seconds) of the total time taken to clean the tank. The time taken between scrubbing and final rinsing could be different for different areas of the tank and would depend on the cleaning procedure. In the case of rotating spray devices, the impingement acts on any given surface for only a certain fraction of the total time, due to the rotating nature of the spraying device. When cleaning complex vessels using spray devices that do not give complete direct coverage, a certain spray time may elapse before wetting of hard to reach areas begins. This could be a result of design constraints. In such a situation, although a half hour wash cycle may clean the soil by a gradually occurring wetting process, a short rinse cycle (for say 3 to 4 minutes) that follows, may not provide adequate time to contact and wet those shadowed areas and rinse away even a freely rinsable cleaning agent.

Action

Action or impingement refers to the shear force acting on the surface. This is unfortunately the least monitored and understood parameter and is often the cause for inadequate cleaning. In a process train, if the action or impingement varies from one area to another due to design or flow constraints, the lowest level of action (corresponding to worst case locations) should be identified. The other cleaning parameters should then be chosen at levels high enough to compensate for the low levels of action, and at levels which meet the acceptance criteria even at those worst case locations. An optimized cleaning process will try to establish similar levels of action across the entire system.

Concentration

In general, the higher the concentration of an aqueous cleaning agent, the better the cleaning. Higher concentrations could increase reaction rates, increase solubilization, reduce surface tension up to a limit. Concentrations above a critical level are required for formation of emulsions. Substrate compatibility and safety may limit the use of high concentrations.

Temperature

Increasing temperature has a strong positive effect on cleaning performance since several mechanisms such as solubility, diffusion, activity of certain surfactants, and reactions like hydrolysis and oxidation are temperature dependent. In the case of certain proteins, however, denaturation can cause a decrease in cleaning effectiveness beyond a certain temperature.

Other Factors Affecting Cleaning Performance

Surface

The chemistry and nature of the surface can determine the extent of adhesion of the residue to the surface as well as the extent of wetting and soil removal by the cleaning solution. The surface energy of clean metals and oxides is very high. This allows fluids to easily wet and spread on the surface and into the micro-irregularities. For example the contact angle for deionized water (surface energy 73 mJ/m^2) on a clean metal oxide surface (many hundreds of mJ/m^2) is less than 5 degrees while that on polypropylene (surface energy 33 mJ/m^2) is greater than 100 degrees. Thus water tends to ball up on a material like polypropylene that has no polar component. Surfaces with a high surface energy will, however, try to lower their surface energy by adsorbing low energy materials such as hydrocarbons. The reactivity of surfaces to soils will depend on the tendency of the surface atoms to act as electron acceptors or electron donors. The surface finish can also be an important factor. A rough surface increases the surface area of contact of the soil and the substrate and, like cracks and crevices, can be viewed as micro-deadlegs.

Soil Levels

High soil levels could saturate a solvent or could deplete the surfactant or other components in a cleaning formulation, rendering one or several of the cleaning mechanisms ineffective. This is particularly possible when using small volumes of cleaning solution for large surface areas, as with the use of spray devices in a CIP system or when cleaning a series of vessels in a train with the same cleaning solution. One way to estimate the typical soil levels in a vessel is to measure the amount of actives or soil in the used cleaning solution in a pre-validation trial. This estimate could then be used to determine, the worst case soil to cleaning solution ratio to be used for a laboratory cleaning evaluation. An unacceptably high ratio could lead to problems such as inadequate cleaning, redeposition of soil, and in the case of solids, plugging of spray devices.

Soil Condition

The condition of the soil on the surface is an important factor in determining cleaning performance. In most cases, if the soil is cleaned while still Awet@ or fresh, cleaning is easier than if the soil were allowed to dry. In this regard, the time before cleaning begins becomes important and should be documented. In some cases, the production time or campaign time may also have to be considered as there could be certain areas of the process system, such as pipes, that may have been exposed to raw material, intermediate or product only at the beginning of the manufacturing process. In certain cases the soil may be baked onto the surface during or after manufacture, making it more difficult to clean. In other cases, such as in tablet presses, the pressure used can be an important factor in determining the condition of the soil.

Mixing

It is desirable for the cleaning solution to be well-mixed. This assures optimum use of the cleaning solution and prevents localized saturation spots. In a static soak, or in areas of minimal mixing and agitation where diffusion is the primary mechanism of removal of the soil away from the surface, the cleaning solution very close to the surface of the vessel could get saturated with the soil. There would be a decreasing concentration gradient of the soil in the cleaning solution as one moved away from the surface. The surface is then exposed constantly to a depleted or spent cleaning solution. This is clearly undesirable. It must be noted that mixing is not necessarily the same as action or impingement discussed earlier. One could have high levels of action and yet inadequate mixing. Consider the case of a long pipe with a heavy cake of soil that is cleaned with a turbulent once-through flow of a dilute detergent. The flow rate and velocity, and consequently action or impingement, would be the same at the beginning of the pipe as it is at the end of the pipe as long as the pipe diameter is the same. The system is, however, not a well mixed system because at the beginning of the pipe, the soil is constantly being cleaned by fresh cleaning solution, while at the other end, it is exposed to a spent solution that is loaded with the soil that is transported through the pipe. In this case one would expect the end of the pipe to be cleaned last or to a lesser extent. In case homogeneity of the solution cannot be easily achieved (as in the case of the pipe example), surface swabbing locations and parameter selection (such as cleaning time or cleaning agent concentration) should account for such worst case locations.

Rinsing

The water rinsing cycle that follows aqueous wash cycles is an important factor that determines performance for critical cleaning applications. Rinsing is similar to washing, except that the residue in the case of rinsing is more easily removable and is solubilized in water readily. This allows for a compromise in one or more parameters such as a reduction in time (of rinsing) or temperature. Rinsing should, however, be performed for a period that is long enough to get complete coverage of the entire surface and removal of all holdup cleaning solutions. If the cleaning agent is easily rinsable, any difficulty encountered in rinsing the cleaning agent out of the system is often indicative of either solution holdup or poor coverage. Therefore, such a situation is often an indication of a poor soil washing step as well. Rinsing should be done as quickly as possible after the washing process to prevent the soil from drying back onto the surface. The quality of the final rinse water should be at least as good as that used in the manufacturing process.

Selecting the Right Chemistry and Parameters

Cleaning agent selection for cGMP applications can involve evaluation of several important factors. Besides effectiveness, these may include consistent quality, consistent and easy long term availability, safety, environmental issues, analytical methods, and overall cost. Determining the most effective cleaning agent for different types of pharmaceutical product soils is best achieved through laboratory evaluation.

Laboratory Evaluation

A good understanding of the chemistry of the soil being cleaned and of the cleaning agent mechanisms, will help in the screening process. Evaluation of cleaning agents and determination of parameters such as cleaning time, temperature and concentration could be done by a laboratory cleaning study. The soil to be cleaned is coated onto small panels or coupons and allowed to air dry or is baked onto the surface in an oven to simulate worst case conditions that might exist in the process. This step requires a good understanding and review of the manufacturing process. The coupons can then be cleaned by various cleaning agents using the desired cleaning process such as agitated immersion in laboratory glassware or under flow conditions as dictated by the process being simulated. The cleaned coupon can then be analyzed for residue by an appropriate method. Laboratory evaluation can give useful information on a variety of issues including the cleaning effectiveness, the potential for the soil to precipitate and redeposit on the surface, the potential foaming issues of the solution in the presence of the residue, the ratio of the soil level to solution volume that the cleaning solution can handle, and the physical state of the soil that has been removed from the surface. Laboratory evaluations can also provide a documented rationale for the selection of the cleaning agent and parameters. The final confirmation of performance can, however, only come from a field process cleaning trial. Since these laboratory evaluations can be time consuming, preliminary screening is best left to suppliers of cleaning agents who have experience in doing these studies.

As discussed earlier, the parameters time, action, concentration and temperature are interrelated to a certain extent. One could, for example, increase the cleaning agent concentration and reduce the cleaning time to get the same level of cleaning performance. However, of the various parameters and factors discussed above, some are easily controllable, while others are not. An evaluation of the process could be done and a suitable cleaning program could be designed based on the considerations discussed below.

Constraints on Parameters

For some of the parameters or factors there could be constraints on the maximum level achievable in the process. This may include a time constraint for completing the cleaning process, a temperature constraint, or a constraint on worst case impingement or action when dealing with existing processes. It is important to consider the worst case conditions in the process system. For example, if a mixing vessel is cleaned by flooding it with the cleaning solution and using a simple agitator for mixing (agitated immersion process), the level of mixing obtained at the dome could represent the worst case. In certain cases, a constraint may exist on a combination of parameters. An example is substrate compatibility. Isocorrosion curves are available for glass lined vessels where the combination of alkali concentration and temperature would determine whether the cleaning agent is substrate compatible or not.

There would also be constraints on the minimum level required for parameters, related to cleaning effectiveness. As an example, for certain types of soils, a static soak, representing the lowest level of action, would not clean a residue no matter what the other parameters may be. The minimum level of any parameter required for cleaning could be determined from laboratory cleaning evaluations or prior experience. Despite these upper and lower constraints, there is usually a wide range available for selecting the level of these parameters, and consequently multiple combinations of parameter values that would give the same cleaning performance.

Consistency of Parameters

For obtaining consistent cleaning, it is important to maintain consistency in the parameters and factors that affect the cleaning process. Certain parameters can be more easily controlled and monitored than others. This will also depend on the cleaning process used. As an example, let us compare the cleaning of a tank with a manual scrubbing process versus a static soak. Only the wash cycle with respect to the four parameters time, action, concentration and temperature are considered for simplicity. The table below shows the constraints imposed by the process on the various parameters.

	Cleaning Time	Action	Concentration	Temperature
Manual Scrubbing	Since the entire surface cannot be scrubbed together, time per surface area is limited	Very high but inconsistent	Limited by worker safety	Limited by safety and heat loss
Static Soak (immersion)	The entire tank can be soaked and so the total time is available	Very low but consistent	Somewhat limited by substrate compatibility	Could be limited by heat loss only

It may be possible to clean the tank using either a manual scrubbing process or a static soak process. By appropriate selection of the parameters, both of these processes could give the same average level of cleaning performance. It is clear from the above table, however, that a manual scrubbing process would have to rely almost entirely on action/impingement while operating at reduced levels of the other parameters. The static immersion cleaning is not a very efficient process due to the very low action or impingement levels possible. However, the very low levels of action can be for by higher levels of other parameters, such as concentration or cleaning time. The key issue here, however, is that in the case of manual cleaning, the action may not be easily reproducible. The process relies almost entirely on a parameter that cannot be consistently monitored or maintained in the system. On the other hand, in the case of the static soak, the action is low, but consistent. To compensate for the low action, we could use higher levels of other parameters such as concentration or cleaning time, both of which can be easily monitored and controlled. This process could therefore be more easily reproducible as it relies on parameters that are reproducible. Can the manual process then be validated? Yes, but not by getting consistency in the performance measured by residue levels, but rather by using a procedure that is an Aoverkill@. The resultant residue levels after cleaning would then not be at a consistent level from one cleaning to another, but could consistently be below the acceptance criterion.

Whatever the application method that is used for cleaning may be, it will involve a certain level of compromise on parameters. It is important to understand the parameters that are critical to the cleaning process and mechanisms, and to select those parameters at levels that are consistently achievable.

Cost of Parameters

Each of the parameters selected, such as time, action, concentration and temperature would also have an associated cost. Some of these parameters may have a greater component of fixed cost associated with them, while others may be operating or variable costs. For example, investing in fixed cost of providing better impingement could reduce operating costs such as cleaning agent concentration. Cleaning time would have both a direct and indirect (or opportunity) cost, and is generally the most expensive parameter. In plants that operate at high capacity utilization levels, the cost of time would typically dwarf the cost of all other parameters combined.

Conclusion

Selection of appropriate cleaning agents and parameters can be achieved by a combination of laboratory cleaning evaluations and a good detailed evaluation of the manufacturing process with respect to the various parameters and factors that influence cleaning performance. An appropriate selection process could simplify validation efforts and optimize the cleaning process.

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