Aqueous Cleaning and Solvent Substitution

in Chemical Synthesis API Manufacturing

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Solvent substitution and the use of aqueous cleaning for API manufacturing processes has been driven by several factors such as the relatively high cost of solvent acquisition, storage, and disposal; increasing regulatory pressures; the inefficiency and often ineffectiveness of the solvent-based processes; and overall economics. Efficient and successful conversion from solvent-based to aqueous-based cleaning is feasible with appropriate investment in equipment modifications and attention to the details of cleaning process design and validation.

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Most active pharmaceutical ingredients (APIs) are manufactured by chemical synthesis, in which fine chemicals and intermediates undergo significant chemical change through a series of multistep processes. These synthesis processes typically include the use of organic solvents and therefore traditionally require organic solvents for process cleaning. A growing trend exists in the industry to move away from solvent-based cleaning to aqueous cleaning whenever possible. The push toward using aqueous cleaning processes has been driven by various safety, regulatory, and economic factors. Successful conversion from solvent-based cleaning to aqueous cleaning requires having a comprehensive understanding of and addressing various issues related to cleaning chemistry, engineering, analytical methods, validation, and the overall economics of the process.

The recent release of the ICH Q7A GMP Guidance for APIs has generated significant interest and discussion worldwide about the validation of API manufacturing processes. However, limited published information is available about the design of an efficient and validatable cleaning process for API manufacturing (1). This article describes current cleaning practices, the issues to be considered, and the author's experience with switching from solvent cleaning to aqueous cleaning for API manufacturing.

Traditional solvent-based cleaning

Synthetic API manufacturing involves many pieces of equipment for reaction and separation processes. Typically these include reactors, condensers, crystallizers, centrifuges, distillation or extraction columns, filters, dryers, and associated pipes. The nature, level, and tenacity of the residues encountered in the process equipment may vary widely even within the same production train. Cleaning reactors, where aggressive and prolonged processing conditions are encountered, may pose a different challenge from the cleaning of separation equipment such as centrifuges or dryers, where slurries or solids may be caked onto the surface. A variety of materials such as glass, PTFE, Hastelloy, stainless steel, and polymers are used in the construction of process equipment. A good cleaning process will take all these variables into account to ensure that all product-contact surfaces are safely and effectively cleaned.

The traditional approach to cleaning has been to use an organic solvent, very often the same process solvent used in the

synthesis of the API. This approach focuses mainly on the solubility of the active ingredient and often ignores the varying effects of the solvent on different types of surfaces, the chemistries involved, and the processing conditions mentioned previously. The most widely used cleaning solvent in the industry is methanol. Other commonly used solvents include acetone, dimethyl formamide, and ethyl acetate. The cleaning process often starts upstream with the introduction of the cleaning solvent into the reactor. Reactor capacity can range from ~50 to 500 gal for a pilot plant to as high as 3000 gal or more for large-scale manufacturing processes. Solvent-based cleaning typically involves agitating a solvent in the reactor vessel, circulating it through pipes, and refluxing the heated solvent through an overhead riser and condenser system. The refluxing process causes the solvent vapors to condense on overhead vapor lines and condensers, thus allowing for wetting of the surfaces and possible residue removal by dissolution in the solvent. Although this type of cleaning is similar to the processing step in a reactor and therefore has advantages, it is often a very slow and gradual process because of the limited level of "action" or mechanical force on the various overhead equipment surfaces. For this reason, it is not uncommon for as many as 5 to 10 solvent boil-outs to be required to clean some tenacious residues.

Table I: Evaluation of detergent chemistry.

	Drug active A1	Drug active A2	Drug active A3
Molecular weight	404	384	287
Process solvent	Ethyl acetate	Isopropyl alcohol	Ethyl alchohol
Cleaning solvent	Methanol	Methanol	Methanol
Solubility in 2.5% D1 at RT	0.06%	0.02%	0.1%
Solubility in 2.5% D2 at RT	0.0%	0.02%	0.4%
Solubility in 2.5% D3 at RT	0.01%	0.02%	0.4%

RT = room temperature

Some of the key advantages and disadvantages of using solvents for API manufacturing processes are described below.

Advantages of organic solvent cleaning

- The API is usually soluble in the organic solvent. Solubility data are often readily available.
- The solvent can be readily available and routinely used in the manufacturing process.
- Solvent residue analysis is simple and may be unnecessary if the cleaning solvent is the same as the process solvent in the next batch.
- Coverage of overhead surfaces is possible by solvent vapor refluxing. This allows difficult-to-reach areas to be cleaned without the use of spray devices or the need for equipment modification.

Disadvantages of organic solvent cleaning

- Residues other than the active ingredient such as degradants that are not soluble in the cleaning solvent may be present on the surface.
- The solubility of a solvent does not necessarily indicate the rate of solubility. Vapor refluxing is a time-consuming process. The action or force acting on the surface during this process is very limited. The residue also has the potential to redeposit in overhead pipes and on surfaces as the solvent evaporates.
- Solvents are flammable and may require special consideration for equipment design, storage, handling, and transportation.
- Environmental issues associated with solvent-based cleaning processes can be significant. Solvents such as methanol are hazardous air pollutants that require the user to comply with specific regulations (2). Applicable regulations in the United States include 40 *CFR* Parts 9, 63 NESHAP, and the pharmaceutical MACT standards. Water effluent limit guidelines are covered under 40 *CFR* Parts 136 and 439.
- The discharge of large amounts of cleaning solvents may be an issue with corporate and community image. In addition, spent organic solvents most often are either recovered or incinerated, thus adding to the overall cost of manufacturing. For this reason, several pharmaceutical corporations have set goals for solvent reduction.
- Not all surfaces in an API process train can be easily cleaned without manual intervention. Organic solvents can be toxic by inhalation, so special safety procedures and protection may be required.

Aqueous-based cleaning

Aqueous-based cleaning processes are the norm in finished pharmaceutical and biotech industries. Two broad categories of aqueous cleaning agents are used in these industries: commodity cleaning agents such as sodium hydroxide or phosphoric acid that are single-component cleaners; and formulated cleaning agents, which are multicomponent cleaners that take advantage of several cleaning mechanisms (3).

Although commodity cleaning agents have widespread use in the biopharmaceutical industry because of their simplicity and ready availability, they have limited soil-suspending and cleaning ability for the tenacious residues typically encountered in the API industry. Formulated detergents take advantage of the synergy of various components in the formulation. Like commodity alkalis, but unlike organic solvents, a formulated alkaline cleaner can include alkalis to enhance solubility and help in the hydrolysis of the residue. Formulated cleaners also can contain surfactants that provide better wetting, surface action, and emulsification, chelating agents that break down complex metals such as calcium and iron, and dispersants that prevent particles from reaggregation.

However, vapor refluxing usually is not an option with aqueous cleaning agents as it is with organic solvents. This is because of the nonvolatile nature of the active ingredients in most aqueous cleaning agents. If aqueous cleaning agents were refluxed, then only the water would vaporize and the cleaning effectiveness in the reactor dome, vapor lines, and condensers would be minimal. Aqueous cleaning therefore requires direct liquid spray or recirculating flow coverage across all surfaces.

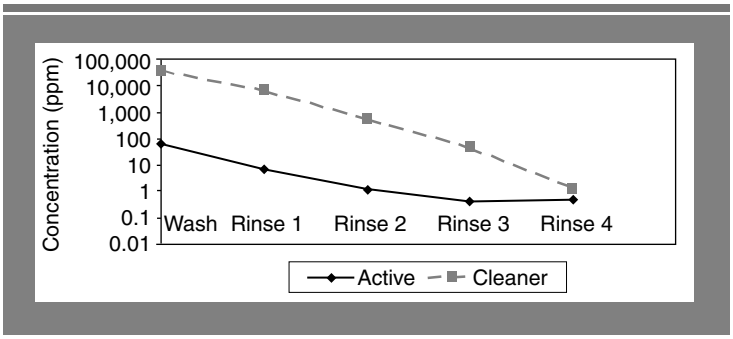

Figure 1: Concentration of active and cleaning agent.

The advantages and disadvantages of using a formulated detergent system for API manufacturing processes are described below.

Advantages of aqueous-formulated detergent cleaning

- Aqueous formulations are not flammable, a condition that reduces storage, transportation, and handling costs.
- Aqueous systems can incorporate multiple cleaning mechanisms, thereby providing more broad-spectrum cleaning effectiveness.
- Aqueous systems do not pose air-emission or environmental image risks as organic solvents do.
- The formulations can be sprayed safely at higher temperatures, thereby allowing for higher levels of two key cleaning parameters: mechanical action and temperature.
- Aqueous systems often are more cost effective for the overall process.

Disadvantages of aqueous-formulated detergent cleaning

- Because liquid coverage across surfaces is essential for cleaning, it may be necessary to install spray devices in vessels and modify associated equipment.
- Cleaning agents often are proprietary formulations and only available from a limited number of suppliers.
- Residue limits for the detergent must be set, and validated analytical methods are required for detergent residue analysis.
- Selecting appropriate cleaning agents may require laboratory cleaning studies or vendor recommendation.

Numerous API manufacturers have weighed these advantages and disadvantages and have adopted aqueous detergent cleaning processes where possible for API manufacturing. However, the process of successfully converting from solvent cleaning to aqueous cleaning is not a simple one. It requires an understanding of the chemistry, equipment, engineering, validation, and cost issues associated with solvent substitution and a process to systematically address these issues.

Issues to be considered in solvent substitution

Selecting the right chemistry. The solubility of an API in an organic solvent is a function of the polarity of the solvent. In the case of aqueous cleaning, solubility is a strong function of the pH of the cleaning solution. Certain functional groups are more soluble in an alkaline cleaning solution and others are more soluble in an acidic cleaning solution. For example, amino acids, diols, triols, organic acids, polysaccharides, saturated oils, and waxes generally are cleaned better with an alkaline cleaner. Aldehydes, alkaloids, amines, bicarbonates, carbonates, ethers, insoluble hydroxides, ketones, metal oxides, pyridines, and pyrrolidines are more likely to be cleaned with an acidic cleaner. However, selecting cleaning agents on the basis of solubility alone may be inappropriate, because other mechanisms may be involved in the cleaning process. Table I lists solubility data of APIs in detergent systems. These detergent chemistries were evaluated in the laboratory and then the cleaning processes were successfully implemented in the field process equipment. For confidentiality reasons. the exact drug active and cleaning chemistries are not disclosed. Three detergents were used: a potassium hydroxide–based detergent D1; a glycolic acid–based detergent D2; and a phosphoric acid–based detergent D3.

Cleaning studies using stainless steel coupons were performed. Approximately 10 g of each active was coated onto an area ~100 cm^2, allowed to dry overnight, and subjected to agitated immersion cleaning. These studies showed that drug actives A1 and A3 could be cleaned from surfaces using a 2% solution of detergents D1 and D2, respectively, at 60 °C for 45 min under agitated immersion conditions.

In the case of drug active A2, cleaning studies showed that it could not be cleaned off coupons by any detergent (D1, D2, or D3) alone. However, detergent D3 in combination with another detergent additive was able to clean active A2 at 60 °C with 90 min of agitated immersion. This demonstrates that the solubility of an API in a cleaning agent may be misleading and may not be a good measure of the cleaning agent's ability to effectively clean that residue from surfaces. Although the solubility of these APIs in the detergents was very low, they were subsequently cleaned successfully from process vessels with the use of aqueous detergent chemistries. These chemistries provided cleaning mechanisms other than solubility, including solubilization, emulsification, wetting, and dispersion.

Selecting the right chemistry and cleaning parameters is very important for the success of a solvent substitution process. Cleaning studies can be conducted in the laboratory by coating the API residue on surfaces, drying or baking them to simulate actual process conditions, and then screening various detergents to determine the right combination of chemistry and cleaning parameters. These parameters include the cleaning time, agitation levels, the cleaning agent concentration, and the application temperature. These cleaning studies should account for worst-case conditions that may be encountered in the process equipment. Among the issues to consider are the soil residue condition (dried, baked, caked), the nature of the surface, surface finish, ratio of the soil to surface area, soil redeposition, and foaming (3).

Equipment design issues. The API industry uses a variety of substrates for manufacturing vessels. The most common of these are 304 or 316 stainless steel, glass-lined, PTFE-lined and Hastelloy substrates. Evaluating the compatibility of cleaning agents with these substrates is important to ensure product integrity and equipment protection.

For example, in the case of glass-lined reactors, the concentration and temperature of alkaline cleaning solutions should be limited because of the possibility of etching glass surfaces by

Table II: API and cleaning agent concentrations.

Cleaning step	API concentration ppm	Cleaning agent concentration
Wash loop A	40.8	4% by vol.
Wash loop B	57.9	4% by vol.
Wash loop C	59.7	4% by vol.
Rinse 1	7.1	6300 ppm
Rinse 2	1.1	54 ppm
Rinse 3	0.4	47 ppm
Rinse 4	0.5	1.3 ppm

overuse of alkaline solutions. Data and technical support from cleaning agent and equipment vendors can be used to determine the iso-corrosion curves for cleaning agents on glass-lined equipment. Also, after using the alkaline cleaning agent, the glass surfaces should be thoroughly rinsed with water, ensuring complete coverage across all surfaces, to avoid localized etching of the glass when the reactors are heated. If data are not available, laboratory substrate compatibility studies should be conducted under typical exposure parameters and conditions.

Cleaning process pipes can be a major challenge in API manufacturing processes. One of the commonly encountered causes of cleaning problems in process pipes is the inadequate flow rate of the cleaning solution. It is recommended that the flow rate of cleaning solutions through pipes have an average velocity $\geq$5 ft (1.5 m)/s. This is a commonly accepted design practice for clean-in-place (CIP) systems in the pharmaceutical and biotech industries. In an API manufacturing plant, it is not uncommon to find larger-diameter pipes in which this high velocity is not feasible. In those situations, a close examination of the pipe layout is necessary to assess the flow coverage, the potential for gas and particle entrapment, and the level of flow turbulence (4). In large-diameter pipes such as overhead risers that lead to condensers, it may be necessary to install spray devices to ensure adequate coverage.

The proper design of process piping is essential for good cleaning performance. When piping systems are not appropriately designed for cleaning, it is important to identify the worst areas and then either modify the piping or develop an appropriate cleaning procedure. Dead legs should be minimized to have a length-to-diameter (L/D) ratio $\leq$1.5. In existing systems where this ratio is exceeded, the flow and coverage in those areas must be examined and the cleaning ability validated. This may involve one or more corrective measures such as increasing the flow rate, reversing the flow direction if appropriate, changing the orientation of the dead leg, reducing the dead leg by pipe modification, diverting the cleaning solution through the dead leg as another loop, or dismantling and manually cleaning those areas.

Ball valves, which are used extensively in API manufacturing, can be difficult to clean. These valves may have to be manually cleaned if adequate CIP methods cannot be demonstrated and validated.

Cleaning strategies. In some processes, eliminating cleaning solvent may involve significant equipment modifications and the installation of several spray devices to provide complete coverage. If this is not feasible, an alternate approach could be to reduce, rather than eliminate, the use of organic solvents. This strategy would involve aqueous cleaning by agitated immersion for the removal of most of the residues from process equipment, followed by a solvent-vapor reflux step to reach some of the overhead areas that the aqueous cleaner cannot cover.

A follow-up solvent flush can be used for API residue-sampling purposes after aqueous cleaning, even in situations in which good aqueous cleaning coverage is established. Another reason for using a solvent after aqueous cleaning is to remove the residual rinse water from the system. The solvent used in this final cleaning step is usually a polar solvent with good water miscibility that often is also the process solvent used in the subsequent batch.

Sometimes a solvent is used to remove or recover the gross product residue from the processing equipment before the use of an aqueous detergent. When this is done, the process solvent of the batch that was just produced is used.

Cleaning validation. General guidelines for cleaning validation are discussed in section 12.7 of the ICH Q7A GMP Guidance for APIs. Industry practice and sample calculations for establishing acceptance criteria of actives in API manufacturing have been discussed in the literature (5). Acceptance criteria for a cleaning detergent should be established using a similar approach on the basis of its toxicity and effects on any subsequently manufactured API, as well as how those APIs are used in finished drug products. When detergent cleaning is performed, whether it is between batches of the same API or different APIs, cleaning validation for detergent removal also must be performed.

Total organic carbon (TOC) analysis is commonly used as an analytical method for detergent residues in the finished pharmaceutical and biotech industries. However, as a nonspecific method, it is not very commonly used in the API industry because of potential interference from background organic carbon coming from the organic solvents used for manufacturing and cleaning. In addition, the water used for cleaning in an API facility may not always be low-TOC water.

Other analytical methods that are used for detergent residues may include ion chromatography, atomic absorption, conductivity, titration, high-performance liquid chromatography (HPLC), and UV spectrophotometry. HPLC is a commonly used method for the analysis of drug actives and for that reason is often a method of choice for cleaning agent residues as well.

Case study

A multinational pharmaceutical API manufacturing company was using large quantities of methanol to clean drug actives from its manufacturing process trains. The original cleaning procedure used as many as 9 to 11 methanol batch refluxes to meet the acceptance criteria of some water-insoluble APIs in a particular process train.

The company decided to evaluate aqueous cleaning procedures to reduce the excessive solvent use. Initially, the company's objectives were to have the same cleaning procedure for all the actives manufactured in the process train and to achieve methanol reduction without the need for equipment modification. Laboratory cleaning studies were conducted using aqueous clean-

Table III: R_{act} and R_{ca} values for each rinse.

Cleaning step	R_{act}	R_{ca}
Rinse 1	~ 8	8.0
Rinse 2	6.4	11.4
Rinse 3	2.75	11.7
Rinse 4	0.8	39

ing chemistries (6). On the basis of the results of these studies, the company converted and validated its cleaning process to use a combination of aqueous cleaning followed by methanol cleaning. A process wash with an alkaline detergent (D1) at a concentration of 2% followed by an acidic detergent (D2) at a concentration of 2%, both at 70 °C, was demonstrated to significantly reduce the residue levels by an agitated immersion process.

The two aqueous cleaning agents (D1 followed by D2) were not required for all residues but were used so that a single cleaning process could be used for product residues that required either an alkaline or an acidic approach. This general procedure helped with matrixing or grouping strategies and with standardized cleaning procedures.

Because this aqueous agitated immersion process did not provide complete coverage across all surfaces (particularly the overhead risers and condensers) and consequently did not achieve complete residue removal, two methanol flushes were required after the aqueous cleaning steps were completed. Nevertheless, this new process was implemented and validated because it significantly reduced the amount of cleaning solvent used and provided a standardized cleaning procedure.

A few years later, driven by the Clean Air Act regulations and increased pressure to improve capacity utilization, the company decided to conduct a cleaning trial in the manufacturing facility to evaluate the possibility of a further reduction in cleaning time and a further reduction or elimination of methanol.

Cleaning trial. For the field trial, a section of the process train was used that consisted of a 1000-gal glass-lined reactor, an overhead riser leading to a condenser, a filtration system at the discharge of the reactor, and a process pump and associated lines.

Laboratory evaluations showed that the drug active that was used for the trial had a water solubility of only 0.025% at room temperature. Laboratory evaluations showed that cleaning could be carried out at lower temperatures if higher concentrations of the detergent were used. It was determined that using ambient temperature saved time. Not heating the cleaning solution would more than offset the additional cost of the increased cleaning agent concentration that would be required.

The cleaning trial was conducted using a 4% solution of detergent D1 at ambient temperature for 30 min, based on supporting laboratory cleaning data. A CIP engineering company designed a manway cover, spray nozzles, and a dual spray ball manifold assembly. The 6-in. riser and 2-in. condensate return lines were cleaned by recirculating the cleaning solution. The highest point in the riser near the condenser had a nozzle. This was used to bleed off any air that was trapped in the large (6-in.) pipe to allow complete liquid coverage in the large-diameter pipe. The bleeding of the cleaning solution was done by inserting a flexible tube into the reactor.

The process was segregated into three loops to ensure coverage of all the surfaces. Loop A consisted of the glass-lined reactor, pump, filter units, and pipes. Loop B consisted of the reactor, pump, vent line, and vent return line. Loop C consisted of the reactor, pump, riser, condenser, and the associated pipes. The centrifugal pump at the discharge of the reactor had a 15-hp motor with 3600 rpm, and delivered ~75 gal/min of flow. The pressure at the pump discharge was in the range of 35–40 psig, depending on the loop.

The aqueous cleaning process consisted of the following steps:

- Each of the three loops was prerinsed once to drain with deionized (DI) water for ~5 min.
- The reactor was filled with ~400 gal of 4%-by-volume cleaning agent in DI water. The solution was recirculated through each of the three loops (A, B, and C, in that sequence) for ~34 to 41 min and finally discharged to drain.
- Four hundred gallons of deionized water was recirculated through the three loops in sequence and then discharged. The recirculation time for each of the three loops was ~6 to 8 min. The process was repeated four times.

Samples were drawn during the wash and water-rinse steps. They were analyzed for active ingredient using UV spectrophotometer analysis and for the cleaning agent by conductivity.

Observations and results. The concentrations of the API and the cleaning agent are tabulated in Table II and illustrated in Figure 1.

After the first rinse, the drop in the cleaning agent concentration between Rinse 1 and Rinse 2 was not as high as expected from the author's prior experience. The rinsing performance can be understood by taking a close look at the numbers. For any rinse, the ratio of actives (R_{act}) is defined as the concentration of drug active in the preceding rinse (or wash) divided by the concentration of active in the present rinse. In a similar manner, the ratio of cleaning agents (R_{ca}) is defined to be equal to the concentration of cleaning agent in the preceding rinse (or wash) divided by the concentration of cleaning agent in the present rinse. The values of R_{act} and R_{ca}, calculated from the data in Table II, are tabulated in Table III for each rinse. For Rinse 1, R_{act} has been estimated from the volume-weighted average of actives in the wash solution for the three loops (A, B, and C).

The wash step and each of the subsequent four water rinses in this trial used the same amount of water (400 gal). Also, earlier studies using the cleaning agent D1 showed that it was very water soluble and very freely rinsable. The implication of this easy rinsibility is that we should expect almost all of the cleaning agent to be present in the rinse water and very little to be adhered to the equipment surfaces after the first rinse.

If we assume that almost the entire amount of cleaning agent residue was in the rinse water, then we could conclude that there was liquid held up in the system approximately equal to the rinse volume (400 gal) divided by R_{ca} Therefore, for Rinse 2, for example, that value is 400 divided by 11.4, or 35 gal. This means that ~35 gal of the rinse water was not drained out of the system at the end of Rinse 1.

Because a holdup of ~35 gal of rinse water was much larger than would be expected for this system, the lines were opened after Rinse 3 to investigate the cause of the low value of R_{ca}. A significant quantity of rinse water was discovered and drained from the flexible hose that connected the two filter housings. The quantity of drained water could not be measured but was estimated

to be ~20 to 25 gallons. After the draining, Rinse 4 was done. As Table III shows, the R_{ca} values increased significantly, to 39. This implies that the holdup volume in the entire system after appropriate draining was now only ~10.3 gal (400 divided by 39).

R_{ca} can be viewed as a rinsibility factor. Clearly, higher R_{ca} values for the rinses are desired. For Rinse 1, the R_{ca} value was low because the cleaning agent that was drained during the wash cycle was not yet rinsed off the surface. The R_{ca} values for subsequent rinses depend on how freely rinsable the cleaning agent is and on the configuration of the process equipment and resultant holdup volume after rinsing and draining. This shows the significance of the need to design process vessels and pipes that are easily drainable. Drainability plays a significant role in preventing cross-contamination and is important for improving cleaning process efficiency and conserving rinse water.

The rinsibility factor is related to the slope of the curve in Figure 1, where the *y* axis is on a logarithmic scale. A process with good liquid coverage using a freely rinsable component such as the cleaning agent in this case will exhibit a straight line. A steeper slope implies more drainable process equipment, a higher R_{ca} value, and consequently a lower rinse-water volume requirement.

By accounting for the drainage of the wash solution and applying an R_{ca} value of 39 for the subsequent rinses (rinse water drained off without holdup, as in Rinse 4), one can calculate that the cleaning agent concentration in the third rinse would have been less than 1 ppm. In other words, if the problem of the holdup in the flexible hose had been detected and proper drainage restored early, the fourth rinse could have been eliminated.

A closer look at Table II also shows that the R_{act} values are approximately equal to R_{ca} values for Rinse 1. This suggests that most of the active ingredient and cleaning agent left behind in the system after the wash step was in the draining solution. However, as the rinsing process continued and as the concentration of the actives dropped, the R_{act} values dropped significantly while the R_{ca} values remained high. This suggests that the contribution of soil coming off system surfaces during the rinsing process became more significant. In other words, either the soil was not as freely rinsed off the surface as the cleaning agent was, or there was a location where adequate cleaning was not achieved. This is also confirmed by the fact that for Rinse 4, R_{act} was <1 (because Rinse 4 had higher levels of active than Rinse 3).

To investigate this, the filter housing, which was the suspected cause, was opened and examined. Some visible bulk active residue, which was caused by inadequate coverage as a result of air entrapped in the system, was discovered. The area was manually cleaned and appropriate measures were suggested to bleed off the air and allow for good coverage in that area for future cleaning.

The other areas of the process were closely examined at numerous locations, including the dome of the reactor and pipe nozzles. All the areas were visually clean.

After the aqueous cleaning, a methanol reflux and flush was conducted using 500 gal of methanol through the three loops. The rinse solvent was analyzed for actives, and the amount of active in the 500 gal of methanol was 6 ppm. The acceptance criterion was 10 ppm for this active.

Further improvements in the aqueous cleaning procedure were made following the trial, and the new aqueous-based cleaning process was adopted at the manufacturing plant.

Conclusion

The case history previously described demonstrates the feasibility of achieving a reduction or elimination of cleaning solvent use. It highlights some of the issues related to solvent substitution and shows that close monitoring of the wash and rinse solutions during a cleaning trial and appropriate analysis of the data can provide invaluable information to troubleshoot and improve the cleaning process.

Solvent substitution and the use of aqueous cleaning for API manufacturing processes has been driven by a number of factors such as the relatively high cost of solvent acquisition, storage, and disposal, the increasing regulatory pressures from the Environmental Protection Agency and the Occupational Safety and Health Administration, the inefficiency and often ineffectiveness of the solvent-based processes, and overall economics. Efficient and successful conversion from solvent-based to aqueous-based cleaning is feasible with appropriate investment in equipment modifications and attention to the details of cleaning process design and validation.

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