Impact of API Physicochemical Properties on Cleaning Method Design and Cleaning Validation

William R. Porter

ABSTRACT
Physicochemical properties of active pharmaceutical ingredients (APIs) and excipients used in the manufacture of pharmaceutical dosage forms play a critical role in the successful design of robust and validated cleaning processes. The development and validation of these methods requires an understanding of the solubility properties and resistance to degradation of formulation components, including both API and excipients. Knowledge and understanding of physicochemical characteristics is critical to cleaning agent selection, cleaning procedure design, worst-case compound identification, and analytical method selection and development. Much of the information needed concerning solubility (i.e., hydrophilicity/lipophilicity, ionizability, surface activity, and temperature effects) and degradation (i.e., hydrolysis, oxidation, photochemical reactivity) is routinely obtained during preformulation studies on new API candidates, or can be efficiently obtained at that time. Points to consider and questions to ask relating to physicochemical property identification that are relevant to cleaning are reviewed.

INTRODUCTION
Development and validation of cleaning processes for equipment used in the manufacture of pharmaceutical dosage forms is critical to the assurance of efficacy, safety, and quality of the final product. The purpose of a cleaning method is to minimize cross-contamination from previously manufactured product when the subsequent product is to be manufactured on cleaned equipment. Cleaning validation serves to demonstrate that the cleaning method can achieve this goal.

Prevention of cross contamination between different product lots manufactured on shared equipment is accomplished by using a validated cleaning procedure (the method). The cleaning method should be developed according to scientific and technical principles, be validated in designated conformance trials, be well controlled in performance, and be monitored and maintained throughout the product lifecycle. The cleaning method is validated by demonstrating that remaining residue on the equipment surfaces is below a calculated acceptable residue level that provides clean equipment that can be safely used for subsequent manufacturing.

Critical to the development of a reliable and robust cleaning procedure is consideration of appropriate scientific and technical knowledge of the properties of the product residue to be cleaned. Fundamental knowledge of the physicochemical properties of the active pharmaceutical ingredient (API) and other formulation components is essential in this regard. Understanding the solubility and stability properties of the residue to be cleaned are vital areas of study. Without knowledge of solubility and stability characteristics of the active drug and...

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inactive residue to be cleaned, the following cannot be determined:

- A rational selection of cleaning agent cannot be made
- A rational cleaning procedure cannot be developed
- Determination of the worst-case compound in a cleaning matrix cannot be made
- A rational analytical testing of residues cannot be accomplished.

The above are fundamental to the development of cleaning methods and the conduct of cleaning validation. Solubility and stability properties are fundamental areas of interest in pharmaceutical R&D, but may not be generally known to cleaning method developers. However, in most pharmaceutical product development programs, much of the physicochemical property information needed to assist developers of cleaning methods will have been obtained as part of preformulation studies typically performed early in the development process. Those charged with developing cleaning methods may have to ferret out this information if knowledge management procedures are not in place in their organization to assure availability of information. Cleaning method development specialists, as customers for preformulation information, may need to make their special needs known to those who actually conduct physicochemical property elucidation studies to ensure that the physicochemical data needed to support cleaning method development is acquired in a timely and economical manner. Submitting a special request for studies to be conducted just to support cleaning method development is not cost-effective and may delay development. It is essential that the cleaning method stakeholders understand what they need and expect from preformulation colleagues and makes those needs known well in advance of the time the information is actually wanted. This review addresses specific applications of fundamental principles of solubility and stability as well as how this information applies to cleaning method development and cleaning validation.

**SOLUBILITY**

The solubility properties of an API are part of the fundamental physicochemical properties determined in preformulation studies. Knowledge of these properties is useful in the development of cleaning methods and in the approach to cleaning at the commercial manufacturing site. At some point in the process of cleaning a surface, at least some of the undesirable residue must be dissolved, emulsified, or suspended to some extent by the cleaning agent, which in most cases is water fortified with additives to enhance the solubilization process. Alternatively, alcohol may be required as a cleaning agent in some cases based on favorable solubility of the API in alcohol. The following is a review of the basic physicochemical concepts that influence solubility. Several publications provide more detailed coverage of this topic (1, 2).

The following topics related to solubility are briefly discussed:

- Hydrophilicity/hydrophobicity (or lipophobicity/lipophilicity)
- Ionization and the effect of pH
- Effect of temperature
- Surface activity
- Liquid and semisolid product vehicle polarity
- Impact of solubility on cleaning procedures and cleaning validation.

**Hydrophilicity/Hydrophobicity (or lipophobicity/lipophilicity)**

Like dissolves like. Water has a high dielectric constant (i.e., a measure of its polarity, or ability to become oriented in space by application of an external electric field). Substances that also exhibit high polarity, such as table salt (an ionic substance) or sucrose (an electrically neutral substance containing many polar hydroxyl substituents) intermix well with water molecules—they are hydrophilic (“water-loving”) molecules. These molecules form solutions in which molecules of the polar substance are dispersed in a sea of water molecules stabilized by dipole-dipole, dipole-charge, or hydrogen bonding interactions. Substances that do not exhibit high polarity, such as animal fats (e.g., glycerol esters of long-chain fatty acids), do not mix well with water. They are hydrophobic (“water-hating”) molecules. There are only limited ways, other than van der Waals’ forces, in which molecules having low polarity can interact with water molecules. The introduction of a hydrophobic nonpolar molecule into liquid water actually forces the water molecules to become more ordered and less random in their orientation, because opportunities for water molecules to engage in stronger interactions, such as hydrogen bonding, are reduced in the direction of the nonpolar solute. Nonpolar (greasy) substances dissolve more readily in nonpolar (lipophilic—“fat-loving”) solvents. Conversely, polar substances have little affinity for nonpolar lipids (i.e., they are lipophobic—
“fat-hating”) and will tend to separate from fatty or nonpolar materials to form a new phase.

The determination of the relative hydrophilicity/lipophilicity of new drug substances is critical to the development of new drug products and methods for analyzing them, in addition to its impact on cleanability. Conventionally, the affinity for a new API for polar and nonpolar media is represented by its octanol-water partition coefficient (3,4). Octanol-water partition coefficients are such important predictors of the behavior of chemical substances in solution that their determination is often one of the first activities performed in characterizing the physiochemical properties of a new API candidate. Because partition coefficients vary by orders of magnitude, typically the base 10 logarithm of the partition coefficient is reported (logP) as a measure of lipophilicity. An increase in logP from +1 to +2 represents a 10-fold decrease in affinity for polar solvents (e.g., water) and a 10-fold increase in affinity for nonpolar solvents (e.g., octanol). Many effective small molecule APIs typically have logP values in the range 2–3, and are, therefore, moderately lipophilic and thus poorly soluble in water. In recent years, the trend has been for medicinal chemists to develop even more lipophilic new drug candidates (logP > 4), which can pose problems for designing effective cleaning procedures. Not only do these lipophilic APIs have poor water solubility themselves, but frequently require incorporation of equally lipophilic excipients into formulations to provide effective drug delivery, thus compounding the cleaning problem.

Ionization and the Effect of pH

The chemical structures of many APIs contain moieties that can dissociate when dissolved in water to form positively- and negatively-charged ions. Ions are far more polar than non-ionized substances and dissolve much more readily and to a greater extent in water than the non-ionized form of the drug substance from which they originated. Thus, solution pH plays an important role in the dissolution and solubilization of many drug substances (5). Typical pharmaceutical excipients, on the other hand, rarely contain moieties that can ionize to any appreciable extent in aqueous solution. However, some excipients, and many APIs, can undergo degradation reactions under conditions of extremely low or extremely high pH, leading to the formation of degradation products that may be ionizable, even though the parent substance from which they were derived is not. Substances that are weakly acidic in aqueous solution tend to be less soluble in acidic cleaning media because the acidity of the cleaning medium suppresses ionization of weak acids. Substances that are weakly basic in aqueous solutions tend to be less soluble in alkaline cleaning media because the alkalinity of the cleaning medium suppresses ionization of weak bases. The manipulation of cleaning solution pH is an easy tool for enhancing solubilization of troublesome residues. Lipophilic residues (e.g., from mixtures containing lubricants such as magnesium stearate) are often difficult to remove from surfaces. Many commonly encountered lipophilic substances are either weak acids or comprised of materials that can undergo degradation under conditions of extreme pH to form weak acids, so highly alkaline cleaning media tend to promote solubilization of such materials. For drugs that are weak bases, alkaline cleaning media can actually render them less soluble. If contamination of surfaces with a weakly basic API is problematic, an acidic cleaner may improve cleanability. Measurement of ionization properties of new APIs is one of the first physicochemical properties determined in preformulation studies; it and lipophilicity are so critical that in silico methods for predicting logP and ionizability are increasingly used very early in the drug discovery process (6).

Effect of Temperature

Temperature plays an important role in solubility and in the cleaning process. In most cases, solubility increases with an increase in temperature. In some cases, the increase is large; in others, the increase is minimal. For a few compounds, solubility actually decreases with an increase in temperature. These effects may be explained by the physical interactions of the molecule of interest with the solvent compared to physical interactions of the molecule with others of its own kind (i.e., in forming a crystalline solid). These properties must be known when developing a rational cleaning procedure, but may only be characterized in a limited fashion during preformulation studies. However, process chemists charged with developing efficient procedures for production of new APIs frequently conduct solubility studies as a function of temperature as part of their normal process optimization work, and should be consulted to learn more about the effects of temperature on solubility.
**Surface Active Molecules**

As we have seen, polar solvents (like water) and non-polar solvents (like octanol) won’t stay mixed for long, even after vigorous physical agitation. The surfaces of each phase tend to actively repel molecules of the other phase, leading to rapid phase separation when disruptive physical forces are removed. The molecules at the surface of adjoining phases interact preferentially with other molecules in the phase from whence they came rather than with their opposite numbers in the adjoining phase. If a substance is added to a physical mixture of a polar and a nonpolar liquid that can reduce this surface activity (a surface-active agent, or surfactant), then it is possible to form an emulsion—globules of one liquid phase within the other liquid phase that remain physically stable for long periods of time. Surfactants are amphiphiles: one portion (typically the larger portion) of the surfactant molecule is nonpolar, while the (smaller) remainder is polar. Surfactants promote wetting, emulsification, and dispersion of suspended solids to enable cleaning. Surfactants generally enhance the ability of aqueous cleaning media to solubilize, emulsify, or suspend less polar substances (7). Some APIs and formulation excipients are also surface-active and may interact to form insoluble residues if mixed with a surface-active cleaning agent of the wrong sort. For example, lipophilic APIs containing a weakly basic moiety capable of ionizing to form a cationic species could combine with an anionic surfactant (e.g., the commonly used sodium lauryl sulfate) to form a salt that may have poor water solubility, thus not only reducing the effectiveness of the cleaning agent but also producing a new hard-to-clean residue.

**Liquid and Semisolid Product Vehicle Polarity**

Pharmaceutical liquid and semisolid liquid products contain vehicles of widely varying polarity. In general, water is a polar vehicle with a high dielectric constant and is a good solvent for polar hydrophilic molecules. At the other extreme are non-polar, low dielectric constant vehicles such as mineral oil or petrolatum that might be used in topical ointment products. These molecules are good solvents for hydrophobic non-ionizable drugs. Between polar solvents such as water and non-polar solvents such as octanol are the semi-polar solvents. Ethanol is representative of this category of solvent, which also includes liquids such as propylene glycol and low molecular weight polyethylene glycols. These liquids have intermediate dielectric constants. Semi-polar liquids are miscible with polar solvents and with non-polar solvents. Semi-polar liquids are often used in product development to enable solution formulations. Semi-polar solvent like alcohol may be used in cleaning for highly insoluble APIs or other troublesome formulation components.

**STABILITY OR DEGRADATION**

Few substances can resist chemical transformation. The stability properties of an API are part of the fundamental physicochemical properties determined in preformulation studies. As development progresses into early formulation studies, additional stability or degradation studies are conducted on prototype formulations or mixtures of the API with selected excipients to study how formulation components alter the stability of the API; these are often called excipient compatibility studies. Fortunately, most API candidates must exhibit “reasonable” chemical and physical stability in order for them to be developed and marketed, so the real challenge to cleaning method developers is to understand whether special conditions to which the API and excipients may be exposed during cleaning operations are sufficiently adverse to cause significant degradation that may impact ease of cleaning.

Validation and compliance personnel must be aware of potential chemical and physical changes in the product residues to be cleaned. Chemical stability refers to residue stability in the presence of oxygen, light, heat, water, acid, base, metal ions, etc., any or all of which may impact pharmaceutical product residues remaining on manufacturing equipment. Physical stability refers to changes where the chemical molecular structure of a solid remains the same, but the physical form and physical properties of a solid may change. This is relevant to cleaning because properties that may change include solubility, hygroscopicity, chemical stability, and other properties. Solid phase transitions can affect cleanability if the result is conversion of a more water-soluble solid form to a less water-soluble form. Unlike chemical reactions, which can destroy an API and convert it to a degradation product that may not be detectable using an analytical method designed to quantify the API, physical changes usually just affect the ease or difficulty of removing the API from the surface. An understanding of how APIs and excipients may degrade or undergo physical form changes during cleaning is essential to the development of rugged and reliable cleaning processes (8–11). Furthermore, this understanding is essential to selec-
tion and development of the appropriate analytical method for use in cleaning validation testing. The techniques for elucidating the effect of cleaning systems on API stability in formulated products are not all that different from experimental methods used in preformulation studies of the degradation potential of the pure API. Indeed, similar experiments could be performed to compare alternate cleaning strategies.

The following topics related to stability are briefly discussed:
- Kinetics of chemical degradation
- Common degradation mechanisms
- Physical stability–phase transformations
- Applications of stability to cleaning procedures and cleaning validation.

**Kinetics of Chemical Degradation**

Chemical degradation reactions of pharmaceuticals and excipients follow the well-established principles of chemical kinetics (8–11). During the course of a chemical reaction, the concentrations of reactants and products change with time until the reaction either reaches completion or equilibrium. The concentrations of the reactants decrease over time, while those of the products increase. The rate of a reaction can be represented either by the decreasing change in the concentration of a reactant or the increasing change in the concentration a product with respect to time.

**Reaction mechanisms.** Reaction mechanisms are well known and explained in discussions of chemical kinetics. An overall reaction may contain a number of elementary reactions. A complete scheme of these elementary reactions represents the actual path of a reaction and is called the mechanism of the reaction. Among the elementary reactions comprising an overall reaction, one of these steps usually proceeds with the slowest rate. This slowest step is called the rate-determining step of a reaction and determines the rate of the overall reaction. Once the reaction mechanism is known, and the rate-determining step is identified, the expression of the overall rate of the reaction may also be readily derived. Reactions may be zero order, first order, second order, etc. depending on molecularity of the reaction. Degradation reactions of API residues with cleaning agents are bimolecular, but appear to be first order because the concentration of the API is limited and the cleaning agent is present in great excess. It is thus called a pseudo first order reaction with respect to the API present in limited amounts.

**Effect of temperature.** The rate of a reaction is affected by temperature. The Q10 rule, attributed to pioneering physical chemist Jacobus H. van’t Hoff, states that the velocity of a chemical reaction increases approximately two- to threefold for each 10 °C rise in temperature. His student, Svante Arrhenius (12), developed this into a more formal theory relating the rate of degradation to absolute temperature:

\[
\ln(k_{g,T}) = \ln(A_g) - \frac{E_a}{RT}
\]

Here \(k\) is the rate constant for reaction mechanism \(g\), \(A\) is a constant known as the Arrhenius frequency factor (the limiting rate as the absolute temperature \(T\) is increased to infinity) that is also characteristic for mechanism \(g\), \(E_a\) is the factor by which the reciprocal of the absolute temperature \(T\) must be multiplied to estimate the degradation rate and \(R\) is the universal gas constant of physical chemical theory. Knowledge of \(E_a\) is important because when degradation reactions are known to occur, they will be accelerated when high temperature cleaning is conducted. Although the design of cleaning methods requires the understanding of degradation reactions in solution, what happens to solid dosage forms prior to cleaning is also important. Advances in this field permit fairly rapid estimation of degradation in solids using accelerated conditions (13). Reactions with larger \(E_a\) values are more sensitive to changes in temperature. As quality-by-design (QbD) initiatives become better established, information on degradation pathways and their sensitivity to temperature effects are increasingly being studied earlier in the pharmaceutical development process. However, it may be the case that the design of cleaning methods might be the first instance in new product development where this information becomes critical to quality (CtQ). If so, consider incorporating studies of API degradation in prospective cleaning media into preformulation studies if these experiments are not already being performed. Minimally, the effect of solution pH on degradation rate should be studied.

**Common Degradation Mechanisms**

Both APIs and excipients can degrade when exposed to environmental stressors. During cleaning operations, pharmaceutical product residues are exposed to water (and possibly to extremes of pH), air, and light (14–18). Water promotes hydrolysis of labile functional groups in both APIs and in some excipients where such groups are present. Air can cause
Oxidation, which is facilitated by the high surface area of residues that contaminate equipment surfaces. Exposure to light can promote photolytic degradation, especially because residues are present as thin layers on contaminated equipment surfaces. Components of cleaning media added to control pH can catalyze hydrolysis reactions. Corrosion products generated either within the manufacturing process or during cleaning operations can also catalyze reactions, particularly oxidation reactions.

**Hydrolysis.** Hydrolysis is by far the most commonly encountered drug degradation mechanism both in solution and also in the solid state. Many drug molecules contain derivatives of functional groups such as carboxylic acids that are readily cleaved by water or hydroxyl solvents. Hydrolysis of such derivatives can occur both in solution and in the solid state in the presence of water. In particular, the presence of hydrogen or hydroxyl ions present at low or high pH catalyzes hydrolytic reactions. Because cleaning media typically are formulated at extremes of pH to facilitate removal of excipient residues, the degradation of APIs containing functional groups susceptible to hydrolysis should be anticipated.

**Oxidation.** Oxidation presents an important drug degradation pathway and is second only to hydrolysis. To some extent, the potential for oxidative degradation can be predicted theoretically (19). Although its significance to drug stability has been recognized, the study of oxidative stability has not been well developed until more recently, partially due to its complicated nature. Many pharmaceutical compounds contain amine functional groups. Amines are known to be prone to oxidation. Oxidation of amine-containing APIs by atmospheric oxygen can occur during hold times when residues are left on equipment prior to cleaning. Reactions with atmospheric oxygen are particularly likely to occur when equipment is first rinsed with plain water and then allowed to sit for some time before final cleaning with a formulated cleaning medium. Damp residues will absorb oxygen from the air and solvent-mediated oxidation reactions can then proceed while the equipment is waiting for final cleaning. Exposure of drug product residues containing APIs having amine moieties to oxidizing agents such as commercial bleach (sodium hypochlorite) or hydrogen peroxide frequently will result in partial or total destruction of the API. Oxidation is frequently introduced deliberately in cleaning processes as a final decontamination step to assure destruction of any remaining API. However, although many oxidation products are more water-soluble and easier to rinse away as a consequence, this is not always true. Specific analytical methods designed to measure API may show the “clean” surface to be free of API itself, while oxidation products produced in the decontamination process remain undetected.

**Photolysis.** According to the Grotthuss-Draper law, no photochemical reaction can occur unless light is absorbed (20, 21). The relevant radiation bands that are most likely to be problematic to pharmaceuticals are visible light (~ 400–800 nm) and ultraviolet (UV) light (~ 200–400 nm). Sunlight in the wavelength range of 200–280 nm (UV-C range) is effectively absorbed by molecular oxygen and ozone in the upper atmosphere and is, therefore, not considered to be important for photolytic degradation of drugs, although many organic substances do absorb strongly in this wavelength range. Borosilicate glass also effectively blocks exposure to UV-C light. Ordinary soda-lime window glass further blocks radiation in the 280–315 nm (UV-B) range. Photochemical degradation is typically studied using artificial lighting to mimic exposure to indoor sunlight in 315–400 nm (UV-A) range, and so exposure to higher energy UV radiation (200–315 nm) is often deliberately blocked (e.g., by use of a soda-lime glass filter). However, manufacturing facilities often are equipped with artificial light sources that may emit UV radiation in the UV-B region (e.g., high-pressure mercury arc lamps) or UV-C region (e.g., quartz tube germicidal lamps) that can induce photochemical degradation not detected in ordinary stress tests. All organic compounds containing aromatic rings (which include most APIs) absorb radiation in the UV-C range. If equipment surfaces contaminated with residues to be removed by cleaning were exposed to such radiation sources, unexpected degradation products could be produced.

**Physical Stability: Phase Transformations**

Physical stability refers to the ability of a solid phase to resist transformation under various conditions. Although in some cases tautomerism may be involved, this section encompasses phase transitions where the chemical molecular structure remains the same (22, 23) but the physical form changes (polymorphism). Many substances have two or more distinct solid forms (polymorphs). Elemental carbon, for example, is most stable at ordinary temperatures and atmospheric pres-
sure as graphite, but under conditions of high pressure, carbon can form another solid phase—diamond.

Various solid forms of a chemical entity may have different physicochemical properties. For example, while diamond is an excellent conductor of heat, it is an electrical insulator; graphite, on the other hand, conducts electricity readily. Some of these properties are relevant to pharmaceutical development, such as solubility or dissolution rate, hygroscopicity, melting point, chemical stability, etc. Extensive efforts are invested early on into the selection of an optimum solid form as an API for downstream development, typically as part of preformulation and chemical process development studies. The understanding of the physical stability of the selected API solid form is minimally necessary to realize the benefit of the selected solid form, to ensure control during the manufacturing processes, and ultimately to assure the quality of finished products containing the API.

Solid phase transitions can affect cleanability if the result is conversion of a more water-soluble solid form (e.g., a salt, amorphous form, unstable polymorph) to a less water-soluble form (e.g., thermodynamically most stable crystalline polymorph of non-ionized parent form of API, hydrated form of anhydrous API, etc.). Some changes can be induced by the cleaning agents used (e.g., precipitation of the free base of an API that is the salt of an amine drug by an alkaline cleaning agent, formation of an insoluble salt by exposure to an incompatible ionic surfactant, etc.). Such changes can sometimes make the API harder to remove from the surface.

As a result of exposure to the various forces (e.g., heat, pressure, dissolution, drying) during manufacturing processes, APIs and excipients may be converted to solid forms that differ in rate and extent of solubilization in cleaning media. The common lubricant, magnesium stearate, is a dihydrate at ordinary humidity and ambient temperature, but when heated in a dry environment, it loses water and converts to an anhydrous solid form with different solubility properties. When exposed to moisture, on the other hand, it converts to a trihydrate form, again, with different solubility properties. Granulation and compaction greatly reduce surface area, which diminishes the overall dissolution rate. Other processes may lead to formation of metastable amorphous or thermodynamically less stable polymorphic solid forms with higher solubility or higher surface area or both. Thus, cleaning procedures that were tested and found to be effective for removing residues from equipment used in one process may fail when used to clean equipment used in a different manufacturing process. That different processes affect cleanability in different ways should not be cause for astonishment; the discussion above may help us in understanding some of the underlying reasons for these differences.

**CLEANING AGENT SELECTION AND CLEANING PROCEDURE DEVELOPMENT**

The cleaning method for the product residue should be consistent with the physicochemical properties—solubility and stability—of the residue to be cleaned. In some cases, these properties can be used advantageously to facilitate cleaning. For example, a basic drug substance may be easily cleaned by use of an acidic cleaning agent. In fact, simply adjusting the pH of a soaking liquid may essentially accomplish cleaning without use of a complex cleaning agent. In some formulations, while the active ingredient is the most critical compound to be cleaned regarding carryover to subsequent product, inactive ingredients such as colorants may be the most troublesome residues to clean. It may be more difficult to remove colored residue from the equipment surface than it is to remove active drug. If this is the case, development of a cleaning method for the colored excipient will be the primary objective in cleaning procedure development; this method must also remove active drug residue. There must be good understanding of the stability properties of the compound of interest. For example, protein molecules may be hydrolyzed by alkaline cleaning agents to form amino acid fragments, which are usually more soluble and easier to clean than the parent molecule. If the compound of interest degrades to an insoluble compound, the cleaning method must consider the solubility properties of the degradation product as well as the solubility properties of the parent compound. Likewise, a cleaning agent that would cause an API or excipient to change physical form and become less soluble would likely make cleaning more difficult—and the cleaning procedure should necessarily be designed to address the newly formed insoluble residue. For example, a tablet formulation containing magnesium stearate as a lubricant may become more difficult to remove from equipment surfaces treated with an acidic cleaning agent, as the magnesium stearate would be converted to stearic acid. Some compounds—active drugs, degradation products, or inactive excipients such as colorants—are so insoluble in water that a non-aqueous solvent such as ethanol is preferred for cleaning.
DETERMINATION OF WORST-CASE COMPOUND IN A CLEANING MATRIX

Multiproduct manufacturing facilities often use a matrix approach for cleaning validation. In this approach, cleaning validation of a worst-case product covers the cleaning of other products that are less difficult to clean. The determination of the worst-case product is based in part on the solubility of the compound of interest. Thorough and complete understanding of solubility, including solubility in acid, alkaline, and neutral pH should be known. Also, solubility in the cleaning agent should be known. An ionizable compound that is highly soluble in an alkaline cleaning agent cannot be claimed to be a worst-case compound just because it is mostly non-ionized and poorly soluble in pure water. Solubility in water is truly irrelevant when the solubility of a compound exhibits significant pH-dependency or is solubilized in cleaning by micellization or emulsification. If the residue to be cleaned is a degradation product of the original active drug, its solubility as a function of pH and in potential cleaning agent solutions must be known to correctly determine the worst-case compound in a cleaning matrix. This assessment cannot be made without knowledge of the stability properties of the compound of interest.

ANALYTICAL METHOD FOR CLEANING VALIDATION

Care must be exercised in selection of the analytical method for cleaning validation to assure that the method quantifies the “worst case” residue, whether that may be a new physical form for the API itself or a degradation product. For example, an analytical method highly selective and specific for the API may not, in fact, be the best choice. Is the parent API the actual remaining moiety on the equipment surface after cleaning with highly acidic or highly alkaline pH? What happens to the target molecule under these rigorous and potentially reactive conditions? It may be more appropriate to develop an assay for both the parent molecule and degradation products or degradation products alone—or even to use a nonspecific method—in these situations. When matrix approaches to cleaning are used to evaluate the effectiveness of cleaning, it is important to understand the solubility properties not only of the parent API, but also the properties of any new physical forms that may be produced by the cleaning process as well as the solubility properties of the most difficult-to-clean degradation products in order to appropriately compare the API and its degradation products to the model hard-to-clean compound. In cases of protein product cleaning, a non-specific analytical method such as measurement of total organic carbon (TOC) is often used to verify equipment cleanliness because the parent molecule may be completely destroyed in the high pH cleaning process. The use of non-specific methods for small molecule APIs could, if practicable, eliminate many of the concerns with respect to chemical and physical fate discussed here.

RECOMMENDATIONS

Validation and compliance personnel should be sure that solubility properties of the residues that must be cleaned from manufacturing equipment are well known and understood. Solubility in various solvent classes should be known. Solubility as a function of pH should be known. The usual pH range for such studies is from pH 1 to pH 8, the normal human physiological pH range, and is covered in typical preformulation studies. However, extending the pH range to pH 12 is useful for cleaning validation because alkaline surfactant cleaners at this pH are commonly used in pharmaceutical manufacturing facilities; you may need to communicate your need for this information to preformulation scientists if it is not being provided to you routinely. The effect of temperature on solubility at optimum cleaning pH should be known. Further, extending these solubility studies to include surfactant solutions at or above the critical micelle concentration is even more relevant to cleaning. Because these special needs of cleaning method stakeholders may not be routinely addressed in preformulation studies, be sure to communicate your requirements early and clearly.

Many hypothetical degradation reactions have been discussed in this review. In any real product development process, the degradation processes that are relevant to a particular drug product are typically identified in laboratory studies well in advance of the need to develop a cleaning process for manufacturing equipment, either in preformulation studies or during the development of stability-indicating analytical methods. Personnel responsible for developing cleaning processes should communicate their need for information on how components of the drug product might degrade during potential cleaning processes to scientists and engineers engaged in those earlier development activities. Appropriate stress
If the API can degrade during the cleaning process, that no contaminating residues of API can be found. ing that surfaces have been sufficiently clean and developing methods for the purpose of demonstrat
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that surfaces have been sufficiently clean and that no contaminating residues of API can be found. If the API can degrade during the cleaning process, then the analytical method must be designed so as to show that API degradation products are also removed by cleaning. This discussion identifies some of the factors that have the potential to complicate the development of a validated cleaning procedure. This is not to say that all, or even any, of the changes in material properties suggested will occur in your manufacturing process; however, when unexpected results are obtained, one or more of the chemical or physical processes described herein may likely be the root cause of the difficulty. The resolution of problems encountered during the investigation of cleaning failures may lead to cleaning process improvements. Careful consideration of potential causative factors outlined in this discussion in seeking resolution of cleaning challenges can lead to process changes that greatly improve not only the cleaning process, but also the scientific and technical basis for the cleaning program.

CONCLUSIONS
A basic understanding of the chemical and physical properties of the materials used to produce pharmaceu
tical products, coupled with an understanding of how processing conditions can lead to changes in these properties through chemical degradation or physical form transformation, should help us to devise cost-effective, appropriate, rugged, and reliable cleaning methods. Knowledge of solubility and stability properties are especially relevant in this regard. Knowledge of solubility and stability properties of residues to be cleaned will enable a rational choice of cleaning agent and development of a rational cleaning procedure. Without knowl
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