# AQUEOUS CRITICAL CLEANING: A WHITE PAPER

## *HOW TO CHOOSE ALKALINE OR ACID PHARMACEUTICAL CLEANERS*

### *The role of pH and Residue in Pharmaceutical Cleaning*

A great deal is known about how pH affects aqueous critical cleaning. The first step is for you to identify the residue that needs to be removed and then determine the optimal pH range that will remove it. By understanding the structure, functional groups, molecular polarity, solubility and molecular weight of the residue being removed, it is possible to determine if an alkaline or acidic cleaner would work best for a given cleaning method. In most cases, simply by choosing the correct acidic or alkaline pH range for the type of residue being removed, you will be able to select the correct type of cleaner. On some difficult, water insoluble residues there can be additional benefits to understand how pH can manipulate the electrochemistry of the residue as well as the substrate it is associated with. If the pH of the cleaner chosen can create the same charge on the residue and substrate surface, a beneficial repulsion between the two can occur that can help facilitate the removal of the residue off the substrate's surface.

### *How to Select the Correct pH Range for the Pharmaceutical Cleaner*

First let's consider how to select the correct alkaline or acidic pH range for the cleaner with respect to the given residue. Typically, alkaline cleaners are used on oily residues and acidic cleaners are used on inorganic residues. The following table outlines the types of chemical structures found in pharmaceutical residues and indicates if they are best cleaned by acidic or alkaline cleaners. Some residues can be cleaned by either, but will tend to lean toward one pH range for most efficient results. At the top of the table is a list of alkaline, high pH cleaners available from Alconox, Inc. You can choose from cleaners intended for manual/ultrasonic cleaning, or machine/spray CIP cleaning in either powders or liquids and with or without phosphates. At the bottom of the table are the acidic low pH cleaners available from Alconox, Inc. It is important to note that difficult-to-classify residues may require bench-scale cleaning verification studies prior to doing larger scale cleaning trials.



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# Residues that are best cleaned by Acidic or Alkaline Cleaners

**Alkaline**
**High pH**

**Acid**
**Low pH**

| Alkaline Cleaners from Alconox, Inc. | | | |
|---|---|---|---|
| **Application:** | **Phosphate:** | **Powders** | **Liquids** |
| Manual/Ultrasonic | With Phosphate | Alconox | |
| Manual/Ultrasonic | Phosphate Free | Tergajet | Liquinox |
| Machine/Spray CIP | With Phosphate | Alcojet | Detojet |
| Machine/Spray CIP | Phosphate Free | Tergajet | Solujet |

**Generally Best cleaned by Alkaline in order from top going down:**
Oils, fats, greases
Alcohols Amino Acids
Diols, Triols
Phosphates
Organic Acids
Acid salts

**Either; Alkaline towards top of list, Acids towards bottom:**
N-heterocyclics
Polysaccharides
Proteins, fermentation
Steroids
Sugars
Ethers and ketones
Pyrrolidines
Pyridines
N-heterocyclics

**Generally Best Cleaned by Acids in order from bottom going up:**
Amines, alkaloids
Amphoteric proteins
Starches
Carbonates and bicarbonates
Metal Oxides
Insoluble hydroxides

| Acid Cleaners from Alconox, Inc. | | |
|---|---|---|
| **Application:** | **Phosphate:** | **Liquids** |
| Manual/Ultrasonic | Phosphate Free | Citranox |
| Machine/Spray CIP | Phosphate Free | Citrajet |

***The Role of pH and Substrates in Aqueous Critical Cleaning***

Understanding the properties of both the residue and the hard surface are important and can be used beneficially to improve the aqueous cleaning process. Often by using an aqueous cleaning solution above or below the defined isoelectric point of the hard surface and the inverse log of the acid dissociation constant (pKa) of the residue, a like – like charge repulsion can be created that facilitates the cleaning process, making it far more efficient.

The isoelectric point of a surface is the pH at which the surface's electric charge is neutral with regard to its acid/base and electron donor-acceptor reactions. Moving to a higher or lower pH will shift the effective surface charge or electron density in a negative or positive direction. Two common hard surfaces in pharmaceutical manufacturing are stainless steel and glass. Stainless steel has an isoelectric point of 8.5 associated with the reactivity of the oxygen in the oxides $Fe_30_2$, $Fe_30_4$, and $Cr_20_3$ on the surface of the metal whereas glass has an isoelectric point of 2.5 associated with the $SiO_2$ on the surface. Raising the cleaner solution pH past the isoelectric point, causes the surface to become more negatively charged.

Likewise, if the residue is an acid or base or amphoteric compound, the charge can also be manipulated by pH. The pKa, of most acids, indicates the pH at which the hydronium ions and conjugate base are present in equal concentrations. Moving higher in pH shifts the equilibrium toward the right, thereby increasing the concentration of the negative conjugate base.

TABLE A: **RELATIONSHIP OF pKa, CONJUGATE BASE AND HYDRONIUM ION CONCENTRATION**

$$HA + H_2O \rightarrow H_3O^+ + A^-$$

| [HA] = acid concentration | [$H_2O$] = water | [$H_3O^+$] = hydronium ion concentration | [$A^-$] = conjugate base concentration |
|---|---|---|---|

$$pKa = -\log [H_3O^+] [A^-]/[HA]$$

Thus, when cleaning acids off of stainless steel or glass, it is desirable to use a cleaning solution with a pH above the pKa of the acid and the isoelectric point of the stainless steel. A repelling negative character between the acid conjugate base residue and the stainless steel surface will result. To apply this concept practically, lets exam stearic acid ($C_{17}H_{35}COOH$) residue on a steel manufacturing tank surface. In this case, stearic acid has an isoelectric point at around pH 5 that drives formation to the negatively-charged stearate ion ($C_{17}H_{25}COO^-$). If an aqueous alkaline cleaner is employed that is equal to or

above pH 8.5, then the stearic acid will predominantly be in the negatively-charged conjugate base stearate ion ($C_{17}H_{25}COO^-$) form. Additionally stainless steel typically has an isoelectric point of 8.5 associated with the reactivity of oxygen in the oxides $Fe_30_2$, $Fe_30_4$, and $Cr_20_3$ on the metal surface, as well as the hydrates and hydroxides formed in aqueous solutions. Therefore, under such alkaline conditions, pH 8.5 or greater, the metal oxides in the stainless steel surfaces will also become negatively charged, setting up an appropriate repulsion between the stearic acid conjugate base and the steel surface. This repulsion is desirable as it facilitates cleaning and removal of the stearic acid residue from the surface.

The reverse holds true for basic residues. By lowering the pH of the residue below the pKa and the isoelectric point of the surface being cleaned positive-positive repulsion may be achieved. At the very least, by lowering the pH, a neutral residue and a positive surface can be achieved, with no attraction that would make cleaning difficult created.

TABLE B: **OPTIMIZING THERMODYNAMIC CLEANING CONDITIONS FOR SURFACE/RESIDUE ELECTROSTATIC REPULSION**

| | |
|---|---|
| Acidic Residues | pH > pKa and isoelectric point of surface |
| Alkaline or basic residues | pH < pKa and isoelectric point of surface |

In conclusion, by evaluating the residue and the substrate being cleaned, you can successfully choose the correct pH range for the cleaner you will need. In the case of cleaners from Alconox, Inc cleaners, once you know the correct pH, by choosing whether you will clean manually or in an automated cleaning system and whether you prefer a powder or a liquid, you can then make a final decision about which cleaner to select.

***For Additional Help with Your Critical Cleaning Challenge***

Alconox, Inc has 60 + years in developing aqueous cleaning solutions for pharmaceutical manufacturing and is able to help solve critical cleaning challenges.

Please contact the Critical Cleaning Experts at Alconox Validation Support or Alconox Cleaning Verification Lab for assistance.

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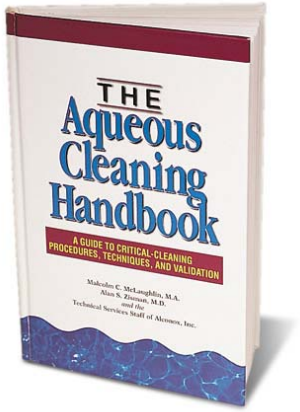
To read more about critical cleaning, request your FREE copy of The Aqueous Cleaning Handbook by clicking here.

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**If you have questions please contact Alconox Technical Support at**

**914.948.4040 or email at cleaning@alconox.com**