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FDA & OTC Antiseptics

A review of consumer antiseptic wash ingredients undergoing FDA challenge

On September 23, 1972 the *New York Times* reported that the U.S. Food and Drug Administration (FDA) put the germ killer hexachlorophene (pHisoHex) under strict control after it was reportedly linked to the death of at least 39 French and 15 U.S. babies. The route of administration was percutaneous absorption from the compounds usage as a bath wash and baby powder. Hexachlorophene was popular and found in practically every kitchen and bathroom in the developed world. On September 6, 2017 the story continues when perhaps a final nail will be hammered into the availability of hexachlorophene. The Federal Register (FR) will inform that the legal status of this antiseptic—and others like it used in cleansing and bathing activity—will be lowered to misbranded. The FDA has been persistently concerned with the local and systemic safety (toxicity) and the infection preventing properties (antisepsis) of these drugs for over 40 years. Now, to their credit they extend their reach to a new product definition: Consumer Antiseptic Wash (CAW). Note the term "wash," for this alone would have made the famous *NY Times* headline unnecessary and saved the children.

Accordingly, because of the stimulation of interest that the new rule has and will engender, we have composed the present paper on aspects of antiseptic science and have chosen to discuss four antiseptics of the many presented in the FR. We give neither advice nor suggestions on their regulatory status but merely portray the laboratory properties that we are asked to track as they will bear on efficacy.

REGULATORY AND TECHNICAL UPDATES ON SOME OTC ANTISEPTICS

Effective on September 6, 2017, FDA bans a list of 29 over-the-counter (OTC) antiseptic ingredients that are currently used or may potentially be used in CAW products.[1] FDA has concluded that there is insufficient evidence that these products are more effective than and as safe as ordinary soap and water. A firm must now show that an antiseptic used for hand or body wash is tested clinically and prevents infection in humans better than classical soap and water. Similarly, it must be applied and then washed off, supported with adequate toxicology, and evaluated for the potential to contribute to bacterial resistance. Three common CAW ingredients—benzalkonium chloride, benzethonium chloride, and chloroxylenol—were deferred from this ruling while data supporting their usage is still being reviewed or submitted.[1]

CAW products include a variety of personal care products intended to be used with water, such as antibacterial soaps, hand and body washes. It is important to note that the new rule does not alter the standing of many of these same ingredients used in other similar ways. Specifically, the final rule does not have an impact on the monograph status of health care personnel hand washes, patient preoperative skin preparations, surgical hand scrubs, or the monograph status of antiseptics for food industry use.

GERMICIDES REVIEWED IN THIS PAPER

With the exception of the deferred ingredients mentioned above, manufacturers selling CAWs containing any of the other antiseptics listed in the FR1 following the final rules effective date (September 6, 2017) will be subject to FDA enforcement. In this paper we choose to review the following four ingredients: phenolics, povidone iodine (PVP-I), chlorhexidine gluconate (CHG) and sodium hypochlorite (Na+ClO-). We note that all the compounds listed in our review are featured in the World Health Organization (WHO) list of essential medicines.

We point out that although the FR mentions only the pure phenol liquid carbolic acid—greater than or less than 1.5%—we choose to educate our readers more with antiseptic science by broadly discussing the entire phenolic group.

Our main purpose in this review is to instruct a technical audience about certain aspects of antiseptic science. To this end we will review and allow the reader to compare and contrast the following traits of product performance: speed, spectrum, resistance, inactivation and mechanism of activity (*Table 2*). The four ingredients discussed represent strikingly different molecular types: cationic/aromatic, pyrrole nucleus, phenolic organic acid and inorganic mineral acid. In addition to the microbiological facts and comments provided in these pages the reader is referred to the excellent review of McDonnell and Russel.[2]

PHENOLICS

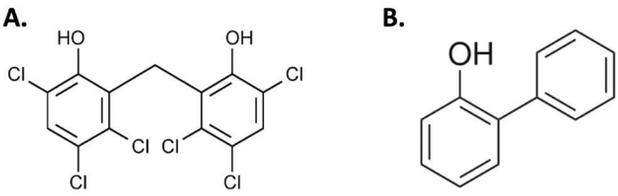
We choose to start with phenolics, which over the years have advanced from the original simple carbolic acid molecule of Lister to a series of dozens of molecules that have been chlorinated, alkylated, and/or fused to the bicyclic or tricyclic form to yield a library of antibacterial, antifungal, and antiviral agents. These compounds are negatively charged organic acids with poor solubility. Although they do not act in seconds or minutes they find use where speed is not important such as in emulsions, soaps, cosmetics, and topical drugs.

Other usages of phenolics

Phenol is commonly found in mouthwashes, scrub soaps and surface disinfectants and is the active ingredient found in some common household disinfectants (e.g. Lysol, Pine Sol, antibacterial dish soaps). Phenolics are effective against bacteria—especially Gram positive bacteria—and enveloped viruses but are not as effective against non-enveloped viruses and spores. These compounds are often inactivated in the presence of hard water and organic material. Compounds of the phenolic class are typically used for decontamination of the hospital environment, including laboratory surfaces and noncritical medical items. Phenolic disinfectants are generally safe except that prolonged exposure to the skin may cause irritation and systemic effects. For this reason the use of phenolics in nurseries is questioned due to potential toxicity in infants (*see Figure 1*).

Spectrum

The antibacterial or antiviral activity of phenolic compounds is related to the length and position of the side chains and halogenation in concert with the pH-dependent degree of ionization of the –OH group.



A. Hexachlorophene. Multi-chlorinated derivative.
B. 2-phenylphenol (OPP). Lacks halogen or side chains.

FIGURE 1: Representative common phenolic molecules.

The data in *Table 1* shows the classical "Broad Spectrum" range of the typical phenolic derivative as opposed to the purely antibacterial range of the typical broad spectrum antibiotic. We point out the slightly greater sensitivity of the Gram positive over the negative. One also notes the sensitivity of filamentous fungi to the phenolic compound, especially the high lipid content containing Trichophyton. This is the type of in vitro MIC (minimum inhibitory concentration) testing no longer accepted by FDA for efficacy of CAW products.

Mechanism

Phenolic agents appear to primarily target the cytoplasmic membranes and inhibit membrane bound enzymes. It is the free hydroxyl group and balance between the hydrophobic and polar groups that attribute to the compounds reactivity. There is an attachment phase to the surface of the organism plus an entry episode not unlike the penetration of the antiviral Amantadine inside of the influenza virion.

Historical note

The antimicrobial activity of phenolic compounds was discovered around 1865 by Joseph Lister, a surgeon in England. At the time, almost all surgeries ended either in death or infection and were described as the result of "bad air." He transferred carboys of carbolic acid (phenol) available at the coalmines to his surgical suite, sprayed it into the air, and applied it to the surgical site. Infections and death rate declined. In the years ahead, chemists and bacteriologists in England and Germany observed that the structure of pure carbolic acid could be altered in virtually hundreds of ways to produce the fascinating field of "Disinfectant Biology."

CHLORHEXIDINE GLUCONATE

Chlorhexidine is a well-known germicide that came into medical use in the 1950s and has characteristics of both antiseptic and disinfectant. It acts in a manner similar to the quaternary ammonium compounds (QACs), but is more versatile in that it has several clinical uses. Along with being used to degerm the skin of the patient and the hands of the healthcare providers, it is also used for cleaning wounds, preventing dental plaque, treating yeast infections of the mouth, and to keep urinary catheters from blocking. Since the 1950s, chlorhexidine has been competing head-to-head with PVP-I as a pre-surgical antiseptic.[3] It is noted that chlorhexidine has a more lasting and substantive effect than iodophors in side-by-side tests (*see Figure 2*).

Spectrum

Chlorhexidine rapidly inactivates lipophilic viruses such as Influenzas, Coronavirus, Herpes, HIV Type I, and Ebola. It is inactive against hydrophilic or naked viruses such as Polio, Norovirus, or the Enteroviruses Coxsackie A/B, and the ECHO group. Hospitals use chlorhexidine as a key tool to protect patients against infections and prevent the spread of organisms like ***Methicillin-resistant Staphylococcus aureus*** (MRSA). Chlorhexidine is effective

TABLE 1: Comparing a germicide (OPP) with an antibiotic (AMX) - (active MIC concentrations)

Organism	Classification	OPP (µg/mL)	AMX (µg/mL)
Bacillus subtilis	G+	100	8
Escherichia coli	G-	200	16
Proteus vulgaris	G-	200	64
Pseudomonas aeruginosa	G-	200	64
Staphylococcus aureus	G+	100	4
Candida albicans	Yeast	100	>200
Aspergillus brasiliensis (niger)	Fungus	75	>200
Trichophyton pedis	Fungus	20	>200

Chlorhexidine is 1,6-di(4-chlorophenyl-diguanido) hexane, a cationic bisbiguanide of the following formula:

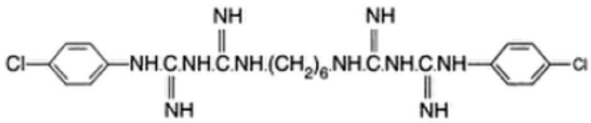


FIGURE 2: Structural formula of Chlorhexidine.

against both transient (viruses) and resident (bacteria) organisms on the skin but is not as effective against spores.

Mechanism

Chlorhexidine is characterized as being a strong base with cationic properties. The compound is said to have hydrophilic (diguanido) and hydrophobic (hexane) groupings, which react with different parts of the microbe. These parts are essential to the electrostatic balance required for the four categories of microstructure germs that the medicinal chemist is concerned with: 1) Gram positive or 2) negative bacteria and 3) enveloped or 4) naked viruses. The significance of the nitrogenous groups is the positive charge that allows the compound to adhere to either the negative surface of bacteria and viruses or to the surface of human skin. It is here that chlorhexidine fulfills one of its most important medical roles as a pre-surgical dressing. There is evidence that when chlorhexidine is combined with alcohol its germicidal effect is potentiated against both bacteria and viruses.

Historical note

Chlorhexidine was patented by Imperial Chemical Industries in Manchester, England (1954) for usage as a bactericide to be used on tissues and instruments. It is constantly compared with povidone-iodine as to their important roles in preventing surgical site infections (SSIs) with a slight edge often given to chlorhexidine. The development of chlorhexidine was based on knowledge gained over the years from analysis of the range and speed of action of the quaternary compounds.

POVIDONE-IODINE (PVP-I)

Povidone-iodine, an antiseptic solution based on a novel form of molecular iodine, is a WHO-recommended agent for dressing wounds and for pre-surgical antisepsis. Since 1821[4] the effective use of iodine as an antiseptic has generally led us to believe that there may be no more powerful killer of bacteria/fungi or inactivator of the viral agent than this halogen. Today the medical practice employs three preparations; (1) iodine tincture, (2) Lugol's iodine and (3) povidone-iodine. The latter is the most useful either for short-term first aid or long term surgeries (*see Figure 3*).

Over the years, tincture of iodine has prevented infections in the hospital, home and battlefield. Despite decades of such success, it has always possessed properties undesirable for practical application: unpleasant odor, staining and painfulness in open wounds. The development of the iodophor carrier in the late 1950-1960s, called "tamed iodine," led to a distinct upgrade in aseptic surgery, preparatory procedures and general first aid treatment from inside the home to the hospital. The magic of the iodophor discovery is in the presence of a "carrier" of the three species to the wound site, not merely the absence of alcohol. Among the 29 antiseptics cited in the September 2016 FR, the iodophor alone supplied data indicating that the compound does not convert an organism to drug resistance.[5]

Spectrum

PVP-I has one of the widest ranges of kill/inactivation without resistance. This agent rapidly—seconds to minutes—works against either the resident or transient flora of the skin including Gram positive and negative bacteria, yeasts and molds including conidial and hyphal forms and a broad range of enveloped and naked viruses. In other words, molecular iodine, as for years in the "tincture" captures the same breadth of activity when weakly bonded inside of the PVP molecule as when dissolved in alcohol and infamously known as "Tincture of iodine." The release of iodine from the carrier provides two ionic and one molecular (I2) form of the germicide. We note that only the latter molecular form is biocidal.

Mechanism

Free molecular iodine released from the carrier penetrates the cell walls of organisms and proceeds to oxidize sulfyhydryl groups. Iodination of amino acids and lipids also contributes to the microbiocidal activity of iodine.[6]

Historical note

The PVP carrier povidone (or polyvinylpyrolidone) is known to have been studied by German and American scientists in World War II as a substitute for "blood plasma," the liquid only part of "whole blood." Povidone-iodine (PVP-I) was discovered in 1955 by HA Shelanski, a toxicologist/microbiologist at the industrial toxicology lab in Philadelphia while doing toxicity studies on the PVP plasma substitute. He determined that when combined with iodine it formed a stable molecule that was less irritating but equally as active as the tincture. He named the new molecule "iodophor." Human clinical trials eventually showed that the compound was superior to other iodine formulations.[5]

SODIUM HYPOCHLORITE (NA+CLO-)

Commonly referred to as bleach, sodium hypochlorite is perhaps the most well known consumer house-hold disinfectant and bleaching agent. Similar to the other compounds reviewed in this report, it appears on the WHO list of essential medicines under the category of disinfectant. The usage of chlorine compounds as bleaching agents and disinfectants date back to the late 17th century. Although the usage of chlorine as a bleaching agent, water/pool treatment and a general purpose disinfectant are well known, its historical use as an antiseptic is less known and will be briefly reviewed here.

During World War I, an English chemist by the name of Henry Dakin prepared a highly diluted sodium hypochlorite/boric acid solution called Dakin's solution in an attempt to treat battlefield wounds. Prior to wound closure, Dakin's solution was used for wound disinfection and irrigation via administration through

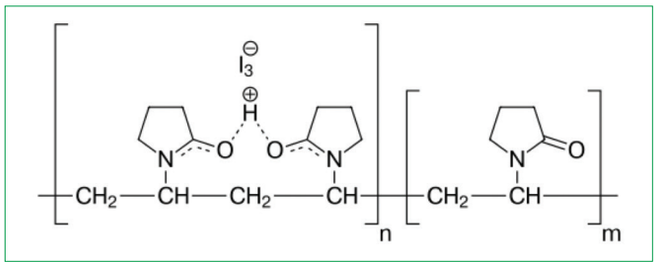


FIGURE 3: Structural formula of Povidone-iodine.

perforated rubber tubing. The solution is credited to have helped significantly reduce the rate of death and amputation during WWI.[7]

Dakin's solution (0.125-0.5%), manufactured by Century Pharmaceuticals, is still used today as a broad-spectrum antimicrobial wound care solution for acute and chronic wounds. Although the antiseptic contains the same active chemical used in the disinfectant, certain dilutions and treatments are performed in order to reduce the inherent skin irritation properties. Common household bleach sold at "removed ~"1-8% sodium hypochlorite is effective against a wide variety of aerobic and anaerobic bacteria, yeast, molds and enveloped and non-enveloped viruses (*see Figure 4*).

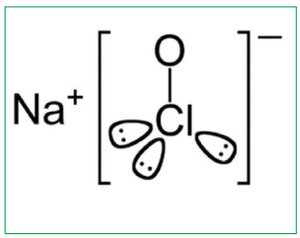


FIGURE 4: Structural formula of Sodium Hypochlorite.

Spectrum

Dakin's solution is a broad-spectrum antimicrobial cleanser effective against aerobic and anaerobic bacteria including common resistant clinical strains, viruses, yeasts and molds. It is based on the reactivity of the chlorine atom, which has proven useful from the home to a terror site as either a disinfectant or antiseptic.

Mechanism

Sodium hypochlorite is a highly active oxidizing agent that targets the sulfyhydryl groups of vital enzymes. The chlorine compound quickly destroys phospholipids and restricts cellular metabolism. In 2008, Winter et al. demonstrated that hypochlorous acid causes the oxidative unfolding and aggregation of certain cellular proteins both in vitro and *in vivo*.[8] Despite extensive research, the exact mechanism has yet to be fully elucidated. We point the reader to the 5th edition of Block[6] for a more in-depth analysis regarding the mechanistic activity of chlorine compounds. Staying on the subject of the unrivaled potency of the chlorine atom we advise our readers of its three main categories of use:

1) Low concentration: human use as a mild antiseptic. Not well known despite being used for decades (Dakin's).
2) Mid concentration: very well known and used in hospitals, laboratories and homes as a disinfectant (Bleach).
3) Super concentration: hardly known. Potent weapon against germ warfare recommended by the EPA in terror attacks (Anthrax).

Historical note

TERROR IN THE EAST: On October 9th, 2001 the Senate Building in Washington was attacked with a weaponized strain of anthrax in the form of letters mailed from Princeton, NJ to Senators Tom Daschle and Patrick Leahy. In the same time frame anthrax letters were sent to several news/media agencies including, ABC, CBS, NBC, the National Enquirer and NY Post. In the ensuing weeks a total of seven people died of respiratory anthrax and dozens more fell ill. With respect to decontamination, the Environmental Protection Agency (EPA) advised that the Hart Senate Office Building be decontaminated and instructed on the use of gaseous chlorine dioxide generated from sodium chlorite. An immense overkill mode was employed for public safety. The main suspect, a bacteriologist in the microbiology lab at Fort Detrick, committed suicide before the Federal Bureau of Investigation (FBI) could bring charges. **CP**

Disclaimer: Nothing in this paper is intended as advice to any manufacturer on matters of efficacy or safety relative to the requirements now needed to prove efficacy for an antiseptic as per the September 6, 2017 FR.

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^structure of povidone
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TABLE 2: Summary Table

Activity		Anionic Phenol	Halogen (Cl_2, I_2)	Cationic (QAC, CHG)	Antibiotic
Inactivation by hard H_2O & organic matter		YES	YES	YES	NO
Develops resistance		VAR	NO	VAR	YES
Percutaneous absorption		YES	NO	NO	NO
Sporicide (bacterial spores)		NO	VAR	NO	NO
Speed (sec. to min.)[1]		NO	YES	YES	NO
Spectrum	Broad[2]	YES	YES	YES	YES
	Complete[3]	YES	YES	YES	NO
Virus	Lipophilic (HSV)	YES	YES	YES	NO
	Naked (polio)	NO	VAR	NO	NO
Mechanism	A. Electrostatic	C	B	A, C	D
	B. Oxidation				
	C. Membrane disruption				
	D. Protein synthesis				

VAR = Variable (time dependent)
[1] In general, speed is concentration dependent.
[2] Gram positive and negative bacteria.
[3] Gram positive and negative bacteria and yeast and molds.