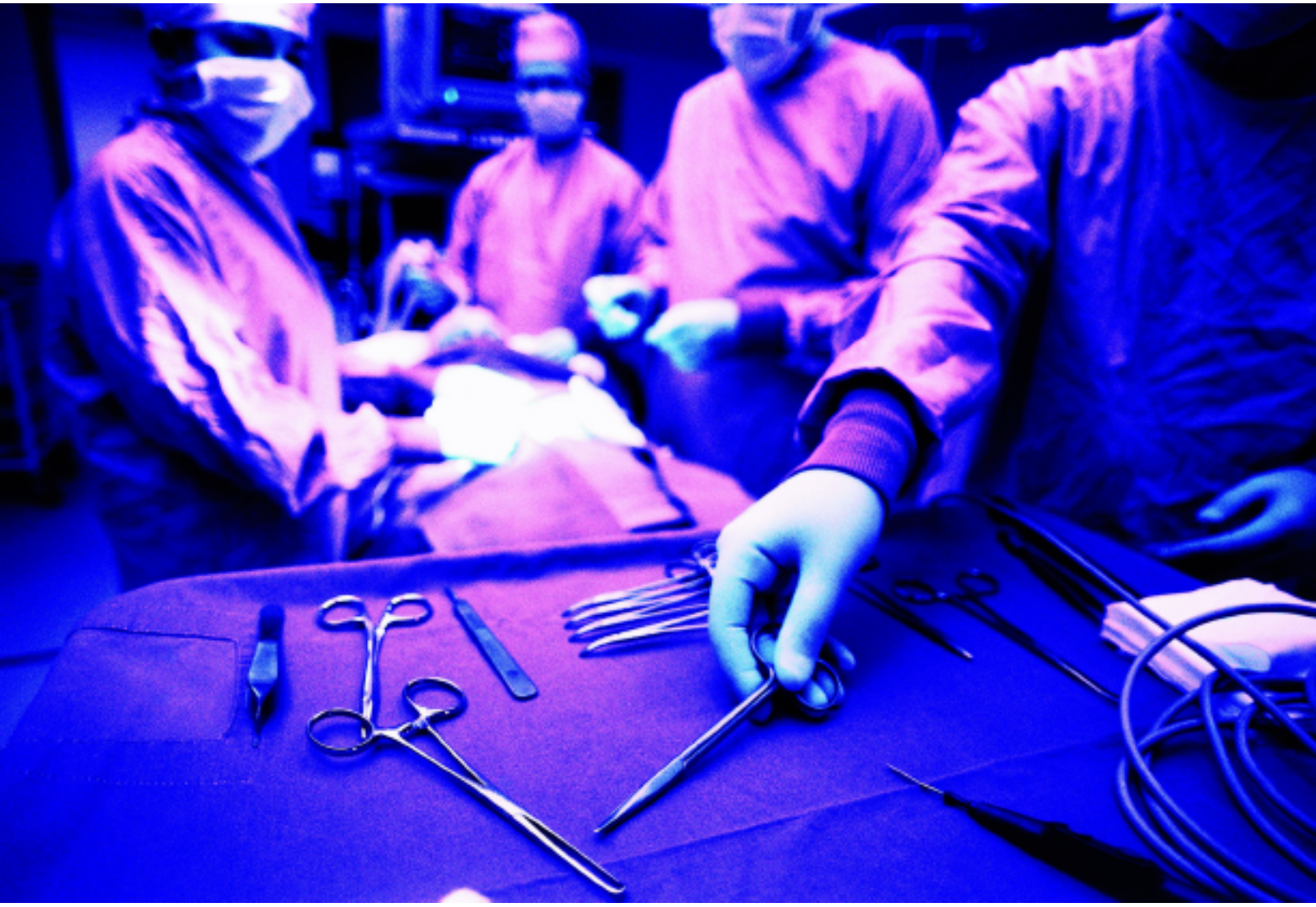
PVP-IODINE

Povidone Iodine Antiseptic Agent



ISP

INTERNATIONAL SPECIALTY PRODUCTS

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INTRODUCTION

Iodine was discovered in 1812 by the French scientist Courtois who isolated this non-metallic essential element while treating seaweed ash with sulphuric acid to recover sodium and potassium compounds. Iodine was named for its deep-violet vapor by Guy-Lussac in 1814 after the Greek word *"ioeides"* meaning violet colored.

While interesting, the new element had several properties which made its application unsatisfactory. Its inherent insolubility in water was overcome by dissolving the iodine in alcohol, but the alcoholic iodine solution itself exhibited serious drawbacks. First, the concentration of the solution constantly varied due to evaporation of the solvent. Furthermore, at concentrations higher than 5% the solutions were found to be irritating to the eyes, skin and mucous membranes. These problems were alleviated to a degree by adding some iodide to the iodine solution to yield the water soluble triiodide, but the irritating effect could not be completely eliminated through this formulation.

Despite these drawbacks, the value of a new disinfectant made from iodine was soon recognized and the water-alcohol solutions were quickly put in use. Lugol's Solution (aqueous solution containing 5% elemental iodine and 10% potassium iodide) was first made in 1829, and *"tincture of iodine"* was listed in the U.S. Pharmacopoeia by 1830.

Over the last century, scientists have developed a number of iodine compounds and preparations to overcome the adverse side effects of iodine, its painfulness on open wounds and the possibility of allergic reactions. The objective was to avoid such incompatibilities without a significant loss of germicidal efficacy. As a result, iodophors, such as PVP-Iodine from ISP, were developed and have succeeded as ideal forms of application.

GENERAL PROPERTIES AND ADVANTAGES

PVP-Iodine (Povidone-iodine), was introduced to the pharmaceutical market as an antiseptic agent in the 1950's and is as effective as iodine itself against a broad spectrum of disease-causing microorganisms.[1,2] It differs from iodine, in that it is less irritating to the skin and does not require iodides or alcohol to dissolve. Additionally, PVP-Iodine stains are water-washable. Early promotional materials refer to PVP-Iodine as *"tamed iodine"* because of its safety. Furthermore, the poison label required for iodine products is not necessary in commercial preparations containing PVP-Iodine.

PVP-Iodine is used in both human and veterinary medicine to kill on contact a wide variety of bacteria, viruses, fungi, protozoa and yeasts. It has also been shown to be effective in controlling some insects. There has been no reported microbial resistance to PVP-Iodine. At the same time, PVP-Iodine is safer and easier to use than classic iodine preparations and has low systemic toxicity. Unlike iodine solutions, it is non-sensitizing and does not cause pain when applied to wounds or mucous membranes. PVP-Iodine forms films that protect open wounds. These films can be washed in water and will not permanently stain skin, natural fibers or hard surfaces. PVP-Iodine is exceptionally easy to use because it is soluble in water as well as in organic solvents, such as alcohols. As a result, it can be formulated in powders, tablets, lozenges, solutions, lotions, gels, ointments, creams, mousses or sprays.

The prolonged, non-selective, anti-microbial action of PVP-Iodine is unparalleled for surface microbiocidal activity and is particularly effective in treating mixed infections. Its effectiveness has been clinically proven for all types of topical applications in both human and veterinary medicine.

INTRODUCTION

TYPICAL APPLICATIONS

- Skin antiseptics
- Surgical hand disinfection (scrubs)
- Wound cleansing
- Minor injury applications
- Treatment of burns
- Treatment of ulcers
- Applications in gynecology
- Dental and oral use
- Veterinary
- Aquaculture

SUMMARY OF PVP-IODINE PROPERTIES AND USES

PROPERTIES	USES
Broad spectrum biocide	Non-selective germicidal action Bactericide, fungicide, viricide, sporicide, amebicide, insecticide, nematocide Lacks the tendency for resistant micro-organisms to develop Effective in dilute solution Unparalleled for surface sterilization and in mixed infections
Detoxified iodine	Low animal and phytotoxicity Non-irritating to skin and mucous membranes Non-sensitizing Does not delay healing or formation of granulation tissue Non-stinging Reduced hazard if accidentally ingested
No detectable vapor pressure	Stable Can be bandaged without danger of burns (but occlusive conditions must be avoided) Retained where applied
Water-soluble	Ease of formulation Uniform concentrations Does not permanently stain
Film-forming	Prolonged germicidal action Adheres to treated surfaces where applied Color delineates treated area
Stable complex	No general odor No loss of iodine Rapid action even in presence of organic matter such as blood, pus, oil, grease, soap, etc.

PHYSICAL AND CHEMICAL PROPERTIES

PVP-Iodine is a stable chemical complex of polyvinylpyrrolidone (PVP) and elemental iodine.[3-5]

ISP supplies both pharmaceutical and technical grades of PVP-Iodine to support multiple applications. Table 1 lists some of the key specifications for each product.

Table 1: Key ISP Product Specifications

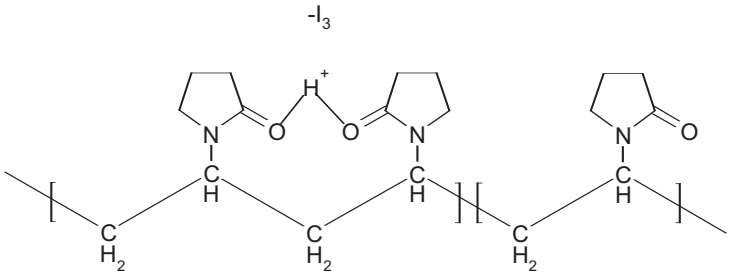
SPECIFICATIONS	PVP-IODINE	IODONE™ 10
Grade	Pharmaceutical	Technical
Pharmacopeia Compliance	USP, Ph. Eur., JP	N/A
Appearance	Free flowing, reddish-brown powder	Free flowing, reddish-brown powder
Available Iodine	11.0 - 12.0%	10.0% Minimum
Iodine	6.0% Maximum	N/A
Loss on Drying	5.0% or 8.0% Maximum†	8.0% Maximum
Ash	0.025% Maximum	N/A
Heavy Metals	20 ppm Maximum	N/A

†Depending on grade.

DESCRIPTION

Chemical Description: Polyvinylpyrrolidone-Iodine complex
CAS Registry Name: 2-Pyrrolidone, 1-ethenyl-, homopolymer compound with iodine
CAS Registry Number: 25655-41-8

CHEMICAL STRUCTURE



PHYSICAL AND CHEMICAL PROPERTIES

SOLUBILITY

PVP-Iodine (Povidone-iodine) is completely soluble in cold water in amounts up to and exceeding 10% (1% available iodine). By contrast, elemental iodine is water-soluble only to 0.034% at 25˚C.

PVP-Iodine is also soluble in:

- ethyl alcohol
- isopropyl alcohol
- glycols
- glycerin
- acetone
- polyethylene glycol

VISCOSITY

As would be anticipated, the viscosity of PVP-Iodine solutions is a function of both the molecular weight of the polymer and the concentration of the solution. Typical data determined at 25˚C for polymer complexes prepared from PVP K-30 is shown in Table 2.

Table 2: Viscosity of PVP-Iodine in Aqueous or Ethanolic Solutions

	Viscosity	
Solution Concentration %	Water mPa.sec	Ethanol mPa.sec
5	2.0	2.0
10	7.0	5.0
15	23.0	20.0

STABILITY

PVP-Iodine can be stored in powdered form without significant iodine loss. Samples kept for three years at 65˚C in glass stoppered bottles without tape or seal showed only 0.5% maximum loss of available iodine. The product should, however, be protected from light and moisture.

Published data show the stability of PVP-Iodine solutions is vastly superior to that of iodine tincture or Lugol's solution.

COMPATIBILITY

PVP-Iodine dosage forms have been formulated successfully as powders, non-oral tablets, liquids, lotions, ointments, gels, mousses and sprays.

If the vehicle or base reacts with iodine, then the available iodine in the final preparation must be determined and adjusted, as necessary, since the germicidal activity of the finished product is dependent only on the level of non-complexed, free iodine. The amount of free iodine results from the iodine/iodide ratio and the molecular weight of the PVP used in the PVP-Iodine complex.

pH

The effective pH-range of PVP-Iodine is between 2.5 to 7 with an optimum between pH 3 to 6. Reducing agents and amino groups react with iodine lowering the amount of available iodine and increasing the amount of iodide. Shift of the iodine/iodide ratio to lower values and reduction in the amount of non-complexed free iodine results in reduced germicidal activity.

Compatibility of PVP-Iodine with other materials should be confirmed to avoid corrosion or incompatibility prior to use on hard surfaces or for disinfection of materials.

PARTICLE SIZE

Average particle size ranges from 90 to 140µ. (Measured by Malvern Mastersizer 2003)

MODE OF ACTION

GERMICIDAL ACTION

The disinfecting characteristics of iodine arise from its ability to substitute for covalently bound hydrogens in compounds containing –OH, -NH, -SH, or CH functional groups. These groups can not only be part of the solvent or other constituents of the formula, but also of the material to be disinfected such as skin, mucous membranes, bacteria, etc.[6]

The exact solution-phase chemistry which yields the germicidal action is not easy to determine owing to the number of reactions which iodine may undergo in solution.

The chemistry of iodine in water can be described by a large number of reactions with eight of these being considered important. These reactions and their respective equilibrium constants are shown in Table 3.

These equations show that in aqueous solution iodine can exist in as many as seven different forms. It is also evident that since H^+ participates in many of the reactions, effects of solution pH are always important to the reaction pathways.

It has been shown that of the seven different forms of the iodine described in the reactions above only hydrated molecular iodine (I_2), hypoiodous acid (HOI) and iodide ion (I^-) influence the antibacterial effect.[7,8]

In pharmaceutical formulations that contain both iodine and iodide, the bactericidal effect can almost entirely be attributed to free molecular iodine.[7]

Table 3: Iodine-containing species in aqueous iodine solutions: Reactions and equilibria[7]

	I_2			I^+	+	I^-			K =	9.9×10^{-9}
I_2	+	H_2O		H_2OI^+	+	I^-			K =	1.2×10^{-11}
I_2	+	H_2O		HOI	+	H^+	+	I^-	K =	3×10^{-18}
	HOI			I^+	+	OH^-			K =	3×10^{-10}
	HOI			H^+	+	IO^-			K =	4×10^{-13}
I_2	+	HOI		I_2HOI					K =	2.7×10^{-7}
I_2	+	I		I_3^-					K =	7.14×10^{-2}
	3HOI			$3H^+$	+	$2I^-$	+	IO_3^-	K =	2.5×10^{-11}

MODE OF ACTION

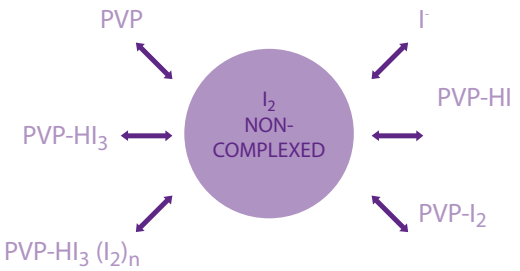
In the presence of polymers having the ability to bind iodine (known as an iodophor property), the chemistry of iodine becomes even more complex. It is presumed that polymeric iodophors with oxygen-containing functional groups (e.g. carbonyl groups) will react with iodine to form donor-acceptor complexes in which the iodine is the acceptor.

In PVP-Iodine the iodophor consists of poly (*N*-vinyl-2-pyrrolidone) where at least two further reactions must be considered:

As is the case with all iodophors, the antibacterial activity of PVP-Iodine is associated with the elemental iodine in the solution.

The difference between a conventional iodine solution and an iodophor is that the latter carries practically all the iodine in a complexed form, so that the concentration of the free iodine in the solution is always very low. This property has the effect of reducing the drawbacks associated with the presence of elemental iodine i.e. high toxicity, high level of irritation and staining power.

The bulk of the iodine exists in the triiodide form, which is in equilibrium with iodide and the active iodine.



In the PVP-Iodine complex, the iodine does not exist as a single species and in fact several forms of iodine have been characterized:

- ***"Available iodine"***
  Contains all the iodine species which can be titrated with sodium thiosulfate
- ***"Iodide"***
  Negatively charged ion; necessary for the complexation of iodine
- ***"Total iodine"***
  Given by the sum of available iodine and iodide.
- ***"Free Iodine"***
  The type of iodine which can be extracted from aqueous PVP-Iodine solution.

BEHAVIOR OF THE PVP-IODINE COMPLEX

Elemental analyses, iodine determinations, and the results obtained using various physical methods have shown that PVP-Iodine can be defined as a system in which for every two amide groups complexed with HI, there are an average of seventeen uncomplexed vinylpyrrolidone units in the molecule. Therefore approximately 80 mole % of the product is actually unaltered poly(vinylpyrrolidone) and hence should behave as such.

The determining factor for bactericidal activity is not the concentration of the *"free iodine"* in the solution but instead is the concentration of *"free iodine"* at the wall of the target bacterium. Polyvinylpyrrolidone itself has no bactericidal effect, but owing to its affinity for the cell membranes is able to deliver the active ingredient to the target.

It was also observed that the microbial action of such solutions increased on dilution, and a gradual decrease in activity only began when the dilution reached 1:100. This behavior seems to be independent of the duration of the interaction between PVP-Iodine and the microorganisms.

MODE OF ACTION

In studies of PVP-Iodine solution equilibria, the content of uncomplexed iodine initially increases with dilution reaching a maximum at a solution strength of 0.1% and then decreases upon further dilution (Figure 1). The other iodine species present in a PVP-Iodine solution exhibit normal behavior in that their concentration decreases on dilution.

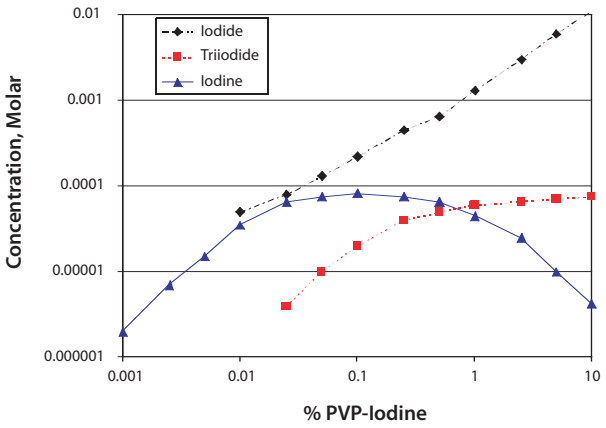


Figure 1: Equilibrium concentrations of PVP-Iodine

Rackur explained this dilution phenomenon by the formation of polymeric aggregates which contain entrapped, uncomplexed iodine.[9] Increasing the amount of solvent causes these aggregates to dissociate hence releasing the entrapped iodine and consequently increasing the antimicrobial efficacy of the solution.

By combining the results of the microbiological studies with the iodine equilibrium concentration curve (as shown in Figure 2) it becomes evident that the maximum iodine concentration and maximum microbial effect coincide. This provides strong confirmation that the concentration of uncomplexed iodine is the critical factor in PVP-Iodine efficacy.

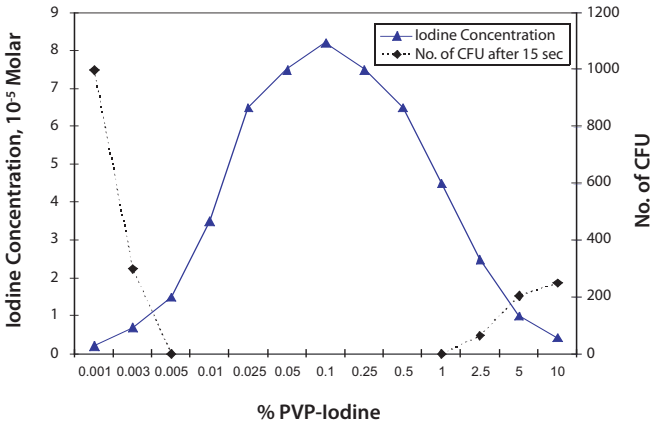


Figure 2: Correlation of the concentration of uncomplexed iodine with microbial reduction after 15 seconds for various concentrations PVP-Iodine.[7]

(Mode of Action Section: Extracts taken from Analytical Profiles of Drug Substances and Excipients – Vol 25 1075-6280/98 Barabas & Brittain and references cited therein)

ANTIMICROBIAL ACTIVITY

IN VITRO BIOCIDAL ACTIVITY

For many years, iodine has been recognized as an effective broad spectrum biocidal agent.[10] The irritancy and toxicity associated with its use have been significantly reduced by using PVP-Iodine.

The microbiocidal action of PVP-Iodine, as discussed earlier, is related to the non-complexed, freely mobile elemental iodine, I_2, the active form of which is polarized by water and hence can be considered to be H_2OI^+ in its final state. This activated iodine reacts in electrophilic reactions with enzymes of the respiratory chain as well as with amino acids from the cell membrane proteins both located in the cell wall. As a result, the well-balanced tertiary structure necessary for maintaining the respiratory chain is destroyed and the microorganism irreversibly damaged. Consequently, PVP-Iodine has a non-specific mode of action.

Biocidal agents have been classically measured for effectiveness by the use of *in vitro* methods. *In vitro* results, however, should be considered only as preliminary findings which should be confirmed under *in vivo* conditions simulating serum load and other organic matter in test samples. PVP-Iodine can react with these materials consuming some of the available iodine and thus reducing its germicidal efficacy.

The *in vitro* biocidal activity of PVP-Iodine has been studied for years against bacteria, yeast and molds, actinomycetes and rickettsia,[11] see Table 4.

SUMMARY

- PVP-Iodine kills microorganisms including bacteria, viruses, yeasts, molds, fungi and protozoa.
- Its microbiocidal activity is that of a non-specific mode of action causing irreversible damage to the microorganism with no tendency to form resistance.
- Electrophilic reaction with enzymes of the respiratory chain located in the cell wall.
- Electrophilic reaction with amino-acids located in the cell wall.
- Damage of the necessary protein tertiary structure destroys the microorganism.

ANTIVIRAL ACTIVITY

There have been reports that PVP-Iodine is effective as an antiviral agent.

Eleven products containing PVP-Iodine were tested for their ability to inactivate human immunodeficiency virus (HIV) in a cell culture system.[12] All of the products completely inactivated the virus at PVP-Iodine concentrations greater than 0.5%, except for the lubricating antiseptic gel, which required 2.5%. Douche and medicated douche products did not inactivate HIV at the concentrations prescribed for usual clinical use (0.33% and 0.25%, respectively) but were effective at PVP-Iodine concentration of 0.5%.

Further studies have shown that PVP-Iodine 0.25% surgical scrub and solution inactivated HIV within seconds *in-vitro*, and if used in clinically achievable concentrations could serve as a surface disinfectant in hospital settings where HIV may be present.[13]

ANTIMICROBIAL ACTIVITY

Table 4: Microbiological Efficacy
Activity of PVP-Iodine versus Bacteria, Yeasts and Molds, Actinomycetes and Rickettsia [54,73]

ORGANISMS (NO. of STRAINS)	RANGE OF PVP-I IN ppm AVAILABLE IODINE	CONTACT OF KILL TIME IN SECONDS
Proteus (41)	100 - 2500	15 - 180
Staphylococcus (36)	66 - 2500	15 - 80
Pseudomonas (36)	25 - 2500	15 - 900
Streptococcus (25)	200 - 2500	15 - 30
Escherichia (23)	200 - 2500	30 - 120
Salmonells (9)	1000 - 2500	15 - 60
Candida (8)	3.75 - 2500	10 - 120
Serratia (6)	200 - 2500	60 - 120
Spores-Baccillus; Clostridium (6)	10000	2 - 5 Hours
Trichomomonas (5)	400 - 2500	30 - 60
Enterobacter (4)	1000 - 2500	60
Klebsiella (4)	500 - 2500	60
Clostridium (4)	1000	30 - 60
Shigella (3)	1000 - 2500	60
Corynebacterium (3)	2500	60
Diplococcus (3)	1000 - 2500	60
Mycobacterium (3)	1000 - 2500	60 - 120
Bacillus (3)	7.5 - 2500	10 - 30
Sarcina (2)	500 - 2500	60
Trichophyton (2)	1000	60
Aspergillus (2)	1000	30
Mima (1)	2500	60
Herella (1)	2500	60
Edwardsiella (1)	2500	60
Citrobacter (1)	2500	60
Providencia (1)	1000	60
Acienetobacter (1)	3.75	10
Epidermophyton (1)	1000	60
Microsporum (1)	1000	60
Pencillium (1)	1000	30
Nocardia (1)	2500	60

ANTIMICROBIAL ACTIVITY

IN VITRO COMPARISON WITH OTHER ANTIMICROBIALS

BACTERICIDE

The antibacterial effect of PVP-Iodine, acetic acid and chlorhexidine gluconate was tested against *Pseudomonas aeruginosa, Staphylococcus aureus and Escherichia coli*. PVP-Iodine was found to be the most effective.[14]

Furthermore PVP-Iodine solution and cream proved to be an effective antibacterial agent against methicillin-resistant (MRSA) as well as methicillin sensitive strains (MRSS) killing all within 30 seconds. This study also demonstrated that PVP-Iodine was more effective than chlorhexidine.[15]

Among the commonly used disinfectants including benzalkonium chloride, chlorhexidine gluconate and PVP-Iodine, the latter was found to yield the most rapid bactericidal effects against both MRSA and MSSA.[16]

Extensive studies were conducted in which 580 Gram-negative bacilli were investigated and 18.2% of the tested *Enterobacteriaceae* were found to be resistant to chlorhexidine digluconate, including 92.1% of those belonging to the *Proteus* strains. Four percent showed resistance to benzalkonium chloride (with 89.5% of the *Proteus* strains), but PVP-Iodine killed all the strains tested.[17]

The behavior of 29 bacterial strains, including *Pseudomonas aeruginosa, Serratia marcescens* and *Burkholderia cepacia* was studied against chlorhexidine gluconate, benzalkonium chloride, saponated cresol and PVP-Iodine. As many as 5 strains of *Pseudomonas aeruginosa* were found to be resistant to chlorhexidine gluconate and benzalkonium chloride, 3 strains of *Burkholderia cepacia* were resistant to chlorhexidine gluconate and 5 of the 8 strains of *Serratia marcescens* tested were resistant to chlorhexidine gluconate and benzalkonium chloride. None of the strains were resistant to saponated cresol or to PVP-Iodine. The level of the bacteria tested was at the concentration recommended for disinfection of hands.[18]

ANTIVIRAL

Out of several disinfectants tested as antiseptics to inactivate HIV in the oral cavity, PVP-Iodine, benzalkonium chloride and chlorhexidine digluconate were found to be effective. PVP-Iodine, however, was the most effective of the three since it also yielded negative results in the HIV-specific plaque forming assay.[19]

Using Type I (Sabin strain) polio virus as the test organism, 5% PVP-Iodine was found to be rapidly virucidal.[20] In the same study, 2% glutaraldehyde was found to be similarly effective. However, 0.2% glutaraldehyde and noxythiolin were found to be less effective, while 0.05% chlorhexidine digluconate showed no virucidal activity.

ANTIMICROBIAL ACTIVITY

PVP-IODINE COMPARISON WITH CHLORHEXIDINE

PARAMETER	PVP-IODINE			CHLORHEXIDINE		
Mode of Action	Activated iodine reacts by electrophilic reactions with enzymes of the respiratory chain as well as with amino acids from the cell membrane proteins both located in the bacterial cell wall. The tertiary structure necessary for maintaining the respiratory chain is destroyed and the micro-organism irreversibly damaged.			Adsorbs onto the bacterial surface causing a disorganization of the bilayered cytoplasmic membrane. The respiratory chain is interrupted, the membrane-bound ATPase is inhibited. At a certain concentration range, lysis of the cell wall resulting in release of the interior of the cell can occur. This can happen to red blood cells and explains why Chlorhexidine is limited to a single application for treatment of open wounds. PVP-Iodine does not have this limiting property.		
Effective pH Range	Range	2.5 - 7		Range	5 - 8	
	Optimum	3 - 6		Optimum	5.5 - 7	
	Vegetative Bacteria	Gram-positive	Y	Vegetative Bacteria	Gram-positive	Y
		Gram-negative	Y		Gram-negative	Y
Microbiocidal Efficacy	Bacterial Spores		Y	Bacterial Spores		N
	Yeasts		Y	Yeasts		Y
	Fungi		Y	Fungi		Y[a]
	Viruses		Y	Viruses		Y[b]
	Bacteriophages		Y	Bacteriophages		N
Use Concentration	10% to 0.01% PVP-Iodine *(10% PVP-I _ 1% available iodine)*			4% to 0.02%		

[a] Fungistatic and fungicidal efficacy is subject to species variation.
[b] Infectivity of some lipophilic viruses e.g. influenza virus, adenovirus and herpes virus is inactivated.

ANTIMICROBIAL ACTIVITY

PVP-IODINE COMPARISON WITH CHLORHEXIDINE

PARAMETER	PVP-IODINE		CHLORHEXIDINE	
Applications	Skin antiseptics	Y	Skin antiseptics	Y
	Surgical hand disinfection	Y	Surgical hand disinfection	Y
	Wound cleansing	Y	Wound cleansing (single application only)	(Y)
	Minor injury applications	Y	Minor injury applications (single application only)	(Y)
	Treatment of burns	Y	Treatment of burns	N
	Treatment of ulcers	Y	Treatment of ulcers	N
	Applications in gynecology	Y	Applications in gynecology	N
	Dental and oral use	Y	Dental and oral use	Y
	Veterinary	Y	Veterinary	Y
	Aquaculture	Y	Aquaculture	N
Properties	• Excellent water-solubility. • Non-irritating and low toxicity. • Polymeric iodophor complex acts as iodine reservoir which replaces used iodine. • Some persistence due to film-forming properties of Povidone. • Susceptibility to the presence of organic matter (reducing the germicidal capacity).		• As base insoluble in water; some salts are readily soluble in water. • Inorganic ions precipitate chlorhexidine as insoluble salt. • Persistent action. • Toxic due to lysis of red blood cells. • Susceptibility to the presence of organic matter, less than PVP-Iodine. • Reversible staining of teeth surfaces when used as mouth rinse.	

ANTIMICROBIAL ACTIVITY

IN VIVO STUDIES

Numerous *in vivo* studies made over approximately 35 years, as well as the widespread clinical use of products containing PVP-Iodine, indicate the efficacy of PVP-Iodine as a therapeutic agent for both humans and animals. Some of the publications supporting the clinical effectiveness of PVP-Iodine are reviewed below.

SKIN DISINFECTION

PVP-Iodine Surgical Scrub is a 7.5% PVP-Iodine solution (0.75% available iodine) containing various agents for wound and skin cleansing. It should be rinsed off immediately after use to minimize skin irritation and healing retardation.

To reduce the presence of micro-organism on skin and prevent infections a PVP-Iodine Topical Solution containing 10% PVP-Iodine (1% available iodine) should be used. The PVP-Iodine film should remain on the skin so that it can act as a continued antimicrobial barrier.

To measure the efficacy of surgical scrubs, samples of scrub juices were taken to establish immediate, cumulative and persistent effects. The immediate effect is the reduction of bacteria found immediately after scrubbing.

A cumulative effect is seen when regular use of the scrub leads to increasing reductions of bacteria. The final measurement, persistence of effect, is defined as a decline in the post-wash bacterial count. Studies with PVP-Iodine scrubs show an effective, extensive immediate effect, a definite cumulative effect and a persistence of effect.[21-24]

PRE-SURGICAL SKIN PREPARATION

Numerous studies indicate the efficacy of PVP-Iodine for pre-surgical skin preparation.[25-28] There is also evidence that it is effective against spores present on the skin.[29]

PVP-Iodine products have been widely used for pre-operative skin preparation and in various surgical procedures and shown to significantly lower subsequent infection rates.[30-35]

TREATMENT OF WOUNDS

PVP-Iodine Topical Solution (10% PVP-Iodine containing 1% available iodine) is effective for ridding and preventing infections, including those with severe ulceration.[36-43]

PVP-Iodine has been shown to be an effective, fast acting and safe wound healing disinfectant.[44,45] It can be used on mucous membranes without danger of burns, and is not only antiseptic but appears to augment wound healing.[46]

TOPICAL APPLICATIONS

Topical PVP-Iodine Antiseptics, Aerosol Sprays, Ointments (5% PVP-Iodine, 0.5% available iodine) and Creams (5% PVP-Iodine, 0.5% available iodine) have been used to prevent microbial contamination in burns, incisions and infected ulcers.[47-52]

BURNS:

When used in the treatment of burns, PVP-Iodine effectively controls bacterial growth and protects the developing epithelium. Unlike many antibiotic agents it has the added advantage in that its continued use does not result in the generation of resistant organisms.[53]

ANTIMICROBIAL ACTIVITY

ULCERS:

PVP-Iodine, in solution or as an ointment, is particularly useful in the treatment of infected external skin ulcers where the maintenance of low bacterial count is of great importance.

PVP-Iodine containing preparations may be bandaged allowing exchange of humidity with the environment, but it is important to avoid occlusive conditions which could cause redness and skin irritation.

These products should not be used on deep wounds or serious burns without consulting a physician. Use should be discontinued if redness, irritation, swelling or pain persists or increases.

SCALP INFECTIONS:

Scalp and skin cleanser containing 7.5% PVP-Iodine has been reported to yield a significantly larger reduction of the microbial count in the scalp and hair versus products without PVP-Iodine.[54]

MINOR SKIN ABRASIONS:

Cuts, bruises and lacerations which demand immediate attention in order to avoid serious infections are suitable for treatment with PVP-Iodine.

GYNECOLOGICAL APPLICATIONS

Douche and vaginal suppositories containing 10% PVP-Iodine have been reported effective in the treatment of vaginal infections.[55-62] These can be used both as a topical and therapeutic agent for the treatment of birth-canal infections and for various forms of vaginitis.

DENTAL AND ORAL USE

PVP-Iodine has been reported as a very effective bactericide against organisms commonly found in the mouth and is able to destroy these within 15 seconds.[63]

Using a mouthwash/gargle product containing 0.5% PVP-Iodine is effective in reducing the bacterial flora in the mouth prior to dental surgery. It can also reduce the number of odor-causing bacteria.[64-68]

PVP-Iodine may cause less staining of the teeth verses chlorhexidine gluconate mouthwash.

PVP-Iodine has also been used to disinfect dental impressions made from silicon rubber and alginate.[69]

VETERINARY MEDICINE

PVP-Iodine products have been used topically in the treatment of various swellings, chronic inflammatory conditions, sprains, bruises, obstinate ulcers and to disinfect the umbilical stump of foals and calves.

Due to its low toxicity and highly effective antimicrobial activity, topical PVP-Iodine applications have particular advantages in treating skin infections of cats, dogs or other animals that lick wounds.

PVP-Iodine has also been found to be highly effective in treating bacterial and fungal fish infections and minimizes infection of fish eggs, thereby increasing the hatching yield.[70,71]

Additionally, scrub and antiseptic solutions containing PVP-Iodine have been reported as highly effective for use on dogs, cats and horses for various pre-surgical procedures.[72]

APPLICATIONS

TOPICAL

USE	PVP-IODINE PREPARATION
Antiseptic skin cleansers for pre-operative scrubbing and washing by surgeons and theatre staff and pre-operative preparation of patients' skin.	Surgical Scrub 7.5% w/v with non-ionic surfactants
Pre and post-operative antiseptic skin cleanser for major and minor surgical procedures.	Topical Solution 10% w/v Topical Alcoholic Solution 10% w/v Where quick drying effect is required
Skin cleanser for treatment of acne vulgaris. General disinfection of the skin.	Skin Cleanser / Liquid Soap 4% w/v
Treatment and prevention of infection in wounds, ulcers, burns and cuts.	Dry Powder Spray 2.5% w/v
Quick drying antiseptic for the treatment and prevention of infection. Useful against herpes simplex, herpes zoster, grazes, abrasions, cuts and wounds.	Antiseptic Paint 10% w/v
Treatment and prevention of infection in minor cuts and abrasions, minor surgical procedures and small areas of burns.	Ointment 10%w/v Dry Powder Spray 2.5% w/v
Treatment of infections in decubitus and stasis ulcers.	Ointment 10% w/v Dry Powder Spray 2.5% w/v
Treatment of seborrhoeic conditions of the scalp.	Shampoo 4% w/v Scalp and Skin Cleanser 7.5% w/v

APPLICATIONS

GYNECOLOGICAL

USE	PVP-IODINE PREPARATION
For vaginitis due to candidal, trichomonal, non-specific or mixed infections. Pre-operative preparation of the vagina.	Vaginal Gel 10% w/v Vaginal Pessaries 200mg Vaginal Douche Concentrate 10% w/v

DENTAL AND ORAL CARE

USE	PVP-IODINE PREPARATION
For treatment of acute mucosal infections of the mouth and pharynx. For oral hygiene prior to, during and after dental and oral surgery.	Gargle and Mouthwash 7.5%w/v Concentrated Solution requiring dilution 1:4 or 1:5 parts with water prior to use

APPLICATIONS

VETERINARY MEDICINE

USE	PVP-IODINE PREPARATION
Skin disinfection prior to injection or surgery.	Topical Solution 10% w/v Topical Alcoholic Solution 10% w/v Where quick drying effect is required
For use as an aid in the control of mastitis and teat sores in cattle. Used as a teat dip or as an udderwash. Suitable for cut teat and udder wounds. May be sprayed on teats at drying-off time to assist mastitis control. May also be used diluted for uterine instillation for endometritis.	Topical Solution (0.5% w/v available iodine) Spray / Mousse
For use on horses, cattle, swine, and sheep for aid in the treatment of foot rot, minor cuts, bruises, abrasions, and burns.	Ointment
As an aid in the treatment or prevention of local infections in cases of wounds, abscesses, burns and fungal infections e.g. disinfection of the naval, removal of horns, castration, ringworm.	Spray / Mousse

AQUACULTURE

USE	PVP-IODINE PREPARATION
Effective against the causative organisms of furunculosis adhering to outside of fish eggs. Also used for disinfection of material and equipment used in handling fish eggs. Bacterial and fungal infection of fish.	Solution (50ppm available iodine)

FORMULATIONS

FORMULATIONS

PVP-IODINE SOLUTION

INGREDIENTS	% w/w
PVP-Iodine	10
Citric Acid Phosphate Buffer Solution	90

METHOD OF MANUFACTURE

1. Dissolve the PVP-Iodine in the buffer solution.
2. The pH of the solution is 4.5.

PVP-IODINE SURGICAL SCRUB FORMULATION 1

INGREDIENTS	% w/w
PVP-Iodine	7.5
Sodium Lauryl Sulfate	15.0
Lauramide DEA	4.0
Water	73.5

METHOD OF MANUFACTURE

1. Dissolve the surfactants SLS and Lauramide DEA in water at 70˚C.
2. Add PVP-Iodine powder whilst stirring until a brown clear viscous solution is obtained.

STABILITY:

Under accelerated test conditions (14 days at 52˚C) the loss of available Iodine is about 12% so that a PVP-I overage calculated to 120% available Iodine should be used.

FORMULATIONS

PVP-IODINE SURGICAL SCRUB FORMULATION 2

INGREDIENTS	% w/w
PVP-Iodine	7.5
Ammonium-Nonoxynol-4 Sulfate	20.0
Lauramide DEA	1.2
Glycerol	20.0
Water	51.3

METHOD OF MANUFACTURE

1. Dissolve the surfactants in water at 70°C.
2. Add glycerol.
3. While stirring add the PVP-Iodine powder until a brown, clear, viscous solution is obtained.

STABILITY:

Under accelerated test conditions (14 days at 52°C) the loss of available Iodine is about 12% so that a PVP-I overage calculated to 120% available Iodine should be used.

PVP-IODINE SURGICAL SCRUB FORMULATION 3

INGREDIENTS	% w/w
PVP-Iodine	7.5
Ammonium-Nonoxynol-4 Sulfate	25.0
Lauramide DEA	4.0
Water	63.5

METHOD OF MANUFACTURE

1. Dissolve Lauramide DEA in water at 70°C.
2. Allow to cool to 40°C and then stir in the PVP-Iodine powder.
3. Add Ammonium Nonoxynol-4 Sulfate until a brown clear viscous solution is obtained.
4. The pH is around 3.5.

STABILITY:

Under storage at room temperature the available Iodine drops after 12 months to about 88% so that a PVP-I overage calculated to 120% available Iodine should be used.

FORMULATIONS

PVP-IODINE MOUSSE
11021-75-1

INGREDIENTS	% w/w
PVP-Iodine	2.000
Oleth-20	0.250
Citric Acid	0.014
Di-sodium Hydrogen Phosphate	0.030
Potassium Iodate	0.100
Sodium Hydroxide (to adjust pH to 5.8)	qs
Deionized Water	to 100.000

METHOD OF MANUFACTURE

1. Dissolve Oleth-20 in water.
2. Dissolve PVP-Iodine in water until homogeneous.
3. Add the rest of the ingredients in the order listed mixing well after each addition.
4. Adjust the pH to about 5.8.
5. Fill with propellant. (10% P/B)

PVP-IODINE SPRAY GEL
10586-83-4

INGREDIENTS	% w/w
Phase I	
Deionized Water	69.5
Aminomethyl Propanol	0.5
Acrylates/C10-30 Alkyl Acrylate Crosspolymer (Carbopol ETD 2020)	0.5
Phase II	
Deionized Water	20.0
Buffer pH 5.5	5.0
PVP-Iodine	2.5
Phase III	
Deionized Water	2.0

METHOD OF MANUFACTURE

1. Disperse the Acrylates/C10-30 Alkyl Acrylate Crosspolymer in the water of Phase I.
2. Dissolve the PVP Iodine in the water of Phase II and add the buffer.
3. Add Phase II to Phase I with thorough mixing.
4. Add Phase III with mixing until clear.

FORMULATIONS

PVP-IODINE VAGINAL DOUCHE

INGREDIENTS	% w/w
PVP-Iodine	10.0
Polyethylene glycol 400	0.5
Poloxamer 407 USP	0.3
Citric acid (0.1 molar solution)	43.2
$Na_2HPO_4 12H_2O$ (0.2 molar solution)	46.0

METHOD OF MANUFACTURE

1. Dissolve the PEG 400 in a mixture of the citric acid and phosphate buffer solutions.
2. Whilst stirring, add the PVP-Iodine and Poloxamer 407 until a clear brown solution is obtained.
3. The pH should be about 4.3.

PVP-IODINE VAGINAL PESSARIES

INGREDIENTS	% w/w	% w/w
PVP-Iodine (micronized)	5	10
PEG 400	10	5
PEG 1500		50
PEG 4000	85	35

METHOD OF MANUFACTURE

1. Melt the different PEG grades by slow warming.
2. Add with permanent stirring the micronized PVP-Iodine in small portions.
3. Continue stirring until a uniform brown suspension is obtained.
4. Pour into 2.0 gram pessary molds.

FORMULATIONS

PVP-IODINE TEAT DIP
10867-148-3

INGREDIENTS	% w/w
PVP-Iodine	5.00
Glycerin	4.00
Polysorbate-20	0.35
Sodium Hydroxide 10% (to adjust pH to 4.5 to 5.0)	qs
Deionized Water	to 100.000

METHOD OF MANUFACTURE

1. Dissolve PVP-Iodine in water until homogeneous.
2. Add Glycerin with mixing.
3. Dissolve Polysorbate 20 and mix until homogeneous.
4. Adjust the pH to about 4.5-5.0. Use Citric Acid solution if necessary.

PVP-IODINE TEAT DIP
10% STOCK SOLUTION

INGREDIENTS	% w/w
Phase I	
PVP-Iodine	10.00
Plasdone® S-630	1.00
Phase II	
Sodium Lauryl Sulfate	0.50
Phase III	
Sodium Biphosphate (Na_2HPO_4)	0.14
Sodium Citrate	0.03
Sodium Hydroxide Solution, 1 molar	2.08
Glycerol	1.00
Deionized Water	85.25

METHOD OF MANUFACTURE

1. Dissolve Phase II into Phase III with constant stirring.
2. Slowly add Phase I until a brown clear liquid is obtained.
3. The pH is 4.5.

REGULATORY AND SAFETY

Because of the product's wide usage and established efficacy, PVP-Iodine is presently included as an antiseptic agent in the USP, Ph. Eur. and JP as Povidone-Iodine. PVP-Iodine sold for medical applications is manufactured according to U.S. current Good Manufacturing Practices.

Toxicity test results, as well as usage for various medical conditions during the past approximately thirty-five years on many thousands of patients, all point to the safety and efficacy of products containing PVP-Iodine.

Compared to other iodine preparations, PVP-Iodine exhibits markedly lower oral toxicity. Consequently, the accidental ingestion of PVP-Iodine solutions is much less hazardous than from equal amounts of available iodine solutions. For this reason, PVP-Iodine solutions do not require the hazardous, poisonous warning labels on bottles that other iodine products must have.

Moreover, animal and human exposure tests have revealed virtually no skin reactions to PVP-Iodine, and only very mild transitory effects on mucous membranes.

These results are in marked contrast to the effects of elemental iodine, which is a primary irritant and sensitizer. Preparations containing elemental iodine with no PVP frequently delay the healing of wounds by inhibiting formation of granulation tissue. PVP-Iodine is unique in effectively minimizing or eliminating these undesirable effects. It may be left in contact with tissue for extended periods of time with no ill effects. Even non-occlusive bandages are permissible, whereas ordinary iodine preparations are not bandaged because the iodine sublimes onto protective coverings causing pronounced irritancy to the tissue.

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