

CHAPTER II

INFORMATION

POVIDONE-IODINE

Synonyms : 2-pyrrolidinone-1-ethenyl-, homopolymer,
compound with iodine
: Betadine (Purdue-Frederick)
: PVP-Iodine (GAF)
: 1-Vinyl-2-pyrrolidinone polymer, compound
with iodine
: $(C_6H_9NO)_n \times I$ [25655-41-8]

Description

Povidone-iodine (PVP-I) is a complex of iodine with povidone. It contains not less than 9.0 percent and not more than 12.0 percent of available iodine (I), calculated on the dried basis (8).

The complex is a yellowish-brown, amorphous powder, and has a slight characteristic odor. Its aqueous solution is acid to litmus. A 10% solution in water has a pH of 1.5 to 2.5 (6,9).

The concentration of free iodine is less than 1 ppm(6). The 99% of iodine is in the complexed state

(10). Sample of 10% PVP-I solution had free iodine values ranging 0.5 - 1.8 ppm (11).

At this point, it seems to be necessary to define some expressions normally used in connection with PVP-I (1).

available iodine = iodine that can be titrated
against sodium thiosulfate.

total iodine = available iodine + iodide.

free iodine = iodine that can be extracted
with heptane from an aqueous
PVP-I solution, or

= uncomplexed iodine that can
be determined in a dialysis
experiment, or

= free iodine that can be
determined in an
electrochemical model.

Solubility

PVP-I is soluble in water and alcohol but practically insoluble in chloroform, carbon tetrachloride, ether, acetone, heptane, hexane, and dichloromethane (6,9,12,13).

The good solubility of the PVP-I complex in water

results from the substantial number of pyrrolidone rings which are free, i.e., which are not involved in complexing. If the proportion of HI_3 in the adduct is increased to the point that the predominant proportion of the pyrrolidone rings participates in adduct formation, the complex loses its good solubility characteristics (10).

Incompatibility

PVP-I is not resistant to reductants, and its biocidal action is considerably reduced in strongly alkaline media. It has also been reported that PVP-I solutions become incompatible with Merfen^R and thimerosal, after several days' storage (14).

A mixture of equal parts of PVP-I solution and hydrogen peroxide 3% exploded about 100 minutes after dispensing. It was suggested that iodine had accelerated the decomposition of the peroxide liberating oxygen and the explosion had been caused by the inadvertent tightening of the cap on the bottle (13).

In a study on the effect of additives coformulated with iodophore PVP-I on the release of bound iodine, ethanol and benzalkonium chloride caused a significant release while polysorbate 80 had the least effect (15).

A pH reduction occurred when PVP-I solution and compound tincture of benzoin were combined in the liquid state. The reduction occurred immediately and continued for 24 hours. The reduction of pH was not observed when dried compound tincture of benzoin was added to PVP-I solution (16).

In the presence of increasing concentration of human serum albumin, the amount of available iodine in PVP-I preparations decreased (17).

Uses

PVP-I is an iodophore which slowly liberates inorganic iodine in contact with the skin and mucous membranes. PVP-I kills both gram-positive and gram-negative bacteria, fungi, viruses, protozoa and yeasts. It is used similarly to iodine and is employed for the treatments of contaminated wounds, preoperative preparation of the skin and vagina candidiasis, vaginal trichomoniasis, acne vulgaris, and other pyogenic or seborrhoeic infections of the scalp or skin. It has also been used in the treatment of eczematoid ringworm (13).

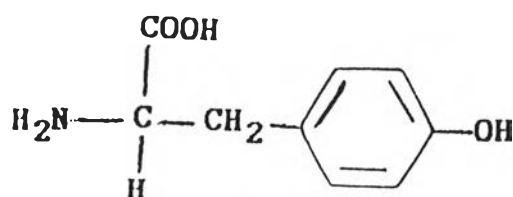
Mode of action

Vratsanos, S.M. et. al.(18) proposed the mechanism for the antibacterial action of PVP-I as a penetration of

the bacterial cell wall, and disorganization of the complex upon its contact with the protein- and lipid-rich cell membrane.

It has been found that iodine inactivated enzymes and proteins by

- reacting with thiol groups in cytoplasm (19).
- reacting with tyrosine (hydroxyl groups) (20).
- halogenation of tyrosine (21).



Tyrosine

Dose

Topical, 0.5 to 10% w/v of PVP-I (0.05 to 1.0% available iodine equivalent)

To the skin, 7.5 to 10% w/v of PVP-I, in various liquid forms, as ointment, or as aerosol; to the mouth and pharynx, 0.5 to 1% solution; vaginal mucosa as 0.5 to 1% solution or gel; for baths, from 30 to 50 ppm. Available iodine equivalents can be calculated by dividing the PVP-I concentration by 10 (6).

Forms of application

In the past, iodine preparations were known, and used as iodine tincture or Lugol's solution. Iodine was not used in other formulations. Only after PVP-I was developed was it possible to produce preparations for a very wide variety of forms of application. PVP-I preparations are therefore now used mainly as aqueous solution and liquids for general and surgical hand disinfection and for treatment of wounds. Formulations for PVP-I gel, cream, ointment, powder, spray, soap, pessary and teat dip are also wellknown (13,22).

Official dosage forms of PVP-I are (6)

Aerosol : 5%

Solution : 5, 7.5, 10 and 30% (some are diluted before use).

Also available as foam, gauze, mouthwash-gargle (0.5%), ointment (10%), shampoo (7.5%), surgical scrub/skin cleaner (7.5%), scrub applicator (2%), scrub solution (2%), swab (10%), vaginal douche (10%), whirl pool concentrate for bathing patients (10%).

The development of PVP-I is also made in the form of water disinfection tablet (23), encapsulated tablets (24,25). The recent development using PVP with a K value of 17 may open up new and improve therapeutic

possibilities for the treatment of large wounds and for use of the product in those body cavities where questions of resorption and excretion are relevant (10).

The interaction between PVP-I

If we examine the structural formula of PVP-I in the USP. monograph, it can be seen that no information whatsoever is given as to the way in which the iodine is bound to the PVP.

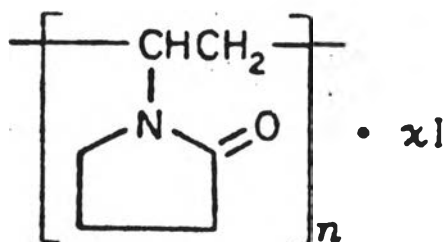


Figure 1 PVP-I USP.XXII

Vratsanos, S.M. (18) indicated that in efforts to discover how iodine was complexed by polyvinylpyrrolidone, PVP, extraordinary difficulties arised due to the nature of the components forming the complex. The polymer components exhibited considerable variation in its structure. Among a number of variables, the length of the chain, stereoregularity and possible branches to the chain were complicating factors. With regard to iodine, complications developed depending on whether iodine interacted alone or in the presence of

sources of iodide ion. Moreover, based on spectrophotometry findings, light absorption at 290 nm was not linearly dependent on concentration of aqueous PVP-I solution. He was convinced that the PVP-I complex underwent continuous structural changes when observed within the extremes of dilute aqueous solution.

Much insight into the nature of the interaction between PVP and iodine has been gained for many years. The details of the interaction were obviously complex. Most papers gave the results that supported each other, some did not. However, complete structure and interaction of PVP-I have not been clarified. The previous discussions have been reviewed as follows.

Spectrum of PVP-I

The absorption spectrum of PVP-I aqueous solution was recorded in Figure 2, together with spectrum of KI-iodine solution (26). The two peaks at 287 and 351 nm for KI-iodine solution were obviously originated from free triiodide anion. PVP-I solution gave the same shape of spectrum though the peaks were slightly red shifted.

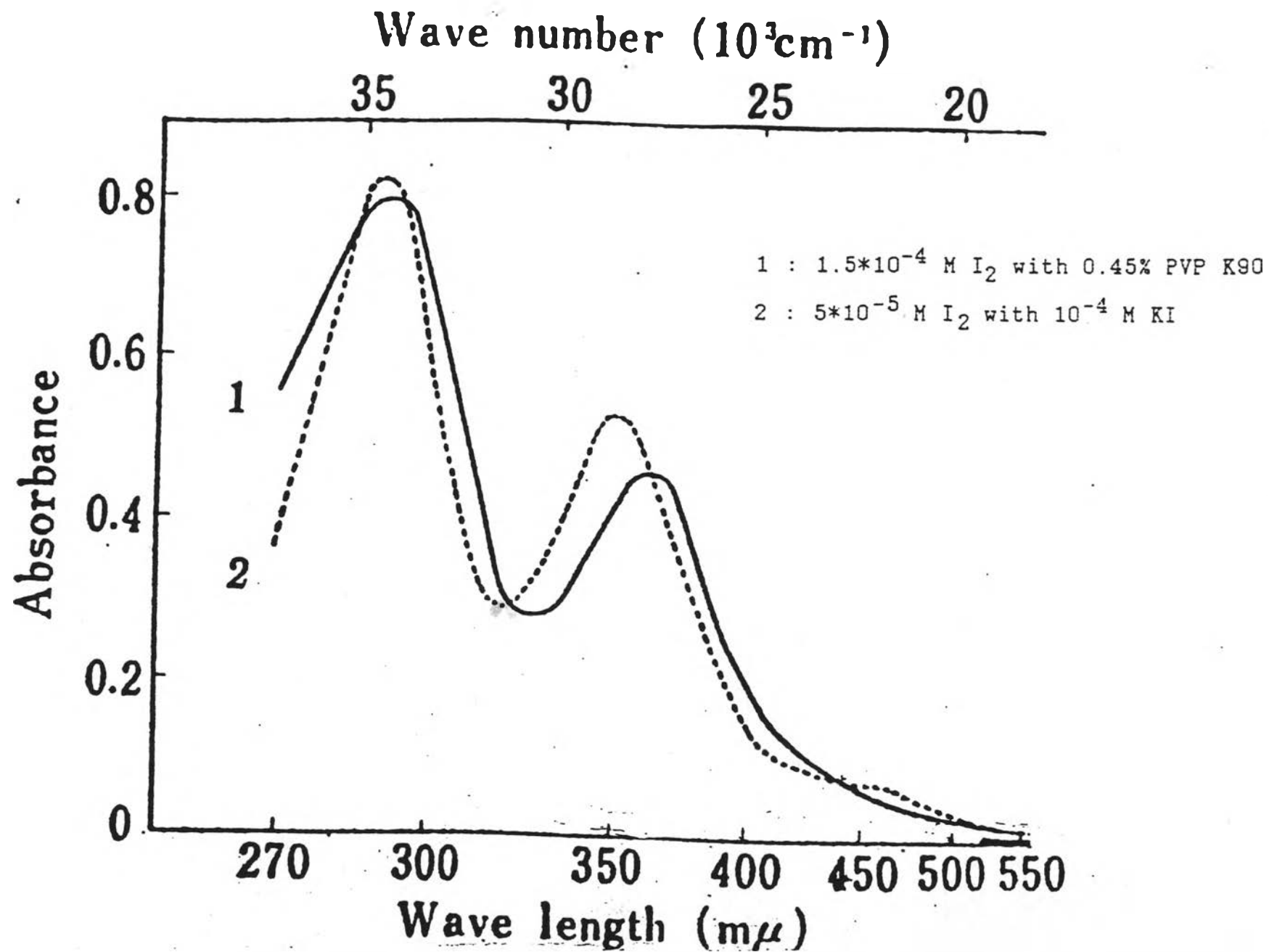


Figure 2 The absorption spectrum of PVP-I aqueous solution.

The reaction of PVP and iodine

The pioneering work in 1954, Oster, G. and Immergut, E.H. (27) showed that PVP altered the ultraviolet absorption spectrum of iodine at 290 nm. This indicated some interaction. They postulated that the first few iodine induced a helical form to PVP and then succeeding iodine atoms entered the interior of PVP helix.

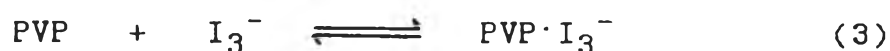
Barkin, S., et. al.(28) reported in 1955 that by viscosity experiments the interaction between iodine and PVP caused considerable changes of shape and size of dissolved polymer molecules.

In 1957, Siggia, S. (1) stated that when powders of iodine and PVP were mixed, there were some chemical reactions between the two; the iodine oxidized unsaturated end groups or residues in the PVP, resulting in formation of an amount of iodide ion so that no further loss of iodine occurred in the powder after the initial preparation.

Kaneniwa, N. and Ikekawa, A. (29) studied the interaction between PVP and iodine in 1974 and reported that iodine molecules were dissociated into triiodide anions or monoiodide anions by oxygen of carbonyl groups of PVP. Formation of N^+ in PVP molecules prevented

iodine molecules from dissociation.

Takikawa, K. , Nakano, M. and Arita, T. (30,31) studied the permeation pattern of iodine in PVP solution through silicone membrane and explained kinetic of hydrolysis of iodine in 1978. They concluded that PVP tended to accelerated hydrolysis of iodine except for the initial period of hydrolysis. Since at the beginning of hydrolysis, only a small amount of iodide was formed and the concentration of molecule iodine was much greater than that of triiodide ion, in the presence of PVP, iodine might form a weak complex with it and was less available for hydrolysis than in the absence of PVP. An alternative explanation was a possible change in activity of water in the presence of PVP. As the time elapse, the concentration of triiodide ion formed according to reaction 2 increased and formed complex with PVP. The possible mechanism of accelerated hydrolysis of iodine in the presence of PVP was complexation of triiodide ion with PVP and subsequent shifts in the hydrolysis equilibrium of iodine.



The state of iodine in PVP-I complex

It has been generally accepted that the complexation of iodine with PVP involves neutral as well as ionic iodine. In most cases the ionic iodine was believed to be the iodide ion.

From electrophoretic mobility study of the PVP-I complex of Barkin, S. (28) in 1955, the result clearly showed the anionic character of the polymer ion. They believed that only at high iodide concentrations could the composition of the complex between PVP and iodine be expressed by the formula $P \cdot I_3^-$, where as at smaller iodide concentrations there might be less than one negative charge per three iodine atom, i.e., $P \cdot I_5^-$, etc. and that a certain minimum number of I^- -ions was necessary in order to form a complex or adduct.

Eliassaf, J. (32) reported in 1966 that in water the tri-iodide ion is the binding species ; iodine molecules was also absorbed in chloroform solution. Also, Morigushi, I., Araki, Y., and Kaneniwa, N. (26) exhibited the absorption spectrum of PVP-I in 1974 and concluded that the complex included a combined tri-iodide anion in the structure.

The result of the investigation of Mokhnach, V.O., and Propp, L.N. (33,34) in 1968 gave conflicting

evidence. They reported that iodine in PVP-I complex existed in both I^+ and I^- states. Their conclusion was encouraged by Cournoyer, R.F. and Siggia, S.'s experiments in 1974 (35,36). They prepared nonsolvent mixing of PVP with crystalline iodine. The iodine was shown to undergo hydrolysis with moisture in the polymer to give iodide (I^-) and hypiodite (IO^-). The ionic forms of iodine appear to associate with the molecular iodine, resulting in the final stable PVP-I complex. The role of the PVP is thought to be that of providing an environment conducive to the hydrolysis and association phenomena involved in the complexation step. The affinity of PVP and iodine for one another is proposed to be the result of the summation of many small interactions between the two species.

Directly opposite, Shenck, H.U., and Simak, P. (10,37) suggested in 1980 that it had been unable to find any indication that solid commercial PVP-I contains any substantial amounts of iodine in oxidation levels -1 and +1, e.g., I^- and IO^- , alongside one another and the quality of the complex is critically affected by whether a sufficient amount of I^- is present.

In 1983, Gottardi, W. (38) again proposed that the amount of iodine which is complex bound to the povidone matrix consists of HI_3^- and I_2^- group.

The bond and the structure of PVP-I complex

Morigushi, I., et. al. in 1969 (26) found that complexation appeared generally dependent of the size of PVP. Therefore, the complexation between PVP and iodine might be attributed to Van der Waals forces or the like as well as charge transfer force. PVP formed a charge transfer complex with iodine in non-polar solvent and the complex was immediately converted into ionic structure in polar media.

Schenck, H.U., et. al. (37) investigated the structure of PVP-I by IR spectroscopy and X-ray structure analysis in 1980. They proposed that in protogenic solvent as methanol or water iodine was complexed to the polymer via a short hydrogen bond between two carbonyl groups of two pyrrolidone rings and that a triiodide anion was bound ionically to this cation. However, it seemed impossible for all pyrrolidone rings to take part in adduct formation (Figure 3). If there were about 18-20 pyrrolidone rings for every hydrogen triiodide, complexation was good and the excess pyrrolidone rings not taking part in the complexation provided the desired water solubility.

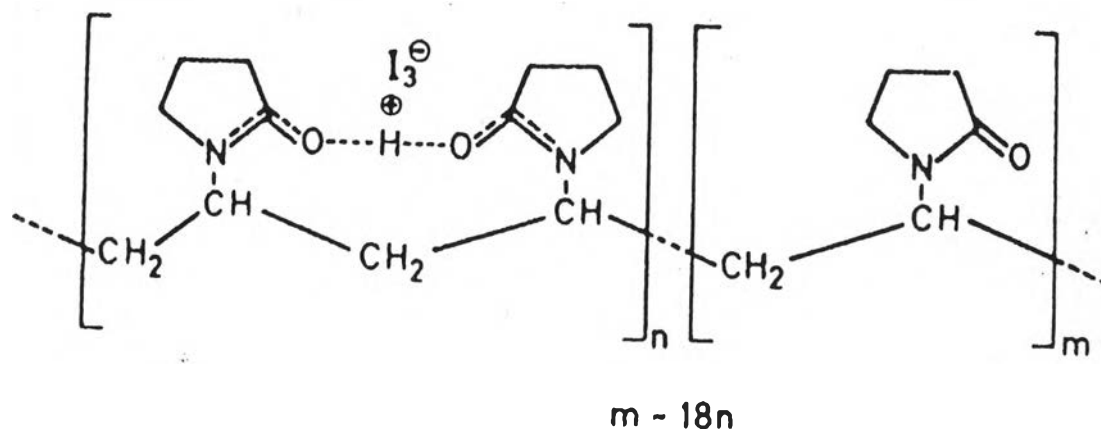


Figure 3 Proposed structure of PVP-I

Sus, T.A., Karaputadze, T.M., and Kirsh, Yu.E. (39) reported in 1981 that the main factor promoting complex formation between I_3^- and vinyl polymers containing an amide side group in aqueous solutions is the participation of H_2O molecules in bonding I_3^- with the carbonyl of the amide group in a partially dehydrated region around the chain by forming H-bond with units of the polymer chain and with the sorbed small molecule.

Based on the spectrophotometric and potentiometric evidences in 1983, Vratsanos, S.M. (18) reported a model of the PVP-I structure. The "stepwise complex formation" and the "chelate effect" were accepted as basic mechanisms. Iodine located in the hydrophobic cavity of PVP chain in helical folding. Each turn of the

helix consisted of about 14 polymer units surrounding one iodine molecule. The 14:1 ratio should be considered rather a structural parameter for the requirement of 14 polymer units to complete one turn of the helix around one iodine molecule. Adsorption of iodine might be the initial process in a stepwise complex formation, and also the final effect after the end-point of the PVP-I interaction. However, it proved more difficult to elucidate whether the chromophores was the iodine molecule or triiodide or a mixture of iodine and iodide in varying proportions.

Factors affecting complexing degree

Eliassaf, J. (32) studied the binding of iodine to PVP in aqueous potassium iodide solutions potentiometrically. The number of monomeric units of PVP binding one molecule of I_2 , increased with increasing temperature and decreased with increasing molecular weight of PVP. The binding capacity of PVP for iodine was increased by addition of sodium sulfate (Na_2SO_4).

Barbara, L. (40) stated that the complexing degree of iodine increased with the molecular weight and concentration of PVP in the aqueous phase.

Kirsh, Yu.E., Karapudtadze, T.A. (41) discovered that the ability of PVP to bind I_3^- ions depended on the

molecular weight of the macromolecule being in the range from 2.5×10^4 to 100 (molecular weight of analogue).

The release of available iodine from PVP-I

Shenck, H.U., et.al.(10) proposed the kinetics of the release of available iodine from PVP-I by stopped-flow method in aqueous solution. The results showed that PVP-I acted as a stable depot for iodine from which iodine is released very quickly if it was consumed by reduction as was the case when it acted as a disinfectant.

Stability study

The older literature includes many examples of stability data that have been presented in much the same manner as product-development reports. There was no the study of pH log profiles of PVP-I solution. Many papers present table showing stability assay results after methods were developed and the PVP-I product were stored under the usual accelerated conditions, or tables indicating compositional changes induced or prevented when modifications were made in the method under study. For example, the study of the effect of moisture content in PVP before mixing with iodine by hot formulation, the table showed percent of H_2O in original PVP and percent loss of available iodine in storage of 10%PVP-I solution at

42 °C for 10 days (26).

Table 2 Percent loss of available iodine in storage of 10% PVP-I solution at 42°C for 10 days

% H ₂ O in original PVP	% loss of available iodine
1.1	12
2.7	6
4.9	2
6.5	1
9.1	1
13.2	1

In the modification of Denzinger, W. (42), 82.5 parts PVP with K-value 31.5 and water content 2.7% was mixed with 3.5 parts ammonium bicarbonate and 17.5 parts iodine and heated 1 hour at 50 °C and 8 hours at 100 °C to give PVP-I with available iodine 11.3%, iodide content 5.6%. Iodine loss 5.3% after 15 hours at 80 °C.

The stability in finished preparations is more difficult to assess because it depends greatly on the adjuvants. A rough guide can be obtained by projecting the results of short-term tests to estimate the long-term stability.

The following simple test is used to assess the stability of PVP-I from BASF manufacturer. Make up a

solution of PVP-I that contains exactly 1% of available iodine. Store it in a glass bottle for 14 days at 52°C. Determine the available iodine and calculate the loss of iodine. The loss of iodine is included in the sales product name, for example, PVP-I 30/06. The first figure indicates the average K-value of the starting PVP. The second figure indicates the percent of iodine loss of the individual PVP-I types under the conditions described above.

Factor affecting stability of PVP-I in powder and solution form

1. Process of the preparation of PVP-I and complex formation.

1.1 preparation method : hot formulation, cold formulation etc.

1.2 the appropriate ratio of PVP to iodine or iodide

1.3 addition of some material in preparation process, e.g., citric acid, sodium bicarbonate.

2. Quality of PVP

2.1 molecular weight of PVP

2.2 moisture of PVP

2.3 PVP preparation

3. pH of PVP-I preparation

4. buffer
5. storage temperature
6. the appropriate container
7. incompatibility

1. Process of the preparation of PVP-I and complex formation

1.1 Preparation method

The original wet process by Shelanski, H.A. in 1949 (2) was prepared by adding a solution of iodine, such as Lugol's solution or tincture of iodine to an aqueous solution of PVP.

To improve the method for preparing PVP-I whereby a more stable composition is formed, there were many applications with different technical method.

1.1.1 Hot formulation :

As disclosed in the paper of Beller, H. and Hosmer, W.A. in 1955 (2), PVP-I composition was prepared by thoroughly mixing dry elemental iodine and dry powdered PVP until a homogenous powdered is obtained (about 6-24 hours), then heating the dry blended material to a temperature of the order of 90-100°C. Some slight stirring was advantageous during this heating in order to assure a uniform product. The heating should be

continued until the ratio of available iodine to iodide ion was substantially 2:1 (for periods of 18 to 24 hours or longer). The heating completed the process of formulation of a complex in which the iodine was chemically available but not free because heating lessened vapor pressure of one sample until zero at 55°C.

1.1.2 Cold formulation :

In 1862, Cantor, A. and Winicov, M.W. (43) discovered cold formulation for preparing PVP-I to improved and simplified the prior art. The complexing of iodine with PVP in aqueous solution can be enhanced by including in PVP-I formulation a source of iodide ion, such for example as HI or an alkali metal iodide in amounts exceeding the amount of iodide formed by interaction of iodine and PVP according to the hot formulation process. The complex was prepared by mechanical blending at room temperature in sealed container for a period of about 24 hours. This method was more convenient than before and of special significance was the fact that the incorporation of iodide in accordance with the present invention permitted the preparations of stable compositions at the practical 1% iodine level containing as little as 3:1 to 5:1 ratio of PVP to iodine. Whereas, heretofore, this was impossible, and the normal practice had been employed

about a 10:1 ratio of PVP to iodine to provide satisfactory 1% iodine solutions.

However, it had been found that the bonding of iodine in this cold formulated composition was inadequate in that the iodine vapor pressure was sufficiently high to develop a distinct iodine odor in closed containers and permit gradual loss of iodine if stored in an open or improperly sealed container.

This problem was not encountered with properly formulated PVP-I complexes prepared by the hot formulating process above mentioned but the hot process was inherently expensive and time consuming, requiring special equipment to accomplish the heating and mixing in a closed system.

Cantor, A., et.al. (44) developed their previous process in 1975. It was discovered in accordance with the new invention that the iodine vapor pressure problem associated with poor complexing of elemental iodine could be completely eliminated. An improved process was prepared by first forming a solid PVP-iodide composition and then cold mixing this material with elemental iodine within a period of about 2-3 hours. The new PVP-iodide composition was prepared by drying solutions containing the PVP and iodide in the proper proportions. The drying

can be accomplished in various ways as for example by evaporation and casting or grinding the resulting solid to a desired particle size, by drum drying to produce a flake material, or by spray drying.

The new approach, therefore, provided the double advantage of substantially shortening and simplifying the formulation or manufacturing procedure as compared with the hot process, and distinctly superior single phase solid product as compared with the product according to former cold process. In this single product, they claimed that the iodine was truly complexed with a substantial elimination of significant iodine vapor pressure during storage of powdered product.

Besides the process above mentioned, there are many papers to develop and simplify the method of preparation. The complexes were prepared both in solid and solution forms. There is no evidence that new method will provide more stable products than former two methods. However, the procedure that is official in pharmacopoeia (26) is as followed. Povidone having an average weight of 40,000 is heated with elemental iodine in the presence of a little water whereby a small amount of the iodine enters into loose organic union with the polymer to form a compound which contains approximately 10% available iodine.

1.1.3 Oxidation process :

In 1960, Arturo Esquefa Sist, D. (45) initiated a new method by adding HI to solution containing PVP and an oxidizing agent (e.g. O, hydrogen peroxide at 5-10°C).

Shetty, Bola Vithal (46) reported that PVP-I might be prepared by reaction PVP with a mixture of iodide and iodate salts, rather than with iodine as in the conventional process. Other oxidizing agents, e.g. bromate, hydrogen peroxide, and persulfate salt might be used in place of iodate. The process was that 10 gm PVP (average molecular weight 40,000) was dissolved in 50 ml distilled water and 1 g potassium iodide was added. When the potassium iodide was dissolved, 0.1 M potassium iodate was added in small portions (about 1 g) until no more free iodide was present. The product contained 9.95% iodine, and was stable over long periods even at elevated temperature.

In 1983, Lorduy Ores, L. (47) again prepared by oxidizing iodide with hydrogen peroxide in an acidified PVP solution at room temperature for 4 hours to yield a solution of PVP-I. The oxidation could be accelerated by heating to 90-95°C for 1 hour. The PVP-I solution was relatively stable for at least 15 weeks.

Franquesa Graner, Roman (48), in 1986, prepared aqueous PVP-I by adding an aqueous solution of potassium iodide to an aqueous solution of PVP, then adding an aqueous solution of potassium iodate, and finally adding sufficient dilute hydrochloric acid to bring about complete reaction of potassium iodate with potassium iodide to form iodine.

1.1.4 Other process :

Nicolas, S. (49) reported, in 1979, that the PVP-I solutions were prepared by adding water to solution of PVP and halogens in solvents having a lower boiling point than, and forming no azeotrops with water (H_2O), and heating to distilled the solvent.

Oita, Nicolae et.al. (50) developed new method in 1978. Soluble complexes of iodine with PVP were obtained by mixing iodine with PVP in 1:3 to 1:5 ratio in a common solvent, preferably 1,2 dichloroethane ($ClCH_2CH_2Cl$), followed by precipitation with petroleum ether.

In 1980, Hafer, P. (51) search for PVP-I preparation. Iodophor powders were prepared by suspending the iodophor-forming organic substance in a solution of iodine in a solvent in which the iodophor-former is insoluble and adding iodide in a solvent that was miscible with the solvent for the iodine. The

experiment was made, 8.5 g PVP was suspended in a solution of 1.1 g iodine in 20 ml ligroin and 0.363 ml 56% hydrogen iodide (HI) in 5 ml acetone added slowly.

Dantas, R, and Green, R. (52) discovered a catalyst for mixing PVP with iodine in aqueous state in 1984. The catalyst was prepared by adding 0.005 part of a 0.012 m solution of mercury- α -(p-hydroxyphenyl) - α - (4-oxo-2,5-cyclohexadien-1-ylidien)-o-toluate (phenolphthalein Hg salt) in ethanol to 1.995 parts 2.5 m potassium hydroxide (KOH).

1.2 The appropriate ratio of PVP to iodine and iodide

The proportions of PVP to iodide in the PVP-iodide composition of latter cold formulation should be in the range of about 2:1 to 8:1. On the mechanically blending elemental iodine with powdered PVP-iodide, PVP:iodine ratio was preferably in the range of about 2:1 to 10:1.

1.3 Addition of some material in preparations process

Saijiro, N. (53) reported that PVP-I aqueous solution was stabilized with potassium iodide. This iodine content in the solution was constant for > 1 year.

On the contrary, Gazarov, R.A., et.al. (54) did not confirm the beneficial effect of potassium iodide (KI), frequently added to the reaction and supposedly participating in the complexing as improving stability of the complex.

Leveen, Harry H. and Joyce, Patrick j. (55) discovered that compounds having prolonged microbiocidal activity contained free iodine, PVP (MW.10,000-500,000) and a high MW. acidic material. These compositions are protected against iodine to iodide conversion and consequent deterioration by the interaction of the alkaline environment.

Denzinger, W. (42) treated powdered PVP with iodine at 70-100°C in the presence of formic acid, oxalic acid or an ammonium salt or amide of carbonic, formic or oxalic. PVP-I prepared by this method with available iodine 11.3%, iodide content 5.6% lost iodine 5.3% after 15 hours at 80°C. They again developed by treating PVP with iodine in the presence of said materials in aqueous solution. Iodine loss was 2.8% in 20 hours at 20°C from the product containing 4.1% available iodine.

Trubitsyna, S.N.(56) reported the effect of addition of citric acid that the yield and iodine content of a PVP-citric acid-iodine complex were independent of

the reaction time, while increasing with rising concentration of PVP. With increasing concentration of citric acid, the yield increased as well but the iodine content decreased due to iodine competition with citric acid. The complex was amorphous and had low thermal stability compared with a PVP-I complex, due to structural deterioration caused by H-bonding between PVP and citric acid.

2. Quality of PVP

Cox, H.L.M.(57) found that the gradual decrease in available iodine content and pH of PVP-I complex solution during storage were minimized by use of PVP of high quality (Plasdone K25 or Plasdone C30) which was only slightly oxidized by iodine.

2.1 Molecular weight of PVP

In practicing of Siggia, S. invention with hot formulation (58), it was preferable to use a PVP having a K value of at least 20, and more preferable about 30. It had been found that PVP of low K-value (and corresponding low molecular weight) consumed more iodine than PVP of higher K-value. Also, the stability of the PVP-I complex obtained when using PVP of low K-value was not as great as the stability of the PVP-I adduct made from PVP of higher K-value. Optimum K-value was about 30. Further

increased in the K-value of the PVP was without substantial effect on the properties of the resulting adduct with iodine, until the K-value became 90, at which time the solubility of the PVP in water, being to decrease substantially.

By consideration of the two BASF PVP-I product (PVP-Iodine 30/06, PVP-Iodine 17/12), the second figure of the product name indicate the iodine loss under the condition previously described (stability study section), we can see that PVP-I of low MW. degrades faster than that of higher MW.. Takikawa, K., et.al.(31) explained that iodine was expected to react with terminal unsaturated groups in PVP. The lower MW. (lower K-value) the larger the number of end groups per gram PVP.

2.2 Moisture of PVP molecule

Siggia, S. (58) also studied the effect of moisture of PVP on the stability of PVP prepared by hot formulation. It was definitely preferable that the moisture content of PVP, blended with the iodine, have a minimum of about 6% moisture content. Maximum stability was obtained in aqueous solutions of the resulting product. Increasing the amount of moisture in the PVP used for blending did not result in further increase stability. The maximum amount of moisture obtained

should be about 15%, since, at higher moisture content, mechanical difficulties in processing arised.

2.3 PVP Preparation

Herrle, Karl et.al. (59) found that PVP-I compound prepared with PVP obtained by free radical polymerization in an alcohol or toluene had a longer shelf life, compared with PVP-I compound prepared with PVP obtained by free radical polymerization in water.

Denzinger, W., et. al.(60) reported that treating iodine with hydrogenated PVP by conventional method gave compounds with improved stability. The 83 parts hydrogenated PVP was mixed with 17 parts iodine powder in a drum for 5 hours at 90°C, giving an adduct which loss 35% iodine in 20 hours at 90°C, compared with 70% when prepared from unhydrogenated PVP.

Karaputadze, T.M. (61) reported that PVP, prepared by the polymerization of vinylpyrrolidone (VP) in system containing hydrogen peroxide (H₂O₂) and ammonia (NH₃), should not be used for the preparation of PVP-I solution because the presence of impurities such as vinyl pyrrolidone decrease the stability of PVP-I. The impurities α -pyrrolidone present in PVP did not affect the stability of PVP-I.

3. pH of PVP-I solution

USP.XXII limits the pH of PVP-I solution not more than 6.

Leveen, Hary H., et.al. (55) informed that PVP-I deteriorated by the interaction in the alkaline environment.

The solutions adjusted to near neutrality by alkaline agent, especially sodium bicarbonate, had tendency to lose their available iodine activity quite rapidly because of the shift of the hydrolysis equation to the right.



4. buffer

It has been revealed (62) that the appropriate method to adjust the neutrality of PVP-I solution with sodium bicarbonate is dry blending 16-20 parts by weight of sodium bicarbonate per 100 parts by weight of the PVP-I composition having an available iodine content from 8-15% and an available iodide content from 0.98 to 5.6% for a period of time ranging from 6 to 36 hours. The resulting product was dissolved in water to form essentially neutral solutions (having a pH range from 6.6 to 6.9).

The complex of PVP-citric acid-iodine system has said to be amorphous and low thermal stability compared with a normal PVP-I complex (56).

The effect of each buffer in PVP-I solution has not been compared.

5. Storage temperature

Cox, H.L.M. (57) prepared PVP-I solution containing iodine 1.15 g, potassium iodide 1.4 g, Plasdone K25 8 g, citric acid 85 mg, sodium phosphate 500 mg and water to 100 ml. Stability was greater at 3°C than at room temperature.

6. The suitable container

Containers that have been designed in PVP-I experiments are glass stoppered bottle (27), brown glass bottle and polyethylene bottle (57). Metal containers are not recommended to use because it will be oxidized by iodine.

However, there are no papers about the effect of containers on PVP-I stability.

7. Incompatibility

It has been found that PVP-I solution is incompatible with compound tincture of benzoin in liquid

state, 3% hydrogen peroxide, ethanol, benzalkonium chloride, and human serum albumin (2,16,18,38).