# CHAPTER I

## INTRODUCTION

Following its discovery in 1811 by the French chemist and saltpeter manufacterer Courtiois of Dijon, who produced iodine by treating seaweed with sulphuric acid, this substance was used in a variety of forms as an antiseptic in medicine. Iodine acts as a multivalent, local, broad-spectrum antiseptic having bactericidal, fungicidal, sporocidal, protocidal, and virucidal properties (1). Iodine, whether as a tincture or a Lugolic solution, has long been used for the fine disinfection of minor wounds. Although iodine formulations are very effective, their range of application is limited by the associated side reactions, includings allergies and pronounced irritation.

In 1949, in the USA, Shelankski developed the iodophores and povidone-iodine (PVP-I) in particular and this represented a dicisive step forward, in that it was now possible to have iodine in which the microbiocidal effectivity was retained, but the disadvantages of iodine previously experienced, such as iodism, asthma, skin irritation, allergy etc.,were virtually eliminated, i.e. with these preparations the therapeutical index was

increased so significantly that the effectivity was virtually ideal and yet the substance was compatible in human (2).

Iodine is strongly "complexed" by PVP. Polyvinylpyrrolidone (PVP) is a water-soluble polymer which is physiologically acceptable to animals and human. It has been used as a blood plasma extender, drug vehicle, suspending agent (protective colloid), and tableting aid. This material, made by the polymerization of vinylpyrrolidone, has the ability to combine with many materials, and thereby often markedly changing their physical and toxicological properties.

The advantages of PVP-I over free iodine (1,3)

1.PVP will solubilize iodine, thereby making possible aqueous solutions of higher iodine content. Iodine alone is soluble to the extent of 0.034% in water at 25$^{o}$C whereas it is soluble to the extent of 0.58% in a 1% aqueous PVP solution under the same condition, a 17-fold increase caused by 1% PVP. It is possible to make aqueous solutions containing 10% of available iodine with the use of large amounts of PVP. Also, PVP-I complex powder is quite water soluble. It is more water soluble than iodine alone.

2.The PVP-I solution and powder are quite stable

to storage since the iodine vapor pressure is reduced essentially to zero, and the PVP-I complex is also quite chemically stable.

3.The oral toxicity of iodine is reduced by the PVP, probably due to the fact that the iodine is not present as such but tied up by the PVP. This permits the internal use of large amounts of iodine without toxic effects.

4.The incorporation of iodine with PVP also eliminates or at least lessens the irritation experienced in the use of other iodine preparations comparable strength. When used in open wounds, the sensation reported range from "no sting" to "very slight sting".

5.Preparations for PVP-I for skin disinfection leave enough stain on the skin to show the surgeon that the surface has been treated but this, unlike the stain left by many other skin preparations, can be removed with soap and water.

To summarize, the general properties and the bacteriological efficacy of conventional iodine solutions are compared againts those of PVP-I solution by the following table.

Table 1 The comparison of the general physiological properties and bacteriological efficacy of conventional iodine solutions against those of PVP-I solutions.(BASF)

| General physiological properties and bacteriological efficacy | Conventional iodine solution | Aqueous PVP-I solution |
|---|---|---|
| -Overall effectivity | ++ | ++ |
| -Influences of impurities (organic substance) | slight | slight |
| -Virus inactivation | ++ | ++ |
| -Toxicity | comparatively toxic | practically non- toxic |
| -Skin irritation | primary irritation | no |
| -Sensitization | do | hardly |
| -Allergies | occur | any |
| -Use on mucous membrane | not possible | possible |
| -Removal of stains from fabrics | hardly | do |
| -Vapour pressure | yes | no |

note ++ = Both preparations showed the same degree of microbiocidal effectivity and virus inactivation.

Today, PVP-I is one of the most important disinfectants used on clinics, medical practice, the household and in animal bleeding. As a result of its advantage over iodine preparations and popularity as a versatile antiseptic, many preparations of PVP-I have received considerable attention from manufacturers. There are many articles about the development of products in powder, cream, ointment, and aerosol spray. However, the general dosage form to formulate is topical solution. The stability in finished preparation depends greatly on the adjuvants and environmental variation. In addition, the problem in formulating solution dosage form is rapid decrease of pH and available iodine.

A general procedure for the preparation of liquid formulations for external use of pharmaceuticals would involve 1) proper selection and use of solvents and vehicles for addition of solid substance in aqueous or non aqueous medium, as the case may require, and 2) in case of incompatibility, determining of the appropriate order of mixing or choice of suitable adjuvants to produce a pharmaceutically acceptable product (4). In addition, a drug product may become a useless and even hazardous therapeutic agent if it reacts with packaging materials or decomposes because of improper storage (5). Solutions to be applied to tissue are liable to cause

irritation if their pH is greatly removed from the normal pH of the applied surface. The external or outer surface of the skin, the epidermis, is the site of medicated application. It is covered with a discontinuous surface film of emulsified lipid. This lipid film usually has a pH on the acid side, from about 4.5 to 6.5, with an average of 5.3 to 5.6. One theory is that the pH of ointment should be about 5.5, so as not to interfere with the normal pH of the skin (4,6). Therefore, pH of topical preparations in manufacturing is always adjusted to nearly the normal pH of the area with which they come in contact. Also, the pH of the sample in the experiments is adjusted to 5.5. The selected buffers (phosphate, acetate and citrate buffer) are commonly used pharmaceutical buffer at pH about 5.5 (7).

Proposed Investigation

The purpose of this investigation is to assess the effects of some selected buffers used in pharmaceutical industry on the stability of PVP-I solution and to find the effective concentration of buffer for PVP-I solution. Other factors that may affect the stability of PVP-I solution such as temperature variation (60, 45, 40, 35$^{o}$C), sources of solvents (single distilled water, deionized water, potable water) and containers (ambered glass bottle, clear glass bottle,

various types of polyethylene bottle) also will be considered.

The outline of this investigation is as followed :

1.Preliminary study on the optimum duration for incubation of PVP-I solutions in stability test.

2.Evaluation of PVP-I solution containing different buffer at various concentrations (0.05M, 0.10M, 0.15M) by accelerated stability testing.

3.Comparison of the effect of each buffer on two considerations. first, ability to maintain pH of the solutions and, second, the effect on degradation of PVP-I (by determining of available iodine remained).

4.Selection of the effective buffer with appropriate concentration.

5.Based on information from 4, the suitable formulation was used to evaluate various solvents (single distilled water, deionized water, potable water) and packaging materials (ambered glass bottle, clear glass bottle, various types of polyethylene bottle).