Physicochemical Basic for the Microbicidal Action of Aqueous Solution of Polyvinylpyrrolidinone-Iodine

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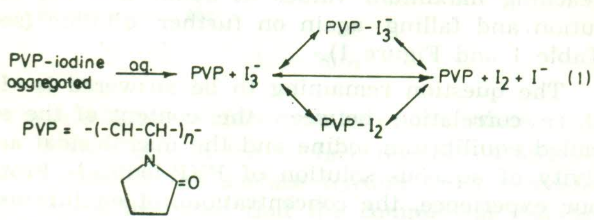
A new potency coefficient, named disinfectant activity coefficient (*k*), for aqueous polyvinylpyrrolidinone-iodine (PVP-iodine) solutions is proposed. The K index, which is a sum of the following four terms: fluidity, surface tension, redox potential and osmolality, gives good correlation with the germicidal activity at different dilutions of PVP-iodine. Mathematical expressions are presented for each term of the K index.

Introduction

At first sight, it might appear as though a substance such as PVP-iodine, which has been known for almost 30 years and which has been used very successfully for over 20 years as a local broad-spectrum antiseptic, requires no further discussion with respect to its analytical aspect. However, as a result of a recent work in this field, it has become necessary to investigate the particular and possibly surprising properties of PVP-iodine[1]. The works of *Gottardi*[2] (1983) and *Pollack & Iny*[3,4] (1985, 1986) may be mentioned as relevant. Moreover, the first part of the 3rd World Congress of Antisepsis, which was held in London in 1984, considered the role of free noncomplex iodine on the effectiveness of PVP-iodine solutions[6].

In antiseptic aqueous solutions containing polymers with iodophor properties, the chemistry of iodine is complex since macromolecules interact with iodine forms:



The iodine moiety of PVP-iodine complex is present in an aqueous iodophor solution in the different thermodynamically stable anionic iodine species and as diatomic iodine. According to many authors[2–5], it is the equilibrium iodine alone that exerts the antiseptic action of the preparation at any given moment. Efforts were directed towards developing methods of measuring the quantitative extent of complexing between the iodine and the organic polymer in order to formulate iodophor antiseptical preparations with improved stability and reproducibility.

The aim of this paper is to propose a new potency coefficient. The significance of the »disinfection activity coefficient of a solution« (*k*) can be described in detail with its relevance to the bactericidal activity of dilute preparations of PVP-iodine solutions.

Materials and methods

Materials

PVP-iodine solutions were provided by the company »Mundipharma GmbH«, Limburg. Solutions of different PVP-iodine mass fractions (10 — 0.05%) were prepared by diluting a $w = 10\%$ PVP-iodine stock solution with sterile water.

Determination of bactericidal activity

The bactericidal activity was examined against *Staphylococcus aureus* by a modified in vitro method recommended in the Guidelines for testing and assessing chemical methods of disinfection[7]. The exposition time was 30s. The bactericidal activity of solutions was expressed by f_{RF} (reduction factor) values:

$$f_{RF} = \log_{10} n_1 - \log_{10} n_2 \qquad (2)$$

where

n_1 = the number of colony forming units per ml without action of the preparation,

n_2 = the number of colony forming units per ml after action of the preparation.

Determination of the physicochemical parameter values

The physicochemical constants were determined at 25 °C.

The viscosity of PVP-iodine solutions with varying concentrations were measured on an Oswald viscosimeter[11].

The surface tension of the solutions was determined with a stalagmometer[12].

For measurements of the total osmolality, a »KNAUER« vapor-pressure osmometer with a universal termistor was used[13].

Results and discussion

Our results obtained for bactericidal activity of PVP-iodine solution in various dilutions are presented in Table 1 and Figure 1.

Our results obtained for physicochemical parameter values of PVP-iodine stock solution in various dilutions are presented in Table 2.

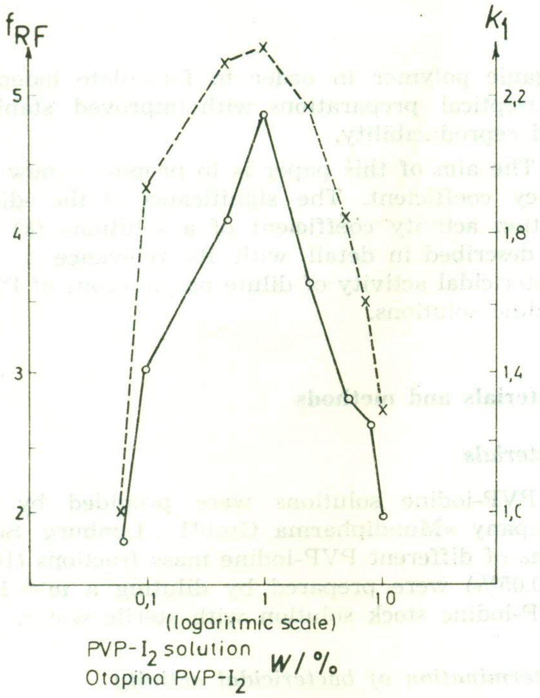


Fig. 1 — *Relationship of reduction factor (f_{RF}) for S. aureus (o———o) and disinfection activity coefficient of solution (k_1) for short action time (x———x) against different concenntrations of an aqueous PVP-iodine solution.*

Slika 1 — *Ovisnost faktora redukcije (f_{RF}) za S. aureus (o———o) i koeficijenta dezinfekcijske aktivnosti otopina (k_1) za kratko vrijeme djelovanja (x———x) i sadržaja PVP-joda u otopini.*

Table 1 — Bactericidal activity of PVP-iodine solution in varying mass fractions on *Staphylococcus aureus*. Exposure time 30 s

Tablica 1 — Baktericidna aktivnost PVP-jodnih otopina različitih masenih udjela za *Staphylococcus aureus*. Vrijeme djelovanja 30 s.

PVP-iodine solution w/%	10	7.5	2.5	5	1	0.5	0.1	0.05
log n_1	6.89	6.89	6.89	6.89	6.89	6.89	6.89	6.89
log n_2	4.92	4.26	4.08	3.25	2.02	2.78	3.87	5.09
f_{RF}	1.97	2.63	2.81	3.64	4.87	4.11	3.02	1.80

Table 2 — *Viscosity (η), Surface tension (σ), Redox potential (μ) and Osmolality (o) of PVP-iodine solution in varying dilutions.*

Tablica 2 — *Viskoznost (η), površinska napetost (σ), redoks potencijal (μ) i osmolarnost (o) PVP-jodnih otopina različitih razrjeđenja*

No	PVP-iodine solution w/%	η mPa · s	σ μN cm⁻¹·10	μ V	o mosmol/l⁻¹
1	10	3.572	41.10	0.586	348
2	7.5	2.137	41.70	0.587	250
3	5	1.478	42.24	0.589	166
4	2.5	1.155	45.21	0.597	66
5	1	1.040	47.55	0.613	26
6	0.5	1.007	57.29	0.625	14
7	0.1	0.975	72.13	0.654	2
8	0.05	0.914	72.11	0.660	0.1

Microbicidal activity of aqueous PVP-iodine solutions

Sifting the literature dealing with the correlation between concentration of aqueous PVP-iodine solution and microbicidal activity it is possible to come to the following controversial conclusions: Bactericidal activity increases with dilution of PVP-iodine solution[8]. Starting from the $w = 10\%$ solution, the content of equilibrium iodine increases, reaching a maximum at about $w = 0.1\%$ solution[2,5]. There is no significant difference between the bactericidal activity of $w = 5\%$ and $w = 10\%$ PVP-iodine solutions tested on *Echerichia coli* $f_{RF\,10\%} = 4.71$; $f_{RF\,5\%} = 4.43$). The content of equilibrium iodine has not been determined[9].

Our results for microbicidal activity of aqueous PVP-iodine solutions show that, starting from a commercially available $w = 10\%$ stock solution, they initially increase as the dilution increases, reaching maximum values at about $w = 1\%$ solution and falling again on further dilution (see Table 1 and Figure 1).

The question remaining to be answered is »Is there correlation between the content of the so called equilibrium iodine and the microbicidal activity of aqueous solution of PVP-iodine?« From our experience, the concentrations of equilibrium iodine, measured potentiometrically and spectrophotometrically, are still far from answering this question. Furthermore, the existing pharmacopoeia specifications are not adequate to predict their microbicidal efficacy.

Disinfection activity coefficient of a solution (k)

As known, the mechanisms by which disinfectants kill or inhibit the growth of microorganisms are complex. Sequential or simultaneous changes of the properties of disinfection solutions often occur, which causes difficulties in differentiating the primary from the secondary effects. The disinfection activity of a solution may be expressed as a function, of at least four characteristic properties, in the general manner of equation (3).

$$\text{disinfection activity} = A_{\Phi} + A_{\sigma} + A_{\text{ch}} + A_{o} \quad (3)$$

We have called this »disinfection activity coefficient of the solution (*k*)«.

The different symbols represent the disinfection activity due to fluidity term (A_{Φ}), surface tension term (A_{σ}), chemical properties term (A_{ch}) and osmolality term (A_o). Each of these will be discussed below.

For a short exposure time to disinfection solution, the fluidity term (A_{Φ}) and surface tension term (A_{σ}) are evidently important in the reaction with microorganisms. These two enable the passive transport of the substance in solution, across a concentration, electrical and osmotic gradient. For the active transport of the substance in solution, the chemical properties term (A_{ch}) and osmolality term (A_o) are responsible.

Aqueous solutions of PVP-iodine mentioned above show a remarkable disinfection activity due to their properties as oxidizing agents. Consequently, the redox potential will be a measure of its chemical activity.

Fluidity term (A_{Φ})

Equation (4) gives the common expression for A_{Φ}

$$A_{\Phi} = 1/\eta \quad (4)$$

where η is the viscosity of the solution.

Surface tension term (A_{σ})

The contribution of the surface tension term to the microbicidal action of a solution is assumed as in equation (5)

$$A_{\sigma} = 30/\sigma \quad (5)$$

where σ is the surface tension of the solution.

With a rise in the surface tension of solution, the value of the surface tension term decreases. It should be noted that the commercial disinfection solution usually contains substances that lower the surface tension.

Redox potential term (A_{μ})

We propose a simple expression for the electrochemical potential of the solution (6)

$$A_{\mu} = -|\mu_{\text{sol.}}| \quad (6)$$

$\mu_{\text{sol.}}$ — potentiometrically measured potential of solutions using platinum electrode.

Since the bacterial surface is normally negatively charged, the oxidizing agents are probably more effective because of the attraction of the oxidizing molecule to the membrane surface.

Osmolality term (A_o)

This contribution may be very important in the *k* of certain types of solutions. On the other hand, the equation for osmolality term (A_o) has to be considerably variable for different kinds of bacteria, even for different bacteria strains.

For short exposure time disinfectant solutions, such as are required for disinfection of hands, we propose the following empirical expression for osmolality term

$$A_{o1} = \{\exp[-a \cdot \log(1 + o)] - \exp[-b \cdot \log(1 + o)]\} \cdot c \quad (7)$$

where *a*, *b* and *c* are constants with values of 0.8, 1 and 17, respectively. Equation (7) is a quantification of osmolality contribution in the disinfection activity of PVP-iodine aqueous solution vs. *Staphylococcus aureus*. But, for broad-spectrum disinfectants, with a more than 120 s prolonged contact time, the expression for A_o will be

$$A_{o2} = 1/2 \log(1 + o) \quad (8)$$

The obtained values for fluidity term (A_{Φ}), surface tension term (A_{σ}), redox potential term (A_{μ}) and osmolality terms (A_{o1} and A_{o2}) of PVP-iodine aqueous solution in varying concentration are shown in Table 3.

Finally, for the short exposure time disinfection solution, the K estimating equation is (9) and for the prolonged contact time disinfectant solution the estimating equation is (10)

$$k_1 = A_{\Phi} + A_{\sigma} + A_{\mu} + A_{o1} \quad (9)$$

$$k_2 = A_{\Phi} + A_{\sigma} + A_{\mu} + A_{o2} \quad (10)$$

The development of Eq. (9) and Eq. (10) is guided by theoretical rather than by statistical arguments. The results for k_1 and k_2 obtained by these equations are shown in Table 3.

Our results for the k_1 evaluated values of aqueous PVP-iodine solutions in fact show that, starting from a commercially available $w = 10\%$ stock solution, the k_1 values initially increase as the dilution increases, reaching maximum at about $w = 1\%$ solution and falling again on further dilution (see Table 3 and Figure 1).

It was pointed out earlier that certain bacteria were more readily killed by dilute aqueous solution of PVP-iodine than by the traditional $w = 10\%$ *stock solution*[2,5,9]. The phenomenon of maximum microbicidal effect of PVP-iodine solutions at specific concentrations can be seen particularly clearly in the case of *Staphylococcus aureus*. In addition, our disinfection activity coefficient of solution (k_1)

Table 3 — *Fluidity term (A_Φ), Surface tension term (A_σ), Redox potential term (A_u), Osmolality term (A_{o1}, A_{o2}), and disinfection activity coefficient of solution (k_1, k_2) of PVP-iodine solution in varying dilutions*

Tablica 3 — *Term viskoznosti (A_Φ), površinske napetosti (A_σ), redoks potencijala (A_u), osmolarnosti (A_{o1}, A_{o2}) i koeficienti dezinfekcijske aktivnosti otopina (k_1, k_2) PVP-jodnih otopina različitih razrjeđenja*

No	PVP--iodine solution w/%	A_Φ Eq. (4)	A_σ Eq. (5)	A_u Eq. (6)	A_{o1} Eq. (7)	A_{o2} Eq. (8)	k_1 Eq. (9)	k_2 Eq. (10)
1	10	0.28	0.73	—0.586	0.89	1.27	1.314	1.694
2	7.5	0.47	0.72	—0.587	0.95	1.20	1.553	1.803
3	5	0.68	0.71	—0.589	1.04	1.10	1.841	1.901
4	2.5	0.87	0.66	—0.597	1.21	0.91	2.143	1.843
5	1	0.96	0.63	—0.613	1.35	0.71	2.327	1.687
6	0.5	0.99	0.52	—0.625	1.39	0.59	2.275	1.475
7	0.1	1.03	0.42	—0.654	1.06	0.24	1.856	1.036
8	0.05	1.09	0.42	—0.660	0.13	0.02	0.980	0.870

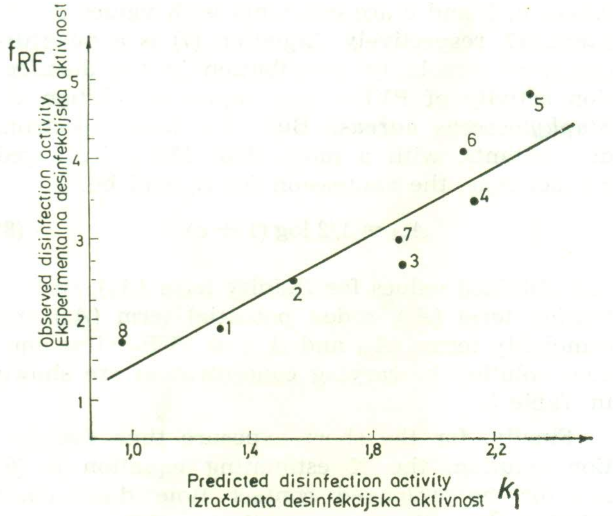


Fig. 2 — *Plot of the observed disinfection activity of S. aureus after an action time of 30 s against the predicted activity of k_1.*

Slika 2 — *Linearna ovisnost eksperimentalnih dezinfekcijskih aktivnosti za S. aureus za vrijeme djelovanja 30 s i izračunatih aktivnosti uz pomoć k_1.*

will be correlated directly with our observed disinfection activity of *S. aureus* after an action time of 30 s (Figure 2). The agreement between the experimental bactericidal activity of solutions, f_{RF}, and the calculated activity, K_1 is analyzed by the linear least-square equation:

$$f_{RF} = a \cdot k_1 + b \tag{11}$$

The following statistical parameters have been obtained for (11): $a = 2.05 \pm 0.31$, $b = —0.65 \pm \pm 0.56$ ($r = 0.94$, SD = 0.39).

From a physicochemical point of view, while the values of the surface tension term and redox potential term in the $w = 1\%$ PVP-iodine solution are not remarkable different from the $w = 10\%$ solution, the variation in the fluidity term and osmolality term provides a suitable opportunity for adjusting the maximum k_1 values (Table 3), thus providing the desired microbicidal kinetics of PVP-iodine solutions.

On the other hand, the k_2 values (referring to the disinfection efficiency for more than 120 s prolonged contact time) show that the $w = 5\%$ PVP-iodine solution has the greatest microbicidal potency (Table 3).

One should always remember the functions used in K calculations are empirical, being chosen because they are easy to handle numerically, and because of their ability to give a quantitative description of disinfection solutions. Therefore, the K shows a potential for being used in design of disinfection solutions. However, more work is needed before the range of its applicability is established.

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List of symbols
Popis simbola

PVP — Polivinilpirolidinon
Polyvinilpyrrolidinone

η — Viskoznost
Viscosity

σ — Površinska napetost
Surface tension

o — Osmolarnost
Osmolality

μ — Redoks potencijal
Redox potential

f_{RF} — Redukcijski faktor
Reduction factor

n_1 — Broj kolonija u 1 ml otopine formiranih bez djelovanja preparata
The number of colony forming units per ml without action of the preparation

n_2 — Broj kolonija u 1 ml otopine formiranih djelovanjem preparata
The number of colony forming units per ml after action of the preparation

A_{Φ} — parametar fluidnosti
Fluidity term

A_{σ} — Parametar površinske napetosti
Surface tension term

A_{ch} — Parametar kemijskih svojstava
Chemical properties term

A_{μ} — Parametar redoks potencijala
Redox potential term

A_{o1} — Parametar osmolarnosti za kratko vrijeme djelovanja
Osmolality term for short exposure time

A_{o2} — Parametar osmolarnosti za produljeno vrijeme djelovanja
Osmolality term for prolonged exposure time

k_1 — Koeficijent dezinfekcijske aktivnosti za kratko vrijeme djelovanja
Disinfection activity coefficient of solution for short exposure time

k_2 — Koeficijent dezinfekcijske aktivnosti za produljeno vrijeme djelovanja
Disinfection activity coefficient of solution for prolonged exposure time

w — maseni udio
mass fraction

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SAŽETAK

Fizičko-kemijske osnove mikrobicidnog djelovanja vodenih otopina polivinilpirolidinon-joda

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Uveden je novi deskriptor polivinilpirolidinon-jodnih (PVP-jodnih) otopina koji smo nazvali koeficijentom dezinfekcijske aktivnosti otopina (k), a dobro korelira s germicidnim djelovanjem PVP-jodnih otopina različitih razrjeđenja. Indeks k predstavlja zbroj od četiri terma: fluiditeta, površinske napetosti, redoks potencijala i osmomolarnosti koji su definirani matematičkim izrazima. U svrhu izračunavanja vrijednosti termova određivana je viskoznost, površinska napetost, redoks potencijal i osmomolarnost PVP-jodnih otopina različitih razrjeđenja. Germicidna aktivnost određivana je kvantitativno in vitro ispitivanjem u odnosu na *Staphylococcus aureus* za kratka vremena djelovanja. Utvrđena je dobra korelacija između k vrijednosti i odgovarajuće germicidne aktivnosti za svako pojedino razrjeđenje.

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