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Advances in antimicrobial polymeric iodophors

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ABSTRACT

Despite centuries of research on this chemical element, the ability of iodine to form complexes with water-soluble polymers and various other molecules remains a topic of great interest. The fascination with iodine and iodophors arises from their remarkable antimicrobial properties against a wide range of pathogens. This review encompasses historical information on iodine and iodophors, showcases existing iodine-containing products available in the market, explores the diverse physicochemical methods employed to study polymer-iodine complexes, and assesses recently published studies on iodophors. Recent advances in this field include the use of new experimental techniques to get new insights into the mechanisms of complexation and structure of these complexes; preparation of iodophors using novel polymers, nano- and micro-particles; and fabrication of antimicrobial surfaces capable of slow iodine release.

1. Introduction

Iodine is a nonmetallic chemical element that belongs to the halogen family. It was discovered by Courtois in 1811 [1] and was named as a new chemical element by Gay-Lussac in 1813 [2]. At room temperature the molecular iodine (I_2) is a bluish-black solid with crystalline appearance and ability to sublime forming a deep violet vapor irritant to mucosal surfaces [3].

Iodine has strong antiseptic properties which was first discovered by Davaine in 1873 [4] and paved the way for its numerous biomedical applications. It is currently well-documented that iodine has bactericidal, fungicidal, virucidal and sporicidal activities [5]. Antimicrobial properties of iodine continue to attract attention of researchers even in the recent decade due to the strong need for combating various infections and preventing their spreading.

The antiseptic applications of iodine expanded substantially with the discovery of its ability to form complexes with some hydrophilic polymers and smaller molecules such as cyclodextrins and surfactants. Nowadays these formulations are commonly called iodophors. The first reaction of this type was reported by Colin and de Claubry in 1814 [6] for the complexes of molecular iodine with starch. This reaction has found numerous applications in analytical chemistry due to the rapid change in colour from yellow/brown typical for solutions of molecular iodine to a dark blue-black of the starch-iodine complex [7]. Some starch-iodine complexes also found applications as antiseptics in wound

care. Iodophors can also be formed by reaction of molecular iodine with some synthetic water-soluble polymers. One of these iodophors is formed through the complexation between poly(N-vinylpyrrolidone) (Povidone) and molecular iodine, which was discovered by Shelanski in 1949 [8,9].

Currently, iodophors are widely used as antiseptic products for disinfection of surfaces, wound treatment, pre- and post-operative care, mouth washes, gargles, and nasal sprays. They may be formulated as solutions, gels, sprays, powders, wound dressing pads and cotton sticks. Fig. 1 shows some examples of commercial iodophors.

Despite over two centuries of research into iodine and iodophors, many fundamental aspects of the complexes formed by this halogen and hydrophilic polymers are still poorly understood. This review aimed to present an analysis of the progress in this field from the physicochemical properties of iodine to the development of modern methods to study polymer-iodine interactions and structure of their complexes, and to the biomedical applications of these systems.

2. Iodine and its physicochemical properties

Molecular iodine is poorly soluble in water, but it is readily soluble in many organic solvents such as hydrocarbons, alcohols, carbon disulfide, ethers, halogen derivatives of hydrocarbons, etc. Iodine solutions in different solvents have different colors with purple, red, brown and intermediate shades (Fig. 2). In solutions of solvents that do not contain

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oxygen (carbon disulfide, chloroform, carbon tetrachloride and hydrocarbons) iodine turns purple; in oxygen-containing solvents (alcohols, water) solvation occurs and these solutions are colored brown and red [10]. The solubility of iodine in water increases strongly at higher temperature and reaches 3.3 g/L at 100 °C [11], compared to its solubility of 0.33 g/L at 25 °C [12]. The solubility can also be enhanced by adding iodide ions causing the formation of soluble tri- and polyiodides [13].

In aqueous solutions, several chemical reactions involving the iodine are possible and these processes result in formation of the following forms: I^- , I_2 , I_3^- , I_5^- , I_6^{2-} , HOI , OI^- , HI_2O^- , IO_2^- and H_2OI^+ . The presence of each form in solutions depends on the concentration of iodide ions and pH of the medium. For example, at $pH \leq 6$, the main forms of iodine are I^- , I_2 , and I_3^- . At high concentrations of iodide ions in solution the predominant forms are I_5^- and I_6^{2-} ; HOI , OI^- , HI_2O^- , IO_2^- and H_2OI^+ . These forms are also typically present in solutions at $pH > 6$ [13]. As the content of iodine in solution strongly depends on the temperature, more than 100 % increase in its concentration is observed with an increase in temperature from 20 to 35 °C. For this reason, temperature should be considered when iodine formulations are administered [14].

3. Interactions of molecular iodine with water-soluble polymers

Molecular iodine is known to have skin irritating properties and it is toxic at high concentrations [15]; therefore, it has limited biomedical applications [16]. Furthermore, the sublimation of iodine at room temperature poses an additional constraint on its applications and storage. The discovery of the complexation of iodine with water-soluble polymers to form iodophors [17], has presented numerous opportunities

to substantially reduce its toxic and irritant characteristics. Moreover, this has allowed to increase the antimicrobial and antifungal activity of its formulations [18]. Iodine can form charge-transfer complexes with natural and synthetic polymers and cyclodextrins, which have low energy of activation and high electrical conductivity [19]. The main mechanism of the complexation is the hydrogen bond-like interactions between I_3^- ions and O-containing functional groups of macromolecules, which includes the charge transfer from iodine to O-containing functional group [20]. For example, Goodwin et al [21] proposed the following model for the structure of complexes formed by iodine with poly(vinyl pyrrolidone) (Fig. 3).

Polyvinylpyrrolidone – iodine complex is a widely studied iodophor that is currently used commercially. In 1979 Schenck first proposed that triiodide anion is bound ionically to the proton which forms intramolecular hydrogen bonds between carbonyl groups of two amide motifs [22]. Goodwin and et al. [21] reported that the structure of povidone-iodine complex includes pyrrolidone units are involved in intermolecular hydrogen bonds along with triiodide anions. The unique property of povidone-iodine is that the antibacterial activity of its 10 % solution increases with dilution and reaches a maximum at a concentration of 0.1 % [23].

Another studied synthetic N-containing polymer-iodine complex is a complex with nylon. As a result of the complexation I_2 - I_3^- species inserted between amide motifs linked by hydrogen bonds [24]. In the other study [25] of iodine-nylon-6 complexes two species of iodide ions were found: I_3^- and I_5^- . I_5^- ions are oriented along the polymer chain axis, whereas I_3^- are oriented perpendicular to the chain axis in uniaxially drawn films and films with planar orientation. The presence and arrangement of iodide ions influence the alignment of nylon-6 chains during the

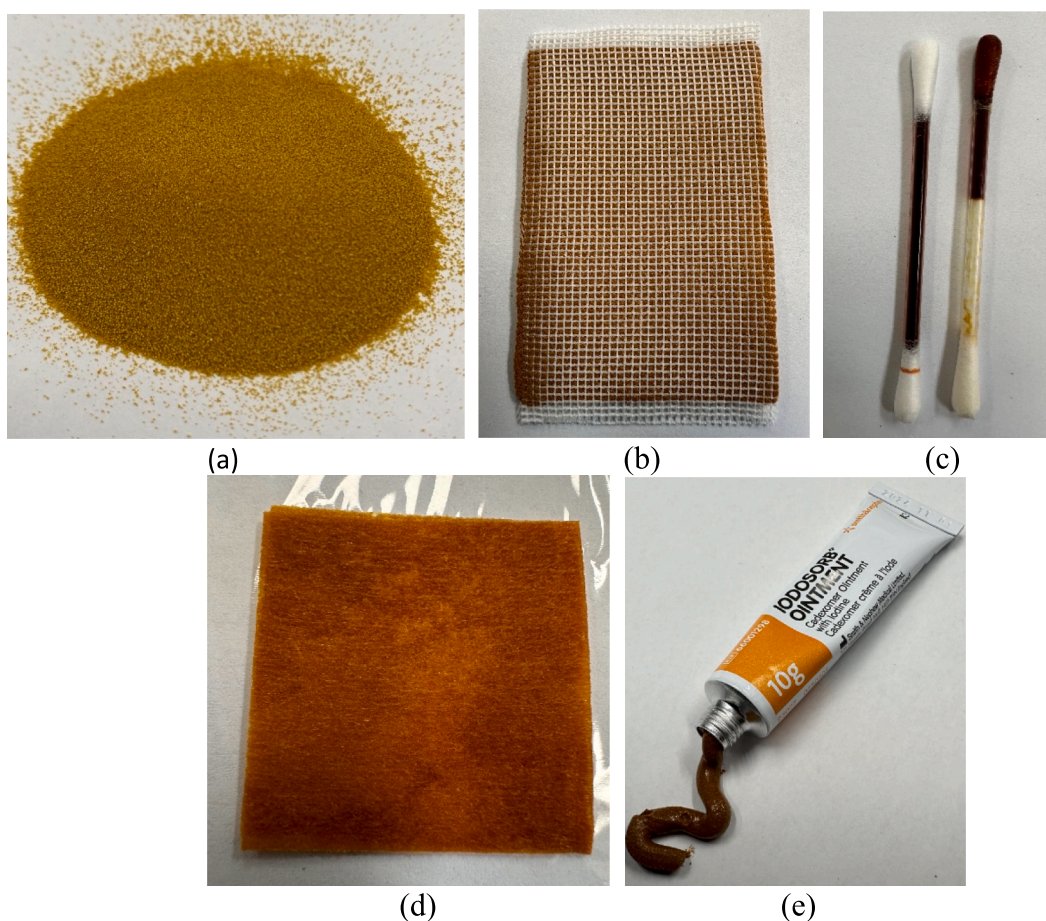


Fig. 1. Examples of different commercial iodophor formulations: Iodosorb powder from Smith & Nephew (a), Iodoflex cadexomer dressing from Smith & Nephew (b), Supvox cotton sticks (c), Povidone-iodine prep pad (d), and Iodosorb ointment from Smith & Nephew (e).

complex formation process. Nylon-6 can form a complex with iodine in its solution and vapors phase [26]. The presence of a solvent (liquid phase) influences the adsorption of iodine on nylon material, leading to the formation of ionic forms of iodine and potentially more complex polyiodide ions. In contrast, when iodine is adsorbed directly from vapors (vapor phase), it mainly exists in a molecular form. This difference in adsorption behavior highlights the importance of the phase (vapor or liquid) in which the iodine adsorption process takes place and the role of the solvent in facilitating these interactions.

Polyurethanes can also form charge-transfer complexes with iodine [27]. Typically, the main iodine species that are involved in the complex are I_3 and I_5 . The results of this study suggest a concentration-dependent relationship between iodine concentration and complex formation. Initially, there is a rapid increase in complex formation with increasing iodine concentration. Iodine can be introduced into polyurethane matrices by two methods: incorporating polymerization and immersing polymeric samples in iodine solutions [28]. Formation of the polymer-iodine complex is caused by intramolecular hydrogen bonding between the lone pair electrons of iodine and amine hydrogen in the polymer. It caused a shift in the N–H stretching band to a lower frequency.

Polyacrylonitrile (PAN) is reported to form complexes with iodine through intermolecular interactions between PAN motifs and I_5 ions [29]. By immersing PAN films in the aqueous solution of iodine and potassium iodide the authors have established that iodine sorption changed the crystalline structure of PAN. They proposed an intercalation model of the PAN-iodine complex [30].

Table 1 presents some examples of polymer-iodine complexes, with the mechanisms of complexation and color of the resulting products. One of a most widely studied complexes of iodine with natural polymers is the product of its interaction with starch, which typically has a dark blue color. This color is observed due to the absorption maximum at $\lambda_{\max} = 650$ nm of the amylose-iodine complex and because iodine has 20% affinity for amylose and <1% affinity for amylopectin. The amylopectin-iodine complex is typically red-purple and has an absorption maximum of 540 nm [11]. The color of the amylose-iodine complex depends on the degree of polymerization of this polysaccharide: when it is 40–130 then the product is blue, when it is 25–40 then the product is red, and when it is 19–25 then it becomes orange. However, when the degree of amylose polymerization is less than 10 the complex is formed as a colorless compound [31].

Other polysaccharides have also been found to form complexes with

iodine. For example, hemicellulose is also able to interact with iodine and the color of its complex depends on the length of the polysaccharide chain. For some hemicellulose-iodine complexes, consisting of 4–6 glucose units no color changes are observed, whereas with increasing number of chains to 8–12 units, this polysaccharide forms a red complex and to 30–35 it will form a blue complex [32]. Similar behavior is also observed for complexes of xylo-polysaccharides with iodine: xylodextrin forms dark purple complex, xylotetraose forms blue complex, xylobiose and xylotriose form light brown complexes. The important factors determining the complexation of hemicellulose polysaccharides with iodine are the ratio of the 1–4 link to other links, which is 1:3 both in linear and branched structures, and the internal configuration of the polysaccharides [33]. Gum Arabic is another example of a natural gum that was reported to form complexes with iodine. This material is a complex mixture of glycoproteins and polysaccharides, mostly composed of arabinose and galactose. The authors [34] have introduced new reactive groups into gum Arabic using acylation reaction and studied the complexation of the resulting product with iodine in ethanol solutions. The results of this study show that iodine interacts with $-C=O$ groups of acylated gum and the amount of iodine available in this complex is about 17.1 %, whereas povidone-iodine contains around 13.5 % of available iodine. The iodophor formed by acylated gum Arabic exhibited excellent antimicrobial activity against *E.coli*.

Cyclodextrins (CDs) are cyclic oligosaccharides prepared from starch using enzyme-catalysed reaction with cyclomaltodextrin glucotransferase. There are three types of cyclodextrins that can be prepared using this reaction (α -, β -, and γ -CDs) and these compounds differ in the size of their cycle. CDs have ability to form complexes with “guest” molecules in aqueous solutions through hydrophobic interactions, hydrogen bonding and van der Waals forces [35]. Complexes of α -CDs with iodine display the highest absorbance of their solutions compared to β - and γ -CD [36]. It is also known that α -CD forms more stable complexes with iodine compared to β - and γ -CD [37]. The mechanism of complexation between CDs and iodine involves inclusion of I^- and I_3^- ions into their cavity [38].

4. Physicochemical methods to study formation of iodophors

Early studies of polymer-iodine complexation were mostly relying on colorimetric techniques; however, the progress in the development of modern physicochemical methods of analysis provided a range of novel opportunities to shed light on the structure and properties of iodophors.



Fig. 2. Molecular iodine dissolved in aqueous solution of KI (1), 1-butanol (2), benzene (3), chloroform (4) and hexane (5) at 0.2 mg/mL.

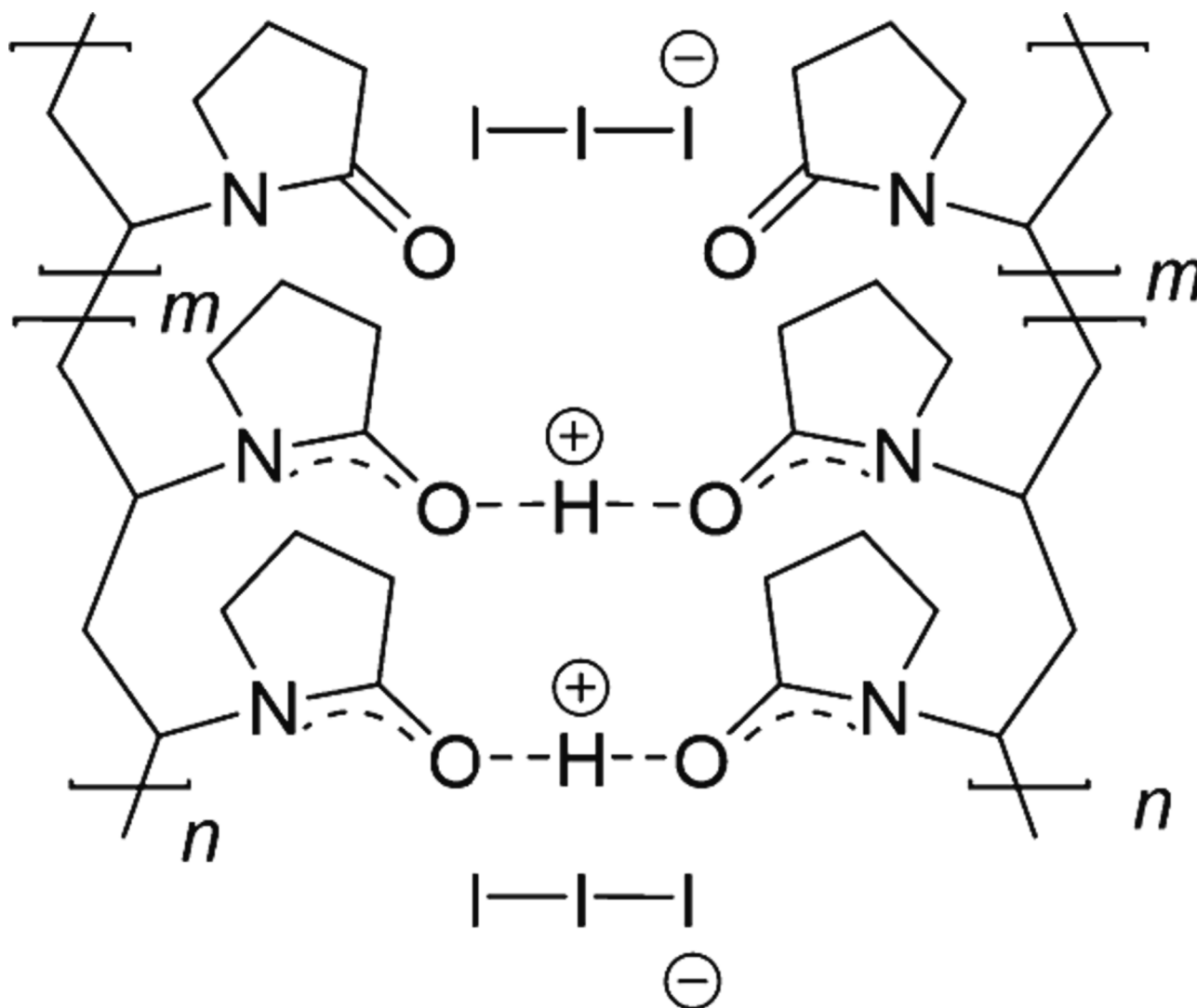


Fig. 3. Structure of iodine complex with poly(vinyl pyrrolidone). Reprinted from [21] with permission from the American Chemical Society.

UV-vis spectroscopy is one of the most common and traditional methods to study the complexation between polymers and iodine in solutions. Spectrophotometric studies provide the main characteristic absorption bands of iodine solution and can detect the changes happening upon formation of iodophors. The spectra with absorption bands at 192–193 and 226 nm are typical for aqueous solutions of iodides [11]. Absorption bands at $\lambda_{\text{max}} = 288\text{--}298\text{ nm}$ and $348\text{--}356\text{ nm}$ are well documented for solutions of iodine and are observed due to the presence of I_3^- ions [51]. Later it was demonstrated that $\sim 290\text{ nm}$ belongs to I_3^- and $\sim 350\text{--}360\text{ nm}$ is due to IO^- oxyanion. The peaks at $450\text{--}460\text{ nm}$ are typical for solvated molecules of iodine [52]. The shift of λ_{max} from 350 to 360 nm to $372\text{--}386\text{ nm}$ is usually observed upon formation of the iodophor complex in the iodine-polymer solution. The UV-vis spectrum of iodine in solutions is also characterized by the presence of a band at 460 nm ; a gradual addition of iodide ions to this solution results in increase in the intensity of the band at 350 nm with the appearance of an isosbestic point at 430 nm , which indicates the presence of an equilibrium in the system [53]. UV spectroscopy has been used to study the effects of the concentration of iodide ions [45], temperature and polymeric charge [54].

FTIR-spectroscopy is a powerful technique that can be used to determine the complex formation constants and to provide information about the polarity of the complex formed. The authors [55] reported the calculations of the complex formation constants of iodine with various

model oxygen-containing organic compounds like acetone, cyclohexanone, ethyl ether and 3-phenylsydnone. They established that the intensity of $\text{C}=\text{O}$ stretching vibrations of the ketone group increases, while the intensity of C-O stretching vibrations decreases upon complexation of these compounds with iodine. These changes were explained by the charge transfer from oxygen atoms to iodine molecules [22]. Ren *et al* [29] used IR spectroscopy to study the complex formation between polyacrylonitrile (PAN) and iodine. They observed some shifts in $\nu(\text{CN})$ and $\delta(\text{CH}_2)$ in the IR spectra of PAN in the presence of iodine. The band shift was also affected by the nature of the counterions present in solutions (K^+ , Na^+ , Li^+). Matsubara and Magill [56] reported an infrared spectroscopy study of the interactions between the iodine and polyamides of thirty-one different structures. It was concluded that the complexation of iodine with polymers proceeds through the involvement of tri-iodide ions.



De Faria and co-workers [42] reported the use of Raman spectroscopy to study the complexation between iodine and PVP in the range of 80 to 1800 cm^{-1} . Strong characteristic vibrations of I_2 and its polyiodide derivatives (I_3^- and I_5^-) were observed in the spectra of iodophors at 112 , 145.5 and 167 cm^{-1} . The spectral data indicated that the presence of I_3^- and I_5^- was dependent on the method used to prepare iodophors. In the study [57] the authors evaluated poly(vinyl amide) coatings with iodine and observed Raman vibrations at 112 and 144 cm^{-1} , which indicates the presence of I_3^- . The absence of a band at 180 cm^{-1} confirmed that free

Table 1
Characteristics of some polymer-iodine complexes.

Polymer	Mechanism of complexation	Color of polymer-iodine complex	Photo of polymer-iodine complexes (Concentration of iodine 0.04 mg/mL, iodide – 0.08 mg/mL, and polymer – 1 mg/mL)	References
Polyvinyl alcohol (PVA)	Inclusion of iodide ions into helical PVA chains	Red, however, if boric acid is added the product becomes blue		[39-41]
Poly(N-vinylpyrrolidone) (PVP)	Formation of donor-acceptor complex	Brown		[22,42]
Polyethylene Glycol (PEG)	Formation of charge transfer complex between with I ₃ ions and oxygen atoms	Non-specific color (Depends on concentration of iodine)		[43-46]
Poly(2-ethyl-2-oxazoline) (PEOZ)	Monomolecular complexation between PEOZ chains and iodine species with conformational changes	Yellow		[47]
Starch	Left-handed helical structure with a polyiodide chain	Amylose forms blue complex and amylopectin forms red one		[48]
Chitosan	Interaction of hydroxyl groups in D-glucosamine moiety in chitosan with primarily I ₃ ions	Non-specific color at room temperature and purple after freezing	 After freezing 	[49]

(continued on next page)

Table 1 (continued)

Polymer	Mechanism of complexation	Color of polymer-iodine complex	Photo of polymer-iodine complexes (Concentration of iodine 0.04 mg/mL, iodide – 0.08 mg/mL, and polymer – 1 mg/mL)	References
Cellulose derivatives	Sandwich structure formed by a pair of neighboring cellulose chains and triiodide species.	Non-specific color		[20]
Pectin	Charge transfer complexation with participation of the carbonyl and hydroxyl groups of pectin and absorption of I ₃ ions, I ₂ and I _n polyiodide ions.	The color of complexes can change from red to black depending on the concentration of the polymer and iodine		[50]

* Photos of iodophors were taken by the authors of this review.

I₂ was not present in the coating. The results also depend on the method of the complex preparation: poly(vinyl amide) coating was saturated by solution of iodine in isopropanol. Lundin et al [58] reported a compositional analysis of kaolin-polymer iodine foams. They observed spectral peaks at 114 and 143 cm⁻¹, which are correspond to the ν_1 (symmetric stretch) and ν_3 (asymmetric stretch) modes of I₃. Molecular distortion of I₃ ion due to the complex formation with the polymer results in an asymmetric environment and activates ν_3 mode. No Raman peaks were observed near 167 cm⁻¹ corresponding to I₅. The symmetric I-I stretching mode of iodine can be near 143 cm⁻¹ but the absence of I-I stretching mode near 255 cm⁻¹ confirmed the presence of I₃.

X-ray diffraction spectra may provide valuable information about the structure of polymer-iodine complexes. Tashiro and co-workers [59] studied the structural features of iodophors prepared by immersion of PVA films cross-linked with boric acid into solutions containing iodine and potassium iodide with various concentrations. Before this study, three different kinds of PVA-iodine complexes were known (forms I, II and III). By immersing the PVA film in a diluted solution of KI/I₂ (0.001–0.05 M) the authors discovered the formation of a new form IV, with a new diffraction pattern. As they demonstrated in this study, this new form of polymer-iodine complex is composed of vertically arrayed I₅ ions surrounded by six PVA chains of plana-zigzag conformation forming the cylindrical structure. These cylindrical structures assemble into the hexagonal lattice (Fig. 4).

Using a combination of X-ray diffractometry and infrared spectroscopy Schenck et al [22] evaluated the structure of complexes formed between iodine and PVP. They proposed the structure of the complex, which involves two carbonyl groups of two pyrrolidone rings associated with a hydrogen proton, which, in turn, is coordinated with the triiodide ion. The crystal structure of cellulose-iodine complex and original cellulose was also studied using XRD in [20]. X-ray photoelectron spectroscopy (XPS) was used by Ma and coworkers [60] to study the interactions between PVP-iodine complexes and polypropylene microplastics. The use of this technique provided an opportunity to identify iodine species in PVP-iodine that interacted with microplastics. Two peaks at 635.55 and 617.98 eV were detected in XPS spectra of polypropylene samples soaked in PVP-iodine in the presence and absence of atmospheric oxygen. These spectral data allowed them to conclude that both I₃ and I₅ present in PVP-iodine are the iodine species interacting with polypropylene. Luo et al [27] have used XPS and UV-vis spectroscopies to study the formation of complexes between polyurethane and iodine. The authors have prepared polyurethane films and immersed these samples into iodine aqueous solutions containing 4 %

potassium iodide. The original polyurethane membrane and polyurethane-iodine membrane were scanned in the work. Two new peaks were observed at 618.8 eV and 630.0 eV in the XPS spectra of the membranes soaked in iodine solutions, which were assigned to I₃ and I₅, respectively. The excellent binding of iodine species by polyurethane was explained by the presence of aromatic rings in the polymer due to the formation of charge-transfer complexes of iodine with electron-rich compounds.

Viscometry is a simple physicochemical method that is commonly used to study the conformational changes of polymers in solutions. Podder and Basu [61] have used this technique to study interactions between polyvinylpyridine (PVPy) and iodine in alcohol solutions. They observed formation of PVPy-iodine complexes, which is accompanied by increase in the polymer solution viscosity. This observation was explained by binding of ionized iodide species to neutral PVPy resulting in polyelectrolyte behavior. It is interesting to note that the values of viscosity were greater when these were measured one, two and three weeks after mixing ingredients. This change explains the mechanism of polymer-iodine complex formation: the transformation of an external complex into an internal one occurs slowly, and it is accompanied by the transformation of a neutral polymer chain into a polyelectrolyte and an increase in intrinsic viscosity. Makhayeva et al [47] has also used viscometric technique to probe interactions of PVP and PEOZ with iodine in water-alcohol solutions. They established that the complexation is accompanied by a substantial reduction in solution viscosity indicating a compaction of polymer macromolecules as a result of the interaction with iodine. A spectrophotometric and viscometric study of the interactions of carboxymethylamylose and diethylaminoethylamylose with iodine in iodide containing solutions was reported by Cesàro and Brant [62]. It was established that an increase in intrinsic viscosity at low values of the degree of saturation occurs due to the absorption of negatively charged iodide ions; a further decrease is associated with the stabilization of iodine-iodide compact structures and the formation of intermolecular aggregates. Bendoraitiene et al [63] also reported a spectrophotometric and viscometric study of interactions between polydiallyldimethylammonium salts and iodine.

Conformational changes happening with macromolecules in solutions upon their complexation with iodine can also be studied using dynamic light scattering (DLS). Makhayeva et al [47] has used DLS to demonstrate that at low iodine to polymer ratios the z-average hydrodynamic radius values of PEOZ drop from 7.6 to 4.8 nm with increase in iodine concentration from 0 to 0.5 mol/L and similar trend was observed for complexes of PVP with iodine. Wang et al [64] investigated the

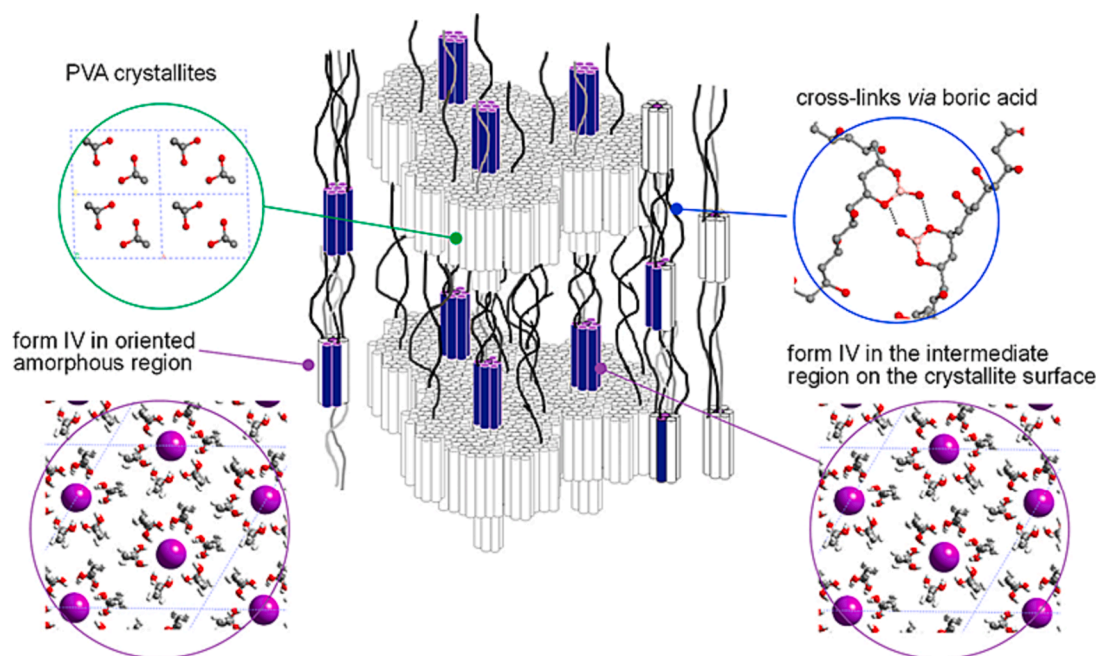


Fig. 4. Structural model proposed by Tashiro and co-workers. The crystalline lamellae are stacked along the drawn direction. The complex form IV is generated in some of the oriented amorphous regions. The oriented amorphous chains are present near the top and bottom surfaces of the crystallites and additionally as the extended tie chain segments in the normal amorphous regions. The cross links are formed in some parts of the amorphous regions through the chemical bonds between the boric acid and the hydroxyl groups of PVA. Reprinted from [59] with permission from Elsevier.

fabrication of a supramolecular amphiphile through binding between double hydrophilic methoxy-poly(ethyleneglycol)₁₁₃-block-poly(L-lysine hydrochloride)₂₀₀ and iodine. The coordination of this block copolymer with iodine has resulted in a change of PEG block from hydrophilic nature to a more hydrophobic one. These changes were observed using DLS.

Isothermal titration calorimetry (ITC) is a powerful physicochemical technique that is commonly used to study interactions between various species in solutions. It provides information about thermodynamic parameters of complexation and stoichiometry of the complexes formed. ITC was used to study the complex formation of iodine with PVP and PEOZ in Ref [47]. It was demonstrated that the complexation of iodine with these two polymers consists of two stages. First iodine molecules/ions bind to several repeating units of the polymer resulting in restriction of the conformational mobility of its macromolecules. These changes are seen on ITC thermograms as phase I characterized by increasing negative enthalpy. The phase II is driven by “one-site” binding event with a possibility for iodine to bind to two monomeric units of PEOZ. Once all PEOZ repeating units are involved in iodine binding, the iodophor undergoes aggregation. In a different study ITC was used to evaluate the binding ability between *E. coli* cells and antimicrobial rubber nanoparticles loaded with iodine [65]. Nanoparticles were titrated to the bacteria suspension. It was established that the interaction between iodine-containing nanoparticles and *E. coli* is enthalpy-driven, based on the negative ΔH and ΔS values recorded and the nature of binding was electrostatic.

Microcolumn liquid chromatography and spectrophotometric technique were used by Munaf et al [36] to study the interactions of iodine and different cyclodextrins (α -, β -, and γ -cyclodextrins). They established that the solutions of iodine exhibit a substantial increase in their optical density in the presence of α -cyclodextrin, whereas the addition of β - and γ -cyclodextrins to iodine leads to only slight increase in the absorbance. The authors attributed this increase in solution absorbance to the increase in the concentration of I_3 ions. The formation of complexes involving I_3 ions was also confirmed by changes in the retention behavior of cyclodextrins. An increase in iodine concentration in the mobile phase increases the retention time of γ -cyclodextrin and

decreases it for α - and β - cyclodextrins in a chromatographic experiment.

Makhayeva et al [47] have proposed a simple method to study the complexation between iodine and water-soluble polymers using a horizontal Ussing chamber with two compartments, separated by a semi-permeable cellulose membrane. This methodology provided an opportunity to determine the iodine partitioning coefficient between the chamber containing polymer-iodine mixture and the chamber with polymer-free solution, which reflected the ability of the polymers to bind this halogen. Based on the values of their partitioning coefficients the studied polymers were arranged in the following order, where the binding ability decreases: PEOZ (50 kDa) > PEOZ (500 kDa) > PVP (360 kDa) > PVP (44–54 kDa) > poly(acrylic acid) (450 kDa). Among these polymers poly(acrylic acid) did not show any tendency to bind iodine.

Overall, the development of novel physicochemical characterization techniques has led to further progress in the studies of iodophors. These methods helped to shed light on the mechanisms of complexation in these systems; however, the presence and involvement of many different forms of iodine-containing ions in solutions still limits our understanding of polymer-iodine interactions.

5. Advanced iodine-containing polymer systems

Polymeric iodophors are extensively utilized as antibacterial and antimicrobial materials, playing a vital role in reducing bacterial pathogens in medical treatments and healthcare practices. They find wide-ranging applications across multiple sectors, including water treatment, medical and healthcare fields as antiseptics, veterinary care for disinfection and sterilization in animal husbandry, food industry as sanitizing agents, agriculture and horticulture for plant disease management, and laboratory research for surface disinfection and decontamination purposes.

Iodophors are strong disinfectants with a broad-spectrum of antimicrobial activities, non-irritation properties, and good stability [66]. Commercial formulations of iodophors are available as adhesive bandages [67], diluted aqueous and ethanol solutions [68], vaginal suppositories [69], patches, antibacterial sponges [70], tampons [71], etc. Some examples of these products are listed in Table 2.

Table 2
Commercially available iodine containing formulations.

Trademark	Main components	Manufacturer	Applications
IoPlex iodophor foam dressing [72]	Iodine complex with PVA	MEDLINE (USA)	Burns, wounds
IodoFoam foam wound dressing [73]	PVA-iodine complex with 8 % iodine (w/w)	Progressive Wound Care LLC (USA)	Provides a protective, soft coating over the wound surface and kills bacteria
Iodoflex 0.9 % Cadexomer Iodine pad [74]	0.9 % iodine complex with cadexomer (modified starch)	Smith & Nephew (United Kingdom)	Bactericidal formulation used against 103 isolates of MRSA and 101 strains of <i>P. aeruginosa</i> (<i>in vitro</i>), for cleaning wounds from exudate and treatment
Iodosorb 0.9 % Cadexomer Iodine Gel [75]			
Inadine™ (PVP-I) Non-Adherent Dressing [76]	10% Povidone Iodine; equivalent to 1.0% available iodine	3M & KCI (USA)	Burns, skin injuries, diabetic foot ulcers, pressure ulcers
10% Povidone-iodine surgical scrub brush sponge with nail clear [77]	10% Povidone-Iodine with minimum available iodine concentration of 0.75% (w/w)	JcMed (China)	Preoperative cleaning of arms and hands
BETApast PRO-N [78]	polyurethane foam with 3% povidone-iodine	MIMS PTE. LTD. (Singapore)	Disinfection and protection of wounds, pressure, diabetic ulcers, burns etc.
BETADINE vaginal pessaries	Povidone-Iodine 10 % w/v	Mundipharma Middle East (UAE)	Specific and unspecific vaginitis, bacterial vaginosis and Gardnerella vaginalis, chlamydia, mycoplasma and herpes, Candida albicans infections, trichomonal infections.
PDI Povidone-iodine Tampons	10 % Povidone iodine solution	PDI Inc (France)	Venipuncture, intravenous administration, renal dialysis, preoperative preparation and other minimally invasive procedures

Recent advancements in nanotechnology and the emergence of novel nanomaterials have had a profound impact on the iodophors sector and triggered strong interest of researchers in the development of iodine-containing formulations. Below we will consider several examples of these studies focused on design of nanoparticles with iodine, preparation of antimicrobial surfaces, formulation of gels and films.

Gao et al [79] reported the design of random copolymers based on N-vinyl-2-pyrrolidone (NVP) and methyl methacrylate (MMA) with the varied MMA to NVP molar ratios (10:0, 8:2, 6:4, 4:6, and 2:8). These copolymers self-assembled into spherical-to-oval shaped nanoparticles in aqueous solutions and were then subsequently loaded with iodine. Antibacterial properties of these nanoparticles were demonstrated in *E. coli*, *S. aureus* and *P. aeruginosa* cultures. Similar strategy was also reported by Borjihan et al [80], who utilized free-radical copolymerization of NVP with acrylonitrile to synthesize an amphiphilic copolymer. After purification and drying this copolymer was mixed with solution of iodine in ethanol to form nano-assembly. Evaluation of antimicrobial activity of these formulations demonstrated good efficiency against *E. coli* and *S. aureus*. The authors [81] reported the

development of polystyrene based functionalised resin using copolymerization of styrene and N-vinylpyrrolidone in the presence of divinylbenzene as a cross-linking agent. The resin was then dispersed in solution of iodine in ethanol for 12 h. It was demonstrated that this resin is suitable for sanitizing bacteria-polluted water using filtration technique (Fig. 5).

There is a strong interest in the use of iodophors either for preparation of antimicrobial surfaces or for disinfection of surfaces. Potentially these antimicrobial surfaces could inhibit the attachment and growth of microorganisms and may play a crucial role in preventing the formation of biofilms. Xing et al [82] reported the development of antibacterial material using UV-induced photo-grafting of poly(N-vinylpyrrolidone) onto the polypropylene film. This material was then capable of absorbing iodine from solutions in ethanol and exhibited antimicrobial activity against *E. coli*, *S. aureus* and *C. albicans*. Gillam et al [83] used plasma polymerization of N-vinylpyrrolidone on different substrates (KBr disks, cotton fabric, silicon wafers and glass slides) and investigated the physicochemical properties of the resulting PVP films. The cotton fabric modified with PVP was then loaded with iodine from alcohol-containing solutions and was subsequently dried under vacuum. Unmodified cotton fabric was used as a control. These materials were then tested and iodine-containing modified fabric exhibited broad spectrum anti-bacterial activity against clinically relevant bacteria (*E. coli*, *P. aeruginosa* and *S. aureus*), including drug resistant strains. It was confirmed that these coatings have biocompatibility and antiseptic properties. Edis et al [84] proposed the use of iodine in combination with Aloe Vera Barbadosensis Miller extract and *trans*-cinnamic acid dissolved in PVP solution for the treatment of sutures, bandages and face masks. The growth of *C. albicans*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae* microorganisms was found to slow down by impregnating bandages and face masks with this antimicrobial formulation.

There has been a growing interest in utilizing iodophors for hand hygiene to prevent the transmission of infectious microorganisms. For this purpose, Vergara et al [85] developed semi-solid formulations based on so-called bigels, consisting of a mixture of an oleogel with a hydrogel. The oleogel was prepared using extra virgin olive oil with beeswax as an organogelator, and α -tocopherol as an antioxidant. The hydrogel was formed using hydroxyethylcellulose, deionised water and povidone-iodine. The bigel was formed by adding the oleogel into the hydrogel with their subsequent homogenisation. The properties of the bigels were strongly dependent on the components ratio with greater iodine release observed from the samples with higher hydrogel concentration (oleogel: hydrogel 40:60). The efficiency of bigel iodophors as hand antiseptics was evaluated in healthy volunteers using finger-streak technique on the surface of the plate count agar. The bigels were found to be easily applied and adhered to the skin surface without dripping. The antimicrobial action of bigels reduced the growth of bacteria on the fingers as early as 1 h after their application.

The development of iodophor-based antimicrobial materials capable of adhering to various substrates underwater was reported by Song et al [86]. They synthesized these materials using free-radical copolymerization of 4-hydroxybutyl acrylate, isobornyl acrylate and N-isopropylacrylamide. Then these terpolymers were dissolved in ethanol and mixed with PVP-iodine and dried under vacuum. The adhesive properties of the films formed were evaluated and it was demonstrated that increasing the content of 4-hydroxybutylacrylate in terpolymers up to 70 % improves the stickiness of these materials both in air and under water. The free iodine was found to be released from this material slowly and continuously to provide a strong inhibitory effect on *S. aureus* and *E. coli*.

Natural polymers such as alginate are commonly used in wound care to produce dressings. Summa et al [87] reported the preparation of a biocompatible film using a combination of sodium alginate with povidone-iodine. It was demonstrated that this material combines excellent wound healing ability typical for alginate and antimicrobial properties of the iodophor, which resulted in faster healing observed in

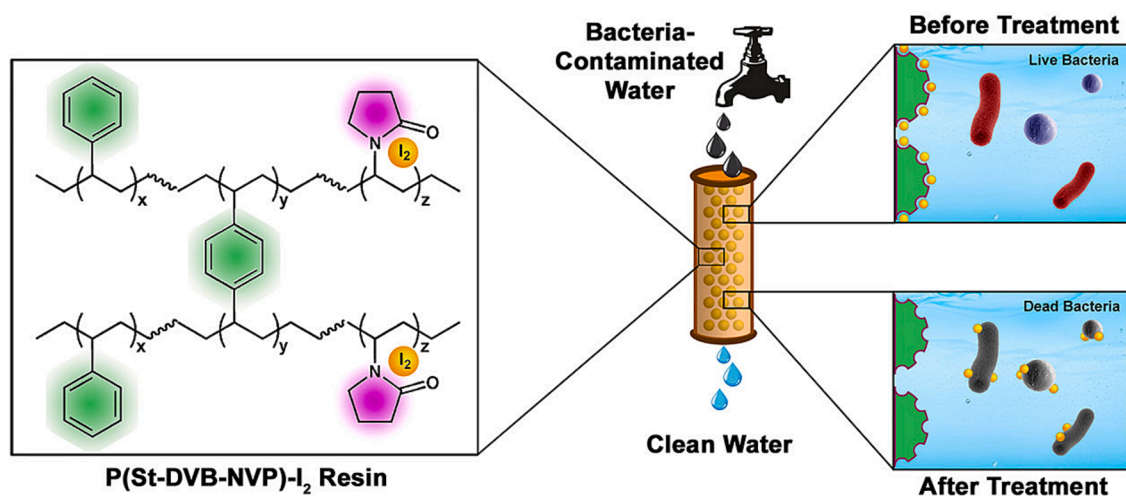


Fig. 5. Styrene-N-vinylpyrrolidone-divinyl benzene resin loaded with iodine and its application for water-purification. Reprinted from [81] with permission from American Chemical Society.

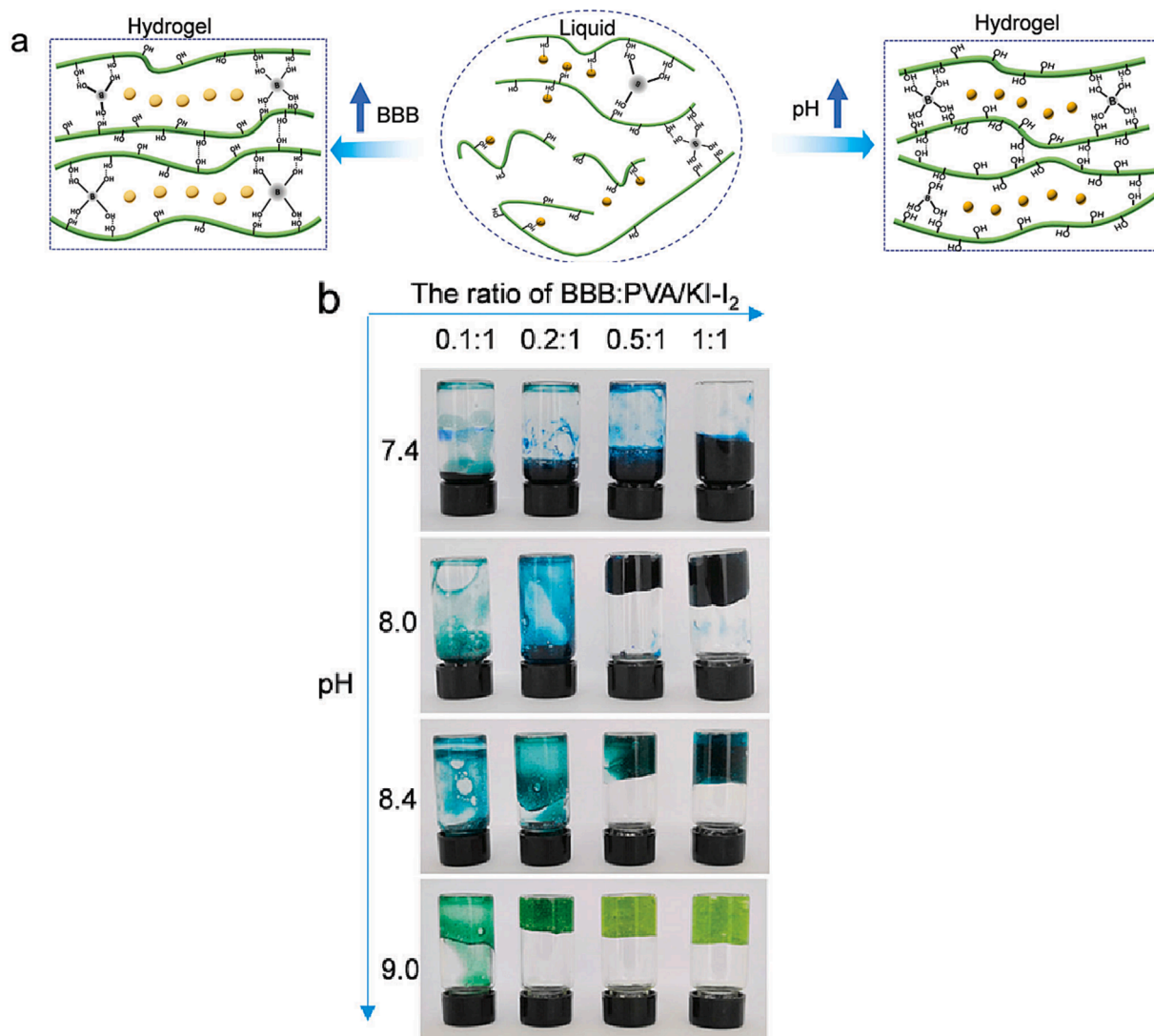


Fig. 6. Formation of hydrogels from poly(vinyl alcohol), iodine and borate buffer (a) and effect of BBB:PVA/KI-I₂ ratio and pH on the properties of the hydrogels (b). Reprinted from [88] with permission from Wiley and Sons.

experimental animal model.

As it is seen from the examples discussed above, the majority of commercial formulations and recently developed iodophors are based on the complexes of iodine with PVP. However, other materials capable of forming complexes with iodine can also be utilized to formulate iodophors. For example, Miao et al [88] reported the preparation of antimicrobial hydrogels based on the blue complex formed by poly(vinyl alcohol), iodine and boric acid. These formulations were prepared by simple mixing poly(vinyl alcohol)/KI-I₂ solution with borate buffer (BBB) in aqueous solution (Fig. 6). The properties of the hydrogels are strongly dependent on the pH value and the volume ratio of the borate buffer and PVA/KI-I₂. The hydrogels exhibited photothermally-responsive iodine release when irradiated with 808 nm near-infrared laser. It was established that a single injection of this hydrogel into MRSA-infected open wound resulted in 5 days healing and this can be further accelerated using laser irradiation.

Chitosan is a cationic polysaccharide that exhibits antimicrobial properties and ability to form complexes with iodine. New nanocomposite consisting of Cu nanoparticles, chitosan and iodine were developed by Mallick et al [89]. Cu nanoparticles with 8 ± 4 nm diameter were synthesized by the reaction of CuSO₄ with hydrazine in aqueous solutions in the presence of chitosan. Then these nanoparticles were mixed with 0.2 M iodine solution in ethanol and the product was purified using centrifugation. The minimum inhibitory concentration of iodine-containing nanocomposite evaluated in *E. coli* was 130.8 µg/mL. Zhang et al [90] reported the preparation of a film based on amphiphilic chitosan and iodine. The amphiphilic chitosan was synthesized by reacting chitin with 2-aminoethyl chloride hydrochloride in the presence of NaOH and then subsequent reaction of poly(aminoethyl) chitosan with citronellal. The solution of this chitosan derivative in 2 % acetic acid was mixed with 5 % w/v iodine in ethanol and the mixture was dried to form a film. This film exhibited a sustained and controlled release of iodine to provide a sustainable antibacterial effect.

6. Conclusion

The ability of iodine to form complexes with water-soluble polymers, cyclodextrins and various other molecules remains a subject of great interest, despite centuries of research of this chemical element. The complexity of transformations between iodine species leads to interesting colour changes in solutions as a result of complexation with polymers and other compounds. These colour changes and other physicochemical properties of polymer-iodine complexes are still poorly understood. The ongoing fascination with iodine and iodophors stems from their exceptional antimicrobial properties against a diverse range of pathogens. This review provided some information on the history and properties of iodine and iodophors, highlighted some existing iodine-containing products on the market, discussed the variety of physicochemical methods used to study complexes of iodine, and evaluated some recently published studies about iodophors. The recent trends in this field include the use of new polymers, colloidal particles and surfaces as well as the development of materials with slow release of iodine.

A number of polymer-based iodophors are already available commercially and are widely used as antiseptic agents and wound dressings. It is expected that the market of iodine containing products will expand further in response to the growing needs in prevention and treatment of infections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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