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Review

Rhodamine B and Rhodamine 6G Based Sensing of Copper Ions in Environmental and Biological Samples: Recent Progress

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Abstract

Metal ions are widely distributed in living organisms and environmental systems, therefore, their monitoring is of great importance. These days, several sophisticated instrumental methods are being used for the detection of metal ions; however, rapid recognition of metal ions requires powerful tools namely, colorimetric and fluorescent chemosensors. In this review, Rhodamine B and Rhodamine 6G based colorimetric and fluorescent chemosensors have been discussed. These methods are simple, involve low cost, lower detection limit, high selectivity, and sensitivity, thereby used to monitor real-time metal ions. Several metal ions were detected with high selectivity and sensitivity with the aid of various derivatives of Rhodamine B and Rhodamine 6G fluorophores conjugated to different ligands. Besides that, this review is focused on the detection of Cu^{2+} metal ions in recent years.

Keywords: sensors, chemosensors, rhodamine chemosensors, environmental samples, biological samples

Introduction

The design of high selectivity and sensitivity chemosensors for detecting the biologically and environmentally significant metal ions has captivated considerable attention [1-3]. Chemosensors signal the presence of a specific analyte of interest and are the molecules of abiotic origin. In mechanism, chemosensors bind to a particular analyte with high selectivity and reversibility which results in a change in some of the properties of the system, like absorption, fluorescence spectra, redox potentials, etc [4, 5]. Sophisticated instrumental methods like inductively coupled plasma mass spectrometry (ICP-MS), atomic absorption spectroscopy (AAS), spectrophotometry, voltammetry, ion chromatography, etc., could be used to detect certain metal ions. Even though these methods are exhaustive, the measurement involves high cost, requires extensive sample preparation, and is considered to be a time-consuming process [6-8]. Therefore, the development of reliable and efficient analytical methods for qualitative as well as quantitative detection of metal ions has drawn continuous research interest in many fields including materials, chemistry, environmental and biological sciences. Chemosensors are the powerful tools to monitor these metal ions *in vivo* and *in vitro*,

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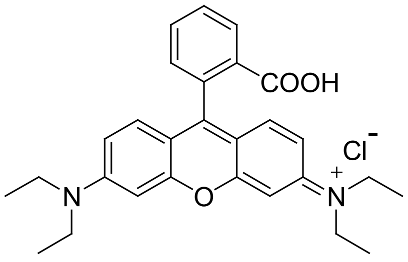
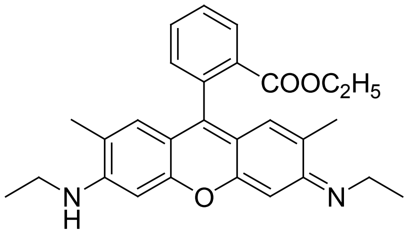


Rhodamine B



Rhodamine 6G

Fig. 1. Structures of Rhodamine B and Rhodamine 6G.

due to their high selectivity and sensitivity, simple operation, low cost, real-time monitoring ability, and short response time [7-10].

Rhodamine B (Fig. 1) is one of the most commonly used dyes which is widely used for labeling pigments, fluorescence standards, and chemosensors. Over the last few years, rhodamine-based probes have emerged as a matter of great interest due to its distinguished photophysical characteristics, namely high extinction coefficients, magnificent quantum yields, excellent photostability, and their ability to bind with various biologically important metal ions [11, 12]. This review focuses primarily on the identification of Cu^{2+} metal ions by Rhodamine B and Rhodamine 6G dependent chemosensors.

Metal Ions Detection Using Rhodamine Chemosensors

Detection of Cu^{2+}

The third most common transition metal ion in the human organism is Cu^{2+} following Fe^{3+} and Zn^{2+}. The function of several physiological processes of organisms and mammals is determined by copper ions [13]. Cu^{2+} is also involved with the active sites of nearly 20 metalloenzymes including laccase, Cu/Zn superoxide dismutase, dopamine β-hydroxylase, tyrosinase, cytochrome c oxidase, and lysyl oxidase. Moreover, Cu^{2+} is an important micronutrient for all known living forms [14,15]. On the other hand, a high concentration of Cu^{2+} is also known to be toxic to living cells and it can cause severe neurodegenerative diseases like Menkes, Wilson, Alzheimer's, and Prion diseases [16]. High intake could also cause anemia and gastrointestinal distress and elevates the risk of lung cancer [17]. Many chemosensors have been reported for sensing Cu^{2+} [7, 18-23] but a convenient, fast, and accurate method is yet to be developed for its detection as this matter is of considerable importance. Sahoo's group reported chemosensor 1 for selective detection of Cu^{2+} in an aqueous medium [24]. In fluorometric titration between chemosensor 1 and Cu^{2+}, enhancement of fluorescence was found to be 130-fold and observed at 574 nm with a very short response time of two minutes. Furthermore, chemosensor 1 (Table 1, Sensor 1) was effectively employed in spinach sapling for the estimation of copper (II) ions from its root, stem, and leaf of the sapling.

Yang et. al developed and synthesized a tetraphenylethene (TPE)-rhodamine hydrazone-conjugate 2 via condensation of rhodamine B hydrazide 2-hydroxy-5-(1,2,2-triphenylvinyl)benzaldehyde [25]. Chemosensor 2 (Table 1, Sensor 2) exhibited aggregation-induced emission behavior in more than 40% water fraction. Upon addition of Cu^{2+}, the absorbance intensity was remarkably enhanced and the solution's color changed from colorless to purple with 1:1 metal-probe complex formation. Moreover, the binding of chemosensor to Cu^{2+} was found chemically reversible by adding an EDTA solution. Ding et. al. reported a fluorescent diarylethene-rhodamine derivative 3 to identify Cu^{2+} and arginine [26] sequentially. Rhodamine derivative 3 (Table 1, Sensor 3) exhibited "turn-on" fluorescence response selectively towards Cu^{2+} in acetonitrile-water (4/1, v/v) media. A linear response was established between Cu^{2+} concentration and fluorescence intensity within the 2-36 μM range. Fluorescence response of 3-Cu^{2+} got quenched with the addition of arginine over other 17 amino acids which demonstrated that sensor 3 has high selectivity towards arginine only.

Selective Detection of Copper Ions (Cu^{2+}) in Solvents

Wang's group reported a rhodamine 6G-based probe 4 (Table 1, Sensor 4) which exhibited selective response towards Cu^{2+} in acetonitrile over the other background metal ions [27]. Upon addition of 6 equivalents of Cu^{2+} to 4, a spirocyclic ring of rhodamine unit was opened, resulting in 250-fold fluorescence enhancement at 557nm with a transition in color to purple, aids in the identification of Cu^{2+} through naked-eye. The detection threshold for Cu^{2+} was 2.5μM when the probe 4-Cu^{2+} complex stoichiometry was 1:1. Wang et. al reported a dual-function optical chemosensor 5 (Table 1, Sensor 5) through condensation of 5-Hydroxymethylfurfural and rhodamine B hydrazide [28]. Chemosensor 5 showed a specific fluorescent response towards acidic pH. Fluorescence intensity of 5 was enhanced by 41 times between pH 7.50 and 3.73 with a pKa value of 5.02 and a change of color from colorless to pink. Furthermore, UV–Vis spectroscopy study and addition of EDTA

Table 1. Chemosensor structure, detection limit and references for Cu^{2+}.

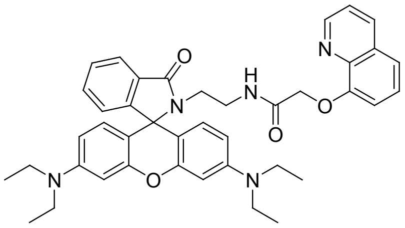
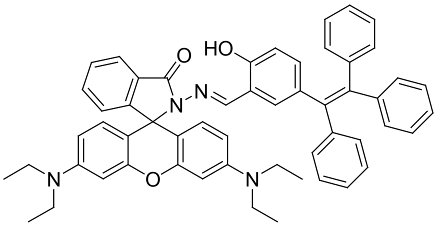
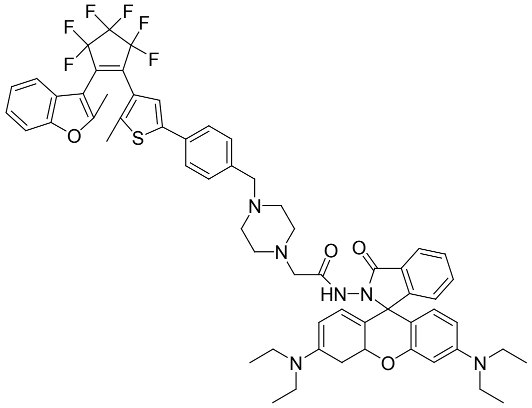
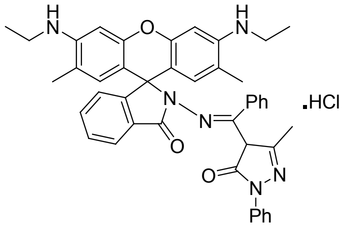
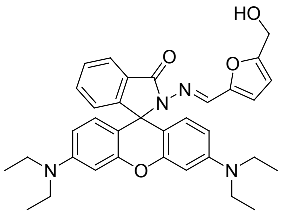
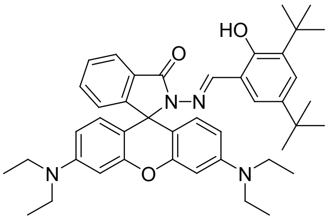
Probe Structure	Analyte	Detection limit	Ref.
 **Sensor 1**	Cu^{2+}	2.2×10^{-6}M	[24]
 **Sensor 2**	Cu^{2+}	10^{-6} mol/L	[25]
 **Sensor 3**	Cu^{2+}	0.28×10^{-6} M	[26]
 **Sensor 4**	Cu^{2+}	2.5×10^{-6} M	[27]
 **Sensor 5**	Cu^{2+}	0.15×10^{-6} M	[28]
 **Sensor 6**	Cu^{2+}	30.75×10^{-9}M	[29]

Table 1. Continued.

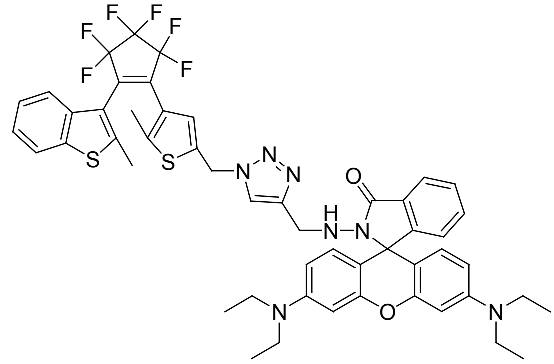
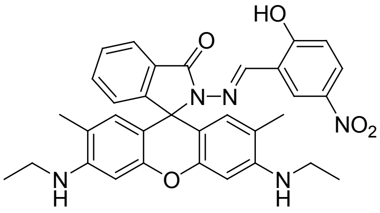
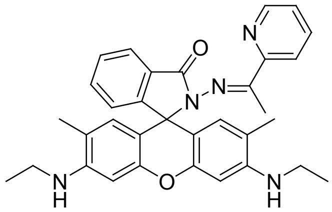
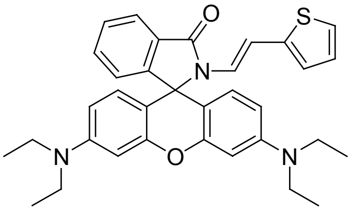
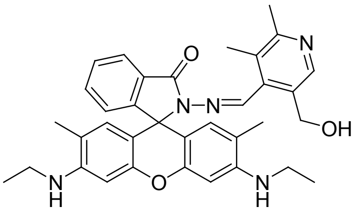
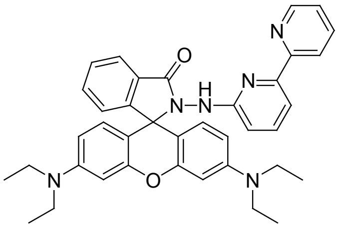
 **Sensor 7**	Cu^{2+}	2.86×10^{-8}M	[30]
 **Sensor 8**	Cu^{2+}	7.19×10^{-6} M	[31]
 **Sensor 9**	Cu^{2+}	0.21×10^{-6} M	[32]
 **Sensor 10**	Cu^{2+}	1.7×10^{-7} M	[33]
 **Sensor 11**	Cu^{2+}	1.0×10^{-6} mol L^{-1} (Absorption spectroscopy) 3.9×10^{-7} mol L^{-1} (Fluorescence spectroscopy)	[34]
 **Sensor 12**	Cu^{2+}	0.739×10^{-9} M	[35]

Table 1. Continued.

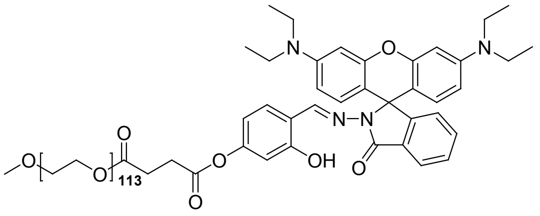
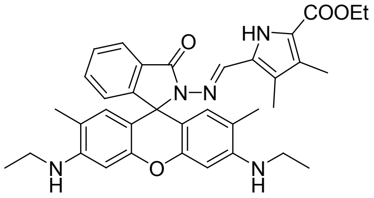
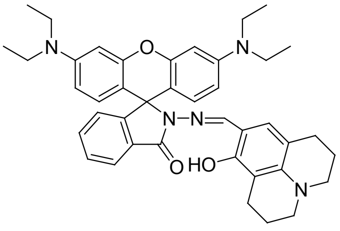
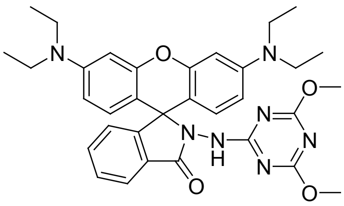
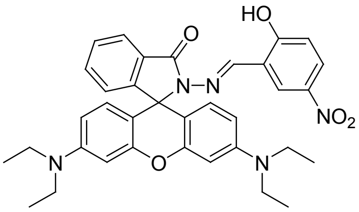
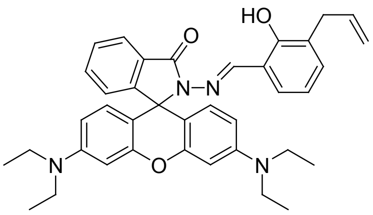
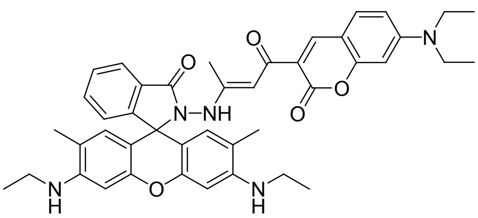
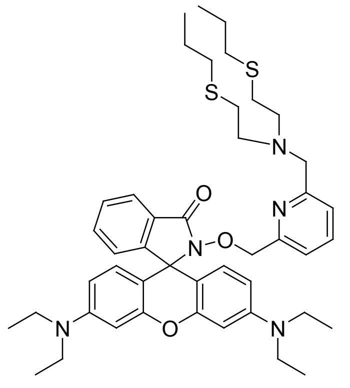
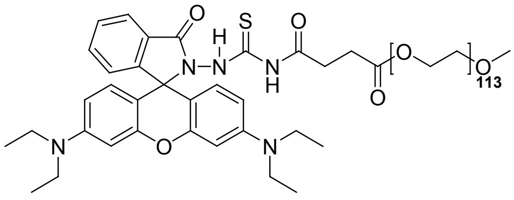
 Sensor 13	Cu^{2+}	2.5×10^{-8} M	[36]
 **Sensor 14**	Cu^{2+}	2.94×10^{-6} M	[37]
 Sensor 15	Cu^{2+}	0.45×10^{-6} M	[38]
 **Sensor 16**	Cu^{2+}	4×10^{-6} M	[39]
 **Sensor 17**	Cu^{2+}, Al^{3+}	4.726×10^{-7} M (Cu^{2+}), 4.43×10^{-7}M (Al^{3+})	[40]
 **Sensor 18**	Cu^{2+}, Al^{3+}	3.21×10^{-7} M (Cu^{2+}), 5.72×10^{-7} M (Al^{3+})	[41]
 **Sensor 19**	Cu^{2+}, Hg^{2+}	6.88×10^{-6}M (Cu^{2+}), 2.86×10^{-6}M (Hg^{2+})	[42]

Table 1. Continued.

 **Sensor 20**	Cu^{2+}, Hg^{2+}	1.63×10^{-6} M (Cu^{2+}), 2.36×10^{-6} M (Hg^{2+})	[43]
 **Sensor 21**	Cu^{2+}, Hg^{2+}	5.92×10^{-7} M (Cu^{2+}), 2.85×10^{-6} M (Hg^{2+})	[44]

experiments showed selectivity and reversibility of probe towards Cu^{2+} in Tris–HCl (10 mM, pH = 7.2) over the other metal ions. A study using Job's plot recorded a 1:2 binding stoichiometry between Cu^{2+} and probe 5.

Chattopadhyay's group synthesized a "turn on" colorimetric and fluorimetric probe 6 (Table 1, Sensor 6) to detect Cu^{2+} ions selectively as low as nanomolar levels in an aqueous medium [29]. The 68-fold increase was observed in fluorescence intensity because of the ring-opening of the rhodamine-B spirolactam network with a color shift to reddish-pink when 3 equivalents of Cu^{2+} was added. The cell imaging study using a fluorescence microscope showed that the probe is non-cytotoxic and it is useful to recognize the distribution of Cu^{2+} ions in live cells.

Xue et. al designed and developed a rhodamine B-consisting diarylethene probe 7 [30]. Fluorescent emission of probe 7 (Table 1, Sensor 7) was remarkably intensified in the presence of protons or Cu^{2+} due to the formation of the rhodamine moiety open-ring. The association constant for 7-Cu^{2+} was 2.86 x 10^{6} L mol^{-1}. The probe was employed effectively for real water sample analysis by spiking an appropriate amount of Cu^{2+}, where % recovery was reported to be 98.6 to 110.9%.

Detection of Copper ions (Cu^{2+}) in the Presence of Environmentally and Biologically Important Metal Ions

Bharadwaj and co-workers developed a new rhodamine 6G derived probe 8 (Table 1, Sensor 8) to detect Cu^{2+} ion over the other environmentally relevant and biologically important metal ions in ethanol-water (1:1, v/v) media at physiological pH (pH 7.2) [31]. Probe 8 bound selectively to Cu^{2+} in 1:1 stoichiometry. The detection limit for Cu^{2+} ion was stated to be 7.19 µM which is below the permitted limit for Cu^{2+} in drinking water (20 µM) set by USEPA. A cell imaging research further revealed that the probe could serve as a possible candidate for the selective Cu^{2+} ion recognition in living cells. Liu et al. reported a novel fluoro-chromogenic rhodamine 6G-pyridine conjugate 9 (Table 1, Sensor 9) for selective Cu^{2+} sensing over other metal ions [32]. After, adding a solution of Cu^{2+} to 9, a "turn-on" response was observed with a remarkable color change from colorless to red. The response of fluorescence intensity of 9 was found linear to Cu^{2+} concentration from 2.0 to 20.0 µM with a binding stoichiometry of 2:1. Further, the probe was tested for sensing of Cu^{2+} in natural water and the recovery was compared with the one obtained by ICP-AES. Comparable recovery results indicated the great potential of a probe for monitoring of Cu^{2+} in real sample analysis.

Identification of Copper Ions (Cu^{2+}) in Aqueous Media

Yang et al. engineered and synthesized a new "off-on" colorimetric rhodamine derivative 10 (Table 1, Sensor 10) possessing thiophene group, for Cu^{2+} identification in aqueous media with high precision [33]. A strong linear response was obtained from 1.0×10^{-6} to 1.0×10^{-5} mol/L between the absorption strength of 10 and Cu^{2+} concentration. Upon incremental addition of Cu^{2+} from 0-4 equivalents to the solution of 10, an absorption band emerged at 561 nm shifting the colorless solution to pink. A rhodamine 6G-based chemosensor 10 reported by Huang et al. exhibited a rapid Cu^{2+} ion identification in an aqueous medium with a color transition towards pink [34]. Chemosensor 11 (Table 1, Sensor 11) showed a very low fluorescence response in the pH range of 2.5-10.5; however, after the addition of Cu^{2+}, significant fluorescence enhancement with pH of 3.5 to 7.5 due to the opening of the rhodamine spirolactam unit. Furthermore, the fluorescence intensity of 11-Cu^{2+} was quenched when the EDTA solution was added, indicating the reversibility of the sensing process.

Yuan et al. developed a "turn-on" fluorescent probe 12 (Table 1, Sensor 12) for Cu^{2+} [35]. For rapid detection of Cu^{2+} an air-dried filter paper from the solution of 12 was immersed in an aqueous solution of Cu^{2+} for several seconds; interestingly, the color of the test strips shifted to purple from colorless with a detection limit of 10μM lower than the approved Cu^{2+} limit in drinking water (1 mg/L) as set by the WHO (World Health Organization). Furthermore, an imaging study showed that probe 12 could be used to detect Cu^{2+} in living cells. A novel water-soluble polymer-based (polyethylene glycol) reversible colorimetric probe 13 (Table 1, Sensor 13) developed by Li's group showed a rapid response towards Cu^{2+} in pure aqueous solution [36]. The chemosensor could detect Cu^{2+} over a wide range of pH 4-10. After the addition of Cu^{2+}, a colorless solution of probe 13 turned to purple within a very short time of 5s, indicating that the probe could be used to detect Cu^{2+} ions in real-time. Association constant of probe 13 coordinated with Cu^{2+} was determined to be 1.01×10^5 M^{-1}.

Sensing Copper Ions (Cu^{2+}) in the Presence of Other Background Metal Ions

Wang et al. reported a ratiometric and fluorescent sensor 14 (Table 1, Sensor 14) Rhodamine 6G hydrazine coordinated to the pyrrole unit, for Cu^{2+} sensing [37]. Probe 14 could be used as a dual-mode sensor. It detects Cu^{2+} from sensor 14- Cd^{2+} complex utilizing ring-opening mechanism and by ratiometric displacement of Cd^{2+} ion. The addition of Cu^{2+} to the solution of 14 exhibited a significant change in absorbance and fluorescence emission at 525 nm and 550 nm respectively, owing to cleavage of spirolactam bond of rhodamine unit. Furthermore, the incremental addition of Cu^{2+} to 14-Cd^{2+} solution, displaces Cd^{2+} to form 14-Cu^{2+} complex indicating ratiometric displacement. Li et. al developed a novel colorimetric probe 15 (Table 1, Sensor 15) from 8-hydroxyjulolidine as source material [38]. Chemosensor 15 showed high selectivity towards Cu^{2+} ions and also exceptional anti-interference ability over the other background metal ions. A 1:1 complex coefficient of 15 to Cu^{2+} was determined by Job's plot analysis. A good linear working range was recorded using 15 for Cu^{2+} from 0-50 μM with a sensing cap of 0.45 μM which is 2 % of the permissible drinking water level of 20 μM as defined by the US EPA.

Simultaneous Identification of Copper Ions (Cu^{2+}) and Aluminium Ions (Al^{3+})

Zhang and co-workers reported a convenient and highly selective probe 16 (Table 1, Sensor 16) for Cu^{2+}, and its chemosensing properties were investigated [39]. An unperturbed absorption spectrum of 16 was noticed in the range of pH 4.0-9.0, indicating that 16 could be used for sample study over an extensive range of pH. With Al^{3+} being added to the probe 16 solution, a marked rise in fluorescence emerged with emission maxima at 580 nm. Interestingly, on the addition of Cu^{2+} to 16-Al^{3+}, fluorescence produced with Al^{3+} disappeared and a unique stable absorption band originated at 564 nm probably due to the paramagnetic effect of the d_9 Cu^{2+} ion. Son's group designed and synthesized 4-nitrosalicylaldimine-based "OFF-ON-OFF" dual reversible sensor 17 with rhodamine B for sensing of Cu^{2+} and Al^{3+} ions [40]. The chemosensor 17 (Table 1, Sensor 17) exhibited fluorescence and optical preference for Al^{3+} and Cu^{2+} in dimethyl sulfoxide-water media over the other common metal ions respectively. With the addition of CN^- and EDTA, the color of 17-Cu^{2+} complex diminished, whereas the fluorescent nature of 17-Al^{3+}, "turned-off" due to the influence of EDTA. The binding constants of 17-Cu^{2+} and 17-Al^{3+} were reported to be 2.18×10^5 and 2.76×10^4 M^{-1} with a binding stoichiometry of 1:1.

Detection of Copper Ions (Cu^{2+}) in the Presence of Aluminium Ions (Al^{3+})

Rai et al. reported a probe 18 (Table 1, Sensor 18) synthesized from rhodamine B hydrazide and allylsalicylaldehyde for Cu^{2+} and Al^{3+} identification in aqueous media [41]. With the introduction of 10.0 Equiv. of Cu^{2+} and Al^{3+} ions to probe 18 solutions, a unique band emerged at 552 nm and 559 nm, respectively, in the UV-Vis spectrum. A "turn-on" fluorescence response appeared with a new band at 587nm when Al^{3+} was added to a solution of 18. Quenching of fluorescence of open-ring form of rhodamine was observed due to chelation enhanced fluorescence quenching (CHEQ). The binding constants for Cu^{2+} and Al^{3+} were calculated to be $6.2 \times 10^4 M^{-1}$ and $1.4 \times 10^4 M^{-1}$, respectively. Xu et al. synthesized probe 19 (Table 1, Sensor 19) based on Rhodamine 6G hydrazone coordinated to coumarin unit at a particular pH for the sensing of Cu^{2+} and Hg^{2+} [42]. The probe detected Cu^{2+} with high selectivity in neutral aqueous media, whereas, Hg^{2+} was detected with fluorescence enhancement at pH 10. Fluorescence intensity linearly corresponds to Cu^{2+} ion concentration ranging from 8-15 μM and absorbance was directly proportional to the quantity of Cu^{2+} ions in the range of 0-30 μM. Upon introduction of 17 Equiv. of Hg^{2+} to 5 μM of probe 19 in acetonitrile/water (9/1, v/v, pH 10.0) media, an enhanced emission band with a fluorescence intensity appeared at 498 nm concerning the concentration of Hg^{2+} ions ranging from 0-20 μM.

Table 2: Pros and cons of sensing and spectroscopic methods.

	Sensing Methods	**Pros**	**Cons**
1	Chemosensors	(1) Convenient for *In Vivo* real-time imaging studies (2) High selectivity and Sensitivity (3) Rapid detection and easy to operate (4) Sample preparation procedures are not complex (5) Convenient for the onsite analysis (6) Few of the chemosensors are reversible (7) Each chemosensor is specific for a particular cation or anion (8) Do not occupy large space (9) Long shelf life and Cost-effective (10) Low power requirements or nil	(1) Detection is pH-dependent (2)Different chemosensors are needed for specific detection (3) Atomic weight of metals cannot be determined
2	Electrochemical Sensors	(1) Specific for analyzing gases and some of the cations	(1) Sensitive to temperature (2) Shelf life is limited (3) Cross-reactivity due to other gases (4) Electrolytes are reduced due to very high temperature and low humidity
	Spectroscopic methods	**Pros**	**Cons**
3	Atomic Absorption Spectroscopy	(1) Quantitative analysis (2) Selective and sensitive	(1) Requires different filters for the detection of different metal ions (2) Onsite analysis is not possible (3) Trained personnel are needed for sample processing and operating the instruments (4) Occupy large space in laboratories (5) High working cost
4	Inductively coupled plasma mass spectrometry (ICP-MS)	(1) Identification of atomic weight of elements (2) Used for simultaneous detection of different elements (3) Selective and sensitive	(1) High working cost (2) Onsite analysis is not possible (3) Trained personnel are needed and require large space in laboratories
5	X-ray photoelectron spectroscopy (XPS)	(1) To determine the binding energy of a particular element. (2) Surface chemistry of metals	(1) Ultra-high vacuum is needed for analysis (2)Trained personnel are needed for sample processing and operating the instruments (4) Maintenance cost is high (5) Not feasible for onsite analysis
6	Electron spin resonance spectroscopy	(1)To detect metals with unpaired electrons or free radicals. (2) Useful for studies of complex macromolecules like proteins with the metal clusters.	(1) Sample solution must contain paramagnetic species (2) Maintenance cost is high
7	Mossbauer spectroscopy	(1) Specifically, to analyze iron	(1) Needs suitable gamma-ray source
8	Ion exchange chromatography	(1) Useful for simultaneous separation, detection, and quantification of different metal ions (2) Amino acids, nucleotides, and large proteins can also be separated	(1) Requires specific columns for separation (2) Need buffer solutions for separation (3) Inconvenient for onsite analysis and maintenance cost is high

Detection of Copper Ions (Cu^{2+}) in the Presence of Mercury Ions (Hg^{2+})

Zang and co-workers developed a dual chemosensor 20 i.e rhodamine B with an NS_2-containing receptor (Table 1, Sensor 20) to sense Hg^{2+} and Cu^{2+} ions in aqueous media [43]. Chemosensor 20 exhibited a colorimetric response towards Cu^{2+}, whereas the “turn-on” fluorescent response showed for Hg^{2+}. Chemosensor 20 exhibited pH-independent response towards Cu^{2+} and Hg^{2+} over a wide range of pH 4.0-9.0. Upon interaction with Cu^{2+}, chemosensor 20 showed a 251-fold absorption enhancement along with a visually detectable change from uncolored to purple. Wang’s group reported a polymer-based water-soluble dual-mode chemosensor 21 (Table 1, Sensor 21) for sensing of Cu^{2+} and Hg^{2+} in a 100% aqueous solution [44]. Probe 21 exhibited not only colorimetric response to Cu^{2+} and Hg^{2+} but also a selective turn-on fluorescent response to Hg^{2+} over the other metal ions that coexist. The binding stoichiometries of 21-Cu^{2+} and 21-Hg^{2+} using Job’s plot analysis were found to be in the ratio of 1:1. Furthermore, the test papers coated with the solution of probe 21 were found relevant for the on-site identification of Hg^{2+} and Cu^{2+} and ions in actual water samples. The pros and cons of sensing methods and spectroscopic methods are shown in Table 2.

Future Perspectives

Chemosensors are organic and susceptible to biodegradation similar to pharmaceutical drugs in the human system [45]. Organic pharmaceutical compounds undergo metabolism by enzymes [46] and used as a therapy, similarly chemosensors can be biodegraded for or after its specific applications [47]. Chemosensors can be effectively utilized to detect and harvest metal ions from biological and environmental matrices, where copper ions are a major cause of environmental concern [48]. Accumulated metallic wastes can be effectively isolated, segregated, and purified for reuse with the assistance of chemosensors.

Conclusions

In this review, recently reported colorimetric and fluorescent sensors originated from Rhodamine B and Rhodamine 6G are summarized. The sensors were classified according to their sensing capability towards specific copper ion. Binding stoichiometry and association constants of some of the sensor-metal complexes were described. Most of the sensors fulfilled the minimum detection limit of these metal ions required by USEPA at physiological pH range in aqueous media. Therefore, sensors fulfilling the criteria set by USEPA were employed to image the cells, and the maximum number of sensors was found to be low or non-toxic with better permeability. More researchers are focused on this creative area of research to develop novel, selective and sensitive sensors for detecting various environmentally and biologically important metal ions.

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Conflict of Interest

The authors declare no conflict of interest.

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