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URINARY IODINE ASSAYS AND IONOPHORE BASED POTENTIOMETRIC IODIDE SENSORS

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1. ABSTRACT

Urinary Iodine has been widely regarded as a biochemical marker for control of iodine deficiency disorders. Based on the Sandell-Kolthoff reaction, most colorimetric assay methods for urinary iodine (UI) determination that have been developed require pretreatment of urine sample. The non-Sandell-Kolthoff methods for UI assay provide alternative approaches for UI assay requiring only simple pretreatment or even without pretreatment. The selective ionophore-based iodide electrodes are highly applicable to the UI assay for large population due to their high selectivity and sensitivity to iodide, amenability to automation and ease of miniaturization. In this report, different assay methods are reviewed, including pretreatment procedures for Sandell-Kolthoff UI analysis. Finally, a summary of the state-of-the-art of the iodide ionophore-based ISEs that are suitable for UI assays are addressed.

2. INTRODUCTION

For adequate synthesis and constant secretion of thyroid hormones T_4 (thyroxine) and T_3 (triiodothyronine), supplementation of iodine is mandatory. Insufficiency of ingested iodine significantly impairs psycho-physiological growth and metabolism, which can transform into iodine deficiency disorders (IDD) (hypothyroidism, goiter, cretinism, mental retardation, etc.). Approximately 1.6 billion people (mostly in developing countries) are currently at risk of IDD (1, 2). Adequate biological levels of iodine can only be maintained through sufficient dietary iodine supplementation. In the clinical laboratory, iodine measurements are used primarily for epidemiological studies. To date, the major application of iodine analysis is to assess the dietary iodine intake of a given population (1, 3). As the majority of ingested iodine is excreted in the urine, the measurement of urinary iodine (UI) excretion provides an accurate approximation of dietary intake (4). In most circumstances, the determination of UI provides little useful information of the long-term iodine status of an individual, since the results obtained merely reflect recent dietary iodine intake. However, measuring UI in a representative cohort of individuals from a specific population provides a useful index of the iodine level endemic to that region (4, 5). Besides estimating the UI concentration in populations, other applications of iodine measurements include determining iodine in milk, food products and drinking water (6). Iodine assays in thyroid or breast tissue have been performed as part of clinical mechanism research studies (7). An ICCIDD/WHO/UNICEF consultation in 1999 endorsed urinary iodine concentration as the most useful laboratory method for assessing iodine nutrition. Advantages are (a) most iodine eventually appears in urine; (b) samples are readily obtainable; (c) the cost is low. The proposed values of average urinary iodine levels as a guide for a region's IDD status are (8): <20 μg/L (severe); 20 – 49 μg/L (moderate); 50 – 100 μg/L (mild) and > 100 μg/L (normal). There have been a number of documents that describe methods for determination of total iodine content in urine.

Methods to determine urinary iodine content have been intensively studied and well developed to meet the epidemiology requirements. For example, an ICP-MS method for determination of urinary iodine, using isotope dilution with iodine-129, was presented by Haldimann et al (9). Although it offers precise results and automated analysis, expensive laboratory instrumentation and highly skilled personnel are required for operation and not suitable for epidemiological assays of a large sample population.

In this work, we extensively review potentiometric sensors using ionophore based iodide-selective electrodes that are applicable to the UI testing. In classic catalytic colorimetry approaches, the so-called "sample digestion" is generally used in order to remove the interfering molecules in urine to insure the reliability of the catalytic reaction. Although conventional ion-selective electrodes (ISEs) based on precipitation membranes or ion-exchanger polymer membranes have been used in UI assays (10), most encounter serious interference from contaminants in the urine samples. Using ion-exchange based ISEs, it has been demonstrated that the significant anions interfering with the ISEs are from Cl^- and SCN^-. The precipitation electrode films are easily contaminated with

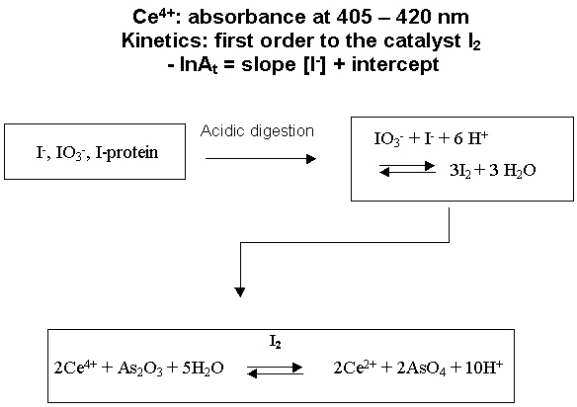

Figure 1. Scheme of Sandell-Kolthoff reaction.

this interfering coating when applied to urine samples. However, recently developed ionophore-based iodide potentiometric sensor techniques exhibit high selectivity to iodide and much lower detection limit, suitable to UI screening assays. More important, no sophisticate, time-consuming, and toxic "sample digestion" is needed. Due to their features including low-cost, rapid and simple-pretreatment, and ease of use, this type of iodide sensor can be applied via automation of the UI assay. In the next section, we summarize eight representative iodide selective ionophores, regarding their performances as iodide selective potentiometric sensors.

3. URINARY IODINE ANALYSIS METHODS

3.1. Sandell and Kolthoff methods

Currently, the most common technique for iodine measurements utilize colorimetric ceric-arsenic assays, which were first proposed by Sandell and Kolthoff (11) (SK method) in 1934. This assay is based on the catalytic effect of iodide in the redox reaction between yellow cerium (IV) and arsenic (III), to yield the colorless cerium (III) and arsenic (V). The reduction in the yellow cerium is measured spectrophotometrically at 410 nm. Sandell and Kolthoff established empirical conditions for the determination of iodine and iodide at concentrations down to 20 parts per billion (ppb), or 20 μg/L. The catalytic reduction-oxidation reaction kinetics has been widely accepted as the kinetic first order in iodine concentration (12, 13). The colorimetric response toward iodine concentration follows the Beer-Lambert law:

$$- ln\,(A_t) = slope\,[I_2] + intercept \quad (1)$$

where A_t is the absorbance at time t of reaction solution, and $[I_2]$ is the iodine concentration. The scheme of this reaction is shown in Figure 1. Automated analyzers have been developed to perform this method based on acid digestion, e.g. the Technicon (Tarrytown, NY) AutoAnalyzer II system. Most of the interfering compounds in urine, which affect the kinetics of the redox reaction in this spectrometric test, are removed by chemical digestion pretreatment of the urine samples. The lower detection limits in linearity of most SK-based assays can reach down to several mg/L (< 20 μg/L) which satisfies the requirements for urine iodine tests. In most clinical laboratories, the wet digestion processes (14), using concentrated chloric acid, is most frequently used rather than dry digestion by alkaline ashing (15, 16). In latter method, the urine specimens are digested using chloric acid or perchloric acid. Both digestion processes are time consuming (several hours) and complicated in operation especially the acidic wet digestion method which has additionally drawbacks in that chloric or perchloric acid are potentially explosive and their usage requires a dedicated fume hood. . Even with these drawbacks, SK-based colorimetric approaches were still regarded as the classic method for UI measurements and are summarized by Dunn et al in 1990s (15).

To improve UI testing with an effective and simple assay approach, many modifications of the SK-based method have been proposed, including changing the digestion procedure to utilize less hazardous methods. Some digestion reagents, e.g. ammonium persulfate (17), H_2SO_4 + $KMnO_4$ + $K_2Cr_2O_7$ (18), instead of the chloric acid, were introduced in UI assays. However, other toxic substances, e.g. brucine, and chromium, were substituted as the reagents, which present significant biological risks to the environment and to the users. A technique using dialysis (19) was proposed to filter interfering components in the urine sample, however, this technique subjects the sample to serious analytical error resulting from interfering substances, such as thiocyanate, that cross the dialysis membrane and participate in the catalytic reaction. K. Tsuda et al (20) substituted ultraviolet (UV) light irradiation for acid digestion in an automated testing system. UV energy produces oxygen and hydroxyl free radicals from the potassium persulfate in a four-step reaction in acidic conditions; the radicals can then react with inorganic iodide separated from iodine-containing organic compounds. This system is sensitive enough to detect concentration of UI <10 mg/L. The within-assay imprecision (CV) was <10% in the UI range of 0.10 – 3.00 μM (10 - 400 μg/L); the between-assay CV was usually < 15% in the same range. Ohashi T. et al. (21) reported a specially designed, sealed, digestion cassette containing a microplate format that can rapidly test UI precisely, with the detection limit of 0.11 μM (14 μg/L iodine). This rapid method makes the assay kit accessible to portable detection devices. More recently, an assay kit with a charcoal purification layer was used to provide a more rapid quantitative measurement (22). A disposable charcoal packed column (Urojod, Merck KgaA, Darmstadt, Germany) is employed to remove the interfering substances prior to the SK method eliminating the need for acidic digestion. This method reported a lower detectable UI level of 100 μg/L (0.79 μM).

3.2. Other methods for UI assays

Besides the SK-methods, other approaches for measuring UI have also been investigated. Automated equipments, e.g. HPLC (23, 24), mass spectrometry (25), ICP-MS (9) provide population assays that are very rapid and precise. However, expensive instrumentation and trained personnel required for these methods are not suitable for epidemiological in-field survey tests, especially

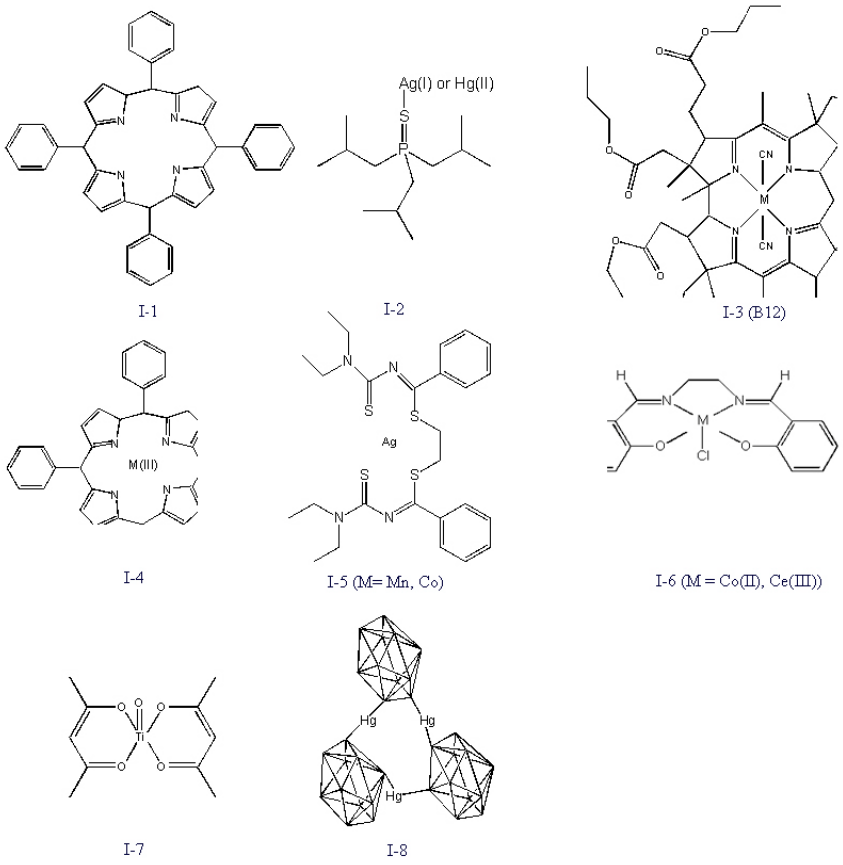

Figure 2. Typical iodide selective ionophores.

in developing countries. The ideal assay method needs to be inexpensive, rapid, and easy-to-use.

Measuring UI with ion-selective electrodes provides a low cost and rapid approach which meets the requirements for in-the-field screening tests. Since iodide is the main excreted form of iodine in urine, which makes up to 90-95 % of total UI, hence urinary iodide is currently the most convenient laboratory marker of iodine deficiency (15). Ion-selective electrodes (ISE) for iodide have been available for many years. The early iodide selective electrodes were based on ionophore free ion exchangers ($\log K_{I,J}^{pot}$ (separate solution method, SSM) (26): Cl^-, -2.0; NO_3^-, -0.7; Br^-, -1.0) or precipitates (27) ($\log K_{I,J}^{pot}$ (SSM) (28): Cl^-, -5.2; Br^-, -2.3). The electrode membrane is formed with AgI precipitates dispersed in silicone rubber, or a pressed mixture of AgI and Ag_2S is utilized. However, the drawbacks of using ion-exchangers and precipitates in electrode membranes limit their application in UI testing. When applied to the measurements in physiological fluids, these electrodes become coated with contaminants and require frequent polishing and washing of the membrane surface; other ions in physiological fluids, e.g. sulfite, interfere with the response behavior, specifically in regard to sensitivity and selectivity. These types of electrodes are therefore not suitable for measurements in urine for a large population sample testing.

3.3. Ionophore-based iodide-ISEs for UI assay

Although commercial electrodes based on anion-exchangers, such as quaternary ammonium salts, can be analytically useful, their selectivity patterns are always correlated solely with anion lipophilicity, resulting in the classical Hofmeister series (ClO_4^- > SCN^- > salicylate$^-$ > I^- > NO_3^- > Br^- > NO_2^- > Cl^- > HCO_3^- > F^-) (29). Recently, examination of a variety of compounds that have strong, yet reversible interactions with target anions has resulted in new ionophores with decidedly non-Hofmeister selectivity toward anions. Iodide selective polymeric electrodes, based on different types of ionophores, have been developed that are potentially applicable to UI detection with high selectivity and biocompatibility. Table 1 lists the commonly used iodide selective ionophores and their response performances in electrode membranes. An ionophore of triisobutylphosphine sulfide (TIBPS) (I-1) (30, 31) demonstrated good selectivity for iodide ($\log K_{I,J}^{MPM}$ (SSM): Cl^-, -5.3; Br^-, -2.5; Ag (I)-TIBPS) but with a somewhat long response time of several minutes. A silver complex of N-thiocarbamolimine-dithioether derivative (I-2) (32) was used as ionophore in other iodide selective electrodes and provided a shorter response time of ten seconds. The detection limit for these ISEs reaches as low as 10^{-8} – 10^{-9} M of iodide. The selectivity coefficient against main interfering ions, like thiocyanate, is $\log K_{I,SCN}^{pot}$ = -2.1. A vitamin B12 analogue with an imidazole group

Table 1. Response performance of iodide ionophores in PVC membrane electrodes

Ionophore	Detection limit (M)	$\log K^{pot}_{I,Cl}$	$\log K^{pot}_{I,Br}$	$\log K^{pot}_{I,SCN}$	Response time	References
I-1 (Ag)	3×10^{-8}	-5.3	-2.5		> 60 sec	30, 31
I-2	7.5×10^{-9}	-4.0	-2.1	-2.2	< 10 sec	32
I-3	10^{-6}	-4.3	-2.5	-2.2	<60 sec	33, 34
I-4 [1]	10^{-5}	-2.8	-2.5	-1.0	<10sec	35
I-5 $\log K^{pot}_{I_3^-,I^-}$: -1.8	10^{-6}	<-6	<-6	-2.6	8 sec	37
I-6	6×10^{-6}	-3.0	-3.2	-2.3	7 sec	47
I-7	3×10^{-6}	-3.4	-3.5	-3.1	8 sec	48
I-8	10^{-9}	-2.1	-1.3	-3.5		49, 53

[1] The electrode membrane in this work is silicone rubber.

coordinated to the metal center (I-3) provided good selectivity for I^- ($\log K^{pot}_{I,J}$ (SSM) (33): SCN^-, -1.6; ClO_4^-, -2.5; salicylate$^-$, -2.1), which is a result of simultaneous interaction of iodide with the metal center and the protonated imidazol ring (34). The porphyrins have been known as the versatile anion selective ionophores, especially when metallized with transition metals. Wakida et al. (35) successfully fabricated an iodide-selective field-effect transistor (ISFET) based on mixed ionophores of quanterney ammonium salt (dimethyloctadecyl-3-trimethoxylsilypropyl ammonium chloride, QAS) and tetraphenylporphyrin (TTP) (I-4) with silicone ladder polymer matrix. Although it was reported to be selective to iodide ($\log K^{pot}_{I,J}$ (SSM): SCN^-, -1; Cl^-, -1.8; SO_4^{2-}, -4.6), the linear response range covers only from 10^{-1} to 10^{-5} M, which is obviously not suitable for UI assay. Meyerhoff, M. et al. (36) studied the potentiometric response to iodide of a glassy carbon electrode coated with a thin, unmetallated, poly(tetrakis(p-aminophenyl)porphyrin) (poly(H_2(p-TAPP))) film. The electrode showed a large dynamic linear range, from 10^{-7} M to 10^{-1} M. Metalloporphyrin derivatives such as (5, 10, 15, 20-tetraohenylporphyrinato) manganese (III) (I-5) have been used to measure triiodide as analyte (37, 38). These electrodes demonstrated selectivity for triiodide ($\log K^{pot}_{I,J}$: Salicylate$^-$, -3.3; Cl^-, <-4) and possessed a detection limit of 10^{-6}M (I_3^-). The electrodes using metalloporphyrin as ionophore usually show a super-Nernstian response, and a large potential change occurs within a narrow concentration range that is generated by forming a dimeric metalloporphyrin structure (39-41). This type of metalloporphyrin has also been applied to develop optical sensors for anions (42-44) and neutral species (45) based on spectrometry and fluorescence methods. The Schiff-base complexes of Co (II) (46) or Ce (III) (47) (I-6) were also used in preparing the highly selective iodide membrane electrodes. However, this type of electrode showed a narrow Nernstian response linear range, from 5×10^{-2} M to 8×10^{-6} M, which is not suitable for UI detection. Very recently, titanium acetylacetonate (TAA) (48) (I-7) was used as iodide ionophore in constructing iodide selective electrodes. The reported electrode exhibited a broad linear response range (10^{-6} – 10^{-1} M) and good selectivity for iodide against interfering anions ($\log K^{pot}_{I,J}$: Cl^-, <-3; SCN^-, < -3; salicylate < -3). Bachas et al. (49) studied the ionophore of 9-mercuracarborand-3 (MC-3) (50) (I-8) and successfully characterized this ionophore in physiological samples. With the very recent breakthrough discovery in potentiometric selective membrane electrodes (51, 52), E. Prestch (53) reported a highly sensitive and selective iodide membrane electrode using ionophore composed of [9]-mercuracarborand-3 (MC3) (I-8) and internal filling solution of Cl-form resin. This electrode used the newly developed ISE model for measuring ultra-low level of analyte in aqueous solution. The lower limit of detection is in the nanomolar range (2×10^{-9} M). The logarithmic upper detection limit was 3×10^{-3} M. In addition, a long lifetime is expected for this system due to its specially designed configuration. The sensitivity of this ISE meets the UI assay requirements and will be potentially applicable to the development of UI assays.

Although these ionophore-based selective electrodes are very selective and sensitive to iodide, most electrodes were prepared with poly(vinyl chloride) (PVC) as the polymeric membrane matrix, the surface at which may be coated by organic substances in the urine samples, hence interfering with the response. No such electrode has been reported for testing iodide in urine samples.

To obtain reliable clinical assay results, the required selectivity coefficients for iodide against the main interfering anions in urine can be calculated according to the methods developed in Simon's group (54, 55) at ETH. The main electrolyte concentration ranges in urine are: I^- > 0.00079 mM (lower limit of IDD); Cl^- 11 – 25 mM; thiocyanate 0.002 – 0.007 mM (non-smoker) and 0.012 – 0.029 mM (smoker). The required selectivity coefficient (with mid-point calibration) of iodide-ISE in urine, against the interfere ions, can be calculated with a tolerable error of 1% as -6.0 for Cl^-; -2.5 for SCN^- (non-smoker) and -3.0 for SCN^- (smoker) (56) which do not meet the calculated selectivity requirements. However, The UI assays for epidemiological studies focus more on trends through the screening of large population samples. Additionally, the SSM selectivity coefficients are obtained at analyte concentrations within Nernstian response linear range. However, because the IDD level of iodide is around 10^{-7} M, which is even below the detection limits of most current available iodide selective electrodes, the reported SSM selectivity coefficients may not be directly used to compare to the calculated required selectivity coefficients.

4. CONCLUSION

Currently, there are few commercial assay kits or devices available in the market for rapid and inexpensive

testing of urinary iodine to provide reliable results for iodine determination without sample pretreatments. Development of rapid, simple, and inexpensive methods is required, especially for developing countries. The selective iodide ionophores are useful compounds in designing the described, new iodide sensors, e.g. ISEs, optodes, ISFET and microfluidic sensing devices, for epidemiological urinary iodine assays. Ionophore-based iodide selective potentiometric sensors are one of the most promising approaches capable of meeting the epidemiological requirements, including lost cost, ease of fabrication and simplicity of operation. Additionally, no complicated pretreatment is required when using potentiometric sensors in such assays. The combination of a microfluidic sensor array with ionophore-based sensing membranes may provide a new methodology to significantly improve the testing speed and accuracy for population screening, lower the cost of population screening, and be applicable to existing automated devices.

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