

Photochemical Stabilization of Fortified Salt to Treat Lymphatic Filariasis and Iodine Deficiency Disorders

Paper Track: Salt and Health

Abstract: Lymphatic Filariasis (LF), also known as elephantiasis, is a devastating parasitic infection which can cause severe deformities and is one of the world's neglected tropical diseases. Haiti is one of four Caribbean countries where the disease is endemic. The Haitian population also suffers from widespread iodine deficiency, which can lead to a variety of health problems and is the leading preventable cause of cognitive developmental disabilities. The University of Notre Dame Haiti Program, in partnership with the Haitian Ministry of Health and others, has a goal of eliminating LF and preventing iodine deficiency disorders through nationwide mass drug administration of diethylcarbamazine tablets and production and distribution of salt co-fortified with iodine and diethylcarbamazine citrate (DEC). Cargill Salt has partnered with this program to provide technical assistance in the manufacture of the co-fortified salt. A challenge to the program was encountered in the early stages of the commercialization process, which has since been resolved. Specifically, the co-fortified salt was initially found to be unstable, resulting in yellow salt that would not sell. The yellow color formation was shown to be due to a photochemical reaction caused by exposure of the product in transparent plastic bags to sunlight. In the presence of sunlight, a series of reactions occur between DEC and iodate in which iodate is progressively reduced to iodide and iodine, forming the distinctly yellow triiodide ion. The product can be stabilized by adjusting the DEC/iodate additive solution to an alkaline pH with a suitable base such as sodium hydroxide. Salt treated with a DEC/iodate solution adjusted to pH 7.2 showed minor discoloration when exposed to sunlight, and adjusting the additive solution to pH 9.2 eliminated all discoloration. The Haiti salt processing plant, owned and operated by Congregation de Sainte Croix-Haiti (CSC), relied on a back titration of the acidic DEC to determine the DEC content of their product. This method was hampered when the DEC citrate solution was pre-neutralized, requiring that a new analytical procedure be developed which could be easily performed by the plant. Since DEC is a buffer system, the pH versus equivalents of NaOH curves were shown to be only slightly affected by DEC concentration. Therefore, it is shown that determination of DEC can be done by measuring the volume of titrant required to adjust the pH of the solution between two discrete points in the buffer region. An accurate ($\pm 0.01\%$ DEC) analysis can be easily and safely performed by this approach.

Keywords: fortification, diethylcarbamazine, iodine, stability, discoloration, filariasis

Introduction

Lymphatic filariasis (LF), or elephantiasis, is a neglected tropical disease caused by parasites transmitted to humans through mosquitos. The disease attacks the lymphatic system, leading to abnormal enlargement of body parts, disfiguration, pain, disability, and social ostracism. The World Health Organization estimates that 856.4 million people in 53 countries remain threatened by LF¹, and it is the leading cause of disability in the world after mental illness. Haiti is particularly hard hit by the disease, where the prevalence of infection was over 60% in some areas when elimination efforts began in 2000. Historically, Haitians have also suffered from iodine deficiency disorders (IDD), which can cause a number of health problems including goiters and mental handicaps. LF is treatable with the drug diethylcarbamazine citrate (DEC), but direct distribution of the drug in Haiti is hampered by the effects of a transient population, illiteracy, and a need for better education of the population about the disease. Fortification of food salt with DEC has proven to be an effective way to supplement Mass Drug Administration for the treatment of LF in China² and co-fortification of salt with DEC and iodine has been suggested as an effective way to efficiently address both LF and iodine deficiency disorder³⁻⁵. In 1993 the University of Notre Dame Haiti Program (NDHP) started with the goal of eliminating LF and preventing iodine deficiency disorders in Haiti by 2020. Cargill Salt has partnered with NDHP to assist Haiti in becoming self-sufficient in manufacturing and selling salt co-fortified with DEC and iodine to support this goal.

A straightforward manufacturing process for co-fortifying salt with iodine and DEC has been published, which simply involves blending salt with a pre-mix or a stock solution of DEC and potassium iodate.⁶ The CSC plant in Port-au-Prince, Haiti uses this process to make a co-fortified salt product called Bon Sel Dayiti. However, efforts to co-fortify salt by this approach in Haiti led to unexpected instability problems. The fortified salt would often turn a deep yellow in color, making the salt unmarketable. The problem was compounded by inconsistency – sometimes the salt would change color, sometimes it would not, and sometimes the salt would turn yellow only to become colorless again over time. An investigation was carried out to determine the cause of the color change and seek a way to prevent it.

Experimental Procedures

Cargill Hi-Grade granulated salt (99.8% NaCl) was used to prepare test samples, and all other chemicals were reagent grade. Lab samples of fortified salt were prepared by blending salt with a stock solution of DEC and potassium iodate (KIO₃) to target 0.3% DEC and 88 ppm KIO₃ in the salt. Samples were analyzed for “free iodine” using the Hach DPD method⁷ with a Hach DR/2500 spectrophotometer. Samples were analyzed for iodate and total iodine by iodometric titration with 5.00 mM sodium thiosulfate using starch as the indicator⁸. Iodide was determined by subtracting the values for “free iodine” (I₂) and iodate from the total iodine analysis. Potentiometric titrations of fortified salt were carried out with a pH meter. 25.00 gram samples of salt were dissolved in 225.0 mL deionized water and titrated with 50.0 mM NaOH while monitoring the pH as a function of titrant volume.

Photochemical Instability of DEC and Iodate

After numerous unsuccessful attempts to reproduce the color change in the co-fortified salt in the laboratory, it was finally discovered that sunlight exposure was driving the color change. The Bon Sel Dayiti product is packaged in transparent, plastic bags to minimize costs. If the product is stored in the dark, it is stable, but when exposed to sunlight it rapidly changes color and stains the packages yellow. However, upon prolonged storage, the salt will eventually become colorless again, though the bags remain stained. Control experiments revealed that the color change only occurred with salt that was fortified with both KIO_3 and DEC. Salt containing only iodate or DEC individually did not become discolored. The yellow stain could be readily extracted from the plastic bags with water to yield a yellow solution which gave a characteristic deep blue color change when treated with starch and which could be decolorized by further treatment with sodium thiosulfate – consistent with iodine being the source of the color.

It appears that in the presence of DEC, iodate is efficiently photochemically reduced. Analogous behavior has been reported in other systems. Iodate has been shown to be photochemically reduced to iodide in the presence of humic acid.⁹ Spokes et. al. reported that iodate is photochemically reduced to iodide in aqueous solution, and that the presence of organic matter is essential for the reaction.¹⁰ The color changes in the co-fortified salt can be understood as arising from the progressive reduction of iodate to iodide. Initially, iodate (IO_3^-) is reduced to “free iodine” (I_2), which is subsequently further reduced to iodide (I^-). I_2 and I^- react to form the triiodide ion (I_3^-). Both iodate and iodide are colorless while “free iodine” and triiodide are yellow or brown in aqueous solution. Thus, it appears that the color changes arise from the photochemical conversion of iodate (colorless) to iodine/triiodide (yellow) and ultimately to iodide (colorless again). To test this hypothesis, 100 gram salt samples treated with DEC and iodate were analyzed for “free iodine,” iodate, and iodide with and without exposure to sunlight. The results are shown in Figure 1. It can be seen that when protected from light, most of the iodine remains in the iodate form in which it was added. However, after 2 hours of sunlight exposure, the iodate has been quantitatively converted to iodide and free iodine (which react to form triiodide and cause a yellow color). There may be some loss of total iodine, perhaps due to sublimation or side reactions with the DEC, though the analyses shown in Figure 1 are intended to be illustrative of the qualitative chemical change rather than being a rigorous attempt to quantify the iodine speciation with high precision (i.e. there may be some analytical error in play). It is worth noting that even the low level of 10 ppm “free iodine” in this sample was enough to cause very noticeable yellow discoloration.

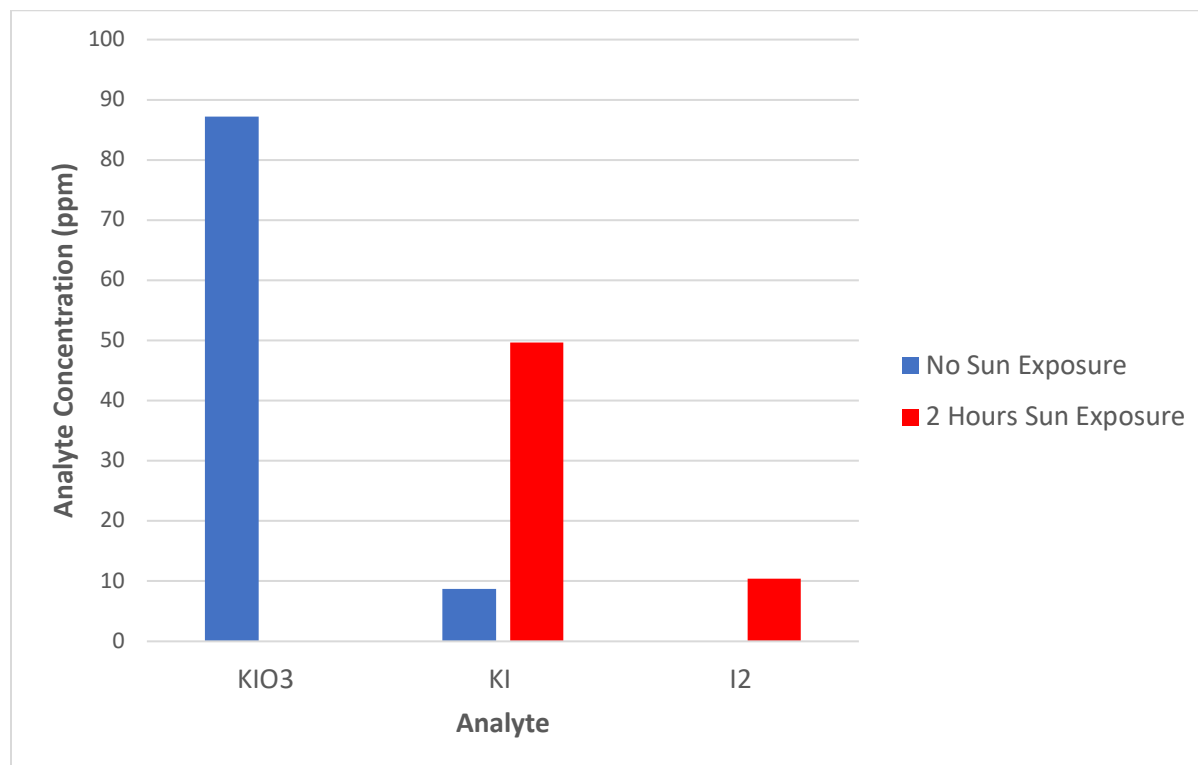


Figure 1. Speciation of iodine in salt treated with 88 ppm KIO₃ and 0.3% DEC citrate (pH 3.6) with and without sunlight exposure

The reduction of iodate is relatively thermodynamically favorable in acidic solution, as indicated by the strongly positive half cell potential in equation 1.



DEC is typically added as the acidic citric acid salt of the free base because the acid salt has much better water solubility. Thus, DEC citrate facilitates the photochemical reduction of iodate both by providing a mildly acidic environment (the pH of the iodate/DEC stock solution was 3.6) and by providing organic material which can serve as a reducing agent. Since the aqueous reduction of iodate is thermodynamically favorable in the presence of acid, tests were run to determine if the reaction could be suppressed by simply raising the pH. This proved successful. A stock solution of 19.7% DEC citrate and 0.58% KIO₃ was adjusted to pH 9.2 with sodium hydroxide and then blended with salt to target the same additive levels as the samples in Figure 1. 100 gram samples of salt treated with the pH adjusted stock solution were analyzed after 2 hours with and without exposure to sunlight, and the results are shown in Figure 2. Whereas Figure 1 shows the iodate rapidly decomposed to iodide and free iodine when exposed to sunlight at the mildly acidic pH of the DEC citrate, adjusting the DEC/iodate stock solution to an alkaline pH of 9.2 in Figure 2 greatly stabilizes the iodate. There appeared to be some small

conversion of iodate to iodide in the pH adjusted sample, but there was no indication of free iodine and there was no color change. The CSC plant has implemented this change in their manufacturing process. They are currently treating salt with a DEC/iodate stock solution which has been adjusted to pH 7.5 with sodium hydroxide, which has successfully eliminated the discoloration problem.

It should be noted that raising the pH of the DEC stock solution shifts the DEC from the protonated form to the less soluble free base, which necessitates a less concentrated stock solution and a higher moisture addition to the salt at a given DEC level. The current Bon Sel Dayiti product contains 0.20% DEC, 40 ppm KIO_3 , and 2.4% moisture. In these laboratory tests it was found that a 19.7% DEC stock solution could be adjusted to a pH of 9.2, but precipitation began when the pH was adjusted above this. Attempts were made to adjust the pH with sodium carbonate, which is lower cost than NaOH, but this did not work as well. It was only possible to adjust the pH to about 7.2 with sodium carbonate. At pH 7.2, the discoloration was greatly decreased but not completely eliminated. Also, neutralization with sodium carbonate results in strong effervescence, which could create safety issues in the plant. As noted above, the CSC plant has found that adjustment of the DEC/iodate stock solution to pH 7.5 with NaOH gives satisfactory stability to the fortified salt.

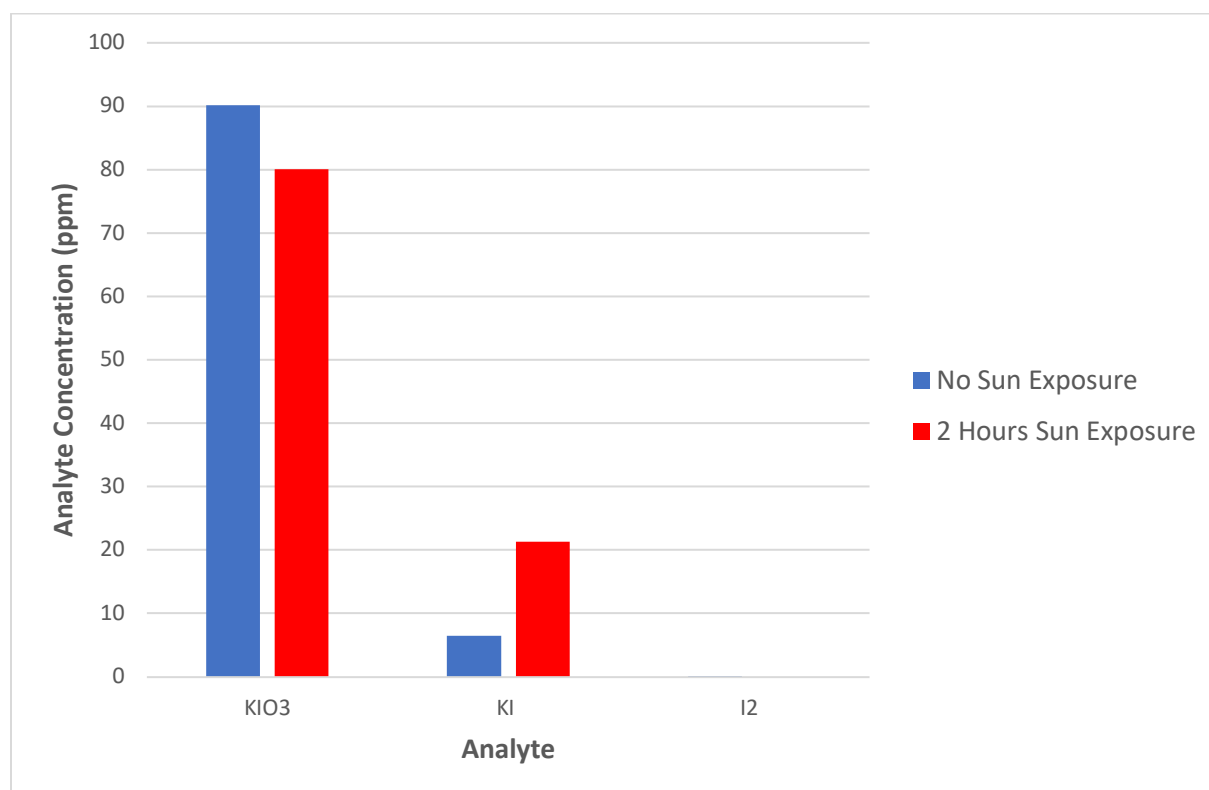


Figure 2. Speciation of iodine in salt treated with 88 ppm KIO_3 and 0.3% DEC citrate (pH 9.2) with and without light exposure

Modification of the Analytical Method for DEC in Salt

A method to analyze the DEC content of fortified salt at the production facility is necessary for quality assurance. HPLC¹¹ and spectrophotometric⁶ analytical methods for DEC have been developed, but they are not practical for use at the Haiti production facility. Weaver et. al.¹² developed a simplified, low-cost analytical procedure for use at the Haiti plant. Since DEC citrate is acidic, it can be accurately analyzed by treating a fortified salt sample with a known quantity of sodium hydroxide (NaOH) and then back-titrating with hydrochloric acid (HCl) to a phenolphthalein endpoint. Unfortunately, pH adjustment to stabilize the DEC introduces uncertainty into this method as it requires that the amount of NaOH added be precisely known, and this is difficult to determine under production conditions. Therefore, a modified method was sought to permit a simple, low-cost analysis of the pH-adjusted product at the plant. Citric acid is a weak, triprotic acid. Therefore, it forms a buffer solution as it is neutralized. The pH of buffers tend to depend primarily on the ratio of conjugate acid and base in solution and not on their absolute concentration. If this holds true for the DEC citrate system, the volume of titrant required to change the pH between two discrete points in the buffer region should be directly proportional to the concentration of DEC.

Titration curves (with 50.0 mM NaOH titrant) measured on 250 grams of 10.0% solutions of salt treated with 0.1% to 0.6% DEC are shown in Figure 3. It can be seen that, as expected, the shape of the titration curves do not change substantially over this range of DEC, and Figure 4 shows that there is a very linear relationship between the volume of NaOH titrant required to change the pH between two points in the buffer region ($R^2 = 0.9998$) and the % DEC in the sample.

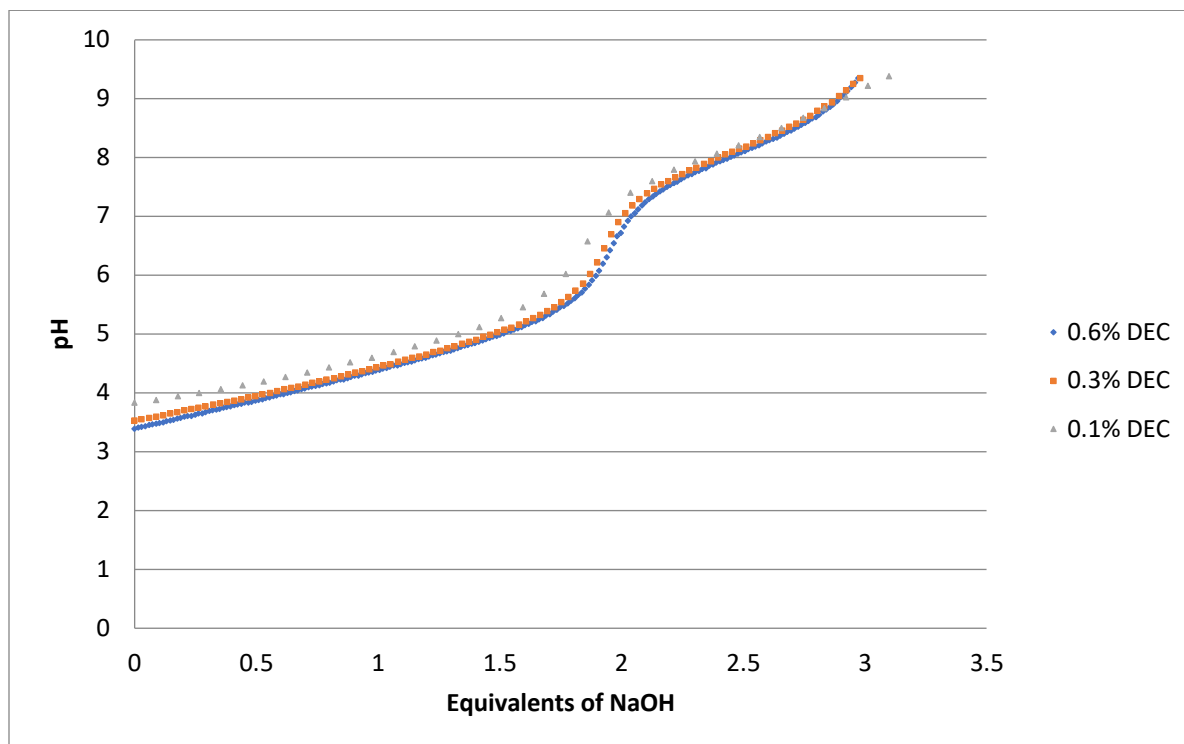


Figure 3. Titration curves of 10% salt solution treated with different levels of DEC citrate.

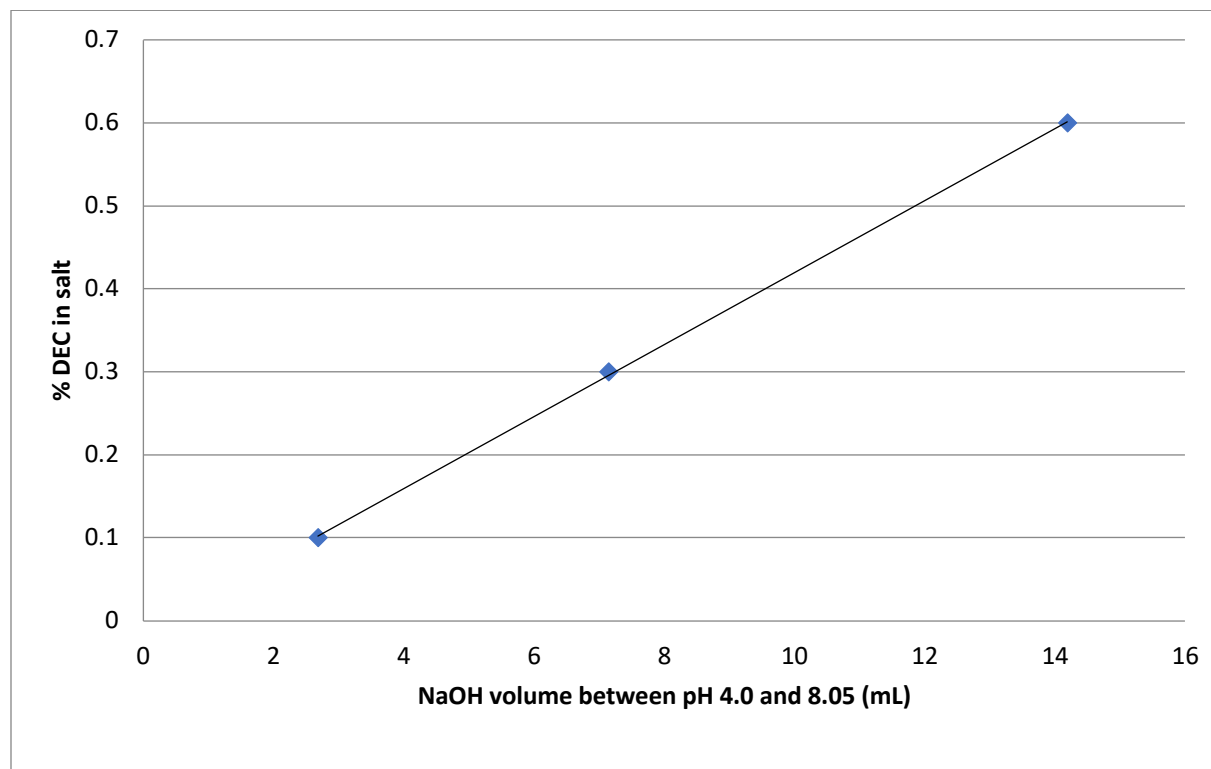


Figure 4. Volume of NaOH required to change DEC fortified salt from pH 4.00 to 8.05.

Therefore, a simple, low-cost, and accurate analysis of DEC in treated salt can be obtained even if the DEC has been adjusted to a higher pH with an unknown quantity of base by this approach. The only additional equipment required beyond that in the method of Weaver et. al. is a pH meter. A typical procedure by this approach would involve first making a standard curve. Lab samples of salt precisely treated with a range of DEC levels encompassing the targeted additive level (e.g. 0.05%, 0.10%, 0.30%, and 0.60%) are prepared and titrated as described above to determine the volume of NaOH required to change the pH from 4.00 to 8.00 (different ranges could be tested, but this range gave accurate results in these tests). A least squares line fit to the volume of titrant required to move the pH between two discrete points versus the % DEC in the samples can then be calculated and used to determine the % DEC in test samples of salt. Salt samples which have been treated with pH-adjusted DEC must first be treated with HCl to take the pH below 4.0 (or whatever the low end of the chosen range is). This approach was tested on a standard sample of pH-adjusted fortified salt treated with 0.30% DEC. A 250 gram sample of 10.0% salt was analyzed. The initial pH of the solution was 9.2. 50.0 mM HCl was added to the solution to adjust the pH to 4.00 and then it was titrated with 50.0 mM NaOH. The titration yielded an analysis of 0.31% DEC, confirming the accuracy of the approach.

Conclusions

Salt fortified with diethylcarbamazine citrate and potassium iodate is photochemically unstable and may turn yellow when exposed to sunlight due to the photochemical reduction of iodate to

free iodine and iodide. While iodate and iodide are both colorless, free iodine is generated as the iodate is reduced, which reacts with iodide forming yellow triiodide. When feasible, salt co-fortified with iodate and DEC should be packaged in opaque packaging to prevent this. However, the photochemical decomposition can be inhibited by adjusting the pH of the DEC. The reduction of iodate is thermodynamically favorable in acidic solution, and the color change can be prevented by adding sodium hydroxide to the DEC/iodate stock solution to adjust the pH to at least ~ 7.5. Raising the pH of the DEC lowers its solubility, necessitating more dilute DEC stock solutions and increasing the amount of water added to the salt for a given treatment level. A simple analytical procedure for DEC in pH-adjusted, fortified salt has been developed. DEC can be accurately determined by measuring the volume of NaOH required to change the pH of a sample between two discrete points in the DEC buffer zone range (such as between 4.0 and 8.0). The procedure only requires a pH meter and standard acid/base titration equipment and reagents. Utilizing this approach, it has been demonstrated that an initial challenge to the effectiveness of the co-fortification process can be satisfactorily overcome – which has ultimately helped facilitate the successful, widespread distribution of co-fortified salt, supporting the elimination of LF, and the prevention of iodine deficiency disorders, in Haiti.

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