

Fortification of salt with iron and iodine to control anaemia and goitre: Development of a new formula with good stability and bioavailability of iron and iodine

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Abstract

Anaemia and goitre are two major nutrition-related disorders. The distribution of iodized salt to control goitre is already widespread, and a method of fortifying salt with iron has been developed to control anaemia. Salt fortified with both iron and iodine would be useful in areas where anaemia and goitre coexist and for anaemia control in countries where the iodization of salt is mandated by law. Studies were carried out to develop appropriate technology to fortify salt with both iron and iodine. Earlier trials indicated that iodine added to iron-fortified salt was highly unstable. Hence, a new formula was developed using sodium hexametaphosphate (SHMP) as a stabilizer. At a 1% level it stabilizes both iron (1 mg/g) and iodine (40 µg/g) quite well. The bioavailability of iron from doubly fortified salt given with a rice-based meal was tested in adult men by the radioisotopic extrinsic tagging technique. The availability of iodine from the doubly fortified salt was compared with that from iodized salt by measuring urinary iodine in adult men after they ingested the salts with a rice meal. The bioavailability of both iron and iodine in the doubly fortified salt was quite satisfactory.

Editorial introduction

The iodization of salt is a feasible, inexpensive, and highly effective means of eliminating endemic goitre and other iodine deficiency disorders that has been adopted by more than 50 countries. Moreover, the International Council for the Control of Iodine Deficiency Disorders, WHO, UNICEF, and the World Bank are very actively supporting the extension of the iodization of salt to those countries in which

goitre still persists as a public health problem. The double fortification of salt with both iodine and iron would be an ideal way to eliminate iron deficiency as well. Establishing its feasibility is particularly important since there is still no effective approach to dealing with iron deficiency in populations on a national level even though its functional consequences are as serious as those of iodine deficiency and even more widespread.

The 1989-90 and subsequent annual reports of the National Institute of Nutrition (NIN) in Hyderabad, India, have contained progress reports on the effort to develop a practical means of fortifying salt with iron that could be employed either alone or in combination with iodine. Many approaches have been explored and a series of field trials conducted by NIN. The Food and Nutrition Bulletin is very pleased to publish the first full scientific report of studies by Dr. Narasinga Rao describing what he believes is a feasible and effective procedure for the double fortification of salt with iron and iodine. This appears to be a major breakthrough in the control of iron deficiency.

The crucial factors in developing a stable combination of iron and iodine in salt are the stability of the iodine compound in the presence of iron after long storage and the bioavailability of the iron in the presence of iodine. These will be influenced by impurities in the salt and its moisture content and by environmental factors such as temperature and relative humidity. As one reviewer suggested, "The presence of impurities in the salt would certainly influence optimum levels of the stabilizer sodium hexametaphosphate (SHMP) and iodine for salt . . . under varying concentrations of magnesium chloride and moisture." The study was conducted using one kind of salt with a specified level of impurities and moisture, but the 1% concentration may not be optimal for the salt of other countries.

Another question raised by the reviewer concerned the reason why the iodine levels in the doubly fortified salt began to fall in the seventh month after having been stable for six months (table 7). If it was because of a seasonal in environmental factors, the timing of the decrease might well be different in other regions or other seasons. This possibility is suggested by the data for the salt iodized with KIO_3 , which show a decrease in iodine from 20 to 12 $\mu\text{g/g}$ after only three months of storage at the 1% level of SHMP. Before the proposed method can be recommended universally, more information must be obtained on the stability of the iodine under a variety of storage conditions.

No matter how convincing any research results may be, international agencies cannot propose them to governments until they have been replicated. It will now be important for nutrition institutions in other countries to repeat these studies under their own conditions. Concerned agencies are urged to provide financial support for such operational research.

Introduction

Iron-deficiency anaemia is prevalent worldwide; the groups most severely affected are women, pregnant women in particular, and preschool children [1]. It often coexists with goitre, or iodine-deficiency disorder; together, anaemia and goitre are the two major nutritional-deficiency diseases in India, as in many of the other developing countries of the world.

The iodization of edible salt is an effective way to control goitre [2], and its use for that purpose is widespread. Salt has also been proposed as a vehicle for iron fortification to combat anaemia. A successful method of fortifying common salt with iron has been developed in India [3-5], and its effectiveness in reducing the prevalence of anaemia has been demonstrated [6,7]. Its large-scale introduction in the country, however, depends on the development of a satisfactory way to fortify the salt with both iodine and iron.

It would be useful and convenient to deliver both iron and iodine in the same vehicle to combat both disorders in areas where they coexist; and, in the many countries where the iodization of salt is mandatory, salt fortified with iron will also have to be iodized even in non-goitre areas. Goitre affects nearly 170 million people in the sub-Himalayan belt of India and some other pockets of the country [8], and, although a programme to distribute iodized salt has been in operation since 1960, it has not had the desired impact because of various operational factors, including in particular the poor supply and distribution of salt in the endemic areas. Therefore, the government has made it a legal requirement that all edible salt in the country must be iodized, and this precludes the manufacture and marketing of salt fortified with iron alone.

The present study thus was undertaken to develop an appropriate technology to fortify salt with both iron and iodine.

Materials and methods

Materials

Salt

Edible salt was purchased from the local market. Most of the edible salt manufactured and marketed in India is the crude salt prepared from sea water, which contains high moisture and other impurities that adversely influence the stability of iron compounds added to it (table 1).

TABLE 1. Composition of edible salt used in India

Component	%
NaCl	94-95
Water	4
Calcium sulphate	0.4
Magnesium salts	0.5-1.6
Insolubles	0.1

Chemicals

Ferrous sulphate, orthophosphoric acid, sodium hydrogen phosphate, potassium iodide and iodate, and calcium iodate were of reagent grade, and other chemicals used in the chemical analysis were of analar grade. All these chemicals were purchased from Sarabhai Merck, Baroda, India. The polyphosphates sodium hexametaphosphate, sodium tripolyphosphate, and tetrasodium pyrophosphate were obtained from Sigma Chemicals Co., St. Louis, Missouri, USA.

Radiochemicals

Fe-ferric citrate and ¹³¹-sodium iodide were obtained from the Bhaba Atomic Research Centre, Trombay, Bombay, India. Fe-ferric citrate was purchased from the Radiochemical Centre, Amersham, UK.

Methods

Fortification procedure

Crude edible salt purchased locally was crushed to a coarse powder (mesh size approximately 10). The powdered salt was mixed thoroughly with ferrous sulphate, potassium iodide or iodate, and other chemicals in the proportions indicated in table 2 until they were uniformly distributed.

TABLE 2. Formula for the double fortification of salt with iron and iodine

Additive	Chemical source	Level
Iron	ferrous sulphate (FeSO ₄)	3.2 mg/g ^a

Iodine	iodide (KI)	52 µg/g ^b
	or potassium iodate(KIO ₃)	67 µg/g ^b
Stabilizer	polyphosphate	1%

- a. Iron, 1mg/g.
b. Iodine, 40 µg/g.

Storage studies

Samples of fortified salt containing iron, iodine, and the stabilizer were stored in glass containers at room temperature and humidity, or in a humidity chamber with relative humidity of about 80%. The samples were monitored at periodic intervals for total and soluble iron (both ferrous and ferric) and iodine content.

For estimating the soluble iron, a sample of fortified salt was dissolved in distilled water to give a 10% solution and filtered, and iron and available iron were estimated in the filtrate. For determining total iron, the salt was dissolved in 1 N hydrochloric acid (HCl). Iron was estimated by the thiocyanate method [9] and ferrous iron by the phenanthroline method [10]. Available iron in the doubly fortified salt was estimated by the in vitro method described earlier [11].

Iodine was estimated by the standard method used for its estimation in iodized salt [12]. At each time point, duplicate samples were drawn from the stored fortified salt to determine iodine content. The averages of the duplicate values, which were very close, are reported.

Iron bioavailability

Iron absorption was studied with radio-labelled iron salt. A small quantity of salt (NaCl, 50 g) was fortified with radioactive FeSO₄, KI, and a stabilizer according to the formula in table 2. Ferrous sulphate labelled with ⁵⁹Fe or ⁵⁵Fe was prepared according to the method of Steinkamp et al. [13].

Seven adult men were selected from the laboratory staff with informed consent. They were apparently healthy, between 25 and 40 years of age, and had normal haemoglobin values. After an overnight fast the subjects were given a rice-based meal (table 3). Five grams of the doubly fortified salt, containing 5 mg of ⁵⁹Fe-labelled iron, was incorporated into the meal in the same way as salt is normally added during cooking. The next day, 5 mg of iron, in the form of freshly prepared ferrous sulphate labelled with the second isotope, ⁵⁵Fe, was given with the meal in a similar way. The radioactivity administered to each subject was 5 µCi of ⁵⁵Fe activity and 10 µCi of ⁵⁹Fe activity.

TABLE 3. Composition of the meal used in the iron absorption study

Ingredient	Quantity	Nutrient	Quantity
Rice	200 g	Iron	9.6 mg
Red gram dhal	30 g	Energy	4,874 kJ ^a
		Protein	29 g
Potatoes	75 g	Phosphorus	685 mg
Onions	25 g	Phytin P	238 mg
Eggplant	50 g	Calcium	439 mg
Oil	10 g	Ascorbic acid	23 mg
Milk as curds	160 ml		

a. 1,165 kcal.

Iron absorption from the fortified salt was determined by whole-body counting of ⁵⁹Fe retention immediately after the subjects had eaten the meal to which ⁵⁹Fe was added and 12 days after the dose, using a shadow-shield whole-body counter designed by the International Atomic Energy Agency, described earlier [3].

At the end of 12 days, 10 ml of blood was drawn from each subject to determine ⁵⁹Fe and ⁵⁵Fe activity by liquid-scintillation counting using a modified method of Eakins and Brown [14]. The percentage absorption of ⁵⁹Fe salt was calculated from the whole-body counting data using the formula given by Callender and Warner [15]. The percentage absorption of ⁵⁵Fe salt was computed from the ratio of ⁵⁵Fe to ⁵⁹Fe in the blood by the formula % ⁵⁵Fe absorption = % ⁵⁹Fe absorption * (⁵⁵Fe/⁵⁹Fe).

Iodine bioavailability

Urinary excretion of iodine reflects the plasma level of inorganic iodine, which in turn reflects absorbed iodide [16, 17]. Inorganic iodine compounds such as those present in iodized salt are reported to be completely absorbed and excreted mostly in urine, with very little excreted in faeces [17]. Hence, the urinary excretion of iodide after a dose of doubly fortified salt was compared with iodide excretion after a dose of iodized salt containing the same amount of iodine to determine the relative availability of iodine from these two fortified salts.

Eight apparently healthy adult men from the laboratory staff were selected for the study. Twenty-four-hour urine was collected for two consecutive days to determine the basal excretion of iodine. On the third day, the subjects were fed a rice-based meal that included 5 g of doubly fortified salt containing 100 µg Of iodine; 24-hour urine was collected for the next two days, and the urinary excretion of iodide was determined. After a lapse of time to allow urinary excretion to reach a steady state, the test was

repeated by feeding the subjects iodized salt containing a similar level of iodine with the meal. The same protocol for urine collection was followed.

Acceptability of the doubly fortified salt

The doubly fortified salt was prepared in bulk according to the new formula and distributed in 0.5 kg amounts to families with different socio-economic backgrounds to assess its acceptability. The families were requested to use the salt for cooking in place of their usual salt. Their observations were recorded in a fashion similar to that used in an earlier study [5].

Results

Effect of adding iodine to iron-fortified salt

A successful method of fortifying salt with iron had been developed earlier (table 4) [5]. Iodine in the form of potassium iodide (KI), potassium iodate (KIO_3), or calcium iodate (CaIO_3) was added to the iron-fortified salt prepared according to the earlier formula (initial level 20 μg of iodine per kilogram of salt) and stored, and the iodine levels were monitored. The iodine rapidly decreased to a negligible level within a few days (table 5). The addition of calcium carbonate (CaCO_3), which is used as a stabilizer in iodized salt, did not improve its stability to any significant extent.

TABLE 4. Formula for iron-fortified salt

Additive	Level
FeSO_4	3.2 mg/g ^a
Sodium acid sulphate	5.0 mg/g
Orthophosphoric acid or NaHPO_4	3.2 mg/g

Source: Ref. 4.

a. Iron, 1 mg/g.

TABLE 5. Stability of iodine in iron-fortified salt stored at room temperature and humidity in

Hyderabad

Iodine source	Iodine level ($\mu\text{g/g}$)			
	Initial	Storage (days)		
		3	15	30
Unfortified salt				
KI	20.0	17.9	15.8	16.0
KIO ₃	20.0	17.6	15.9	15.8
CaIO ₃	20.0	17.4	14.9	14.6
KI + CaCO ₃ ^a	20.0	20.0	20.0	20.0
KIO ₃ + CaCO ₃ ^a	20.0	20.0	20.0	20.0
Iron-fortified salt				
KI	20.0	3.3	2.0	1.1
KIO ₃	20.0	1.5	1.5	1.5
CaIO ₃	20.0	1.4	1.4	1.4
KI + CaCO ₃ ^a	20.0	8.7	8.2	7.1
KIO ₃ + CaCO ₃ ^a	20.0	5.7	5.2	4.4

a. 400 $\mu\text{g/g}$.

These experiments indicated that the iron-fortified salt developed earlier cannot also be fortified with iodine. Another substance to stabilize both iron and iodine was therefore sought.

Effect of polyphosphate compounds on the stability of iodine in iron-fortified salt

A series of studies [18-20] have shown that polyphosphate compounds can chelate iron and improve iron absorption from cereal-based meals [20]. The usefulness of a polyphosphate as a stabilizing agent in the doubly fortified salt was therefore explored. Salt was fortified with FeSO₄ and KI using different polyphosphates at a 1% level, and the colour, the stability of the iodine, and the solubility of the iron

were monitored. As shown in table 6, all of the polyphosphates stabilized the iodine to some degree, but two of them led to discoloration of the salt during storage; it was only with sodium hexametaphosphate (SHMP) that no colour developed.

TABLE 6. Effect of polyphosphates on the stability of iodine in salt fortified with iron and iodine during storage at room temperature and humidity in Hyderabad

Stabilizer and iodine source	Iodine level ($\mu\text{g/g}$)			Colour development
	Initial	Storage		
		1 mo	3 mo	
Sodium hexametaphosphate (SHMP)				
KI	20	20	20	no colour
KIO ₃	20	15	12	no colour
Sodium tripolyphosphate				
KI	20	20	17.5	pale brown
KIO ₃	20	15.5	12.5	pale brown
Tetrasodium pyrophosphate				
KI	20	17.5	14.5	dark brown
KIO ₃	20	13.2	8.5	dark brown

Note: Stabilizer, 1%. Iron, 1 mg/g. Iron was 100% soluble throughout the storage period with all three polyphosphates.

In the presence of the polyphosphates, the iron remained in a water-soluble form, presumably because of the iron-chelating effect. The *in vitro* iron availability [11] remained at 38% throughout the storage period. We concluded that SHMP is a preferred stabilizer when fortifying salt with iron and iodine.

Optimum level of SHMP

To determine the optimum level of SHMP to stabilize iodine, salt was fortified with FeSO₄ and KI to provide 1 mg of iron and 20 μg of iodine per gram of salt. The salt, with different levels of SHMP, was stored at room temperature and humidity, and the iodine levels were monitored (table 7). The maximum stability was seen with 1% SHMP; at this level the iodine was stable for six months, and increasing the

SHMP level did not improve stability. The iodine level tended to decline beyond six months of storage, and decreased to 13 µg/g by eight months. Stability was better with KI than with KIO₃; after storage for three months with 1% SHMP, the iodine levels were 20 µg/g and 12 µg/g respectively. Also, stability was better under high humidity than room humidity.

TABLE 7. Stability of iodine in salt fortified with iron and iodine with different levels of SHMP stored at room temperature and humidity in Hyderabad

Iodine source	SHMP level (g/100 g)	Iodine level (µg/g)						
		Initial	Storage (months)					
			1	2	3	6	7	8
KI	0.6	20	20	12	6	—	—	—
	0.8	20	20	11	3	—	—	—
	1.0	20	20	20	20	20	13	13
	1.2	20	20	20	20	20	12	12
	1.5	20	20	20	20	20	13	12
KIO ₃	0.6	20	20	12	6	—	—	—
	0.8	20	20	19	16	—	—	—
	1.0	20	20	14	12	—	—	—

Iron, 1 mg/g.

Optimum level of iodine

The storage studies were repeated with doubly fortified salt containing 40 µg of iodine per gram, the maximum currently permitted in India, and stored for twelve months. As shown in table 8, the iodine level remained stable for six months and then decreased to 25 µg/g by twelve months.

TABLE 8. Stability of iodine in simple iodized salt and in doubly fortified salt containing 1% SHMP and 40 µg of iodine per gram stored at room temperature and humidity in Hyderabad

Additives	Iodine level (µg/g)	
	Initial	Storage (months)

		1	3	6	9	12
Iodized						
KI	40	40	40	40	30	25
KIO ₃	40	40	40	40	30	25
Doubly fortified ^a						
KI + FeSO ₄ + SHMP	40	40	40	40	30	25
KIO ₃ + FeSO ₄ + SHMP	40	40	40	40	30	25

a. Iron, 1 mg/g.

The level of iodine required in salt at the point of consumption to meet nutritional needs is 15-20 µg/g (with a daily intake of 10-20 g of salt). The government of India has specified the level of 40 µg/g at the point of production to ensure an adequate level at the point of consumption, allowing for losses during transportation and storage. The normal turnover time of salt in India is around six months.

Our studies thus indicate that doubly fortified salt with 1 mg of iron per gram and an initial iodine level of 40 µg/g, with 1% SHMP used as a stabilizer, would continue to provide an adequate level of iodine even after prolonged storage.

Bioavailability of iron and iodine

Before the doubly fortified salt could be recommended for use in the community to control anaemia and goitre, it was necessary to demonstrate satisfactory bioavailability of the iron and iodine when the salt is consumed with predominantly cereal-based diets.

The mean absorption of iron from the doubly fortified salt when consumed with a rice-based meal was 6.1%, and that from ferrous sulphate alone added to the same meal was 3.9% (table 9). The two mean values are not significantly different ($p > .2$) when tested by analysis of variance. The ratio of the two values is 1.56, which is higher than the ratio of 0.8 observed with iron-fortified salt earlier [5] but is significantly different from unity only at the 10% level ($p < .1$).

TABLE 9. Absorption of iron from doubly fortified salt in humans Iron absorption (%)

Iron source ^a	Iron absorption (%)	Ratio of absorption from two sources

	Mean + SEM	Range	
$^{59}\text{FeSO}_4$ in fortified salt	6.1.* \pm 1.29	2.9-12.4	} 1.56** \pm 0.25
$^{55}\text{FeSO}_4$ alone	3.9* \pm 0.38	2.3- 5.5	

Note: 7 subjects; Hb level 140-170 g/L.

a. Given with a rice-based meal (table 3). source provides 5 mg of iron in addition to that in the meal

* Difference between 3.9 and 6.1 not significant ($p > .02$).

** Significantly different from unity only at the 10% level ($p < .1$).

Results of the iodine-absorption study are shown in table 10. Analysis of variance indicates that the increase in urinary iodine excretion over the basal level after consumption of the doubly fortified salt was not significantly different from the increase observed with iodized salt ($p > .4$). The availability of iodine from the two salts was comparable and was not affected by the presence of either iron or SHMP. This must be confirmed by iodine-balance studies carried out over relatively long periods of time [21].

TABLE 10. Availability of iodine from doubly fortified salt

Iodine source	Urinary excretion of iodine ($\mu\text{g}/24$ hr; mean \pm SEM)		
	Baseline	1st day	2nd day
Doubly fortified salt ^a	174 \pm 11.7	201 \pm 11.3	181 \pm 13.4
Iodized salts ^b	124 \pm 11.3	163 \pm 9.9	138 \pm 7.1

Note: 8 subjects.

a. Iodine (from KI), 20 $\mu\text{g}/\text{g}$; iron (from FeSO_4), 1 mg/g; SHMP, 1 %.

b. Iodine (from KI), 20 $\mu\text{g}/\text{g}$.

Difference between the increases in iodine excretion from the two sources over the baseline levels not significant ($p > 4$).

Acceptability of the doubly fortified salt

The doubly fortified salt was well accepted by families of different socio-economic backgrounds. Its use in regular cooking was not associated with any change in the colour or taste of the food.

Discussion

When KI or KIO₃ was added to iron-fortified salt, the iodine was extremely unstable. Therefore, a new formula was developed using SHMP as an iron-chelating agent, in which iodine is quite stable, and the bioavailability of both iron and iodine is satisfactory. Of the several polyphosphates tested, only SHMP produced a stable doubly fortified salt that did not develop any colour.

Adding SHMP or iron did not compromise iodine absorption. Added at 1%, SHMP presumably chelates all the iron (1 mg/g) in the doubly fortified salt and keeps the iron soluble, thus preventing its interaction with the iodide. The suggested level of iodine to be added is 40 µg/g since even after 12 months of storage, the amount in the salt is 25 µg/g.

The doubly fortified salt appears to be quite satisfactory with respect to stability and bioavailability, and it provides adequate levels of iron and iodine to prevent deficiencies when 10-15 g is consumed per day. The 10-15 mg of iron provided by this quantity of salt consumed daily can supplement the regular diet of the population to keep them in iron balance.

The stabilizer SHMP belongs to a group of linear polyphosphates with the general formula (NaPO₄)_n, which are used as additives in food processing for their chelating and stabilizing properties [22]. The acceptable daily intake of these polyphosphates depends on their contribution to the total intake of phosphorus in the diet [23]. The acceptable total daily intake of phosphorus is 30 mg per kilogram of body weight (1.8 g for a 60 kg man). The doubly fortified salt with the proposed level of 1% SHMP would contribute only 70 mg of phosphorus even at the maximum level of salt intake of 20 g per day. Thus, the stabilizer is quite safe for human consumption.

The present formula lends itself to the manufacture of doubly fortified salt, iron-fortified salt, or iodized salt. By omitting iodine where it is not needed, one can obtain an iron-fortified salt that appears to be superior to the product developed earlier [5] with respect to the stability and bioavailability of the iron.

The fortified salt can be manufactured either by dry mixing or by a spraying process in a screw-type blender. In the latter, a solution containing FeSO₄, KI, and the stabilizer can be sprayed at the ratio of 25 ml per kilogram of salt and the salt subsequently dried. The quality of the salt and the iodine stability are not affected by either the source of raw salt or the season in which it is manufactured.

The great advantage of the use of potassium iodate demonstrated in the 1960s [24] was that it made possible the iodization of the kind of crude moist salt sold without special packaging in most tropical developing countries. The process proposed does not require that the salt be refined, dried, or specially packaged. Our studies indicate that the stability of the iodine in the doubly fortified salt is even better

under humid conditions (relative humidity in excess of 80%) than under dry ones.

Cost is an important consideration in the use of doubly fortified salt for combating anaemia and goitre. The major costs are associated with the SHMP, FeSO₄, and KI and with the processing. They work out to about 1.5 US cents per kilogram. This would have to be added to the selling price of cooking salt, which in India varies from 4 to 8 cents per kilogram.

The doubly fortified salt is acceptable for use in cooking. Since the iron is fully chelated and water-soluble, it is less likely to interact with other food components. Before large-scale distribution of the salt is begun as a national programme to control anaemia and goitre, it is essential that its efficacy should be established in well planned community trials. Such trials are currently under way.

Acknowledgements

The author gratefully acknowledges the expert technical assistance of C. Vijayasarithy and S. Ranganathan.

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