Kirk-Othmer Encyclopedia of Chemical Technology.

L-MONOSODIUM GLUTAMATE(MSG)

Monosodium glutamate (MSG), more specifically monosodium L-glutamate, is used in large quantities as a flavor enhancer throughout the world. The industrial production of MSG began in Japan in the early 1900s. Its annual production was estimated at more than 350,000 tons in 1988 (1). The world capacity for production of MSG approximates 500,000 tons per year and continues to increase. The demand for MSG is expected to increase in developing countries as its use in commercially prepared, packaged foods, ready made soups, and as a table seasoning increase in Western and Asian countries.

L-Glutamic acid was first isolated in 1886 (2) from the acid hydrolyzate of wheat gluten and thus named Glutaminsäure; its structure was identified chemically in 1890 (3). In 1908 the ability of glutamate to enhance the flavor of foods was discovered (4). This research (4) was based on the hypothesis that besides the usually recognized four taste elements of bitter, sour, salty, and sweet there was another group of taste substances in foods. A kelplike seaweed harvested around Japan, known as konbu, *Laminaria Japonica*, had been used for many centuries in Japan to improve the flavor of soups and other foods. Kikunae Ikeda isolated the flavor-enhancing part from extracted kelp soup with hot water and identified its taste-enhancing component as sodium glutamate. Immediately he filed a patent application (5) and commercial production of MSG began in Japan in 1909.

1. Properties

Monosodium L-glutamate [142-47-2], $C_5H_8NO_4Na{\cdot}H_2O$ (mol wt 187.13) crystallizes from aqueous solution at room temperature as rhombic prisms. Its structure, as determined by x-ray crystallography (6), indicates that the sodium ions are coordinated octahedrally by four (3α and 1γ) carboxyl oxygen atoms and two water molecules as follows:

crystal system: orthorhombic
space group: $P2_12_12_1$
$z = 8$ (2 formula units in the asymmetric unit)
$a = 1.5267(9)\text{nm}$, $b = 1.7937(9)\text{nm}$, $c = 0.5562(4)\text{nm}$
$V = 1.520\ \text{nm}^3$, $D_x = 1.635\ \text{g/cm}^3$, $D_m = 1.63\ \text{g/cm}^3$

Commercially preferred crystals for use as flavor enhancement are obtained by crystallization in the presence of amino acids such as alanine (7).

The solubility of MSG may be expressed by the following equation (8):

$$S = 35.30 + 0.098t + 0.0012t^2$$

where S is % of anhydrous monosodium glutamate in a saturated solution at t°C and the remainder at equilibrium is the monohydrate. Below -0.8°C, MSG crystallizes as the pentahydrate (8). The filtered pentahydrate loses its water of crystallization upon exposure to air to become the extremely porous monohydrate (9). A 3% aqueous solution of MSG at 25°C has a pH of 7.

Crystalline MSG is less hygroscopic than sodium chloride. The critical humidities of MSG are 96.0, 94.8, and 90.0 at 20, 30, and 50°C, respectively. MSG loses its water of crystallization at 120°C; intramolecular dehydration occurs at 155°C. The decomposition temperature is 225°C.

The α-carbon of glutamic acid is chiral. A convenient and effective means to determine the chemical purity of MSG is measurement of its specific rotation. The specific optical rotation $[\alpha]^{20}_{D}$ of a solution of 10 g MSG in 100 mL of 2 *N*HCl is $+25.16$. Besides L-glutamic acid [56-86-0], D-glutamic acid [6893-26-1] and the racemic mixture, DL-glutamic acid [617-65-2], are known. Unique taste modifying characteristics are possessed only by the L-form.

L-Glutamic acid does not racemize in neutral solution, even at 100°C. Deviation of pH from neutral to greater than 8.5 results in thermal racemization with loss of taste characteristics. Racemization in neutral solution occurs at 190°C after formation of the lactam, 5-oxo-L-proline, pyroglutamic acid [98-79-3].

GRAPHIC FILE NAME

The reaction is very slow in neutral solution, but the equilibrium shifts toward the lactam rather than glutamic acid. Under strongly acidic or alkaline conditions, the ring-opening reaction requires a very short time (10). Therefore, neutralization of L-glutamic acid should be performed cautiously because intramolecular dehydration is noticeable even below 190°C.

Racemization also occurs in the presence of microbial racemase. As for other amino acids, the racemase that is specific for glutamic acid is found in *Lactobacillus fermenti*.

L-Glutamic acid is split into α-ketoglutaric acid [328-50-7] (2-oxo-pentanedioic acid) and ammonia by glutamate dehydrogenase. By the reverse reaction, L-glutamic acid is synthesized from α-ketoglutaric acid, a component of the tricarboxylic acid (TCA) cycle of glycolysis. Whereas glutamate transaminase is nonspecific for the pairs of keto-acids and amino acids, L-glutamic acid is the only amino acid in mammalian tissues that undergoes oxidative deamination at an appreciable rate. The formation of ammonia from α-amino groups of other amino acids requires their conversion to the α-amino nitrogen of L-glutamic acid (11). Thus, L-glutamic acid is a key substance in metabolism of amino acids.

Glutamic acid dehydrogenase is widely distributed in microorganisms and higher plants as a catalyst in the synthesis of L-glutamic acid from α-ketoglutaric acid and free ammonia. Transaminase is contained in a wide variety of microorganisms.

2. Production

2.1. Classical Processes

From 1909, when industrial production of MSG started, until 1965, when the extraction process ended, wheat gluten, separated from wheat flour by washing the starch from the dough, was the main raw material (12). It was used because crude dried gluten (12% as nitrogen) contains as much as 25% L-glutamic acid, the highest content among industrial raw materials. Crude gluten was hydrolyzed by heating with hydrochloric acid. After concentration under reduced pressure, the hydrolyzate was cooled after adding concentrated hydrochloric acid to crystallize L-glutamic acid hydrochloride [138-15-8], L-glutamic acid can be easily separated from other amino acids in the form of its hydrochloride because of its very low solubility in concentrated hydrochloric acid. The hydrolyzate suspends relatively large amounts of humic material formed by the reaction of amino acids and

carbohydrates. Filtration and hydrolysis are very troublesome processes in terms of the equipment required and the environment. Several improvements have been made in the crystallization of the hydrochloride; the filtered wet hydrochloride contains less than 30% of L-glutamic acid, not sufficient to warrant its use as a raw material for the manufacture of pure MSG. The crude hydrochloride is dissolved in hot water and filtered again to separate the humic substances formed after the first filtration. The pH of the refined filtrate is adjusted with caustic soda or ammonia to 3.2, the isoelectric point of glutamic acid, to precipitate L-glutamic acid crystals. Since its solubility is less than 1 g/100 mL-water at room temperature (0.86 g per 100 mL at 25°C), the yield of more than 90% purity L-glutamic acid crystals is very high. The glutamic acid crystals appear as both the metastable α- and stable β-forms. The α-form consists of prismatic crystals which are easy to filter, whereas the β-form needle crystals are difficult to filter. Control of crystallization conditions of α-crystals are required (13). The crude L-glutamic acid crystals are suspended in water and neutralized with caustic soda or sodium hydroxide. The solution is decolorized with activated carbon to produce a transparent solution and MSG is crystallized under reduced pressure. The crystals of MSG are then separated from the mother liquor by centrifugation and dried for packaging.

In the United States and some European countries, beet-sugar-waste molasses, or Stefen's waste, has been used as raw material for MSG production. The 2-pyrrolidinone-5-carboxylic acid [98-79-3] contained in beet sugar as by-product, is hydrolyzed at weakly alkaline pH, and moderate temperature (eg, pH 10.5–11.5, at 85°C for 2 h) to avoid racemization (14). The pH of the hydrolyzate is adjusted to 3.2 with a mineral acid to precipitate crystals of L-glutamic acid. The L-glutamic acid crystals obtained are transformed to MSG as described above.

2.2. Fermentation Process

In the early 1950s, the excretion of small amounts of amino acids in the culture medium of *Escherichia coli* was reported (15) and it was found that addition of excess ammonium salts resulted in an increase in the accumulation of amino acids in the culture medium. In 1957, a new strain of *Micrococcus glutamicum* (afterwards renamed *Corynebacterium glutamicum*) which accumulates large quantities of L-glutamic acid was discovered (16). This novel method enabled yields of L-glutamic acid of about 30% based on the weight of glucose incubated in its cultivating broth, and was immediately applied for industrial production. This discovery led to the fermentation production of many other amino acids by inducing various artificial mutants (17).

Glutamic acid-producing microorganisms are distributed widely throughout the natural environment. They are classified taxonomically as the *Micrococcus*, *Brevibacterium*, *Corynebacterium*, *Aerobacter sp.* and *Microbacterium genera*. Most of these microorganisms are gram-positive, nonspore-forming, nonmotile, and require biotin [58-85-5] for growth. They all have intense glutamate dehydrogenase activity and oxidative degradability, to both L-glutamic acid and α-ketoglutaric acid.

The carbon sources for biosynthesis of glutamic acid include acetic acid and the commonly used carbohydrates (18). For industrial production, molasses and starch hydrolyzate are generally used at present. In L-glutamic acid fermentation, the accumulation of L-glutamic acid is governed not only by its biosynthesis in the bacterial cells but also by its secretion. Biotin is one of the vitamins essential for cell growth, but a biotin concentration in the culture medium sufficient for cell growth makes the cell membranes impermeable for L-glutamic acid and results in poor accumulation (19). The critical biotin content of the cells for L-glutamic acid production is 0.5×10^{-6} g/g-dry cells (20). The limited amount of biotin is believed to cause incomplete biosynthesis of oleic acid [112-80-1], which results in a decrease of the phospholipids in the cell membrane and makes the membrane permeable. If an excessive amount of biotin is added, the result is a dramatic reduction of the L-glutamic acid excreted and accumulation of lactic and α-ketoglutaric acids. This specific function of biotin applies to all microorganisms requiring biotin.

Molasses is useful as a raw material for L-glutamic acid fermentation, except that it requires processing to depress its excess biotin concentration. To reduce this activity, surface active substances (C_{16}–C_{18} saturated fatty acid esters of polyoxyethylene) (21) are added at an early stage of production to retard microorganism propagation. Furthermore, the addition of sugar at a concentration of culture media below approximately 10% is necessary so as not to retard propagation. Additional sugar is fed during fermentation to obtain a higher concentration of excreted L-glutamic acid. This technology made possible a concentration of approximately 80 g/L of L-glutamic acid. Ammonium salts or a solution of urea or gaseous ammonia are convenient nitrogen sources for the fermentation, not only as the initial medium but also to maintain the pH of the culture at 7–8 for microbial growth and product formation. The culture medium becomes acidic because of assimilation of ammonium ions and formation of L-glutamic acid. Gaseous ammonia can be used advantageously to maintain neutral pH and avoid dilution of the culture medium, resulting in the high accumulation of glutamate in the fermentation broth, because it does not contain OH^- ions or water.

Microorganisms require several minerals such as ferrous and potassium ions which play important roles in glutamic acid fermentation. Other important culture conditions include regulating aeration stirring. The biosynthesis of L-glutamic acid is performed under regulated aerobic conditions. When oxygen is not sufficiently dissolved, lactic and succinic acids accumulate and reduce accumulation of L-glutamic acid. On the other hand, an excess of dissolved oxygen results in the formation of α-ketoglutaric acid. The need to regulate oxygen transfer led to the development of novel technologies for measuring the rate of oxygen transfer, which include the use of sodium sulfite solution. By using this technique, the optimal oxygen transfer rate was determined (22). The pressure of dissolved oxygen must strictly be kept above 1 kPa (0.01 atm) by aeration and agitation in the industrial fermentor. The air, sterilized by passing through sterile filtration such as glass wool, is fed to the industrial fermentor as well. Carbon dioxide is formed during fermentation and causes the cultivation medium to foam heavily. Mechanical defoaming alone does not provide sufficient control; chemical antifoaming agents and biochemically inert silicone oils are employed as well.

The optimum temperature for fermentation is 30–37°C depending on the microorganisms used. Regulation of the temperature using heat exchangers installed inside of the fermentor is indispensable. Fermentation is an exothermic reaction, and the temperature critically affects not only propagation of microorganisms but also the formation of L-glutamic acid. L-Glutamic acid is synthesized biochemically through the glyoxylate cycle as an oxaloacetate generating system without carbon dioxide fixation, and through phosphoenol pyruvic acid [138-08-9] to form oxaloacetic acid [328-42-7] with carbon dioxide. Several mutants with high phosphoenol pyruvate carboxylase activity (23) or low isocitrate lyase activity (24) have improved productivity of L-glutamic acid and the extent of carbon dioxide fixation.

Progress in fermentation technology has made it possible to raise the accumulation and the yield of L-glutamic acid above 100 g/L and 60% based on the total amount of sugar. Application of genetic engineering techniques for further improvement is also in progress.

An industrial fermentor of capacity up to several hundred kiloliters equipped with aeration and stirring devices, as well as other automatic control systems, is used. The cultures must be sterilized and aseptic air must be used owing to the high sensitivity to bacterial contamination of L-glutamic acid fermentation.

In industry, microorganisms used for L-glutamic acid fermentation are usually preserved under lyophilization, or when stocked for short periods, preserved by keeping below $-10^{\circ}C$. To refresh the microorganisms, stocked in either form, they are inoculated on a strip of an agar medium composed of yeast extract and/or polypeptone, sodium chloride, and agar at an optimal temperature for them. The refreshed microorganisms are then cultivated in a liquid medium in a flask with a sterilized stopper and shaken vigorously. Then they are transferred into a small fermentor to let them propagate to appropriate volume for seed culture. Fermentation takes about 35–40 hours. In the initial stage of fermentation, the propagation of microorganisms is solely observed, but in the middle stage, accumulation of L-glutamic acid emerges. The end of the process is determined by an increase in pH in the medium whereupon the increase in concentration of L-glutamic acid ceases.

Sterilized fermentation broth, either in the fermentor or through a heat exchanger with steam, is transferred to another vessel and then centrifuged to remove the microorganisms and other insoluble organic substances. After the clarified broth has been concentrated under reduced pressure, the pH of the broth is adjusted to 3.2 using hydrochloric or sulfuric acid to recover L-glutamic acid crystals in the α-form. These crude L-glutamic acid crystals are converted to MSG through decolorization and crystallization processes as discussed previously.

3. Uses

Monosodium L-glutamate elicits a unique taste, known as "umami", which is different from the four basic tastes of sweet, salty, sour, and bitter. Multidimensional graphs of sensory tests show that taste similarity scores of MSG, and of meat, fish, and vegetable stocks which are naturally high in glutamate, fall outside the spaces characterized by the four basic tastes. This suggests that glutamate is not simply a mixture of the four basic tastes, but is an independent basic taste. This concept also comes from studies in physiology, electrophysiology, biochemistry, food chemistry, and nutrition, and basic research on taste receptors (25). A synergistic effect occurs between glutamate and nucleotides such as 5′-inosinic acid [131-99-7] and 5′-guanylic acid [85-32-5] found in meat, fish, vegetables, and mushrooms. Through this effect, even a small addition of glutamate to a food containing the nucleotides remarkably enhances "umami" seven to eight times as much as the original "umami" of the food (26). The taste threshold of MSG is around 0.03% in aqueous solution.

The intensity of "umami" increases linearly with a logarithmic increase in the concentration of MSG. The synergistic effect of MSG with 5′-ribonucleotides is expressed by the following relation

$$y = u + Auv$$

where u and v are the respective concentrations of MSG and 5′-ribonucleotides. A is a constant: 1200 for disodium 5′-inosinate(IMP) and 2800 for disodium 5′-guanylate(GMP), and y is the equivalent concentration of MSG alone. In some commercial "umami" seasonings, 5′-ribonucleotide is added to take advantage of the synergistic effect with MSG (27).

L-Glutamic acid is used as a neutralizing agent for basic compounds, for example, arginine glutamate [4320-30-3] is employed as a pharmaceutical and raw material for cosmetics. Glutamic acid hydrochloride is proposed as an acidifying agent in the stomach. As an amphoteric electrolyte it may be applied as a chelating agent or a builder for a detergents. Sodium pyroglutamate [28874-57-3] obtained by dehydration of L-glutamic acid with heating and then neutralization by sodium oxide is used as a component of a natural moisturing factor for human skin because of its hygroscopic property (28).

4. Safety

Monosodium L-glutamate is metabolized in the same way as glutamic acid coming from any digested protein. After oral ingestion, glutamate is absorbed from the intestine by an active transport system. During this process, a large proportion is metabolized to alanine and α-ketoglutarate, which enters the tricarboxylic acid cycle. Glutamate is further metabolized in the liver to give glucose, lactate, glutamine, and other amino acids. Consequently, blood glutamate levels do not rise significantly unless very large doses are administered. Blood glutamate levels rise transiently when large doses are ingested on their own, but the co-ingestion of foods that contain metabolizable carbohydrate increases the metabolism of MSG and eliminates or greatly attenuates this rise. Human infants, including premature infants, metabolize glutamate similarly to adults (29, 30).

The acute toxicity of MSG is low (31); the oral LD_{50} for humans, calculated on the basis of doses administered in different ways to various animals, would represent a single dose greater than 1 kg for a person weighing 70 kg. In contrast, the oral LD_{50} for sodium chloride in rats is 3.75 g/kg body weight (32).

The main use of MSG is as a food ingredient, and so its safety when used in the diet is the most important aspect of its safety for use. Both short term and chronic toxicity studies on MSG in the diet of several species at doses of up to 4% (approximately 6–8 g/kg body weight per day) in the diet showed no specific toxic effects, and no evidence for carcinogenicity or mutagenicity. Reproduction studies of up to three generations did not reveal any adverse effects of dietary MSG ingestion. Fertility, gestation, viability, and lactation indexes or the pre and post weaning performance of offspring were unaffected. In primates, it was found that the placenta serves as an effective barrier to the transfer of glutamate from the mother to the fetus. The glutamate level of human milk is hardly affected by the oral ingestion of large doses of MSG.

The demonstration that injected or force-fed neonatal rodents given extremely high doses of MSG showed evidence of brain lesions, has led to much additional research to determine any possible link between neurotoxicity and human use of MSG (33). However, no evidence from animal tests indicates that MSG in the diet causes brain damage in humans (34).

Numerous experiments on rodents, as well as dogs and monkeys, with dosage levels up to 43 g of MSG per kilogram of body weight have failed to show any link between dietary use of MSG and brain damage. In the case of dogs and monkeys, even experiments involving injection of MSG have not shown any effects on the brain.

An anecdotal report in 1968 triggered interest in Chinese Restaurant Syndrome (CRS) a reaction associated with transient subjective symptoms of burning, numbness, and a tight sensation in the upper part of the body. Possible association with food ingredients such as MSG was suggested. No objective changes in skin temperature, heart rate, ECG, or muscle tone were observed, and no correlation was seen between plasma glutamate levels and symptoms. In 1979 a survey by questionnaires of more than 3000 people in the United States was conducted. Only 1.8% of those surveyed acknowledged that they experienced possible CRS feelings (35). Only 0.19% of those with symptoms attributed them to eating in Chinese restaurants. These feelings were also found to occur after consumption of spicy tomato juice, orange juice, coffee, and tea. In 1986, self-identified MSG responders were challenged in a properly controlled double-blind study, and it was concluded that the link between MSG and CRS was not supportable (36). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded in 1987 that properly-conducted double-blind studies among individuals who claimed to suffer from the syndrome did not confirm MSG as the causal agent (30). JECFA is a scientific advisory body to the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations.

In 1981, Chinese Restaurant Asthma was reported following capsule administration of MSG to several asthmatics (37). However, the researchers failed to account for other allergens to which the subjects could have been exposed and did not utilize the scientific practice of a "control" substance which would have helped to determine if glutamate triggered this response. In a double-blind crossover study, chronic asthmatics were challenged with MSG or a placebo. No decrease in pulmonary function was observed (39).

JECFA reviewed the safety studies of glutamate and endorsed its safety by allocating an Acceptable Daily Intake (ADI) for L-glutamic acid and its monosodium, potassium, ammonium, calcium, and magnesium salts as being "not specified." The scientific committee for food of EC concurred (40).

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