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Clinical Applications of Magnesium Hydride

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Abstract

Oxygen sustains the lives of human a unique element. However, oxygen is unwanted and harmful when it is over tension to introduce oxygen-derived free radicals in the cells. Hydrogen and oxygen are both involved in the genesis of life that exists on Earth and metabolism in vivo, so it is not strange to exert a biological effect. Recently, scientists have found that hydrogen is an essential physiological regulatory function with antioxidant, anti-inflammatory, and antiapoptotic protective effects on cells. Using therapeutic hydrogen includes different delivery methods, such as inhalation of hydrogen gas, oral hydrogen water, and injection of hydrogen-saturated saline. In clinical applications, magnesium hydride hydrolysis instead of traditional metallic magnesium is effective in increasing the theoretical hydrogen storage capacity by two times. The hydrogen-water comes across as being an excellent choice to produce from magnesium hydride hydrolysis on-demand because its antioxidant activity cannot store.

Keywords: hydrogen, method, metallic magnesium hydrolysis, magnesium hydride hydrolysis, oral hydrogen-dissolving water, hydrogen gas inhalation, hydrogen-saturated saline injection, reversible osmosis

1. Introduction

In 2007, Oshawa et al. [1] have the first reported that inhalation of only 2% hydrogen gas could selectively reduce oxygen-derived free radicals and improve cerebral ischemia-reperfusion injuries. However, the underlying mechanism is still not precise; the protective effects of the small amount of hydrogen on oxidative stress draw much attention for developing the hydrogen biology. Since that, hydrogen biology becomes a hotspot in the medical research, more than 500 papers related to almost all diseases. Lots of evidence shows molecular hydrogen in cells, and organisms exerting the antioxidant, anti-inflammatory, and antiapoptotic for oxidative stress on some types of infections. Why is this discovery significant? Inhalation of hydrogen below the flammability limit of 4.6%, drinking containing saturated hydrogen water, and injection of containing saturated hydrogen saline could exert therapeutic biological effects for selectively eliminating the toxic free radicals, such as hydroxyl free radicals, superoxide radical in vivo. We can treat the reactive oxygen species-caused oxidative stress disease by administrating reductive drugs, such as vitamins. However, it would eliminate all reactive oxygen species [2]. Cells maintain metabolism through oxidizing food into energy species in vivo. Therefore, cells produce reactive oxygen free radicals to help to absorb nutritious substances, which is a unique phenomenon for biological organisms. But over the tension of free radicals can seriously affect the physiological functions, and even lead to death. Oxidative stress damage likes a peeled apple will turn brown with an injury.

What are free radicals? Free radicals are molecules and atomic groups with "unpaired" electrons. Owing to unpaired electrons, they will snatch free electrons of other molecules in vivo to match with them. After snatching electrons, they will turn molecules of the robbed electrons into newly free radicals. Finally, it will induce the "chain reaction of free radicals" so the unbalance of free radicals will cause the cells crisis. Hydrogen has the lightest weight with one proton and one electron, and the molecular hydrogen a nonradical, nonreactive, nonpolar, highly diffusible neutral gas, which can arbitrarily penetrate the cell membrane into nucleus and mitochondria to neutralize the highly reactive oxygen species in vivo. At a low concentration, hydrogen does not react with the characterized as large in number, low in activity, and beneficial reactive oxygen species, such as hydrogen peroxide, nitric oxide. This phenomenon is called the selectively neutralizing highly reactive free radicals. It means that low concentration hydrogen can be limited to deal with high reactive cytotoxic oxygen species and not to kill all the free radicals. Till now, hydrogen has been shown to have a therapeutic effect on over 170 different human diseases and animal models, including in antioxidant activity [1, 3–9], ischemia-reperfusion injury [2, 10–14], Parkinson's disease [15, 16], cancer [17], retina [12], chondrocytes [7], diabetes disease [18], irradiation-induced lung damage [8], mitochondrial disease [9], and cardiac disease [13, 19].

When hydrogen was focused on its biological effects in multiple diseases by scientists in recent years, the method of hydrogen applications is that we have to resolve it for adequately applying its antioxidant, anti-inflammatory, and antiapoptotic function for oxidative stress [1–19]. This antioxidant effect of molecular hydrogen has been proved. However, molecular hydrogen is not the same as hydrogen gas. Hydrogen water contains both atomic and molecular hydrogen. It is essential continuously to study the medical effects in vivo for hydrogen bioresearch. Producing high-quality hydrogen water method for clinical applications is one of the critical points in the study. Although, many scientists have studied hydrogen-associated techniques including magnesium rod hydrolysis, electrolytic water containing sodium chloride, and electrolyzed water by polymer membrane patents [20–22]. We found that the related methods of producing hydrogen dissolving in water were still limited. This chapter shows a new way of magnesium hydride hydrolysis by reacting with tap water. It is provided to increasing the theoretical hydrogen production amount by more than two times, solving the drawbacks that the rate of metallic magnesium rod hydrolysis is too low, the risk of internal explosion of the hydrogen-oxygen electrolysis process itself, and the cost of pure water electrolysis by polymer membrane method is too high. The magnesium hydride hydrolysis belongs to alkaline water efficiently enhances the saturated hydrogen dissolving in water, and the smallest hydrogen molecule passes nanometer-filter of reversible osmosis transformed into fresh high-content hydrogen water.

2. Materials and methods

At room temperature, the concentration of hydrogen molecule dissolving in tap water is only 8.65×10^{-7} mg/L. At such a low level of hydrogen, there is no therapeutic effect in clinical applications. The saturation-hydrogen of 1.6 milligram/Liter [20–22] in water is more than million times of hydrogen concentration in tap water. This value is considered the hydrogen dissolved in water at room temperature to its maximum state. The amount of hydrogen will reduce if hydrogen escapes from the water surface equaling to the pressure at sea level, which is 101.325 kilopascal (one-atmosphere pressure). Hydrogen, under saturation condition, has been found to be able to exert its protective effects in the biological system [1–19]. Hydrogen is the minimum mass gas molecule with relatively steady reducibility, a valuable chemical property of redox reaction in metabolism. It has been accepted that hydrogen cannot directly interact with substances in the biological body, and that is why, we get hydrogen dissolving in water by oral or injection with saturated hydrogen saline. Since 2007, plenty of trials have been done using hydrogen inhalation medicine in treating ischemia-reperfusion injury at 1 or 2% hydrogen concentration for 35 min. Subsequently, a lot of researchers have shown that a small level of hydrogen has therapeutic effects on a variety of diseases. Even in pure oxygen gas environment, it is not flammable or explosive when the hydrogen concentration is less than 4% or over 95%. **Table 1** shows several delivery methods for hydrogen administration in vivo. In the following section, we introduce the means of producing hydrogen molecules, such as hydrogen from metallic magnesium rod hydrolysis [20], sodium chloride ionic water-electrolyzed hydrogen [21], and pure water through polymer membrane-electrolyzed hydrogen [22]. Later, we will explain and compare them with a specific mention as below.

Administration	Delivery methods	Characteristics
Hydrogen gas	Inhalation gas mixture of $H_2 < 4\%$	Rapid, unsafe, acute oxidative damage
Hydrogen water	Oral intake H_2 water <1.6 mg/L	Low cost, safe, convenient
Hydrogen saline	Intravenous injection by saturated H_2 saline	Accurate dosage
Hydrogen solution	Eye drop, bath immersion	Low cost, safe, convenient
Increased intestinal hydrogen amount	Drug	low cost, convenient

Table 1. Hydrogen delivery methods.

2.1. Magnesium hydrolysis

Metallic magnesium is one of the soluble materials in our body, such as bone material and blood vessel stents. It is safe to use as a medical therapy. However, magnesium reacts violently with steam at high temperatures, such as burning or explosion with water vapor. It is active as a reductant agent for oxidizing water into hydrogen with a standard oxidation potential of +2.356 V. If we throw a small piece of magnesium into cold water, it reacts very slightly. Hydrogen gas is slowly released, because magnesium hydroxide is coated on its surface in the reaction. White-colored magnesium hydroxide mixed with water is called emulsion of magnesium milk which is used to neutralize excess stomach acid in treating constipation disease. Magnesium hydroxide is a base hardly soluble in cold water, while it can react with acid to generate a salt and water in a neutralization reaction. We expressed the chemical response according to the standard reduction potential of magnesium [23].

$$Mg_{(s)} \rightarrow Mg^{+2}{}_{(aq)} + 2e^{-}\ E^{0} = -2.372\ V \tag{1}$$

$$2H_2O_{(l)} + 2e^{-} \rightarrow H_{2(aq)} + 2OH^{-}\ E^{0} = -0.828\ V \times 2 \tag{2}$$

Magnesium hydrolysis in redox reaction would be spontaneous ($E > 0$). However, the rate of magnesium hydrolysis is gradually slow down because $Mg(OH)_2$ is highly insoluble in water. Therefore, the total reaction of magnesium hydrolysis is as below.

$$Mg_{(s)} + 2H_2O_{(l)} \rightarrow H_{2(aq)} + Mg\,(OH)_{2(s)} \tag{3}$$

In the solution, two hydroxide ions combine with one magnesium ion to form magnesium hydroxide while leaving insufficient hydroxide ions to conduct the electrons. So, it cannot complete all the hydrolysis reaction despite the escaping hydrogen gas.

Magnesium hydrolysis producing hydrogen-rich water [20] is the most simple and cheap method for oral hydrogen. While drinking hydrogen water, magnesium hydroxide may also take in. There is no potential harm to the human body as a gastric acid inhibitor. If in a day we drink 2 liters of hydrogen water, the intake is 18 mg and will not exceed the limit of 300 mg per day.

2.2. Electrolysis of ionic water

Drinking electrolytic water has used for health care in Japan more than half a century. Commercially available electrolytic water generator [21] is called ion water electrolyzed. The core device of electrolytic water generator includes a pair of anode/cathode electrodes and ionic membrane. The electrolytic reaction has a standard electrode potential of −1.23 V. It means that it at least requires a potential difference of 1.23 V between anode and cathode to split water. The electrochemical reaction includes oxidation at the anode,

$$H_2O_{(l)} \rightarrow 0.5O_{2(aq)} + 2H^{+}{}_{(aq)} + 2e^{-}\ E^{0} = -1.23\ V \tag{4}$$

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reduction at the cathode,

$$2H^{+}_{(aq)} + 2e^{-} \rightarrow H_{2(aq)}\ E^{0} = 0\ V \tag{5}$$

and the overall redox reaction.

$$H_2O_{(l)} \rightarrow 0.5O_{2(aq)} + H_{2(aq)}. \tag{6}$$

Electrolysis of water would be not spontaneous due to $E^0 = -1.23$ V < 0. Therefore, it needs electrical power to drive electrolyzed water reaction. Electrolysis of water has advantages of simple, low cost, and convenient use. However, if it connects to the tap water, the water may contain part of chlorine or salt residues. The residual chlorine content of electrolysis of water will be 15–20% higher than the original tap water. Apart from chlorine, there is ozone in the water at the anode, and ozone has a pungent odor, a harmful effect on human health. Ozone is a strong oxidant which can also damage the lung causing lung bleeding and death. Therefore, the potential crisis in electrolyzed water generator may originate in improper design or use. For example, many manufacturers to reduce costs will not take the initiative to use gas-tight devices to separate the hydrogen and oxygen further, resulting in hydrogen and oxygen confluence, so that the machine is under explosive risk. Also, the hydrogen gas is generated at the cathode, so the solutions become more and more alkaline. The human body is not suitable for drinking too high-pH-value water. When the alkaline electrolytic water enters the stomach, it will be in a neutralization reaction with acidic gastric acid. Therefore, adjusting the human body's pH value by alkaline electrolytic water is lack of scientific basis.

2.3. Electrolysis of pure water

Recently, the green energy market has sprung up, and a new technology called "polymer proton conducting membrane" of electrolytic production of hydrogen from pure water has emerged. Such electrolyzed pure water is the reverse reaction of "hydrogen fuel cell of power generation," which fuel cell directly transforms the chemical energy of hydrogen and oxygen into electricity. The only by-product is pure water. Japan has spared no effects to promote hydrogen fuel cell technology, TOYOTA, and Honda automotive company have also developed hydrogen fuel cell-powered electric vehicles. It uses pure water and electricity to produce hydrogen and oxygen. Due to high hydrogen production efficiency and high safety factor, the purity of hydrogen can reach over 99.999%. The polymer proton-conducting membrane is manufactured by DuPont Inc. as a solid electrolyte, which does not require dissolved ions in water. Instead, the higher the purity of water, the better can protect the core device of membrane electrode assembly without accompanying other by-products. The electrochemical reaction is as below.

$$H_2O_{(l)} \rightarrow 2H^{+} + 2e^{-} + 0.5O_{2(g)} \text{ at the anode} \tag{7}$$

$$2H^{+} + 2e^{-} \rightarrow H_{2(g)} \text{ at the cathode} \tag{8}$$

Water molecule splits at the anode to form two positively charged hydrogen ions (H^+), two electrons (e^-), and a half oxygen molecule (O_2). The two electrons flow through an external circuit and the two hydrogen ions selectively move across the polymer electrolyte membrane to the cathode. At the cathode, the two hydrogen ions combine with the two electrons from the external circuit to form one hydrogen molecule (H_2). The gas-tight polymer of proton exchange membrane prevents the oxygen at the anode from passing through the layer to the cathode, completely isolating the oxygen from the hydrogen gas, avoiding the internal explosion of the electrolysis process. Electrolytic water maintains at a neutral state of pH equal to 7 during the process of electrolysis. Furthermore, the amount of hydrogen production at a 3 Ampere/cm^2 of current density is five times higher than that of the ion-electrolyzed water. The volume of pure water electrolyzed system can be smaller and lighter. Although the polymer electrolyte membrane has many advantages mentioned above, it is still costly to use. Also, it cannot use tap water to be another problem because metal ion, chlorine, carbon monoxide in the solution will poison the platinum catalyst, and its price cannot compete with the other products.

2.4. Comparison of methods

The method of magnesium hydrolysis of producing hydrogen water was invented by Dr. Hidemitsu Hayashi, who was the heart surgeon being responsible for clinical medicine. He began to study the medical benefits of hydrogen water in 1985 and published a report on hydrogen water treatment 10 years later. The magnesium rod consists of magnesium powders packed in a porous polyethylene resin (see **Figure 1**). The mild chemical reaction between magnesium and water lead to the generation of hydrogen bubbles and the formation of magnesium hydroxide on the surface of magnesium. This simple and effective process produces hydrogen antioxidant solution, which is more alkaline than that of pure water [20].

The ion-electrolyzed water system for producing hydrogen water was Akiyama Hiroyuki's invention [21], and the commercial product of both of acidic water and alkaline water has completed. The electrolytic water system includes an electrolysis generating unit, a reading display, and a control unit. It selectively makes and takes out a plurality of acidic-oxidation water and hydrogen-reduction water with a given pH value which is based on a series of operation modes. The reading unit reads the information stored in the external touch panel carried by the user. The control unit determines the operation mode; the ion electrolysis system is operated to improve the usability by a plurality of people [21].

Wang Dong invented the electrolyzed water system based on the polymer electrolyte membrane [22] as shown in **Figure 2**. The electrolyzed water-generating device provides high-purity hydrogen and oxygen for the fuel cell, including the front end plate, diffusion plate, conductive plate, special plate, flow field plate, membrane electrode, rear special plate, buffer plate, rear end plate, and other units, each unit is pressure-resistant. Water and gas flow field plates and conductive plates made of titanium alloy and other corrosion resistant alloys. The carbon fiber paper is used as the membrane electrode diffusion layer. The membrane electrode is a high-activity electrode prepared by proton exchange

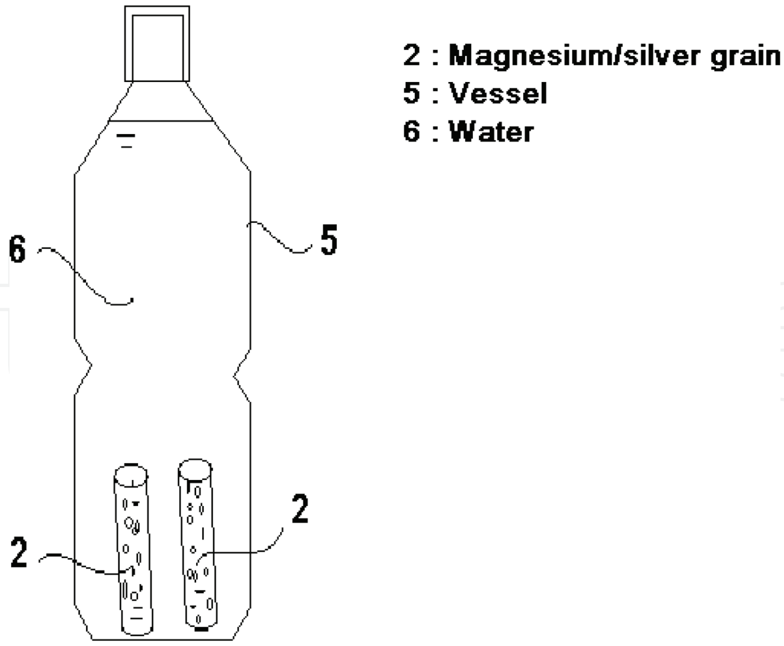

Figure 1. Method of magnesium hydrolysis for producing hydrogen-rich water [20].

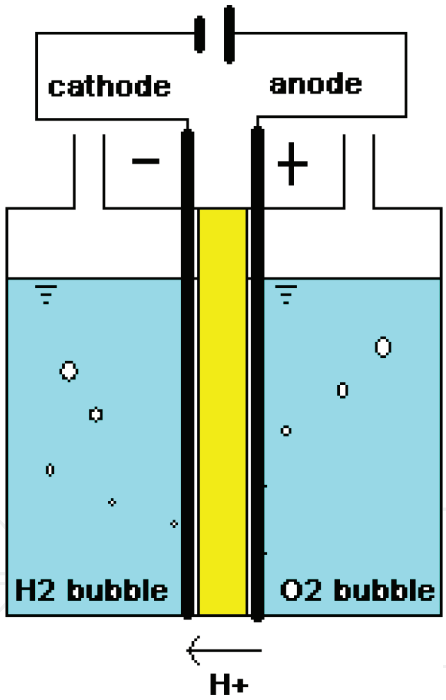

Figure 2. Polymer electrolyte membrane electrolyzer [22].

membrane and composite platinum metal catalyst and carbon black. The working medium of the invention is pure water, has no pollution to the environment, can recycle, and the generated hydrogen water is high in purity and does not need complicated purification and treatment.

Methods	Magnesium hydrolysis [20]	Ion-water electrolysis [21]	Pure-water electrolysis [22]
Theory	Magnesium hydrolysis	Electrolyzed water	Electrolyzed water
Purity	100%	70–98%	100%
Reaction rate	Low	Medium	Medium
Water	Tap water	Ion water	Pure water
By-product	Mg^{+2}, OH^{-}, $Mg(OH)_2$	Cl_2, HClO, O_2, O_3	None
Safety	High	Explosion, toxicity may be possible	High
Cost	Low	Medium	High

Table 2. Three primary producing hydrogen water methods [20–22].

Table 2 listed the comparison between three primary producing hydrogen-water methods. This seemingly theoretical capacity of hydrogen, purity, reaction rate, etc. indeed relevant for real clinical application scenarios. As in many cases, the water of various sources whether or not is readily on site or therefore needs to transport the necessary amount of pure water or distilled water for use. We attempt to improve the conventional methods of producing hydrogen-water by using magnesium hydride hydrolysis. The double capacity of hydrogen sources of magnesium hydride hydrolysis originates as half from the hydride ions and half of the water protons. Thermodynamically, magnesium hydride on contacting with water to produce hydrogen-water is favorable and the by-product of magnesium hydroxide. However, in practice, not only the reaction kinetics is extremely slow but also the insoluble passivation layer of magnesium hydroxide soon coated on the outer surface to impede water entering. For example, the reaction yield of magnesium hydride hydrolysis at room temperature is below 1% after half an hour.

3. Results and discussion

In this section, we give a systematic study on the method of magnesium hydride hydrolysis for producing hydrogen-water. At first, this method provided to an increasing the theoretical hydrogen amount by two times than that of the technique of magnesium hydrolysis. The hydrogen-water produced from this method belongs to alkaline water. At room temperature, the reaction is prolonged because the low reaction kinetics and the surface are gradually covered with an insoluble layer of hydroxide on the outer to hinder response continuously. However, it can activate by using citric acid as a chelating agent. Like, citric acid can dissolve metal oxides by making them dissoluble. Citric acid belongs to a weak organic acid that has the chemical formula $C_6H_8O_7$. In biochemistry, the citric acid acts as an intermediate in the citric acid cycle occurred in the metabolism of all aerobic organisms. The chemical reaction of the citric acid cycle is the source of two-thirds of the food-derived energy in higher living creatures. Hans Adolf Krebs also received the 1953 Nobel Prize in Physiology Medicine for the discovery. In this study, citric acid acts as both of a catalyst to activate reaction kinetics and a chelating agent to inhibit the magnesium hydroxide formation over the complete

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course of the reaction, which is the limiting step of magnesium hydride hydrolysis. These effects are advantageous. The by-product, citrate magnesium, also is a vital component of bone in the human body.

The system of producing hydrogen-water, as shown in **Figure 3**, includes a reactor, reverse osmosis unit, valve, pump, control unit, digital display, water input, hydrogen-water output, hydrogen-water for therapeutic use, magnesium hydride block, and tap water input. **Figure 4** shows the porous structure of magnesium hydride of 35 × 35 × 17 in millimeters which was manufactured by direct hydrogenation processes using a low-cost combustion synthesis [24, 25]. The block of magnesium hydride is made by a light gray crystalline powder (99.9% in purity by mass) under high pressure and temperature of 200 bars and 500°C with magnesium iodide catalysts. The porous structure facilitates the water molecules to enter into magnesium hydride inside to generate hydrogen.

The chemical reaction is expressed below.

$$MgH_{2(s)} \rightarrow Mg^{+2}{}_{(aq)} + 2H^- \tag{9}$$

The magnesium hydride hydrolysis reaction shows a similar qualitative process. At the beginning of the response, water molecule reacts with magnesium hydride to release magnesium ions and negative hydrogen ions. And then, the negative hydrogen ions continuously split water molecules releasing hydrogen gas and hydroxide ions. Therefore, we can observe a steep increase in pH value.

$$2H^- + 2H_2O_{(l)} \rightarrow H_{2(aq)} + 2OH^{-} \tag{10}$$

While the reaction reached the observed equilibrium of pH 11.0, more and more magnesium hydroxide precipitated on the outer surface of the magnesium hydride from the initially supersaturated solutions state. It is in excellent agreement with the observed pH of saturated solutions of magnesium hydroxide in the literature [23, 25].

$$Mg^{+2}{}_{(aq)} + 2OH^{-} \rightarrow Mg\,(OH)_{2(s)} \tag{11}$$

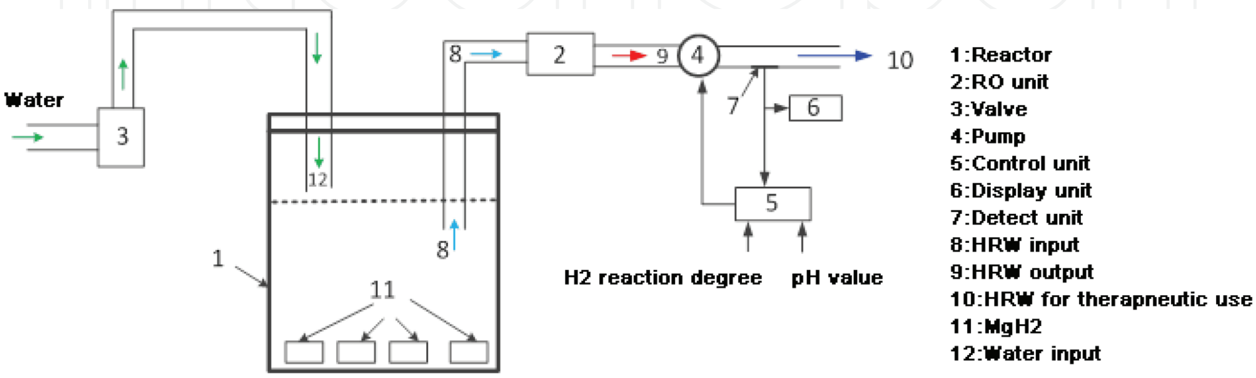

Figure 3. The method of magnesium hydride hydrolysis producing hydrogen-water.

Figure 4. Magnesium hydride (the external size of 35 × 35 × 17 millimeter, Bio-Coke Ltd. Japan).

That is to say, if we carefully control the pH in the hydrolysis reaction less than 11 with magnesium ions concentration less than 0.007 mol per liter, the supersaturated solution state in the solution will not occur. The insoluble magnesium hydroxide layer will not form on the surface to impede hydrolysis reaction. Magnesium hydride is split extremely slow to the hydrogen-saturated state (0.8 mM). The pH-dependence of the hydrolysis behavior of magnesium hydride seems reasonable. Furthermore, we repeatedly inject a small amount of citric acid solution before supersaturation state. The citric acid as a chelating agent can effectively reduce the concentration of magnesium ions and hydroxide ions to generate the soluble magnesium citrate.

$$3MgH_{2(s)} + 2\,C_3H_4(OH)(COOH)_{3(aq)} \rightarrow 6H_{2(aq)} + Mg_3\left[C_3H_4(OH)(COO)_3\right]_{2(aq)} \quad (12)$$

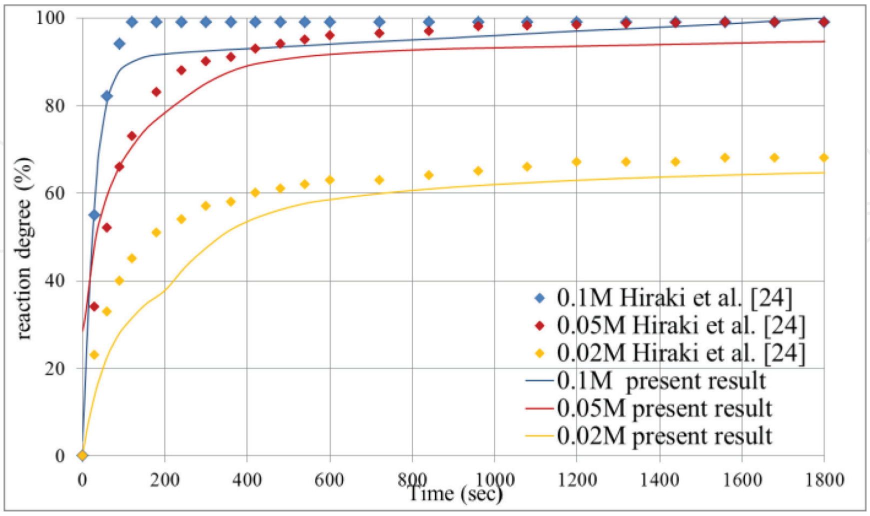

Figure 5. Reaction degree measured in the present result, which also compared with the data of [26].

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The reaction percentage was calculated by:

Reaction degree in % = H_2/H_2 in theoretical value in Eq. (12).(13)

The above behavior has also confirmed in our experiments with a stoichiometric amount of citric acid. For applications, the system injects a small amount of citric acid solution by a sequence of multiple separate times of various steps. To overcome the insoluble passivation layer, the mole ratio of citric acid to magnesium hydride is 2:3. About five times the mass of citric acid compared to magnesium hydride is necessary. **Figure 5** shows the measured reaction degree of magnesium hydride hydrolysis for 0.02, 0.05, and 0.1 moles of citric acid per one-liter-pure water. This data also compared with the literature of Hiraki et al. [26]. The time of dissolving molecular hydrogen as shown in the figure was sufficient for continuous use of 30 min for clinical applications. Finally, citric acid can completely prevent the insoluble passivation layers of magnesium hydroxide and thus significantly increase the reaction kinetics and yield.

4. Conclusions

The magnesium hydride hydrolysis is a very promising method to generate saturated hydrogen water since it is cheap, nontoxic, with a very long shelf life to give a two-times storage capacity of hydrogen than that of metallic magnesium. However, pure magnesium hydride hydrolysis reacts extremely slow and incompletely with water. At room temperature, the yield of hydrogen is less than 1% after half an hour. The addition of a small amount of citric acid solution highly increases the reaction kinetics and hydrogen yield. The kinetics and yield strongly depend on the pH in the solution, which can be adjusted by acids. This technology can serve as a superior replacement for magnesium hydrolysis, avoiding the danger of magnesium burning in oxygen. It is also a significant weight reduction in clinical applications while comparing with other methods of generating hydrogen-water. However, a small amount of molecular hydrogen on oxidative stress by efficiently neutralizing reactive oxygen species only explains part of the phenomena. Now, it is challenged by increasingly accumulated evidence. The future needs to prove the clinical effectiveness, and the evidence in the hydrogen molecular mechanism, medical, and biological effects.

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