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论文题目：The fabrication of a magnesium hydride-based micro-composite material as a local sustained hydrogen supplier and its hydrogen release properties

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The fabrication of a magnesium hydride-based micro-composite material as a local sustained hydrogen supplier and its hydrogen release properties

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Abstract

In recent years, the discovery of the biological reactivity of hydrogen gas has opened the door to hydrogen therapy. It has been found that hydrogen gas has a distinct antiinflammation and antioxidation effect and also plays a positive role in the treatment of the Covid-19. However, current administration methods of hydrogen, including direct inhalation of hydrogen gas, drinking hydrogen-rich water, and injection of hydrogen-rich saline, have the defects of low hydrogen bio-availability, limiting the efficacy of hydrogen therapy. Notably, site-specific hydrogen supply can achieve a higher hydrogen concentration at local lesions, which is in great favor of the treatment of inflammation-related diseases, especially osteoarthritis. Unfortunately, there is yet no effective means of local hydrogen supply for augmented efficacy. On the other hand, magnesium is not only a new biodegradable biomedical material developed in recent years, but also a potential hydrogen storage material with up to 7.6% theoretical hydrogen storage. In this work, based on the hydrolysis hydrogen release reaction of magnesium hydride, a micro-composite material as a local sustained hydrogen supplier is proposed and fabricated, which hopefully provides a safe and reliable hydrogen administration method for site-specific antiinflammation. In the materials, the of reaction degree was controlled by citric acid through adjusting the PH value of the reaction system; at the same time, poly (lactic-co-glycolic acid)(PLGA) was used as the carrier to control the hydrogen-release rate. The experimental results show that, compared with the direct hydrogenation reaction of magnesium hydride with citric acid aqueous solution, PLGA-coated magnesium hydride micro-particles can effectively realize slow and sustained hydrogen release. And further, by changing the ratio of coated reactants, the rate of hydrogen release and the PH value of the composite system can be effectively regulated.

Keywords: Magnesium hydride; Hydrogen therapy; Microfluidic system; Hydrogen release; PH value

Contents

1. Introduction

Hydrogen is a colorless and odorless gas that exists widely in natural world. In recent years, Hydrogen not only shows great advantage and potential in the field of new energy, the research and application of hydrogen in medical field has also attracted more and more attention. Since Professor Ohta of Japan Medical University discovered the therapeutic effects of hydrogen in 2007 and published his first article[1] in Nature Medicine, more than 1300 hydrogen-related papers have been published till now worldwide. Although the mechanism of molecular hydrogen as a new type of effective therapeutic agent remains unclear yet, hydrogen plays a distinct role in the treatment of inflammation/oxidative stress-related diseases, such as osteoarthritis, diabetes, arteriosclerosis, Alzheimer's disease, and so on [2-5]. During the epidemic period of corona-virus, a mixture of hydrogen and oxygen gas was used to treat the Covid-19. Furthermore, academician Nanshan Zhong was invited by the Journal of European Respiratory to publish a review article, introducing the experience of epidemic prevention and control, and announcing the latest clinical treatment progress. In this article, it is mentioned that hydrogen/oxygen mixed gas inhalation resulted in a major amelioration of dyspnea in most patients with Covid-19 in a pilot investigations, and has therefore been endorsed by the latest Recommendation for the Diagnosis and Management of Covid-19 document [6]. At present, the widely accepted therapeutic principle of hydrogen is the selective antioxidation mechanism [7], in which molecular hydrogen can selectively scavenge hydroxyl radical, nitrite anion and other highly cytotoxic reactive oxygen species (ROS) produced during metabolism, without reducing other physiological necessary ROS , such as O_2, H_2O_2, and NO. It is this unique biochemical property of selective antioxidation, combined with the high bio-safety, simple preparation and application, and strong diffusion capacity, the so-called 4S characteristics of hydrogen [8-10], making hydrogen a new potential treatment agent for a variety of diseases, attracting more and more attention in medical field.

Currently, the administration methods of hydrogen include direct inhalation of hydrogen gas [11], drinking hydrogen-rich water [12], injection of hydrogen-rich saline [13], and having hydrogen bath[14]. Hydrogen has entered the Japanese market as early as the last century. China also included hydrogen in food additives in May 2015 and promulgated relevant national standards (GB31633-2014). However, Because of the low solubility of hydrogen in aqueous solution [15], and the high diffusivity of hydrogen, when using these methods to supply hydrogen to human body, the concentration of hydrogen, both in body fluids and in inflammatory sites where

lesions occur, such as joints, is very low, less than the dose required for treatment or anti-inflammatory; in the meantime, the duration time of the interation between hydrogen molecule and diseased tissue is also hard to maintain sufficient long. In this way these treatment methods limit the medical efficacy of hydrogen, blocking the clinical application and development of hydrogen medicine.

Obviously, site-specific hydrogen supply can achieve a higher hydrogen concentration at the local tissue of the lesion, which is in great favor of the treatment of inflammation-related diseases, especially osteoarthritis. Therefore, a local sustained hydrogen supplier system is required that can continuously release a high dose of hydrogen to realize site-specific hydrogen delivery, solving the above-mentioned two problems of low hydrogen concentration and short duration. It has become an urgent task to achieve localsustained and controlled release of hydrogen in the field of hydrogen-based medicine [16].

Magnesium is a biomaterial with good bio-compatibility. Mg^{2+} is the fourth-richest metallic ion in human body after K^{+}、Ca^{2+}、Na^{+}; in addition to, magnesium is an active element which can react violently with water even at room temperature, contributing to its application as a biodegradable medical implant material, which is non-toxic and harmless to human body. Actually, the hydrolysis reaction of magnesium rod is also widely used to make hydrogen-rich water [17]. The chemical reaction of magnesium in contact with water/body fluids is:

$$Mg + 2H_2O = Mg(OH)_2 + H_2 \uparrow$$

Though Mg and its product Mg^{2+} are harmless to humans, the reaction should not be directly used for local hydrogen supply in human body. This is because :1) The amount of hydrogen released is limited. After a certain reaction time, a large amount of magnesium hydroxide is attached to the surface of the magnesium rod, hindering further contact of magnesium with water, resulting in the termination of the reaction. Experimental results show that at 40℃, The hydrogen production of magnesium rod placed in water for 10 hours is only about 0.7 ppm [18]. 2) Hydrogen releasing speed is not controllable. Early in the reaction, Hydrogen release is too fast, not only producing cavitation, causing necrosis of the surrounding tissue, but also not achieving the purpose of sustained release of hydrogen at pathological tissue. 3) This reaction generates OH^{-1}, alkalizing the nearby solution (increasing PH value). This is not conducive to cell survival, and it may even lead to cell death.

In order to use the hydrolysis reaction of magnesium as local hydrogen supply material, Wan et al. [19] try to use the poly (lactic-co-glycolic acid)(PLGA) coated on the outside of magnesium particles to block the contact between water and

magnesium, thus reducing the rate of hydrogen release. This method successfully solves the problem that the rate of hydrogen release is too fast and not controllable in the initial stage of the reaction. However, the problem of solution alkalization still exists with the reaction, and further, the amount of hydrogen release of the materials system needs to be further improved.

In view of these problems above, this paper puts forward a way of preparing local, slow and sustained hydrogen-release medical material based on magnesium hydride. Moreover, the preparation process and influencing factors of the materials are investigated, and the influence and the law the configuration of the material system have on the reaction of hydrogen release are analyzed and discussed, in order to provide a safe and reliable hydrogen supplier for local anti-inflammation.

2. Materials and Methods.

2.1 Idea

An ideal local hydrogen supply medical material should have the highest possible hydrogen release amount and a controllable hydrogen release speed. Magnesium is a potential hydrogen storage material with up to 7.6% theoretical hydrogen storage capacity which ranks the third only after lithium and aluminum among metal. Magnesium hydride, the product of Mg after storing hydrogen, will undoubtedly improve hydrogen release capacity of the system while retaining all the advantages of magnesium metal as a biomedical material. Therefore, magnesium hydride is proposed as the hydrogen supply material. The stability of magnesium hydride is higher than that of magnesium, so it is necessary to react with acid solution to release hydrogen. Citric acid is a weak organic acid, which is often used as food additive and is safe for human body. Therefore, citric acid is used to react with magnesium hydride in the experiment. The chemical reaction formula is as follows:

$$3MgH_2 + 2C_3H_4(OH)(COOH)_3 = 6\,H_2 + Mg_3[C_3H_4(O\,H)(COO)_3] \quad (2)$$

Compared with the hydrolysis reaction of magnesium (1), it can be seen that the amount of hydrogen released by magnesium hydride increases by 2 times with reactants of the same mass.

To control the reaction rate between magnesium hydride and citric acid, magnesium hydride particles were coated with poly(lactic-co-glycolic acid) (PLGA) to block the contact between magnesium hydride and citric acid. With the continuous infiltration of citric acid solution, magnesium hydride and citric acid react gradually and continuously to achieve the purpose of slow release of hydrogen. Citric acid can also neutralize $Mg(OH)_2$ and regulate the PH value of solution to avoid the adverse

effects of alkalization. PLGA is a kind of slow-releasing drug carrier commonly used in the field of medicine. Its degradation products are lactic acid and hydroxyacetic acid, which are also by-products of human metabolism, so PLGA is safe for human body and has no toxic side effects. In order to further control the hydrogen release rate, a certain proportion of citric acid particles can also be coated to delay the reaction between partial magnesium hydride and citric acid, thus obtaining different hydrogen release rates. Therefore, the influence and law of material system configuration (reactants in coating and their ratio) on hydrogen release will be studied.

To achieve PLGA coating of magnesium hydride or citric acid, the current preparation of drug micro-particles is usually done by magnetic stirring; recently developed microfluidic techniques have shown great superiority in the preparation of emulsions or micro-particles with good dispersivity and controllable particle size and morphology, attracting great attention. However, the study of micro-fluidic micro-particles has just started and the technology is not well developed. In this work, PLGA coated magnesium hydride or citric acid micro-particles will be prepared by both microfluidic technology and magnetic stirring. The suitable preparation process and influence factors will be investigated, and the effects on the morphology and quality of micro-particles will be compared and analyzed.

2.2 Materials

The sources and specifications of the raw materials used in the experiment are shown in Table 1. The solid powder was weighed by ZA120.4 analytical balance with accuracy of 0.1 mg, and the liquid was measured by glass measuring tube with the capacity volume of 10 ml.

Table 1. The and specifications of the raw materials used in the experiment

Raw Materials	Source	Specification
MgH_2	Shanghai Jinjin Le Industrial Co. Ltd	Particle size 800 mesh，purity≥98.0%
Poly(lactic-co-glycolic acid) (PLGA)	Shanghai Yuanye Biotechnology Co. Ltd	Molecular weight 10k~20k，PLGA75：25
Dichloromethane (DCM)	Shanghai Aladdin Biochemical Technology Co., Ltd	Chromatographic level，purity≥99.9%
Poly(vinyl alcohol) (PVA)	Shanghai Aladdin Biochemical Technology Co., Ltd	Alcoholization 87.0~89.0(mol/mol), CPS 4.6-5.4
Citric acid	Shanghai Aladdin Biochemical Technology Co., Ltd	Analytical reagent，purity≥99.5%

2.3 Preparation of coated micro-particles

The basic idea of micro-particles preparation is to employ the immiscibility properties of water phase and oil phase, to first disperse MgH_2 solid powder in oil solution of PLGA in DCM (oil phase), that is, wrap it in PLGA, and then, oil phase are 'sheared' by PVA aqueous solution (water phase) to form a single-emulsion droplets in water phase. When all the solvent volatilizes, the PLGA coated MgH_2 micro-particles (MgH_2@PLGA) can be made.

The device for preparing micro-particles by micro-fluidic technology is shown in figure 1, mainly includes injection pump (XF-101PD), syringe, micro-channel, capillary and collection beaker. Among them, Micro-channel is T-junction channel, which is made of glass. The chip structure and size of the channel is shown in Figure 1(b). The capillary is made of PTFE, a size of 0.8 mm inner diameter *1.6 mm outer diameter. The syringe is made of polypropylene, a capacity volume of 20 ml. In the experiment, water and oil phases are pushed into the channel from the syringes by adjusting the pressure of the injection pump. At the intersection of T channels, the oil phase is subjected to shearing and compression of the water phase from both sides, together with the squeezing from the channel at the neck, becoming dispersed emulsion droplets, sequentially going through the micro-channels, and finally collected in the beaker. To prevent the accumulation of droplets, the collected emulsions were subjected to magnetic stirring, at a speed of 1000 rpm / min; Similarly, For the purpose of preventing the accumulation and precipitation of MgH_2 powder particles in the oil phase syringe, the oil phase injection pump was slightly flipped and oscillated every 5 minutes.

In the experiment, the volume ratio of water to oil is adjusted in the range of 1:0.1~1:0.02. Flow velocity ratio between water and oil is adjusted in the range of 4:1~2:1. The amount of DCM is adjusted, according to the amount of PLGA, within 10~40 mg mL^{-1}. The amount of PLGA is determined by the amount of MgH_2 / citric acid solid powder needed for the reaction. According to dispersion, the concentration of MgH_2 powder was determined to be 5 mg mL^{-1}. The concentration of PVA aqueous solution was determined to be 5%. After a large amount of experiments, the optimum processing parameters for the stable preparation of the micro-particles are determined as follows: volume ratio of water phase to oil phase 1：0.1, water phase flow velocity 100 uL/min, oil phase flow velocity 25uL/min, ratio of water to oil flow velocity 4:1, DCM additive amount 20 mg mL^{-1}.

After the emulsion was prepared, the micro-channel was cleaned by DCM for half an hour immediately, and then the glass chip was heated in a tube furnace to let the PLGA adhered to the channel wall completely evaporate. The heating parameters

are as follows: Heating from room temperature to 350℃, the rate is about 3.3℃/ min, and holding for 15 minutes at a temperature interval of 50℃. When the temperature rises to 350℃, it is kept for 6 hours and then cooled to room temperature with the furnace.

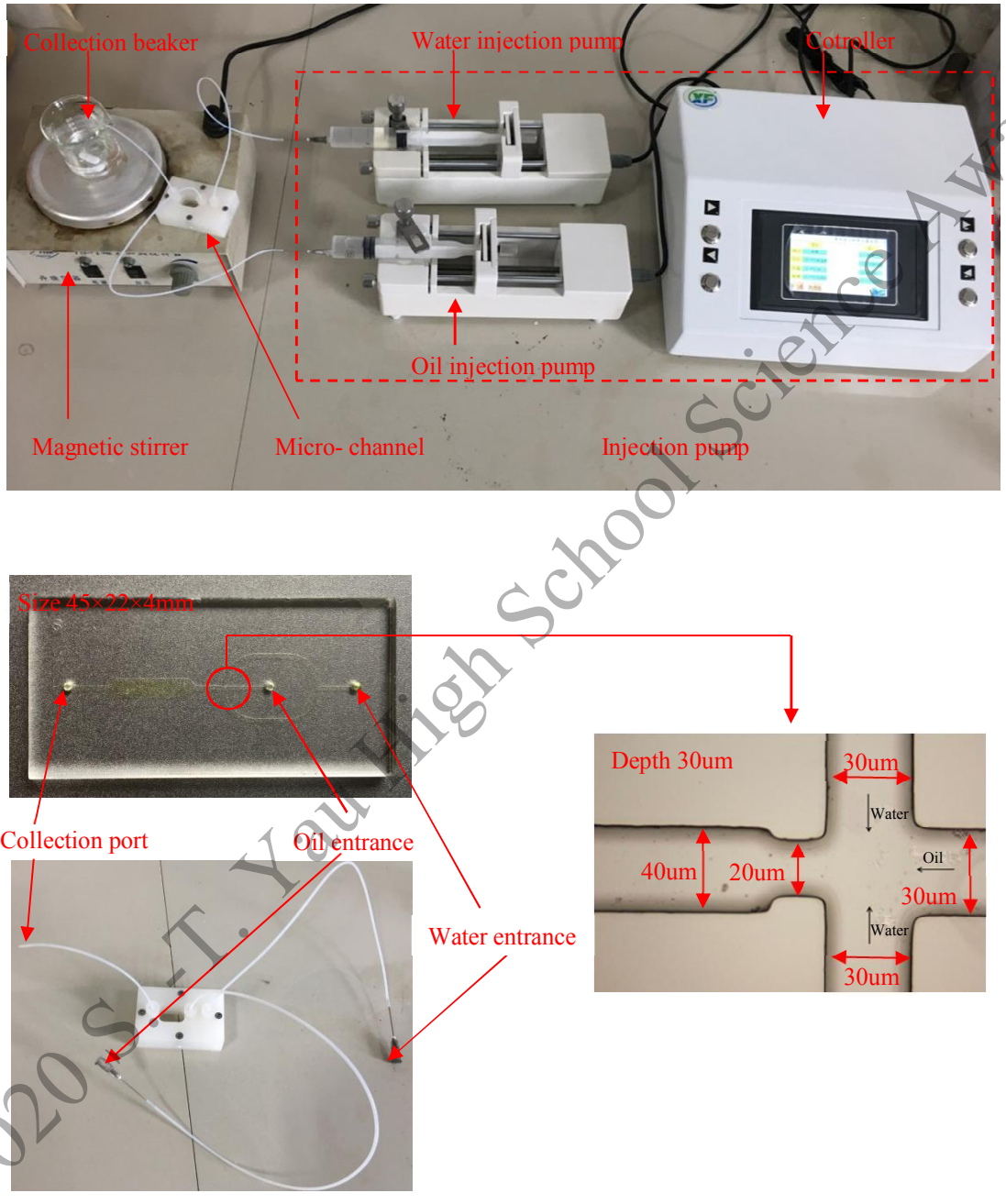

Figure 1. Microfluidic system for preparation micro-particles. a) Composition of the microfluidic system; b) Chip structure and size of the T-junction channel

In the experiment of preparing micro-particles by magnetic stirring, the water phase was stirred by Than Rui 78-1 magnetic stirrer. At the same time, the oil phase

was sucked by syringe and dripped into the water phase while oscillating. The Formulation of water and oil phases is consistent with the optimum parameters determined by the microfluidics method.

The emulsified micro-particles obtained from the experimental were magnetically stirred for 4-5 hours at room temperature. After DCM fully evaporated, the materials was filtrated by filter paper, and then dried to collect the powder, which is washed later with deionized water. After the PVA outside the micro-particles were fully removed, they were filtered and dried again, and finally the targeting micro-particles powder was obtained.

2.4 Morphology characterization

To know the morphology and quality of MgH_2@PLGA micro-particles under different preparation conditions, and to explore the process and mechanism of hydrogen-release reaction between MgH_2@PLGA micro-particles and citric acid, powder samples under different conditions were observed and analyzed by Neophot 30 optical microscope (OM) and Quattro S scanning electron microscope (SEM).

In the observation using OM, a small amount of powder was placed in distilled water, stirred with glass rod. Then the solution was dripped onto the slide. Afterwards, the covering glass was placed and the excess liquid around the cover glass was sucked by filter paper. The glass slide containing the sample was placed on the sample holder of the optical microscope and the reflector is covered before sample observation.

In the observation using SEM, a small amount of powder was placed in alcohol, shaken by ultrasonic cleaning machine for 5 min. Then a small amount of solution was dripped on the surface of a single crystal Si slide. Afterwards, the surface of Si slide was gently dried with ear washing ball. Finally, it is placed in the sample room for observation.

To explore the process and mechanism of hydrogen release in the reaction between MgH_2@PLGA micro-particles with citric acid, the samples during the reaction were taken for sample preparation and SEM observation. A small amount of MgH_2@PLGA powder dissolved in distilled water was shaken with ultrasonic cleaning machine for 5 min, and then added with an appropriate amount of citric acid powder. Afterwards, an appropriate amount of alcohol was added to the reaction solution to promote sample drying. After a certain degree of reaction occurring, a small amount of mixture was dripped on the surface of a single crystal Si slide and dried overnight before observation in the sample room of SEM.

2.5 Measurement of hydrogen-release amount and solution PH value

To study the effect PLGA coated magnesium hydride particles have on delaying

the hydrogen release rate, and the influence of the ratio of coated reactants (magnesium hydride and citric acid) on hydrogen release rate and solution ph value of the system, experiments were conducted to test the evolution of hydrogen release and solution PH value during the reaction for three representative reaction systems. The compositions of the three reaction systems, named No.1, No.2 and No.3, are shown in Table 2. No.1 was the contrast group, free MgH_2 was used to react with citric acid, with a molar ratio 3:2. For No.2, MgH_2@PLGA was used to react with citric acid, with a molar ratio of MgH_2 to citric acid the same as that of No.1, 3 to 2. For No.3, MgH_2@PLGA micro-particle powder was still used, with the molar ratio of MgH_2 to citric acid remaining at 3:2, but a quarter of the citric acid was in the form of citric acid@PLGA micro-particle powder, and the remaining 3/4 of citric acid without the coating of PLGA. All three systems react in the same volume of deionized water, with concentrations of citric acid being 0.05 mol/l.

Table 2. Compositions of the three reaction systems

Group	Solid Phase	Liquid Phase（concentration）	MgH_2：Citric acid（molar ratio）
No.1	MgH_2	Citric acid aqueous（0.05mol/l）	3：2
No.2	MgH_2@PLGA	Citric acid aqueous（0.05mol/l）	3：2
No.3	MgH_2@PLGA、Citric acid@PLGA	Citric acid aqueous（0.375mol/l）	3：2

All three groups were reacted in 25 ml eggplant type flasks. The volume of hydrogen released from the reaction was measured by drainage method, and the PH value of the solution was continuously monitored by PH meter. The reaction and measurement devices are shown in Figure 2. Among them, the PH meter is the Mik-PH8.0 industrial PH meter; the capillary tube is made of material PTFE, with a size of 0.6 mm inner diameter * 1 mm outer diameter; the burette is a 50 acid one, with indexing value being 0.1 ml.

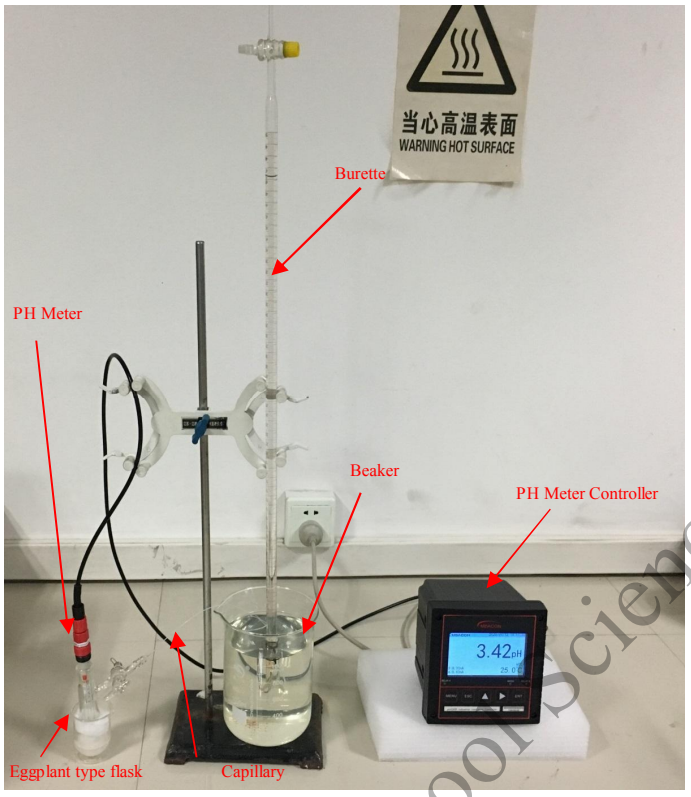

Figure 2. Reaction and measurement (for hydrogen-release amount and solution PH value) devices

3 Results

3.1 Morphology of as-prepared micro-particles

Figure 3 shows the morphology of the as-perepared micro-particles made by microfluidic system. According to figure 3 (a), which is taken under a scanning electron microscope (SEM) at a magnification of 500 times, the particles exhibit core-shell structures. That is to say, the particle has a black core with a white outer layer. They are MgH_2 particles coated by PLGA. Moreover, it can be seen that these particles are about the same size, averagely in the range of 15~20um. They gather in small clusters. These clusters spread out uniformly overall. More details can be obtained under a higher magnification of 5000 times, which is shown in 3 (b) and (c). It can be observed that the white particle has a rough surface, basically round-shaped, forming a core-shell structure. In addition, the PLGA coating is covering almost all MgH2 particles inside, with few narrow cracks on it.

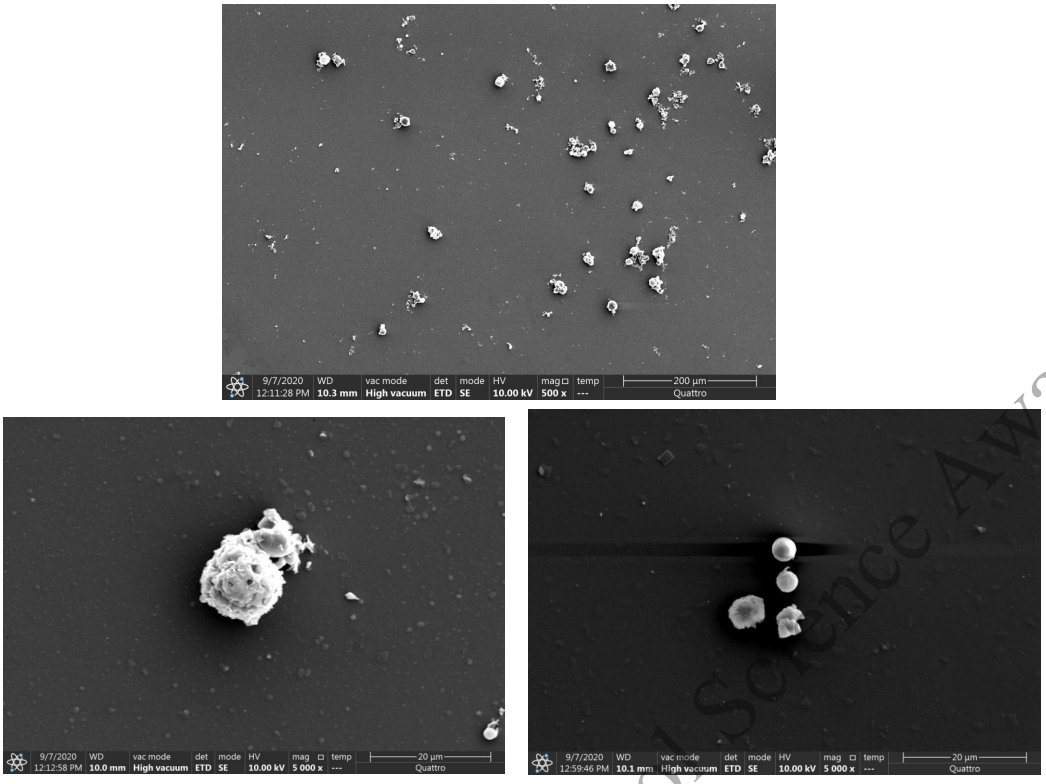

Figure 3. SEM morphologies of the as-perepared micro-particles

3.2 Morphology of as-reacted MgH_2@PLGA micro-particles

To sudy the hydrogen release reaction and its mechanism of MgH_2@PLGA with citric acid, the morphology of the micro-particles during the reaction was observed, as shown in Figure 4. it is interesting to note that, as the particle being eroded by the solution, its surface becomes more smooth, and it has a nearly regular ball-shape structure. With erosion by citric acid, as can be seen from figure 4 (c) and (d) , more cracks start to appear on them, which indicates that the PLGA coating starts to dissolve slowly into the water, thus allowing the infiltration of citric acid solution inside the particles to react with MgH_2.

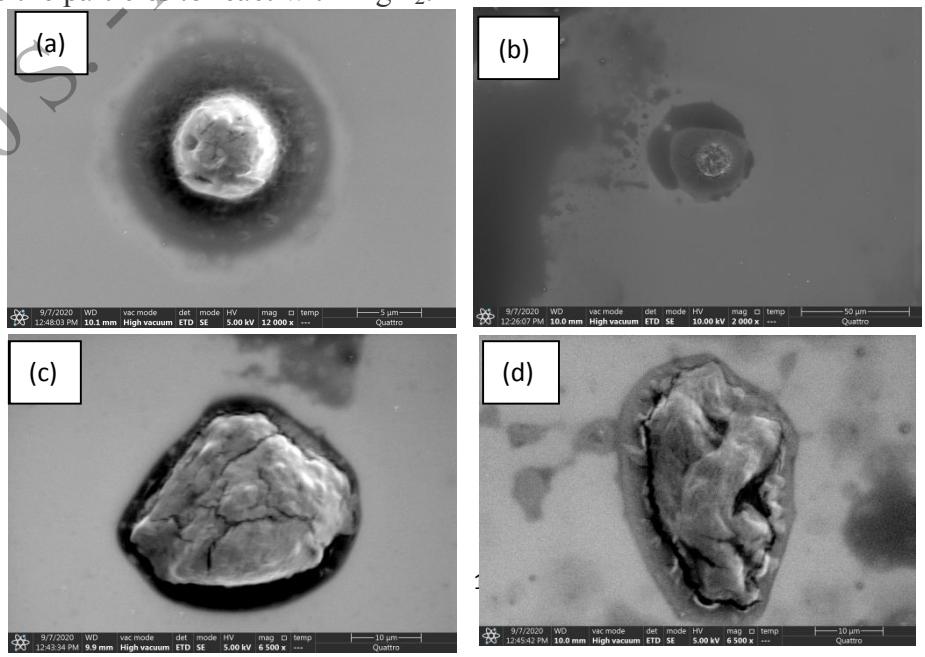

Figure 4. SEM morphologies of as-reacted MgH_2@PLGA micro-particles

3.3 Comparison of the micro-particles made by microfluidic system and magnetic stirring

Figure 5 is the morphology of the particles made by magnetic stirring, showing an irregular shape combined with uneven surface, whereas the micro-particles made by microfluidic system are much regular in shape comparatively (seen Figure 3). This difference can be clearly observed by optical microscope. From figure 6, we can see some particles of relatively similar size in a 200 times metallographic view. The size of the micro-particles obtained by magnetic stirring, on the other hand, has two scales. A large-scale particle can be observed at 200 times metallographic view with its size larger than that of the microfludic-made one. Small-scale particles can be observed at a 500 times magnification (Figure 7), where are hardly ever signs of microfludic-made particles. It should be mentioned that although the size of the micro-particles made by magnetic stirring is not homogenous, these particles of two different sizes may have the potential to help us adjust the rate of hydrogen release during practical application.

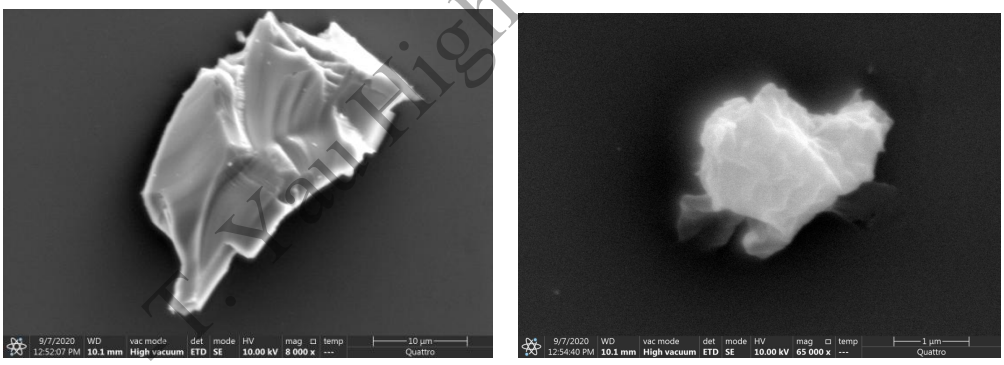

Figure 5. SEM morphologies of the micro-particles made by magnetic stirring

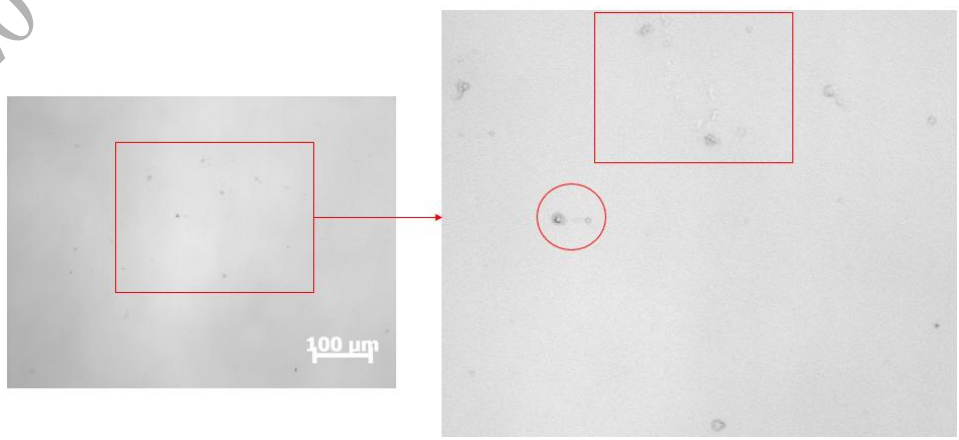

Figure 6. Optical microstructures of the micro-particles made by microfluidic system

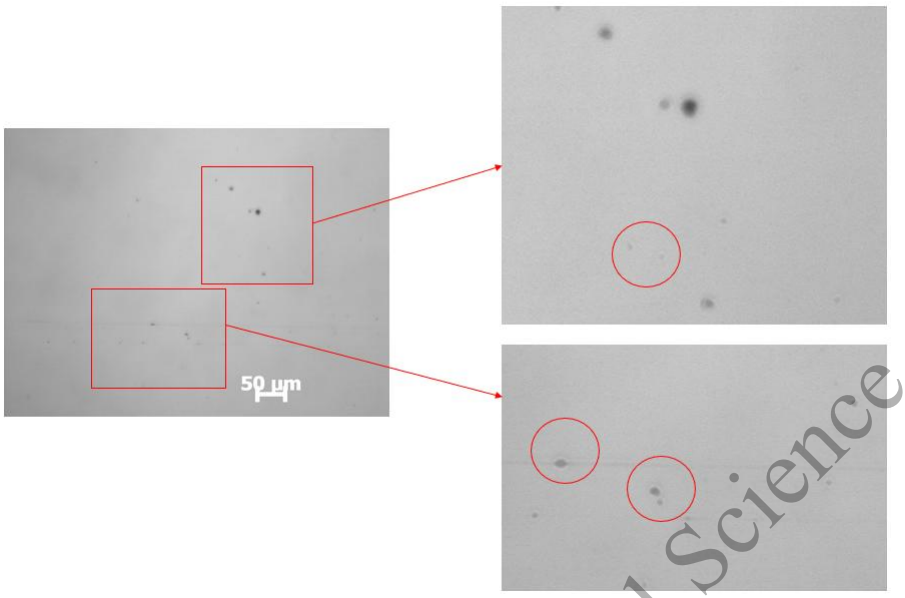

Figure 7. Optical microstructures of the micro-particles made by magnetic stirring

3.4 Evolution of hydrogen during reaction

The evolution of hydrogen released during the reaction for the three different reaction systems are shown in Figure 8 (a) and (b). It illustrates that, for the No.1 reaction system, 10 minutes after the experiment began, approximately 90.9% of hydrogen was released. In contrast, only 25.0% of the hydrogen was emitted even 20 minutes after the beginning of the No.2 experiment, showing a much lower rate of reaction. According to figure 8(b), 24 hours after the reaction took place in the No.2 experiment, 36.8% of hydrogen was released, indicating that the reaction was happening continuously in a slow rate. Comparing the No.1 and No.2 reaction systems, it is obvious that the PLGA coating of MgH2 has done a indispensable job in slowing down the rate of the reaction between MgH2 and citric acid.

Based on Figure 8(a), the No.3 experiment suggests that there are 23.2% of hydrogen emitted during the first 20 minutes of the reaction, which, in contrast with the second experiment, means that 1/4 of the PLGA-coated citric acid has slowed down the rate of the reaction. All curves from these three experimental systems show a relatively high slope in the initial stage of the reaction. This indicates that the uncoated citric acid from all three systems speeded up the speed of reaction. According to Figure 8(a), 2 hours from the beginning of the No.3 system, 45.2% of hydrogen is released, and then, the reaction took place in a relatively low speed. According to figure 8(b), during the first 14 hours of the No.3 system, approximately

58.1% of hydrogen is reacted, and afterwards, a sharp increase in the rate of the experiment appeared. 24 hours after the beginning of the No.3 system, 76.8% of hydrogen is released. In comparison among the three experiments, a sharp increase in the third one has created a distinctive contrast with the former two, suggesting a time when the PLGA coating of the 1/4 citric acid is dissolved, allowing MgH_2 to react with it. This phenomena means that the strategy of coatng a certain amount of citric acid in order to maintain a longer reaction time is achievable and realistic.

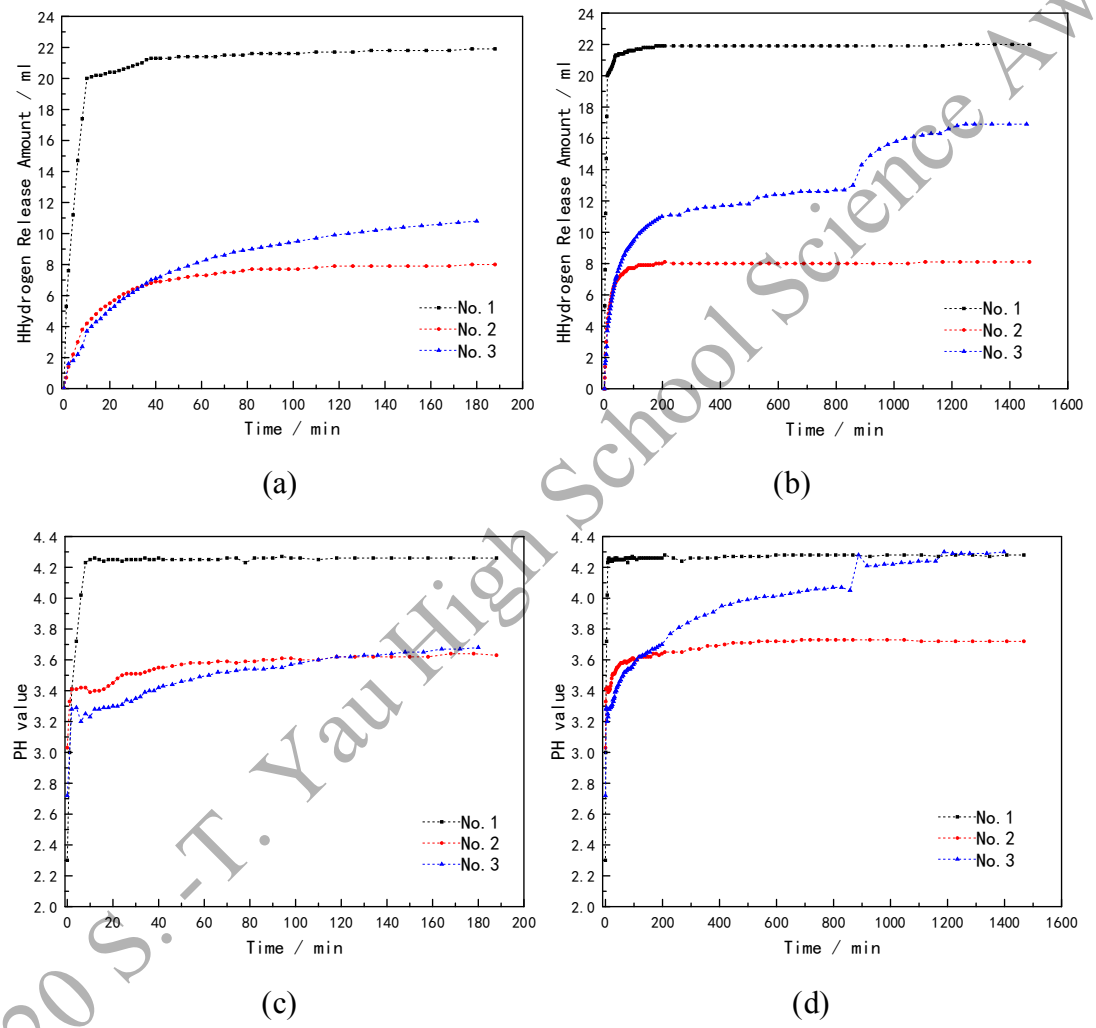

Figure 8. Variation of hydrogen release amount ((a) and (b)) and solution PH value ((c) and (d)) with reaction time for three different reaction systems。

3.5 Evolution of solution PH value during reaction

Our data on the PH value variation with to time of the three reaction systems is consistent with the data obtained on the amount of hydrogen released. According to Figure 8(c) and (d), the PH value of the No.1 system increased from ~ 2.7 to 4.25

within the first 10 minutes, and reached 4.28 within the first 24 hours. In contrast, the PH value of the No.2 and No.3systems increased from ~ 2.7 to 3.45 and from~≈ 2.7 to 3.3 within the first 20 minutes. The data also showed that the PH value of the No.2system reached 3.72 within the first 24 hours, and the third one reached 4.3. Within the first 2 hours of the reaction, the PH value of the No.3system reached 3.62. The sharp increase from the No.3 system took place from approximately 14 hours to 16 hours after the start of the reaction, when the PH value increased from ~ 4.10 to 4.22.

4 Discussions

4.1 Factors that influence the quality of micro-particles.

4.1.1 Shaking syringe to prevent the gathering of small particles inside

The solution we initially collected from microfluidic method contained a large number of small globules and large white flocculants, affecting the quality of the product. With the injection of oil phase and water phase from syringe into the micro-channel, the number of globules in the solution decreases and the number of flocculants increases. This is because of a large number of white flocculants near the wider buffer port of the chip in the micro-channel. This phenomena has led us to the conclusion that the MgH_2 and PLGA particles in the long stationary oil phase solution tend to converge gradually in the injection tube, causing unexpected white flocculants. In this way, it is essential to shake the oil-containing syringe five minutes a time in order to avoid the gathering of small particles inside the solution. Furthermore, because DCM is volatile, this phenomenon leads to the rapid decrease of solvents, and therefore causes the formation of large amounts of precipitates, leading to large white flocculants.

4.1.2 The influence of flow velocity on micro-particles

We initially set the water phase velocity to 40μL/min, and the oil phase velocity to 10μL/min. However, due to the high viscosity of particulate matter in the oil phase, the liquid can not be injected into the channel. When the flow rate of oil phase was tentatively increased to 20μL/min, there then appeared droplets of spherical objects in the micro-channel, intermittentely rather than continuously. In this way, the shear capacity of the water phase relative to the oil phase is weakened, and it contributes to the formation of large amount of white flocculents in the channel. The faster the oil phase flows, the high the productivity is, however, the poor product quality is. And vice versa, the faster the water phase flows, the smoothly the emulsion go through the

channel, but the low the productivity is. Further, combined with the formula of the oil phase, the optimum processing parameters can be achieved.

4.2 Materials of micro-channel —Why choose glass-based micro-channels rather than polymer-based ones

The basic manufacturing method of polymer-based micro-channels is to make the mold made of silicon die a micro-protruding shape by lithography and development. Then polymer materials are covered on the mold and solidified to form it. A traditional way is to use PDMS as this polymeric material. PDMS is a viscous liquid and has good adhesion with silicon wafer. The cured PDMS is viscous, soft, and elastic, so PDMS channels and cover plates can adsorb and bond with each other. Furthermore, the cured PDMS is hydrophobic and waterproof, thus ensuring that the subsequent flow of liquid into the channel does not leak. Besides, droplet formation can be observed because PDMS is transparent.

Several criteria which shows PDMS is suitable as a channel raw material can be summarized in the following. (a) It is liquid at room temperature and has good adhesion to silicon wafer ;(b) It is soft and elastic (cuttable) after curing and sticky; (c) Its curing material is hydrophobic, waterproof and transparent.

Nevertheless, due to the miscibility our chosen oil phase solvent DCM with PDMS, PDMS cannot be adopted as the raw material for micro-channels. Comparing the physiochemical properties of other potential materials, PDV and PTFE, to that of PDMS , neither of them is a suitable one.

PVC liquid is not transparent, and it can also be dissolved. At room temperature, the transparency of liquid PTFE is not ideal after curing by adding curing agent. Moreover, the cured PTFE is non-viscous, so the resulting channel and cover plate can not achieve effective bonding as PDMS (the method of PTFE bonding is usually special solution treatment or high temperature bonding, which may destroy the channel). Moreover, according to the physical properties of PTFE capillary, the solidified PTFE is hard and unfavorable to the channel assembly and connection. To sum up, PTFE may not be suitable as channel raw materials.

The preparation method to make glass mold is to shape the Cr-plated glass surface by lithography. The depressed photoresist channel morphology was formed on the glass surface after lithography. Furthermore, the glass-corroding agent was added to it to corrode the channel of a specific predetermined depth, and then the former glass was punched and bonded with covering glass at high temperature. Glass-based

micro-channels are hydrophobic, waterproof and transparent. Furthermore, its insolubility with PVA and DCM also contributes to our employment of it.

5 Conclusions

A magnesium hydride-based micro-composite material as a local sustained hydrogen supplier is fabricated and its hydrogen release properties are studied. The main conclusions are as follows:

1) A way of preparing local, slow, and sustained hydrogen-release medical material based on magnesium hydride is proposed.

2) PLGA-coated magnesium hydride micro-particles can effectively realize slow and sustained hydrogen release. For free magnesium hydride system, approximately 91% of hydrogen is released in 10 minutes; Comparatively, for the PLGA-coated magnesium hydride system, only ~37% of hydrogen is released in 24h. And further, by changing the ratio of coated reactants , the rate of hydrogen release and the PH value of the composite system can be effectively regulated.

3) The optimum processing parameters for preparation of the PLGA-coated micro-particles by microfluidic system are determined as follows: volume ratio of water phase to oil phase 1：0.1, water phase flow velocity 100 uL/min, oil phase flow velocity 25uL/min, ratio of water to oil flow velocity 4:1, DCM additive amount 20 mg mL^{-1}.

4) Coated micoro-particles made by microfluidic system are much regular in shape and about the same size of about 15~20 um. In contrast, the size of the micro-particles obtained by magnetic stirring has two scales, which may be utilized to regulate hydrogen release rate in application.

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