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NO tablet: autonomous generation of therapeutic nitric oxide in air through redox-promoted CO_2 adsorption

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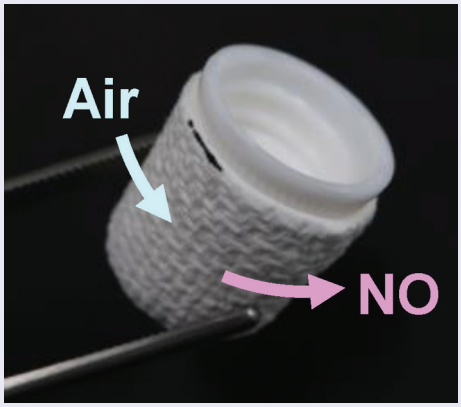
ABSTRACT

Inhaled nitric oxide (iNO) is a powerful therapy for the treatment of various cardiopulmonary and respiratory diseases. However, access to iNO therapy is often limited by the necessity of cumbersome gas tanks and/or elaborate gas blending apparatus. Here, we report a lightweight, inexpensive, and maintenance-free tablet that autonomously generates a therapeutic quantity of NO in air. The tablet is composed of a thimble filter paper containing a powdery mixture of nitrite (NO_2^-)-type layered double hydroxide (NLDH) and ascorbic acid loaded on silica gel ($AASiO_2$). NLDH by itself generates trace amounts of NO in the air due to the left-shifting of the protonation equilibrium of NO_2^- by aerial CO_2 and H_2O ($2[NO_2^-]_{LDH} + CO_2 + H_2O \rightleftharpoons 2HNO_2\uparrow + [CO_3^{2-}]_{LDH}$), which is followed by disproportionation of $2HNO_2$ to NO, NO_2 and H_2O. In contrast, it was found that the protonation equilibrium can be shifted to the right side when volatile acid products (HNO_2 and NO_2) are readily converted to neutral NO over the $AASiO_2$ reductant. Based on this, even a single tablet (containing 0.30 g NLDH and 0.90 g $AASiO_2$) generates 5 ~ 20 ppm NO at 0.5 L/min for 24 h, which is sufficient to be useful for the relief of severe hypoxia caused by persistent pulmonary hypertension of the newborn (PPHN). Moreover, the tablet can be activated by exhaled breath for high-dose iNO therapy (80 ~ 180 ppm for several hours), revealing its potential utility for treating viral pneumonia. The NO tablet can be stored stably over long periods at ambient temperature in a gas barrier bag and has the potential to break the logistical, financial, and operational barriers that have long existed for the widespread implementation of iNO therapy.



IMPACT STATEMENT

A lightweight, inexpensive, and maintenance-free tablet that generates a therapeutic quantity of NO gas in air opens up broad opportunities for treatment of various cardiopulmonary and respiratory diseases.

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KEYWORDS
Nitric oxide; medical device; critical care; layered double hydroxide; CO_2 adsorption; equilibrium shift

1. Introduction

Nitric oxide gas (NO) exhibits a wide range of beneficial physiological effects (e.g., as vasodilator, antioxidant, anti-inflammatory, anti-viral/anti-bacterial, platelet anti-aggregant, signal transducer), and its target delivery to the affected area is of crucial importance in medical applications [1–3]. Inhaled NO (iNO) vasodilates only ventilated regions of the lungs

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without causing a reduction in systemic blood pressure, thereby improving oxygenation of arterial blood and cardiopulmonary conditions [3–5]. Thus, iNO has been applied and tested for the treatment of different cardiopulmonary and respiratory diseases, such as persistent pulmonary hypertension of the newborns (PPHN), pulmonary hypertension crisis during cardiac surgery or lung transplantation operations, acute respiratory distress syndrome (ARDS), viral pneumonia (including COVID-19), chronic obstructive pulmonary disease (COPD), bronchitis, ischemia-reperfusion injury (IRI), cardiac arrest, etc. [3–8]. However, the widespread adoption of iNO therapy has been limited by the requirement of heavy gas storage tanks and/or elaborate gas blending apparatus (involving feedback controller and NO/NO_2 sensors), especially in developing countries and hospitals in remote areas [4,5]. For example, the incidence of severe PPHN is reported at 0.2% of live-born term infants, which results in a significant contribution to morbidity and mortality [9]. For further perspective, in the United States the average cost of 5 days of iNO for PPHN is about $14,000 [10]. To overcome these issues, several different approaches have been proposed for low-cost, on-site generation of NO, including pulsed discharge methods [10], electrochemistry [11], reducing agents [12], or porous materials [13].

Previously, we have reported NO-generating solid materials based on a layered double hydroxide (LDH) containing nitrite anions (NO_2^-) [14,15]. LDH is a clay mineral comprised cationic hydroxide layers $Mg^{II}_yM^{III}(OH)_{2(y+1)}$, where M^{II} and M^{III} are, respectively, divalent and trivalent metal cations (y is in the range of 2–4), with charge-balancing anions and H_2O incorporated in the interlayer spaces [16,17]. Interlayer anions are exchangeable not only at liquid–solid interface [18] but also at air-solid [14,19–21] and solid–solid [14,15,22] interfaces. Due to the strong affinity of LDH for carbonate anion (CO_3^{2-}) [23], the nitrite-type LDH (NLDH) generates HNO_2 vapor in air by a CO_2-driven protonation equilibrium:

$$2[NO_2^-]_{LDH} + CO_2 + H_2O \rightleftharpoons 2HNO_2\uparrow + [CO_3^{2-}]_{LDH}, \quad (1)$$

which is followed by disproportionation of HNO_2 according to:

$$2HNO_2 \rightarrow NO + NO_2 + H_2O \quad (2)$$

as shown schematically in Figure 1(b) [14]. However, since the acidity of HNO_2 (pK_a = 3.16) [24] is stronger than that of H_2CO_3 (pK_a = 3.6) and only 0.04% CO_2 exists in air, the protonation equilibrium lies in favor of the left-hand side of eq.1 and NLDH alone generates only trace amounts of NO (<0.5 ppm) in air. For this

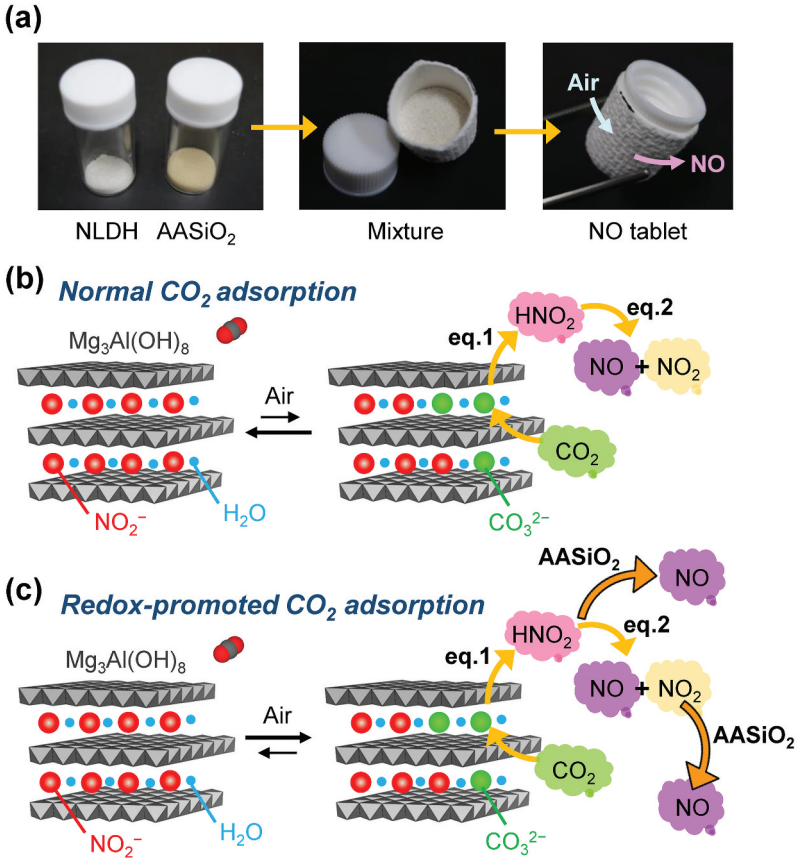

Figure 1. NO tablet and its reaction mechanism. (a) NO tablet prepared from a mixture of NLDH and $AASiO_2$ in a thimble filter paper (Φ_{inner} = 18 mm, L = 25 mm). (b,c) Schematic presentation of NO generation from NLDH through normal (b) and redox-promoted CO_2 adsorption (c).

reason, the generation of therapeutic levels of NO (5–20 ppm in breathed air) from NLDH requires a steady high level of CO_2 (e.g., 4%) to force the protonation equilibrium (eq.1) to the right-hand side. Another approach is to utilize a mixture of NLDH and iron(II) sulfate heptahydrate ($Fe^{II}(SO_4)\cdot 7H_2O$), in which a humidity-triggered solid-state anion exchange reaction occurs between NO_2^- (in the interlayer) and SO_4^{2-} (in the sulfate salt)

$$2[NO_2^-]_{LDH} + SO_4^{2-} \rightleftharpoons 2NO_2^- + [SO_4^{2-}]_{LDH} \quad (3)$$

with subsequent direct reaction of NO_2^- with Fe^{2+}

$$NO_2^- + Fe^{2+} + H_2O \rightarrow NO + Fe^{3+} + 2OH^- \quad (4)$$

as is also shown schematically in Figure S6 [14,15]. This solid-state anion exchange reaction occurs effectively only under high relative humidity (>90% RH) so that this system requires continuous feed of humid air. Thus, for application to iNO therapy, NLDH-based NO generators require consistent and elevated levels of either CO_2 or H_2O.

Here, we report a lightweight (thumb-size), inexpensive, and maintenance-free tablet that autonomously generates therapeutic NO when placed in ambient air (Figure 1(a)). The tablet comprises a powdery mixture of NLDH and ascorbic acid loaded on silica gel ($AASiO_2$). Although NLDH alone generates trace amounts of NO in ambient air due to left-shifting of its protonation equilibrium (eq.1) [14], the equilibrium can be drastically shifted to the right if volatile acid products (HNO_2 and NO_2) can be rapidly converted to neutral NO over $AASiO_2$ reductant [12] (in other words, if HNO_2 and NO_2 are actively eliminated from the equilibrium) (Figure 1(c)). The tablet can be stored safely in a gas barrier bag, and a single tablet (containing 0.30 g NLDH and 0.90 g $AASiO_2$) generates 5–20 ppm NO at an airflow of 0.5 L/min for 24 h, a rate which offers effective relief from severe hypoxia caused by PPHN. Moreover, exhaled breath can also activate the tablet for high-dose iNO therapy (80–180 ppm), revealing its potential utility for treating viral pneumonia [3,6]. We believe that the NO tablet treatment has great potential to relieve the logistical, financial, and operational barriers which have long existed to the widespread adoption of iNO therapy. It will be of particular benefit for home-based therapy, at hospitals in remote locations, for use in critical situations (e.g., emergencies, COVID-19, etc.), and in developing countries where important infrastructure is lacking.

2. Results and discussion

2.1. NO generation from NLDH-$AASiO_2$ mixture

NLDH was prepared by a two-step anion exchange reaction starting from carbonate-type LDH ($Mg_3Al(OH)_8(CO_3^{2-})_{0.5}\cdot 2H_2O$) by initial synthesis of chloride-type LDH ($Mg_3Al(OH)_8(Cl^-)\cdot 2H_2O$) according to our previous reports, with its chemical formula estimated to be $Mg_{3.1}Al(OH)_{8.2}(NO_2^-{}_{0.88}, NO_3^-{}_{0.04}, HCO_3^-{}_{0.17}, Cl^-{}_{0.10})\cdot 2H_2O$ involving 12.3 wt% NO_2^- as an NO source [14,15]. $AASiO_2$ was prepared using the modified procedure of Lovich et al. (see SI for details) [12]. Lovich and coworkers reported that ascorbic acid was activated when loaded onto silica gel, allowing NO_2 to be fully converted to NO over $AASiO_2$. This inspired us to combine NLDH and $AASiO_2$ to convert volatile acid products (HNO_2 and NO_2) from NLDH to NO, leading to a shift to the right-hand side of the CO_2-driven protonation equilibrium (eq.1). Thus, powdery NLDH and $AASiO_2$ were mixed with spatula (without grinding) in a glass bottle and then loaded in a thimble filter paper. After closing the thimble filter paper with a plastic cap (Figure 1(a)), the as-prepared tablets were located inside a plastic syringe with constant airflow (Figure 2(a)). First, we investigated the optimal mixing ratio of NLDH:$AASiO_2$ and found that NLDH:$AASiO_2$ = 1:2–1:3 (w/w) is optimal from the viewpoints of gaseous NO generation and total sample amount as shown in Figure 2(b) (at high ratios the sample weight is unreasonably large although NO generation increases only weakly). Thus, the mixing ratio has been fixed at 1:3 in the following experiments. As shown in Figures 2(c,d), respectively, the generated NO concentration is proportional to the number of NO tablets and inversely proportional to the flow rate, indicating that each tablet generates independently a similar quantity of NO. As expected from eq.1, CO_2 in air is indispensable for NO generation. The removal of CO_2 from the air led to the cessation of NO formation (Figure 2(e)). Under normal room conditions, NO generation is largely unaffected by temperature (Figure 2(f)) and humidity (Figure 2(g)), which is in contrast to the previously reported NLDH-$FeSO_4$ system, which only operates under high humidity (Figure S1) [14,15]. The tablet generates a small amount of NO under dry conditions (<5% RH) due to inefficient protonation of NO_2^- in NLDH (eq.1) (Figure 2(g)), which suggests stable preservation of the tablet under dry conditions. To prove this hypothesis, the tablet was dried well under vacuum at 60 °C for one day and then sealed in a gas-barrier bag together with a zeolite-type strong desiccant. The well-dried tablet recovers its NO generation capability in 2 h without significant change in NO generation (Figure 2(h)). Notably, the dry tablet can be preserved even at 60 °C for four weeks (Figure 2(i)), which corresponds to ca. 1-year preservation at room temperature (RT) (based on the Arrhenius-type acceleration model [25]). It is noted that the undried tablet is not preservable at 60 °C, undergoing severe deterioration even during 1 day (Figure S5). From 0.30 g of NLDH containing 0.80 mmol NO_2^-, 0.62 mmol of NO is generated in 3 days. Thus, it is estimated that 78% of NO_2^- is released as NO (Figure S2). During NO generation, the intensity of the infrared (IR) band due to NO_2^- in NLDH

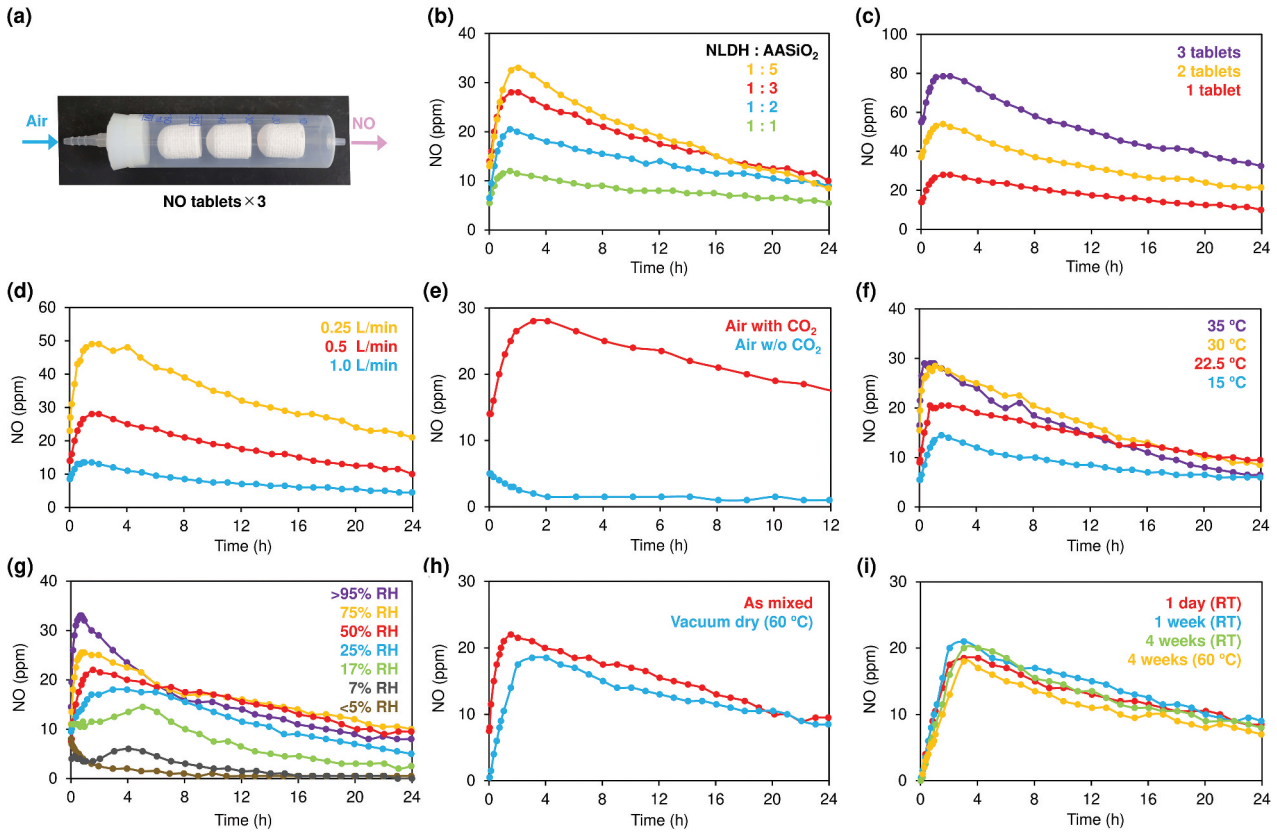

Figure 2. NO generation from a mixture of NLDH and $AASiO_2$. (a) Experimental set-up (three tablets located in a 60 mL plastic syringe (Φ_{inner} = 29 mm)). Effect of (b) mixing ratio, (c) number of tablets, (d) flow rate, (e) CO_2, (f) temperature, (g) humidity, (h) drying, and (i) preservation. NO concentration was monitored by an electrochemical sensor. Unless noted, one tablet containing as-mixed NLDH (0.30 g) and $AASiO_2$ (0.90 g) was tested at RT (22.5 ± 2.5 °C) under constant airflow (0.5 L/min, 50% RH).

was gradually attenuated with a concurrent increase in the intensity of IR bands due to CO_3^{2-} (Figure S4). Importantly, NLDH alone showed no apparent change in its IR spectrum. Thus, these results support that CO_2 adsorption by NLDH is promoted by proximal $AASiO_2$, leading to greater NO generation.

2.2. Activation of the dry tablet by H_2O and CO_2

When the dry tablet was wrapped in wet tissue for 3 min, NO generation was initiated immediately (Figure 3(a), Figure S7), enabling the possibility of prompt supply of iNO therapy to patients. We also tested exhaled breath (containing ca. 4% CO_2 and 100% RH) for activation of the dry tablet (Figure 3(b)). Although it takes ca. 30 min to fully activate the NO tablet, a high concentration of NO (80–180 ppm) could be generated for several hours. Recently, Chandrawati and coworkers reported a mask-type wearable device for low-dose iNO therapy by using a mixture of $NaNO_2$-embedded nanoparticles and pure water containing lemon juice and sucrose solution [26]. The disposable device will be beneficial for use in developing countries and at sites remote from hospitals. When installed on a mask-type device, our tablet will offer low- and high-dose iNO therapy depending on the activation mode. On the one hand, in Figure 3(c), the tablet is exposed only to air, leading to the long-term delivery of low-concentration NO gas (as shown in Figure 3(a)). On the other hand, in Figure 3(d), the tablet is continuously exposed to exhaled breath, leading to short-term delivery of high-concentration NO gas (as shown in Figure 3(b)). We anticipate that the former device (low-dose) will be useful for relaxation of chronic cardiopulmonary diseases such as chronic obstructive pulmonary disease (COPD) [8], and the latter device (high-dose) will be useful for anti-viral/bacterial application including airway sterilization and improving oxygenation of arterial blood [3,6].

2.3. Control of NO concentration

NO concentration can be controlled according to relative humidity (RH) or CO_2 levels in the airflow feed, while response time and variable NO concentration are in a reasonable range (Figure 4(a,b)). Some delays in response (~10 min) are presumably due to limited diffusion of feed air through the thimble filter paper and slow adsorption/desorption of H_2O/CO_2 from NLDH-$AASiO_2$. More precise and prompt control could be

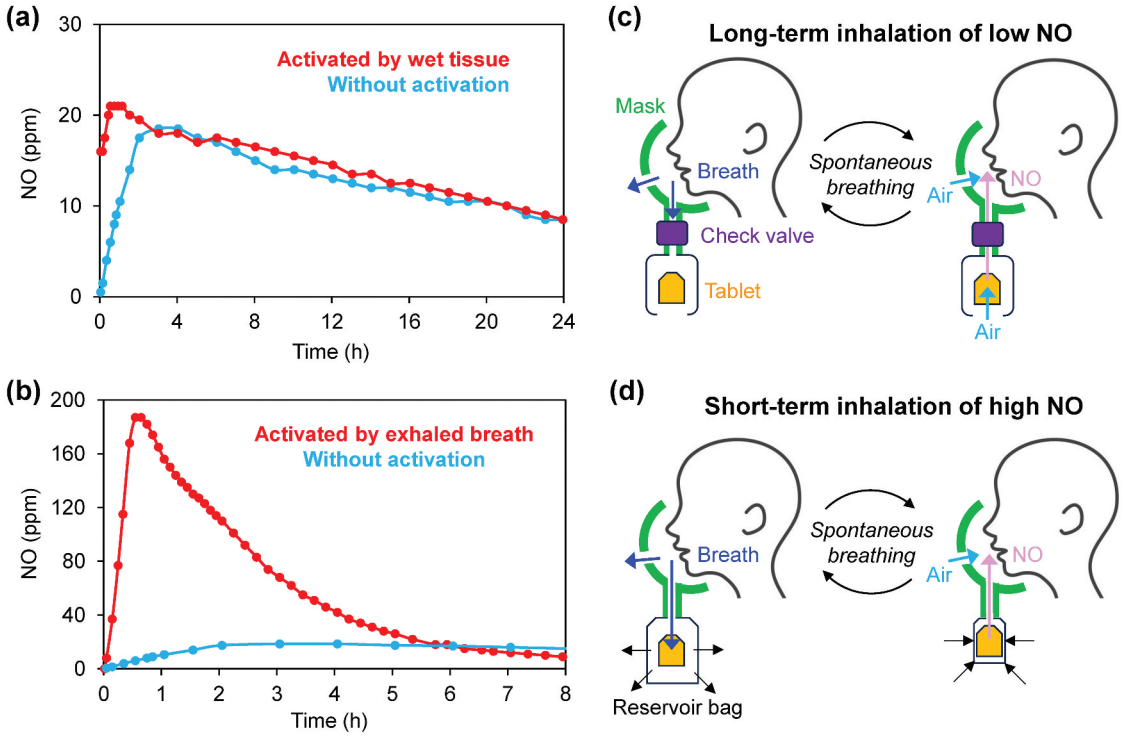

Figure 3. Activation of the dry tablet. (a) NO generation from a single dry tablet after wrapping in wet tissue for 3 min. After removing the wet tissue, the experiment was performed under airflow (0.5 L/min, 50% RH). (b) NO generation from a single dry tablet under exhaled breath flow (0.5 L/min). Proposed mask-type devices for (c) low-dose and (d) high-dose NO gas inhalation.

achieved when excess NO was removed by an activated carbon adsorbent, followed by NO dilution using the NO-depleted air (Figure 4(c)). By adjusting the flow rate of the two lines (with and without activated carbon), the NO concentration was stabilized within 1 min.

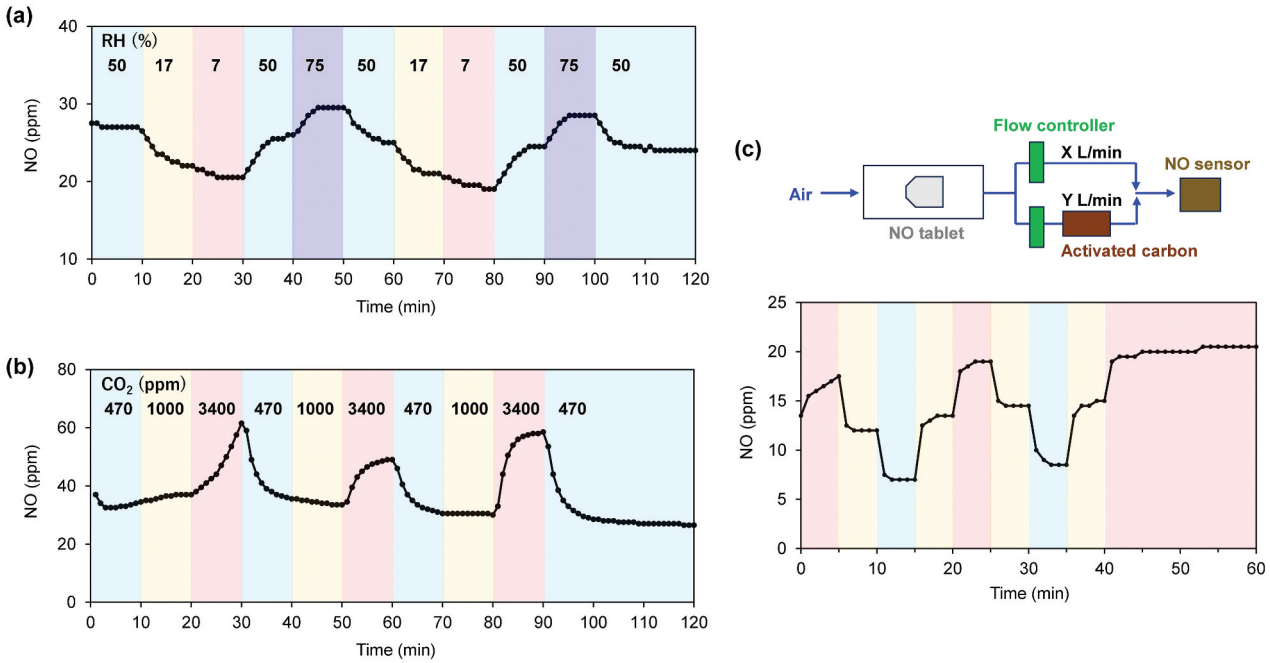

Figure 4. Control of NO concentration. Control of NO concentration by (a) RH and (b) CO_2 concentration. (c) Control of NO concentration by partial removal of NO with activated carbon adsorbent (6.0 g). Red (X = 0.5 L/min, Y = 0 L/min), yellow (X = 0.33 L/min, Y = 0.17 L/min), and blue region (X = 0.17 L/min, Y = 0.33 L/min) denote variation of flow rate in upper and bottom lines. A single dry tablet activated by wet tissue wrapping was used. Unless noted otherwise, experiments were performed at RT (22.5 ± 2.5 °C) under airflow (0.5 L/min, RH = 50%, CO_2 = ca. 470 ppm).

2.4. Analysis of NO and NO_2 gases

In addition to the electrochemical sensor used above, NO generation was confirmed by other analytical methods, including chemiluminescence and selective detector tubes. As shown in Figure 5(a), the chemiluminescence reaction ($NO + O_3 \rightarrow NO_2 + O_2 + h\nu$), which is fully selective to NO over other NO_x, is consistent with the result obtained by the electrochemical sensor. Moreover, the detector tube for separate analysis of NO and NO_2 (GASTEC No. 10) indicates a color change only for NO (ca. 20 ppm), with NO_2 concentration being below the detection limit (<0.5 ppm) (Figure 5(b)). After a precise analysis of NO_2 by a different type of detector tube (GASTEC No. 9P), it was found that NO_2 was present at only 0.025 ppm, which is similar to atmospheric levels and much lower than the permissible level of NO_2 (1 ppm) determined by the Occupational Safety and Health Administration (OSHA) [27].

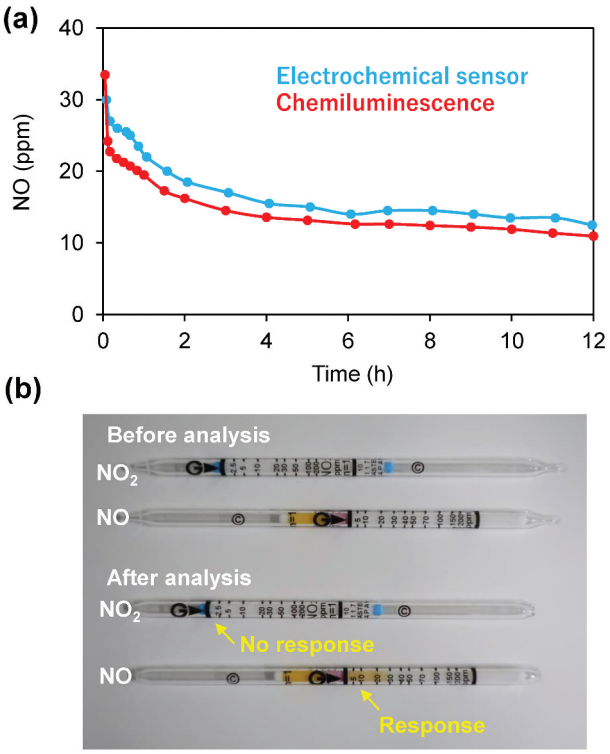

Figure 5. Analyses of NO gas. (a) Comparison of electrochemical and chemiluminescence analyses of NO generated from a single dry tablet (activated by wet tissue) under airflow (0.5 L/min, 50% RH). Note that NO_2 levels are consistently below the detection limit of the electrochemical sensors (< 0.5 ppm). (b) Analysis of NO by detector tube (GASTEC No. 10). The detector tube for NO_2 is based on the formation of nitroso-*o*-tolidine from NO_2 and *o*-tolidine. The detector tube for NO is based on the formation of NO_2 from NO and Cr^{6+}, followed by the detection of NO_2 by *o*-tolidine. Two detector tubes are connected in series, and NO is monitored after NO_2.

3. Conclusions

A tablet containing a powdery mixture of NLDH and $AASiO_2$ exhibits autonomous generation of NO gas in ambient air based on a redox-promoted CO_2 adsorption reaction. The tablet is lightweight, inexpensive, and readily available for NO inhalation therapy. The dose of NO can be controlled by selecting the number of tablets used and the activation mode, and even a single tablet provides sufficient NO to be useful for relief of severe hypoxia due to PPHN. Further improvements of the tablet are possible, including by optimizing the morphological and chemical characteristics of the NLDH used (e.g., particle size, Mg/Al ratio, reaction temperature, decarbonization method [15], drying conditions, pH, solvent used, other additives, and surface functionalization), the properties of $AASiO_2$ used (e.g., loading amount of AA, particle size, water content, other reducing agents, inorganic carrier), and the filter container (e.g., size, shape, breathability). This is currently underway in our laboratory. We believe this NO tablet has strong potential to break the logistical, financial, and operational barriers which have long existed to the widespread adoption of iNO therapy, revealing the true power of NO gas for the treatment of acute and chronic cardiopulmonary and respiratory diseases.

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Disclosure statement

NIMS filed a patent on the NLDH-based NO generator and iNO system.

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Supporting information

The Supporting Information is available for materials, methods, NO generation data, IR study, and miscellaneous data.

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