ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Tamper-Proof Time–Temperature Indicator for Inspecting Ultracold Supply Chain

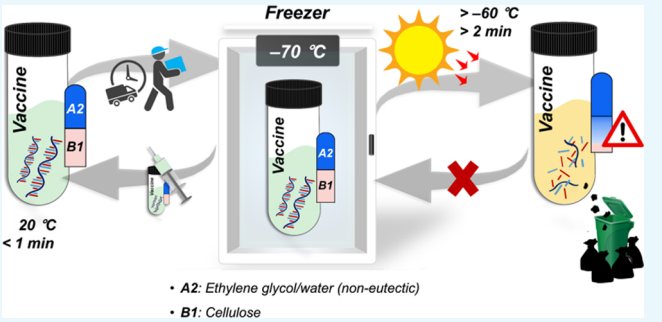
Lam Tan Hao, Minkyung Lee, Hyeonyeol Jeon, Jun Mo Koo, Sung Yeon Hwang,* Dongyeop X. Oh,* and Jeyoung Park*

Cite This: *ACS Omega* 2021, 6, 8598–8604

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: In the precarious situation caused by the COVID-19 pandemic, the use of messenger ribonucleic acid (mRNA) vaccines is promising for prevention against the infection. However, this type of vaccine has not been effectively commercialized because it needs to be stored and transported at ultracold conditions. mRNA vaccines exposed to undesired temperatures may not show any visible changes but can deteriorate and cause negative effects. Consumers' demand for vaccine authenticity requires logistics to develop a robust monitoring tool to ensure the integrity of ultracold supply chain from manufacturing until vaccination. Here, we report a time–temperature indicator (TTI) that can detect a relatively small change in temperature within subzero ranges, for example, from −70 to −60 °C, which cannot be achieved by current TTIs operating at room temperature. A dyed noneutectic ethylene glycol/water mixture that melts near the mRNA conservation temperature (−69 °C) diffuses into a white absorbent and leaves a colored trace. In addition, the heterogeneous ice particles in the noneutectic mobile phase can prevent absorption during short-term exposure to room temperature. Therefore, the proposed TTI will not record inevitable "meaningless" short-term exposure to room temperature during the cold supply chain but monitor the "meaningful" relatively long-term exposure above −60 °C. These findings help facilitate the safe distribution of the COVID-19 mRNA vaccines.



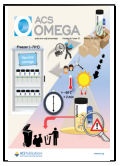
INTRODUCTION

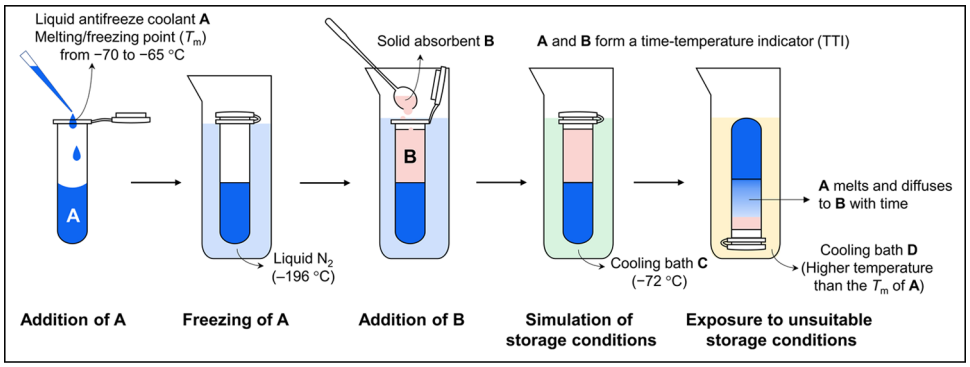
The coronavirus pandemic (COVID-19) has led to drastic human life loss and devastating economic consequences.[1] The urgent need for vaccines prompted an international response; more than 120 vaccine candidates have been developed within five months of the pandemic. Among them, messenger ribonucleic acid (mRNA) vaccines developed by Pfizer-BioNTech and Moderna have emerged as the frontrunners because they offer the highest preventive effect of >95%.[2]

However, mRNA vaccines are highly unstable because RNA molecules are hydrolyzed at ambient temperatures, thus limiting their commercialization.[3] While conventional vaccines can be stored in refrigerators at 2−8 °C, the two mRNA vaccines must be kept at subzero temperatures. After manufacturing, the Pfizer-BioNTech vaccine must be frozen at −70 °C and Moderna at −20 °C for up to six months during the distribution until the end use. Thawed vaccines are stable for 2 h at room temperature during dilution for vaccination, but once thawed or diluted, they cannot be refrozen for continuous shipping according to the current regulatory standards.[4] Moreover, when kept outside of the prescribed temperature/time combinations, the vaccines can be degraded. Vaccination of impotent vaccines provides no protection against the disease and may result in serious side effects. This will eventually cause mistrust in the prevention strategies adopted worldwide. Therefore, there is an urgent need to identify and discard mRNA vaccines that were exposed to and thawed at undesired temperatures at least once, ensuring the delivery of only licensure, originally frozen vaccines to end users.

A time–temperature indicator (TTI) is a simple and smart device that records thermal history.[5] TTIs irreversibly respond to temperature and indicate the exposure time of perishable products and drugs at undesirable temperatures, generally room temperature.[6,7] Many TTIs have been developed and commercialized based on different working principles. Chemical and biochemical TTIs change color based on reactions of small molecules or catalyzed by microorganism enzymes, respectively.[5] However, as heat is generally required

Received: January 22, 2021
Accepted: February 26, 2021
Published: March 11, 2021





• Coolant **A**

Code	T_m (°C)	Components
A1*	−69	EG/water (68:32 v/v)
A2*	−69	EG/water (40:60 v/v)
A3	−70	EtOH/water (80:20 w/w)
A4	−65	EtOH/water (77.5:22.5 w/w)

*A1: eutectic mixture (single-phase melting)
*A2: non-eutectic mixture (double-phase melting)

• Cooling bath **C/D**

Code	T_m (°C)	Components
C	−72	MeOH/water (69:31) with dry ice
D1	−60	MeOH/water (62.5:37.5) with dry ice
D2	−40	MeOH/water (50:50) with dry ice
D3	0	Ice water
D4	20	Room temperature

• Absorbent **B**: **B1**: cellulose powder, **B2**: SAP powder

Figure 1. Experimental design of the proposed diffusion-based TTI at subzero temperatures.

for the reactions, these types of TTIs usually respond to high-temperature ranges[5,8] and thus are not suitable for vaccines that can be sensitive to exposure within subzero ranges. In addition, potential health risks associated with compounds or microorganisms used in these TTIs remain concerning.[5,6] Although new TTI technologies, such as those based on self-healing materials,[6] are still being developed, physical diffusion-based TTIs can offer several considerable benefits. Their working principle is simply based on the diffusion of a colored compound through a substance with increasing time/temperature, leaving a colored trace that can be easily detected.[5,8] Moreover, they can operate at low-temperature spans,[8] which is suitable for pharmaceutical products like vaccines. Unfortunately, the use of TTIs for monitoring storage and distribution at subzero temperatures as low as −70 °C has not been reported because the supply chain for mRNA vaccines is a completely new logistic challenge for health care systems. If the temperature of mRNA vaccines is elevated only from −70 to −60 °C for a long time, the vaccines are apparently intact but can lose their function.[9] As the relentless COVID-19 pandemic necessitates the commercialization of mRNA vaccines, a TTI that can sense a relatively small temperature change of 10−20 °C elevation from the required −70 °C is necessary to securely distribute the mRNA vaccines on a global scale, including developing countries with relatively poor cold supply chain systems.

Herein, we report a tamper-proof TTI that can monitor the integrity of ultracold supply chain. The subzero TTI consists of a color mobile phase and a white stationary phase. The color mobile phase is a noneutectic ethylene glycol (EG)/water mixture with a melting temperature (T_m) of −69 °C. At temperatures above its T_m, the melted mobile phase diffuses into the white absorbent and leaves an easily detectable color trace. The TTI is tamper-proof because the diffusion process is irreversible. The noneutectic melt system contains heterogeneous ice particles, which effectively prevents the permeation of the absorbent for a short time when exposed to room temperature. Thus, this TTI does not record "meaningless" inevitable short-term exposure (<1 min) at room temperature in the cold supply chain (e.g., transfer of a vaccine from a shipper to a freezer or vice versa) but instead monitors the "meaningful" relatively long-term exposure (>2−5 min) above −60 °C.

RESULTS AND DISCUSSION

First, it is important to design an appropriate experimental setup to effectively carry out the diffusion experiment conducted at ultracold temperatures (Figure 1). A cylinder-type 2 mL tube containing 1 mL of a dyed coolant was frozen in liquid nitrogen (−196 °C). After the coolant was completely frozen, the upper cap of the tube was opened and a white solid absorbent was filled. Then, the tube was moved to a new cooling bath (−72 °C), barely maintaining the solid state, which was then ready to be exposed to temperatures higher than the T_m of the coolant. The TTI performance was investigated by inverting the tube inside the cooling bath at testing temperatures (from −60 to 20 °C) to induce gravitational diffusion of the liquefied coolant.

Second, a suitable coolant was chosen considering its T_m, phase-change mode, and viscosity. A mixture of EG and water, which is used as a coolant in automobiles, is a good candidate for the subzero TTI because of the following reasons: (1) the eutectic composition has a low T_m of −69 °C, (2) other noneutectic compositions consist of both ice and liquid above T_m and thus are expected to adjust the diffusion rate, (3) the relatively high viscosity of EG does not hastily change the TTI performance, and (4) the components are universal and accessible.

A series of subzero TTIs consists of a coolant (dyed mobile phase) denoted as "**A**" and an absorbent (stationary phase) denoted as "**B**." At temperatures above the T_m, the coolant diffuses into the absorbent due to the absorption force. The coolant was a binary mixture of organic solvent/water, and its T_m can be controlled by varying the ratio of the mixture component. **A1** and **A2** are EG/water mixtures with an analogous T_m of −69 °C. However, **A1** is a eutectic mixture

https://dx.doi.org/10.1021/acsomega.1c00404
ACS Omega 2021, 6, 8598−8604

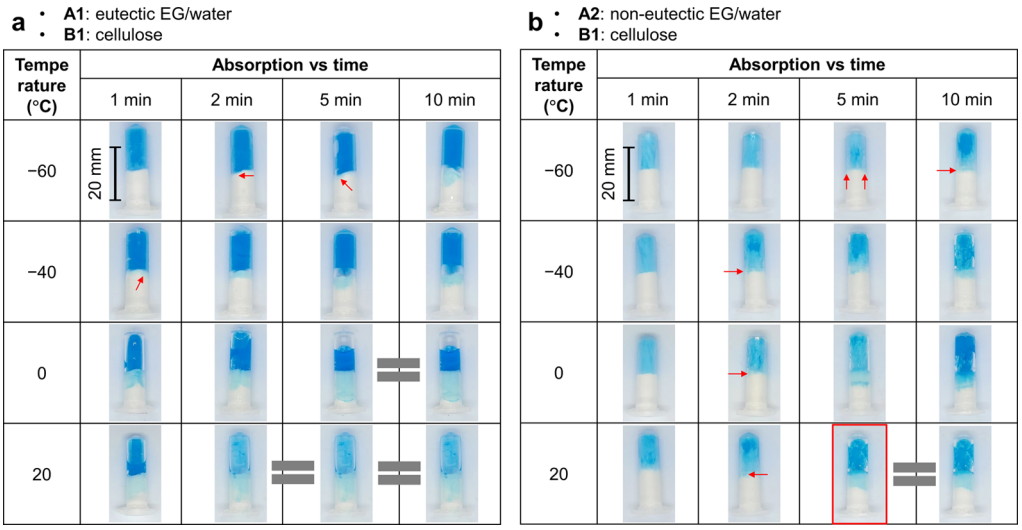


Figure 2. Diffusion of (a) eutectic (**A1**) and (b) noneutectic (**A2**) EG/water coolants into the cellulose (**B1**) absorbent at different exposure durations (1, 2, 5, and 10 min) and temperatures (−60, −40, 0, and 20 °C). The symbol "=" indicates the same diffusion distance of the blue coolants in the white absorbent.

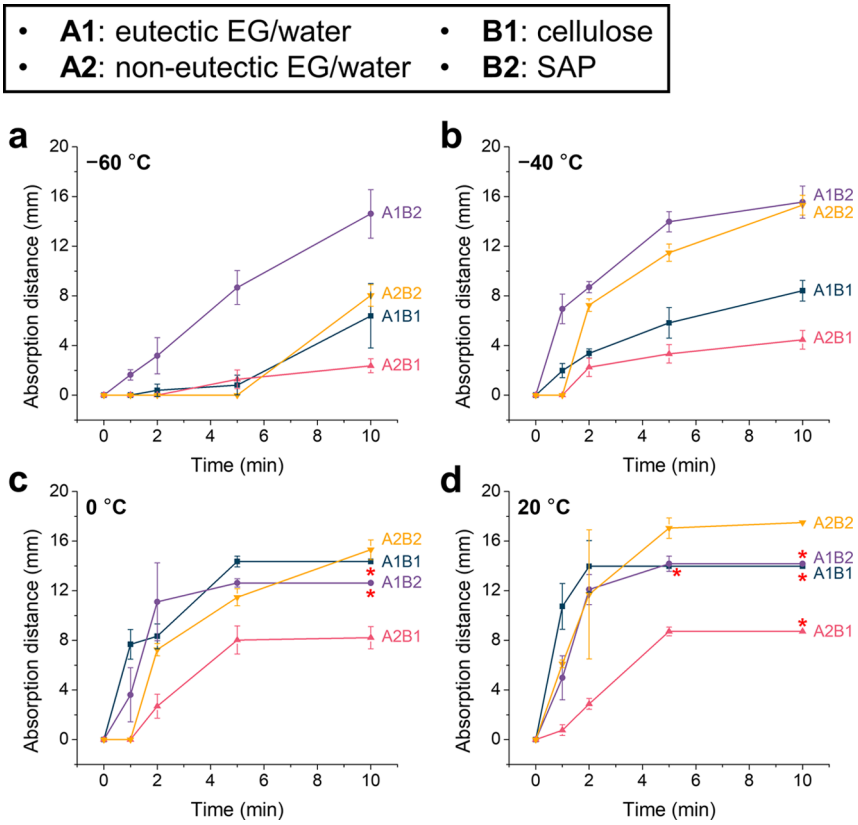


Figure 3. Time-dependent absorption distances of different TTIs at (a) −60, (b) −40, (c) 0, and (d) 20 °C. The data are expressed as means ± standard deviations of quintuplicate samples (n = 5). In some instances, leaching and swelling of the absorbent caused by complete melting of the coolant result in inaccurate determination of the absorption distance. Therefore, these data points are arbitrarily considered identical to previously investigated time points and are indicated by red asterisks (equivalent to symbol "=" in Figure 2 and Figure S5).

(EG/water of 68/32, v/v) with single-phase melting, while **A2** is a noneutectic mixture (EG/water of 40/60, v/v) with double-phase melting, where solid ice particles are present in the melting EG/water solution (Figure S1a and Table S1). It is expected that the heterogeneous mixture of EG/water and ice in the **A2** melt can prevent the stationary phase from quickly absorbing the mobile phase. In addition, control mixtures of ethanol (EtOH)/water with T_m values of −70 °C (**A3**) and −65 °C (**A4**) were prepared to investigate the effect of viscosity on the TTI performance. It is theoretically well established to calculate the viscosity of binary mixtures based on the temperature and mixture composition (Supporting Information).

https://dx.doi.org/10.1021/acsomega.1c00404
ACS Omega 2021, 6, 8598−8604

As absorbents, cellulose (**B1**) and cross-linked poly(acrylic acid) (superabsorbent polymer, SAP) (**B2**) were chosen because they both have abundant surface hydrophilic groups that can provide the absorption force (Figures S2−S4). However, the water absorption capacity of SAP is ∼500 g/g,[10] which is more than 20 times higher than that of cellulose microcrystals (∼5−27 g/g).[11] Thus, we intended to acquire two absorption modes, **B1** for normal and **B2** for rapid. Cooling baths to maintain subzero temperatures of −72, −60, and −40 °C were prepared using mixtures of methanol (MeOH)/water and dry ice, which are denoted by "**C**" or "**D**."

When eutectic **A1** was used as the coolant, absorption was detectable within 2 min even with cellulose **B1** at −60 °C (Figure 2a). At the set temperature, the absorption distance increased with the passage of time, and the change in the distance increased as the temperature increased. An abrupt change is not a desirable feature of a TTI because essential momentary transfer of frozen vaccines between different locations at room temperature must occur in the real world and the TTI should not record such short-term exposures. Surprisingly, the noneutectic coolant **A2** exhibited rare movement into **B1** after 1-min exposure at 20 °C (Figure 2b). After 5 min at −60 °C and 2 min at temperatures above −40 °C, noticeable changes were observed. When **A2** melts, two phases coexisted: the solid water (ice) appeared as lighter blue distributed through the liquid EG/water as darker blue. In addition, the melting rate of ice (forward reaction) in **A2** is hampered by the slow absorption of cellulose as the liquid phase is not quickly removed from the equilibrium ice (solid) ⇄ water (liquid). The solid ice can block the absorption of the melting liquid into absorbent **B** by acting as an obstacle and reducing the contact area of liquefied EG/water with cellulose. Thus, the much more retarded absorption of noneutectic **A2** than eutectic **A1** prevents a short-term change in the **A2B1** system up to 20 °C.

SAP (**B2**) is suitable for more sensitive TTIs operating over short-time ranges because it absorbs the melting coolant faster than cellulose **B1**. Both **A1B2** and **A2B2** showed faster diffusion than their **B1** counterparts (Figure S5). At 20 °C, the absorption rate of noneutectic **A2** exceeds that of eutectic **A1**, which can be explained as follows: (1) higher absorption and thus immediate removal of the melting liquid by **B2** induce a forward melting reaction of solid ⇄ liquid and (2) the kinematic viscosity of the **A2** liquid is lower than that of the **A1** liquid (Table S1). The photographs at 20 °C/5 min showed that **A2** still has some icy parts (lighter blue) in **A2B1** but is completely liquefied in **A2B2** (marked as red square boxes in Figure 2b and Figure S5b). This observation supports our hypothesis. The overall time-dependent absorption distances of different TTIs at various temperatures are shown in Figure 3.

The diffusion-based TTI is tamper-proof and irreversible, so the absorbed dye cannot be restored to its original state. The diffusion distance achieved did not shift when the TTIs exposed to −40 and 20 °C were frozen again at −72 °C (Figure 4).

The coolants consisting of EtOH/water mixtures have 35 and 3 times lower kinematic viscosities than EG/water mixtures at −60 and 20 °C, respectively (Table S1). Even at −40 °C, the melted coolant was quickly absorbed into the absorbent within 1 min (Figure S6). The absorption pattern was similar when the T_m of the coolant was increased although **A4** was expected to melt more slowly than **A3**. Because of its much lower viscosity than aqueous EG, aqueous EtOH was quickly absorbed within a short time even with cellulose (Figure S7). Therefore, it is concluded that EtOH/water mixtures with low viscosities were not suitable for subzero TTIs.

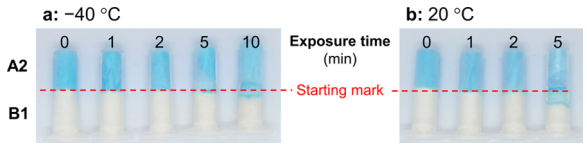


Figure 4. Photographs of the **A2B1** TTI showing irreversible absorption of **A2** into **B1** after exposure to (a) −40 °C and (b) 20 °C followed by freezing back at −72 °C, indicating a permanent warning sign.

During the distribution of COVID-19 vaccines to clinics, the vaccine vials need to be exposed outside of the storage temperature for a short duration when transferring from one freezer and/or shipper to another. The TTI should not record such a short-term exposure; otherwise, abrupt short-term absorption can lead to an incorrect perception of the vaccine status and prodigal discharge of effective vaccines. In this respect, we carried out cyclic tests of repeated exposure at 20 °C for 50 s and freezing back at −72 °C for 5 min. **A2B1** showed rarely noticeable absorption during 10 cycles, while **A1B1** exhibited a noticeable change after the fourth cycle (Figure 5). As discussed earlier, the retardation of absorption due to blockage of liquid diffusion by the solid ice allows the TTI to effectively withstand repeated short-term room temperature exposure. By contrast, the **B2**-based TTIs showed abrupt absorption even with noneutectic **A2** after the first cycle and continuously absorbed the coolants as the cycle continued. Due to the more rapid absorption by SAP than that by cellulose, the transfer of vaccine vials incorporating SAP-based TTIs requires a shorter exposure time. When the exposure duration at 20 °C was reduced to 30 s, **A2B2** showed rarely noticeable absorption until the 10th cycle (Figure S8). It is suggested that noneutectic **A2** can be developed with two sensitivity-controlled TTIs: normal mode with **B1** and sensitive mode with **B2**.

To demonstrate the applicability of our TTIs for monitoring the status of the mRNA COVID-19 vaccine, we fabricated a vaccine vial prototype incorporating the ultracold TTI. The **A2B1** TTI was selected as an ideal TTI because of its stability within a short-time range and detectable absorption over a long-time range. The prototype consisted of a 5 mL glass vial containing the vaccine tightly adhered to a reversed 350 μL glass compartment containing the TTI (Figure 6). When exposed to room temperature (20 °C) for up to 1 min, no appreciable absorption in the TTI was observed, in good agreement with the tolerance time of the vaccine. Under appropriate storage conditions, the TTI also showed no observable absorption after one month (Figure S9), suggesting its stability. Absorption of **A2** to **B1** occurred when the TTI (as-prepared or stored at −80 °C for one week or one month) was exposed to more than 1 min at 20 °C, resulting in an irreversible warning sign in the TTI (Figure S9 and Movie S1).

The sensing behavior of the **A2B1** TTI is reproducible in the form of a 2 mL test tube or a 350 μL insert of the vaccine prototype. Furthermore, phase diagrams and diffusion/absorption are well-established concepts, and information on phase diagrams of different organic compounds can be easily retrievable. The technique to fabricate the TTI is also simple,

https://dx.doi.org/10.1021/acsomega.1c00404
ACS Omega 2021, 6, 8598−8604

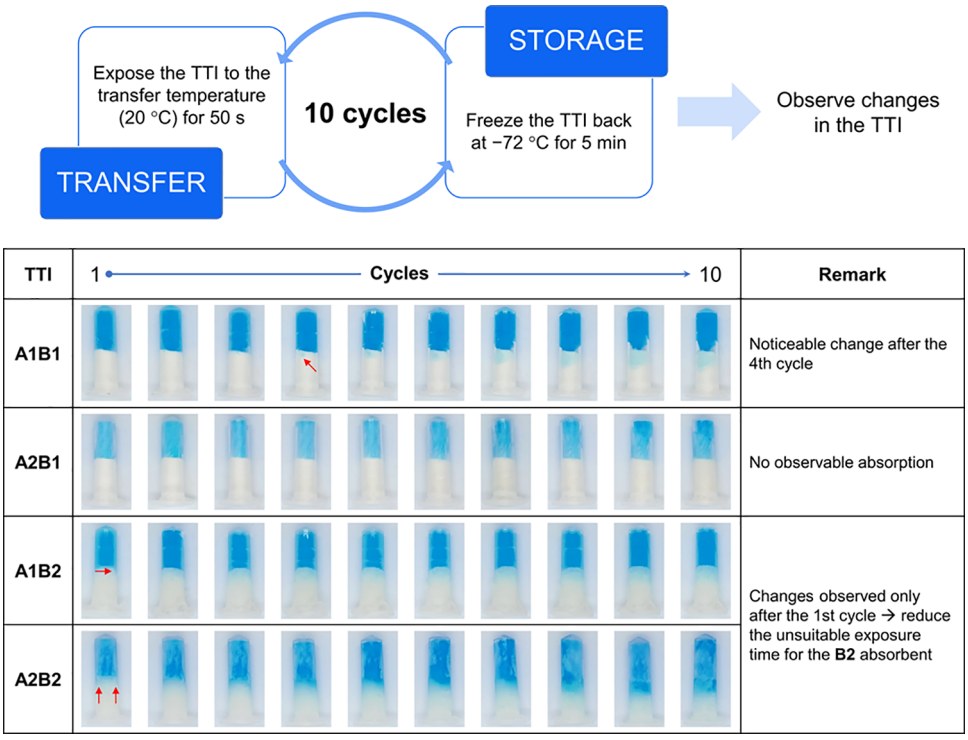


Figure 5. Response of different EG/water-based TTIs to 10 cycles of 5 min freezing at −72 °C and 50 s exposure at 20 °C, simulating the transfer of the vaccine.

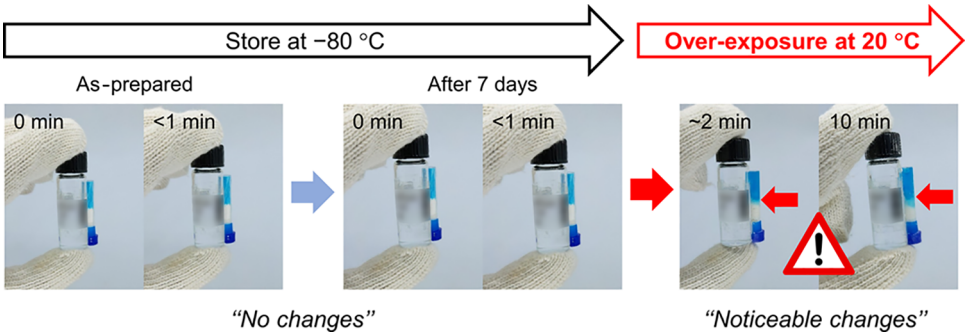


Figure 6. Prototype of the vaccine vial incorporating the **A2B1** TTI.

combined with readily available materials (*e.g.*, EG, water, cellulose, and liquid nitrogen). These factors open up a great possibility for an industrial scaleup. Manufacturers can tailor the properties of the TTI to their own needs. For example, the TTI can be fabricated as a separate entity incorporated in a vaccine lot/package, making it more convenient for batch evaluation and large-scale tracing of the distribution system. Alternatively, a TTI sensing the required frozen temperature of the Moderna's vaccine (−20 °C) can also be flexibly developed by employing the D-sucrose/water phase diagram (Figures S1d and S10). This TTI responded to long-term but not short-term changes at 0 °C and can withstand up to six cycles of storage (−20 °C, 10 min)/exposure (0 °C, 30s). To optimize the performance and realize the full potential of the TTI for ultracold supply chain, studies on factors (such as compositions of the coolant or particle size of the absorbents) influencing the absorption behavior of the TTI will be needed in the future.

CONCLUSIONS

Highly sensitive, reliable, and tamper-proof TTIs that can monitor subzero temperatures for mRNA vaccine ultracold supply chain were developed based on the principle of diffusion of coolants (organic solvent/water mixture) that melt at superlow temperatures. The melting coolant permeated into the absorbent when exposed to temperatures as low as −60 °C, at which the mRNA vaccine can become malfunctional. Most importantly, as a coolant, the EG/water mixtures should be noneutectic. The heterogeneous ice particles in the noneutectic coolants prevented the permeation of the absorbent after few minutes of exposure to room temperature. As a result, the TTI did not record the inevitable "meaningless" short-term exposure to room temperature during the cold supply chain, for example, the time from a refrigerator truck to a freezer in a hospital but monitored the "meaningful" relatively long-term exposure above −60 °C. The developed TTI immediately responded to temperature changes and performed reliably as a thermal history recorder through irreversible liquid diffusion. Thus, it is tamper-proof. The

https://dx.doi.org/10.1021/acsomega.1c00404
ACS Omega 2021, 6, 8598−8604

operating temperature and the response time are simply controlled by adjusting the T_m of the mobile phase (coolants) and the absorption capacity of the stationary phase (absorbents). Moreover, because the proposed TTI is composed of compounds with low toxicity (EG, cellulose, and EtOH), potential chemical hazards related to its use and its effects on the vaccine efficacy can be eliminated, expanding the application scope of the TTI. Considering the current scenario, wherein urgent supply of mRNA vaccines is required, we hope that the findings of this study will assure safe vaccine distribution.

EXPERIMENTAL SECTION

Materials. Antifreeze materials including EG anhydrous (Cat. No. 324558, 99.8%), EtOH (Cat. No. 459844, ≥ 99.5%), and D-sucrose (Cat. No. S5016) were purchased from Sigma-Aldrich (USA). MeOH, which is used in cooling baths, was purchased from SK Chemicals (South Korea). Double-deionized water was purified from tap water using a Milli-Q Integral 3 water purification system (Millipore, USA) with a final resistivity of 18.0 MΩ cm at 25 °C. Crystalline cellulose powder of 20 μm was purchased from Sigma-Aldrich (Cat. No. 310697). SAP was extracted from baby diapers (Huggies Magic, South Korea). Food colorings were purchased from Bread Garden (South Korea). All the materials were used as received without further purification.

Preparation of the TTI for ultracold conditions. The TTI comprising of two components, that is, coolant **A**, which freezes at ≤ −65 °C, and absorbent **B**, was prepared as shown in Figure 1. The coolant **A** was produced at room temperature by thoroughly mixing EG or EtOH with double deionized water in an appropriate ratio according to the phase diagrams (Figure S1). Food colorings (50 mg mL^{-1}) were then added to dye the mixtures to visualize the changes in the TTI. The EG solutions were dyed blue with Blue 1, and the EtOH solutions were dyed green with Fast Green FCF. Then, 1 mL of the coolant **A** was pipetted into clear 2 mL microcentrifuge tubes (Tarsons, USA), which were then attached to a floating rack for freezing in liquid nitrogen at −196 °C for 15 min. The solid absorbent **B** was carefully added on top of the frozen **A** to tightly pack the tube, that is, ∼1.5 g of cellulose powder and ∼0.9−1.0 g of SAP, thus obtaining the TTI for ultracold conditions.

Time−Temperature-Dependent Change of the Ultracold TTIs. Subzero temperatures were maintained using cooling baths comprising of different MeOH/water mixtures (Figure 1 and Figure S1) as a liquid carrier and dry ice as a cooling agent. The temperature was maintained at 0 °C using a water/ice cooling bath, and the room temperature was set at ∼20 °C with a thermo hygrostat (Century Co., South Korea). First, the TTIs were placed in a cooling bath **C** at −72 °C, which is just below the melting/freezing point (T_m) of the coolant **A**. This condition represents an appropriate storage condition for Pfizer-BioNTech's COVID-19 vaccine; hence, no change takes place in the TTIs. The TTIs responded to improper storage temperatures for the vaccine by continuously submerging them to the corresponding cooling baths **D** or exposing them to room temperature. The tubes were placed in an inverse position so that melting liquid **A** could be gravitationally absorbed into absorbent **B**. Changes in the TTIs were monitored at 0, 1, 2, 5, and 10 min after the exposure and were quantified as absorption distances. For accuracy, the absorption distance was determined using the photographs taken of the TTIs. The scale was calibrated between two pixels using the length of TTI tubes as 35 mm. The absorption distance was measured from the initial **A**/**B** boundary to the maximum absorption point of **A** into **B** at five different positions (n = 5) across the tube.

Cyclic 20 °C Exposure Tests. The TTIs were exposed to 20 °C for 30 or 50 s, representing the vaccine transfer time. Subsequently, the TTIs were frozen back at −72 °C in cooling bath **C** for 5 min, representing appropriate storage conditions for the vaccine. A total of 10 transfer−storage cycles was carried out and photographs of the TTIs were taken after each cycle to observe any change in the TTIs.

Fabrication of a Vaccine/TTI Prototype. First, the insert was tightly attached to the vial in an inverted position using a thermally cured double tape adhesive, which allows strong adhesion at ultracold temperatures. EtOH was filled into the vial to represent the vaccine content and the vial was tightly closed. Next, the prototype was inverted and 200 μL of the dyed **A2** mixture was pipetted into the insert. **A2** was frozen in a freezer at −80 °C for 3 h, instead of using liquid nitrogen, to prevent thermal shock that may break the glass. The prototype was then placed into a cooling bath maintained at −72 °C and **B1** was added on top of frozen **A2** to fill the insert, which was finally sealed with a plastic cap to complete the prototype. Changes in the prototype were recorded after 7 or 30 days of storage in the −80 °C freezer and after exposure to 20 °C.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c00404.

Determination of the phase composition and phase percentage of the coolants, viscosity calculation of the coolants, characterization of the absorbents, phase diagrams of aqueous mixtures of EG, EtOH, MeOH, and D-sucrose, SEM images and particle size distributions of the absorbents, ATR-FTIR spectra of the absorbents, diffusion of eutectic and noneutectic EG/water coolants into SAP, diffusion and absorption distances of two different EtOH/water coolants into cellulose and SAP, performance of the **A2B1** vaccine prototype after storage for one month, development of a −20 °C TTI using a D-sucrose/water mixture and cellulose, temperature-dependent parameters at equilibrium for the coolants used in this study, and coefficients for calculating the fluid's absolute viscosity (PDF)

Operation of the subzero TTI for inspecting vaccine vial when exposed to 20 °C (MP4)

AUTHOR INFORMATION

Corresponding Authors

Sung Yeon Hwang − *Research Center for Bio-based Chemistry, Korea Research Institute of Chemical Technology (KRICT), Ulsan 44429, Republic of Korea; Advanced Materials and Chemical Engineering, University of Science and Technology (UST), Daejeon 34113, Republic of Korea;* orcid.org/0000-0002-4618-2132; Phone: +82-52-241-6313; Email: crew75@krict.re.kr; Fax: +82-52-241-6349

Dongyeop X. Oh − *Research Center for Bio-based Chemistry, Korea Research Institute of Chemical Technology (KRICT), Ulsan 44429, Republic of Korea; Advanced Materials and*

https://dx.doi.org/10.1021/acsomega.1c00404
ACS Omega 2021, 6, 8598−8604

Chemical Engineering, University of Science and Technology (UST), Daejeon 34113, Republic of Korea; orcid.org/0000-0003-3665-405X; Phone: +82-52-241-6316; Email: dongyeop@krict.re.kr; Fax: +82-52-241-6349

Jeyoung Park − *Research Center for Bio-based Chemistry, Korea Research Institute of Chemical Technology (KRICT), Ulsan 44429, Republic of Korea; Advanced Materials and Chemical Engineering, University of Science and Technology (UST), Daejeon 34113, Republic of Korea;* orcid.org/0000-0002-9369-1597; Phone: +82-52-241-6315; Email: jypark@krict.re.kr; Fax: +82-52-241-6349

Authors

Lam Tan Hao − *Research Center for Bio-based Chemistry, Korea Research Institute of Chemical Technology (KRICT), Ulsan 44429, Republic of Korea; Advanced Materials and Chemical Engineering, University of Science and Technology (UST), Daejeon 34113, Republic of Korea;* orcid.org/0000-0001-9791-6071

Minkyung Lee − *Research Center for Bio-based Chemistry, Korea Research Institute of Chemical Technology (KRICT), Ulsan 44429, Republic of Korea*

Hyeonyeol Jeon − *Research Center for Bio-based Chemistry, Korea Research Institute of Chemical Technology (KRICT), Ulsan 44429, Republic of Korea*

Jun Mo Koo − *Research Center for Bio-based Chemistry, Korea Research Institute of Chemical Technology (KRICT), Ulsan 44429, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c00404

Notes

The authors declare the following competing financial interest(s): All authors are inventors of the patent application (Appl. No.: KR 10−2020-0152923, Filed: 16 Nov 2020, Assignee: KRICT).

■ ACKNOWLEDGMENTS

This research was supported by the KRICT Core Project (SS2142-10).

■ REFERENCES

(1) Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update; https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/ (accessed 21 Jan 2021).

(2) Kim, J. H.; Marks, F.; Clemens, J. D. Looking beyond COVID-19 vaccine phase 3 trials. *Nat. Med.* **2021**, *27*, 205−211.

(3) Crommelin, D. J. A.; Anchordoquy, T. J.; Volkin, D. B.; Jiskoot, W.; Mastrobattista, E. Addressing the Cold Reality of mRNA Vaccine Stability. *J. Pharm. Sci.* **2021**, *110*, 997−1001.

(4) UK department of Health and Social Care, Information for Healthcare Professionals on Pfizer BioNTech COVID-19 Vaccine. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940565/Information_for_Healthcare_Professionals_on_Pfizer_BioNTech_COVID-19_vaccine.pdf , (accessed 12 Feb 2021).

(5) Wang, S.; Liu, X.; Yang, M.; Zhang, Y.; Xiang, K.; Tang, R. Review of Time Temperature Indicators as Quality Monitors in Food Packaging. *Packag. Technol. Sci.* **2015**, *28*, 839−867.

(6) Choi, S.; Eom, Y.; Kim, S.-M.; Jeong, D.-W.; Han, J.; Koo, J. M.; Hwang, S. Y.; Park, J.; Oh, D. X. A Self-Healing Nanofiber-Based Self-Responsive Time-Temperature Indicator for Securing a Cold-Supply Chain. *Adv. Mater.* **2020**, *32*, 1907064.

(7) Romano, L.; Portone, A.; Coltelli, M.-B.; Patti, F.; Saija, R.; Iatí, M. A.; Gallone, G.; Lazzeri, A.; Danti, S.; Maragò, O. M.; Camposeo, A.; Pisignano, D.; Persano, L. Intelligent Non-Colorimetric Indicators for the Perishable Supply Chain by Non-Wovens with Photo-Programmed Thermal Response. *Nat. Commun.* **2020**, *11*, 5991.

(8) Suppakul, P.; Kim, D. Y.; Yang, J. H.; Lee, S. B.; Lee, S. J. Practical Design of a Diffusion-Type Time-Temperature Indicator with Intrinsic Low Temperature Dependency. *J. Food Eng.* **2018**, *223*, 22−31.

(9) Pardi, N.; Hogan, M. J.; Porter, F. W.; Weissman, D. mRNA vaccines — a new era in vaccinology. *Nat. Rev. Drug Discov.* **2018**, *17*, 261−279.

(10) Zohuriaan-Mehr, M. J.; Kabiri, K. Superabsorbent Polymer Materials: A Review. *Iran. Polym. J.* **2008**, *17*, 451−477.

(11) Cruz, J.; Leitão, A.; Silveira, D.; Pichandi, S.; Pinto, M.; Fangueiro, R. Study of moisture absorption characteristics of cotton terry towel fabrics. *Procedia Engineer.* **2017**, *200*, 389−398.