

Polymer Vesicles with Upper Critical Solution Temperature for Near-infrared Light-triggered Transdermal Delivery of Metformin in Diabetic Rats

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 Electronic Supplementary Information

Abstract Near-infrared light (NIR) triggered transdermal drug delivery systems are of great interest due to their on-demand drug release, which enable to enhance drug treatment efficiency as well as reduce side effect. Herein, a NIR-triggered microneedle (MN) patch array has been fabricated through depositing the photothermal conversion agent and anti-diabetic drug-loaded polymer vesicles with upper critical solution temperature (UCST) into dissolvable polymer matrix. The UCST-type polymer has a clearing point temperature of 41 °C and the drug-loaded polymer vesicles present excellent NIR-triggered and temperature responsive drug release behavior *in vitro* due to the disassociation of polymer vesicles upon NIR irradiation. After applying MNs to diabetic rats, significant hypoglycemic effect is achieved upon interval NIR irradiation and the blood glucose concentration can decrease to normal state for several hours, which enables to achieve the goal of on-demand drug release. This work suggests that the NIR-triggered MN drug release device has a potential application in the treatment of diabetes, especially for those requiring an active drug release manner.

Keywords Diabetes; Upper critical solution temperature; Near-infrared light; On-demand drug release; Polymeric vesicles

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INTRODUCTION

Complete drug release and efficient drug usage rate are two critical factors in the treatment of diseases.^[1–3] The efficacy of drug is not only directly related to its potency, but also affected by many factors such as pharmacokinetics, internal distribution, drug intake, immune clearance and biological toxicity.^[4,5] For this reason, intelligent drug delivery platforms are of great interest for the researchers in the past few decades since they can effectively deliver the cargo to the targets,^[6,7] thus increasing the therapeutic efficacy and lowering the side effect of drug. For the smart drug delivery systems, stimuli-responsive nanocarriers have become an ideal choice to break through the above obstacles.^[8–10] The stimuli contain endogenous signals such as pH,^[11–14] glucose,^[15,16] enzymes,^[17,18] hypoxic environment,^[19] H₂O₂,^[13,15,20] and exogenous signals such as temperature,^[21,22] light,^[23–25] magnetic field,^[26,27] electric field^[28]

and ultrasound.^[29,30] Among the above mentioned stimuli, light is of great interest due to its cleanness, rapid response and on-demand drug control.^[31–33] However, most responsive polymers are sensitive to UV light. But it is worth noting that in most cases UV-light is unable to reach deep tissue because of its limited penetration depth.^[34] Moreover, UV light will exert damage to the normal cell, which causes great side effect to healthy cells.^[35] Compared to UV light, near-infrared (NIR) light is more advantageous for chemotherapy due to its nontoxicity and deep penetration.^[36] However, the NIR-triggered drug release system usually contains photothermal conversion agent, which can effectively convert NIR light to heat. Therefore, NIR-triggered drug release systems can be constructed by combination of temperature-responsive polymeric nanocarriers with photothermal conversion agents.^[36]

Temperature-responsive polymers used in drug delivery systems are mainly composed of lower critical solution temperature (LCST) polymers and upper critical solution temperature (UCST) polymers.^[37] Upon increasing temperature to above phase transition temperature, the LCST-type polymer chains will change from extended state to shrunken form, while the UCST-type polymer will change in an opposite

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trend.^[38–40] For this reason, the UCST-type polymers are more promising in the field of drug delivery for the complete drug release from the nanocarriers. On the other hand, most UCST polymers are highly sensitive to the concentration and ionic strength such as zwitterionic polymers,^[40,41] which prevent the application of UCST polymers in biomedical fields. Recently, the development of UCST polymers allows to prepare the UCST-type polymers such as poly(*N*-acryloyl glycineamide) and ureido-derivative polymers possessing robust and repeated phase transition temperatures, which are independent on polymer concentration and ionic strength.^[42]

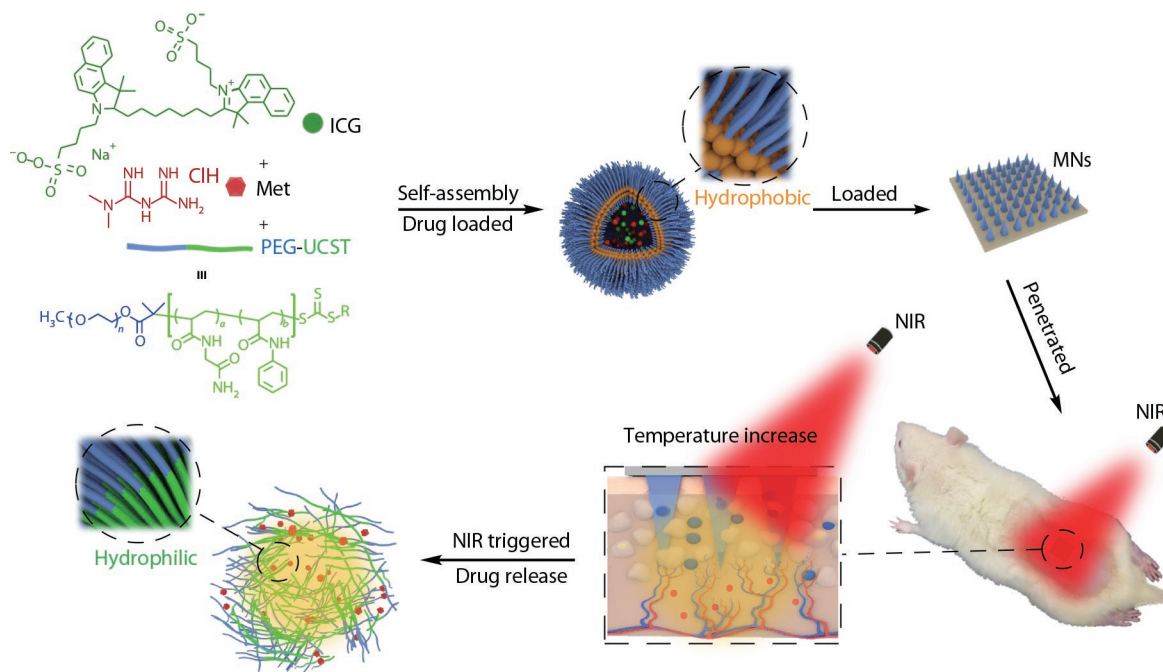
On the other hand, as a new type of drug delivery intermediate, microneedles (MNs) acting as a drug reservoir and a tool for drug delivery have been widely explored recently.^[43,44] Compared with traditional oral administration and injection administration methods, micron-sized MNs deliver cargo through skin, which overcomes gastric acid barriers, bleeding and pain barriers.^[45–47] Therefore, this transdermal drug delivery provides a significant boost on painless administration, sustained drug release and improvement of drug utilization efficiency.^[45,48–50] In this work, a NIR-triggered drug delivery device based on MNs was established by integrating the temperature-responsive polymeric vesicles with MN patches for the treatment of diabetes (Scheme 1). First, a UCST-type block polymer (BCP) poly(ethylene glycol)-*b*-poly(*N*-acryloylglycinamide-*co*-*N*-phenylacrylamide) (PEG-*b*-P(NAGAm-*co*-NPhAm)) with a clearing point temperature of 41 °C was synthesized. The metformin (Met, anti-diabetic drug) and indocyanine green (ICG, photothermal conversion agent) were encapsulated through the self-assembly of PEG-*b*-P(NAGAm-*co*-NPhAm) in aqueous solution. Upon NIR irradiation, the temperature of solution could increase from room temperature to 45 °C, which is higher than the clearing point temperature of PEG-*b*-P(NAGAm-*co*-NPhAm). Therefore, the

core of P(NAGAm-*co*-NPhAm) was dissociated and the encapsulated drug was released from the nanoparticles. By incorporating the drug-loaded vesicles into the poly(vinyl pyrrolidone)/poly(vinyl alcohol) (PVP/PVA) microneedles, the NIR-triggered MN patches were successfully prepared. After administration of the as-prepared MNs into diabetic rats, effectively hypoglycemic effect was achieved upon NIR irradiation. This work suggests the NIR-triggered MN drug release device has a promising application in the treatment of diabetes that specifically requires an active drug release manner.

RESULTS AND DISCUSSION

Characterization of UCST-type Polymers

Actually, several kinds of UCST-type polymer including poly(acrylamide-*co*-acrylonitrile), zwitterionic polymers such as sulfobetaine-based methacrylate polymers have been reported. However, the above mentioned UCST-type polymers have many disadvantages such as high toxic monomer of acrylonitrile, the high sensitivity of clearing temperature to ionic strengths and polymer concentrations of polyzwitterions, which brings much inconvenience to the further application. Herein, we chose the biocompatible poly(*N*-acryloyl glycineamide) and polymers containing ureido-derivatives as a UCST polymer, where the clearing point temperature is independent on the ionic strength and polymer concentration.^[42] Moreover, it is well-known that the clearing point temperature of poly(*N*-acryloylglycinamide-*co*-*N*-phenylacrylamide) (P(NAGAm-*co*-NPhAm)) segment is greatly dependent on the fraction of NPhAm unit.^[51,52] In order to prepare a polymer with suitable clearing point temperature for drug delivery, three block polymers (BCPs) with different feed ratios of NAGAm/NPhAm were prepared by reversible addition-fragmentation chain transfer (RAFT) polymerization using PEG macro RAFT agent



Scheme 1 NIR-triggered drug delivery system of MNs and transdermal drug administration on diabetic rats.

Table 1 Molecular characterizations and clearing point temperatures of three BCPs with different feed ratios.

Code	[NAGAm]/[NPhAm]/[CTA]/[AIBN] ^a	Compositions ^b	M_n ^c (kDa)	D_M ^c	Clearing point (°C) ^d
BCP1	160:40:1:0.2	PEG ₄₅ - <i>b</i> -P(NAGAm ₆₃ - <i>co</i> -NPhAm ₃₈)	13.2	1.21	–
BCP2	170:30:1:0.2	PEG ₄₅ - <i>b</i> -P(NAGAm ₇₃ - <i>co</i> -NPhAm ₂₄)	12.8	1.23	41
BCP3	180:20:1:0.2	PEG ₄₅ - <i>b</i> -P(NAGAm ₈₁ - <i>co</i> -NPhAm ₁₈)	13.5	1.26	32

^a Monomer feed ratios; ^b Compositions were calculated from ¹H-NMR spectra; ^c Number-average molecular weight and polydispersity were characterized from GPC analysis; ^d Clearing point temperatures were determined for 0.1 wt% solutions in PBS with a heating rate of 1.0 °C/min.

(PEG-DDMAT) (Scheme S1 in the electronic supplementary information, ESI). The ¹H-NMR and gel permeation chromatography (GPC) results indicate the successful preparation of three BCPs (Figs. S1–S3 in ESI) with a narrow polydispersity within 1.26. Moreover, the polymerization degrees of NAGAm and NPhAm in three BCPs were calculated from the specific protons belonging to NAGAm and NPhAm by comparing with PEG protons (Fig. S2 in ESI). The detailed molecular characterizations of three BCPs are summarized in Table 1. We can see that the polymerization degree of NAGAm increases while NPhAm unit decreases with an increasing monomer ratio of [NAGAm]/[NPhAm].

After ensuring the successful synthesis of three polymers, the temperature-dependent phase behavior of three block copolymers was characterized by the measurement of turbidity. As shown in Fig. 1, the BCP2, PEG₄₅-*b*-P(NAGAm₇₃-*co*-NPhAm₂₄), presented a suitable phase transition behavior with a narrow temperature ranging from 38 °C to 44 °C, while the other two either cannot be fully soluble in water (PEG₄₅-*b*-P(NAGAm₆₃-*co*-NPhAm₃₈), BCP1) at studied temperature ranges or had a low clearing point temperature that was not suitable for further application (PEG₄₅-*b*-P(NAGAm₈₁-*co*-NPhAm₁₈), BCP3). The narrow phase transition of UCST polymer could be attributed to the narrow molecular weight distribution of the UCST-type polymer and uniform distribution of the NPhAm unit in the core block. As a result, we selected PEG₄₅-*b*-P(NAGAm₇₃-*co*-NPhAm₂₄) (BCP2) as the UCST-type polymer for following studies. Moreover, the clearing point temperature of PEG₄₅-*b*-P(NAGAm₇₃-*co*-NPhAm₂₄) polymer was determined to be about 41 °C, which was suitable for photothermal applications in bio-related field.

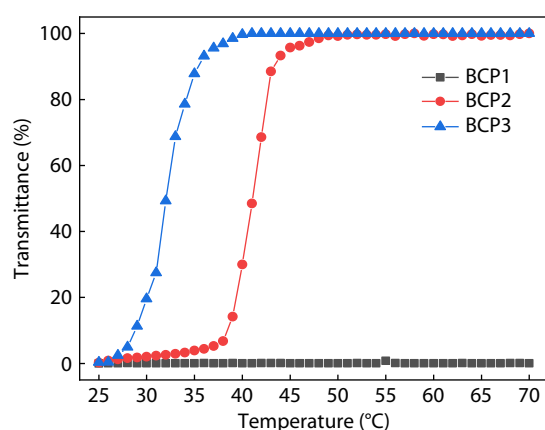


Fig. 1 Turbidity measurement curves of three block copolymers with different compositions. BCP1 (PEG₄₅-*b*-P(NAGAm₆₃-*co*-NPhAm₃₈)), BCP2 (PEG₄₅-*b*-P(NAGAm₇₃-*co*-NPhAm₂₄)) and BCP3 (PEG₄₅-*b*-P(NAGAm₈₁-*co*-NPhAm₁₈)) in PBS from 25 °C to 70 °C.

Characterization of Nano-vehicle

The self-assembled morphology of PEG₄₅-*b*-P(NAGAm₇₃-*co*-NPhAm₂₄) in PBS solution (0.01 mol/L and pH=7.4) was examined by dynamic light scattering (DLS) and transmission electron microscopy (TEM), respectively. Polymer vesicles of PEG₄₅-*b*-P(NAGAm₇₃-*co*-NPhAm₂₄) with an average size of 86 nm were observed by TEM observation after self-assembly processing (Fig. 2a), where the P(NAGAm₇₃-*co*-NPhAm₂₄) segment formed the wall of vesicles while the PEG₄₅ block acted as corona to stabilize the particles. Moreover, the hydrodynamic diameter of the vesicles determined from DLS is about 104 nm, which is slightly larger than that observed from TEM. Since the P(NAGAm₇₃-*co*-NPhAm₂₄) block presented UCST behavior, the hydrodynamic diameter change of vesicles with temperature was examined by DLS. As shown in Fig. S4 (in ESI), the hydrodynamic diameter of aggregates decreased with an increasing temperature and the size decreased to about 20 nm at the temperature above clearing point temperature. This result showed the block copolymer was almost dissolved at elevated temperature ranges. Meanwhile, the TEM morphology also showed no obvious aggregates observed at 50 °C, implying the thermal responsiveness of the vesicles.

After loading with ICG and Met, the size of vesicles was increased from 86 nm to 112 nm, which was detected by both TEM observation and DLS results. The particle size distribution determined from DLS result further demonstrated the size of a small fraction of drug-loaded vesicles was increased to about 1000 nm, which was possibly due to the fusion of vesicles. Moreover, the drug loading content (DLC) and encapsulated efficiency (EE) of both Met and ICG were calculated by standard curve measured by an ultraviolet-visible spectrophotometer (Fig. S5 in ESI). According to the standard curves of ICG and Met in Figs. S5(a) and S5(b) (in ESI), the EE of ICG and Met were calculated as 95.1% and 39.8% respectively, and the DLC of ICG and Met were calculated as 4.8% and 76.1% respectively. Herein, the high loading efficiency of ICG is attributed to the high mass feeding of ICG. As described in ESI, mass feeding of ICG is only 6 mg while the Met is high to 100 mg, so most ICG could be encapsulated into the polymer vesicles. On the other hand, higher loading capacity of Met is a very important factor to evaluate the efficiency of current device. Therefore we added high mass feeding of Met to increase the loading capacity of Met, which in turn results in the low loading efficiency of Met.

In Vitro Temperature-stimulus/NIR-triggered Drugs Release and Cytotoxicity of UCST@Met-ICG

ICG was used as the photothermal conversion agent for the NIR-triggered drug release. For the estimation of the best ICG concentration, different concentrations of ICG were applied at a designated laser irradiation level (808 nm, 0.4 W/cm²).

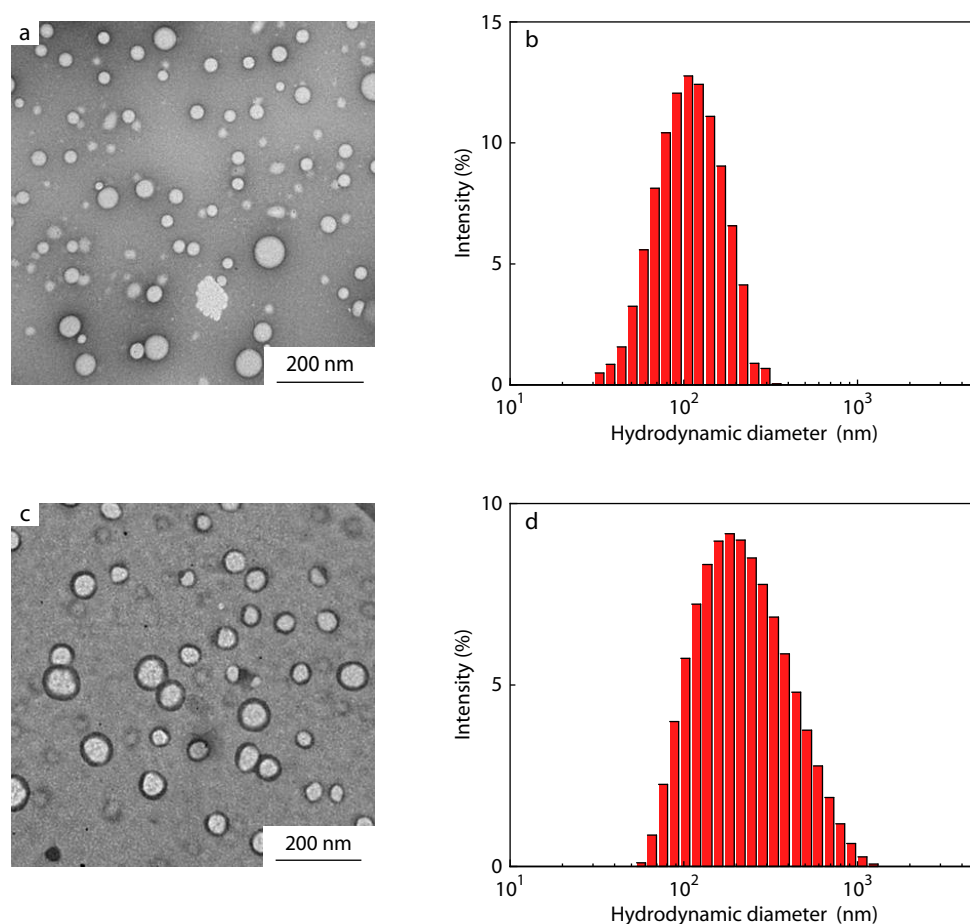


Fig. 2 Characterizations of self-assembled vesicles of UCST-type polymer (feed ratio of NAGAm/NPhAm=170:30) and drug loaded nano-vehicle of UCST@Met-ICG. (a) TEM morphologies and (b) corresponding size distribution of UCST-type polymer; (c) TEM morphologies and (d) corresponding size distribution of UCST@Met-ICG. The TEM samples were negatively stained with 1 wt% uranyl acetate (UA) aqueous solution.

Fig. S6 (in ESI) showed that 20 $\mu\text{g/mL}$ of ICG was the best concentration for the thermoresponsive drug release since the solution temperature will be stable at 48 $^{\circ}\text{C}$ after NIR irradiation, which was higher than the clearing point temperature (41 $^{\circ}\text{C}$). Therefore, the concentration of UCST@Met-ICG was fixed at 0.42 mg/mL , in which the effective ICG concentration was about 20 $\mu\text{g/mL}$. For a better regulation of solution temperature, the photothermal behavior upon NIR irradiation of UCST@Met-ICG was examined to show whether the solution temperature was suitable for the drug release. As shown in Fig. 3(a), the temperatures of UCST@Met or PBS solution without ICG does not change significantly under NIR irradiation. In contrast, the temperature of UCST@Met-ICG PBS solution rapidly increases to 42 $^{\circ}\text{C}$ within about 90 s under NIR irradiation and then the temperature remained stable, indicating an excellent photothermal behavior of ICG. Meanwhile, the temperature after NIR exposure was above the clearing point temperature of PEG₄₅-b-P(NAGAm₇₃-co-NPhAm₂₄), which was better for the phase transition in PBS.

To further investigate the drug release upon NIR irradiation, the temperature-dependent Met release behavior from polymer vesicles was explored in PBS. As shown in Fig. 3(b), an acceptable drug leak of Met can be observed at 25 $^{\circ}\text{C}$ and the

release amount level off at about 18%. However, when the temperature increased to 37 $^{\circ}\text{C}$ that was lower than clearing point temperature, a faster drug release was detected, indicating that the drug-loaded nanocarrier presented a temperature responsive behavior. When the temperature further increased to 45 $^{\circ}\text{C}$ that is above the clearing point temperature of UCST polymer, a significantly fast drug release can be observed. And the final drug release level could reach 80%, suggesting that the polymer vesicles were disassociated at the temperature above clearing point temperature and large amount of drug was released.

The characterization of NIR-triggered drug release behavior of UCST@Met-ICG was further performed at an ambient temperature of 37 $^{\circ}\text{C}$. As shown in Fig. 3(c), about 30% of drug is released from the vesicles in 2 h without NIR irradiation. However, when the solution was exposed to NIR light for 5 min, a significant increase of drug release is detected in the following 1 h, and then the release rate slowed down. Upon for the second NIR irradiation, the drug release rate increased again, but the release rate was not so sharp as the first NIR irradiation.

Subsequently, to evaluate the cytotoxicity of the drug nanocarriers, human breast adenocarcinoma (MCF-7) cells

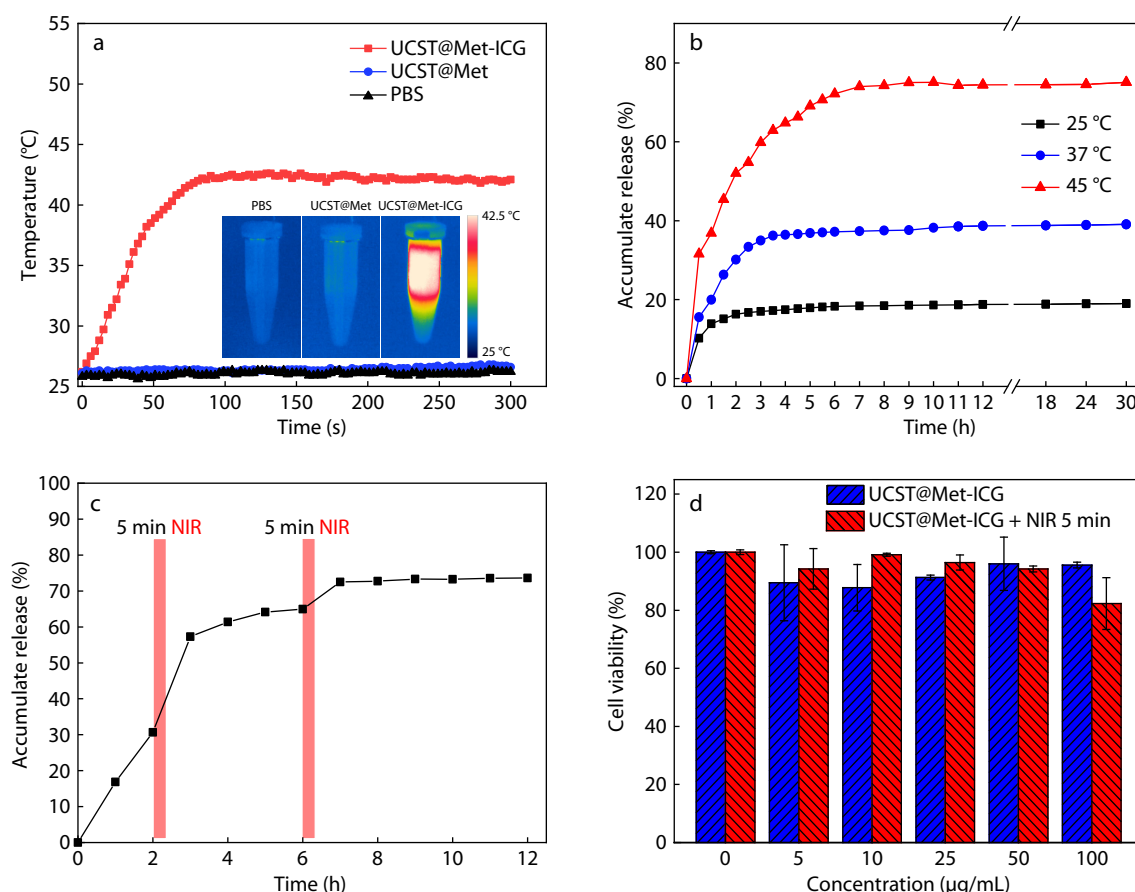


Fig. 3 (a) Photothermal curves of PBS, UCST@Met, UCST@Met-ICG (ICG concentration was 20 µg/mL) under continuous NIR (808 nm, 0.4 W/cm²) irradiation; insets show real-time thermographic images of PBS, UCST@Met, UCST@Met-ICG irradiated by NIR (808 nm, 0.4 W/cm²) at 5 min; (b) Accumulate release of Met at 25, 37 and 45 °C for 30 h; (c) Accumulate release of Met at 37 °C for 12 h and with NIR (808 nm, 0.4 W/cm², 5 min) “open” at the 2nd and 6th hour; (d) Cytotoxicity assay measured by CCK-8 assay of MCF-7 cells co-cultivation with UCST@Met-ICG and UCST@Met-ICG irradiated by NIR (808 nm, 0.4 W/cm²) for 5 min, respectively.

were incubated with the PBS solution of UCST@Met-ICG. The cell survival rate was determined by the CCK-8 assay, as shown in Fig. 3(d). The results showed over 80% of MCF-7 cells survived over a wide range of concentrations with or without NIR irradiation, indicating that this drug delivery system had relatively low cytotoxicity and it was suitable for applying in drug delivery.

Skin Penetration Assay and Local Temperature Change upon NIR Irradiation in Rats

The drug-loaded vesicles were then further integrated with PVA/PVP-based microneedles to achieve transdermal drug release. As shown in Figs. S7 and S8 (in ESI), the morphology of MNs was characterized by a digital microscopy and a scanning electron microscopy (SEM). Each needle had a rectangular pyramid shape and uniform size of about 500 µm in height. To evaluate whether the microneedles meet the mechanical requirements for penetrating skin, a universal testing machine was used to determine the stress-strain curve of each microneedle at different pressures. As shown in Fig. S8(b) (in ESI), the fabricated MNs exhibit excellent mechanical performance. A break force for each microneedle is determined as 0.35 N with a displacement of 0.5 mm, which meets the mechanical requirements for skin penetration.

R6G was used to visually characterize the dissolution of the MNs and the penetration behavior of nanoparticles after the MNs penetrated into the skin *in vitro*. The fluorescence images of pierced diabetic rat skin frozen sections taken by confocal laser scanning microscopy (CLSM) after 5, 10 and 30 min are shown in Fig. S8(c) (in ESI). Strong red fluorescence can be observed around the skin surface after the insertion of MNs on the back of diabetic rats for 5 min. Meanwhile, strong red fluorescence was observed in the deeper tissues with the time increasing, which implies more and more drug-loaded nanocarriers were diffusing into deeper tissues.

To characterize the local skin temperature after application of drug-loaded MNs on diabetic rat under NIR irradiation, an infrared thermal imager was used. As shown in Fig. 4(a), there was no significant temperature change in the skin position of using UCST@Met MNs under NIR irradiation. In contrast, the UCST@Met-ICG MNs had a significant temperature increase on skin surface under NIR irradiation for 5 min (Fig. 4b). Moreover, the temperature-time curves clearly show that the maximum temperature could reach about 45.5 °C within 2.5 min and there is no obvious change in the next 2.5 min. For a control group, the temperature only increased about 1 °C after NIR irradiation for 5 min, indicating no phototherm-

al effect.

NIR Trigger Drug Delivery *In Vivo*

Five experimental groups were used to evaluate the feasibility of NIR-triggered UCST-type drug delivery system integrated with MNs patches for drug delivery. The blood glucose concentrations of each group with time are shown in Fig. 5(a). The blood glucose concentration of normal rats without any treatment (Group I) is stable at a level of about 117.4 mg/dL. In

contrast, the blood glucose concentration of type-2 diabetic rats (Group II) is maintained at a level of about 467 mg/dL. The blood glucose concentrations of experimental rats in Met MN group (Group III) decrease rapidly after administration, and reach a minimum of 55.3 mg/dL at 2.5 h. The subsequent increase in blood glucose concentration may be caused by the biological metabolism of Met. The blood glucose level of the experimental group (MNs loaded with UCST@Met-ICG +

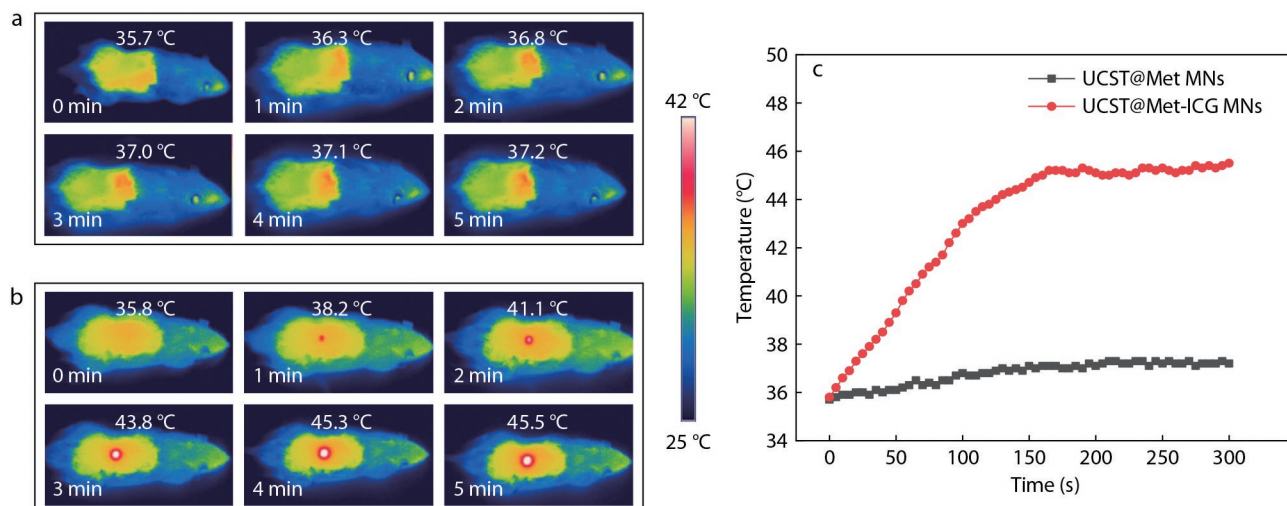


Fig. 4 Real-time thermographic images of diabetic rats under NIR (808 nm, 0.4 W/cm²) after (a) UCST@Met MNs and (b) UCST@Met-ICG MN administration. (c) The temperature curve of penetration site on diabetic rat skin under NIR (808 nm, 0.4 W/cm²) within 5 min.

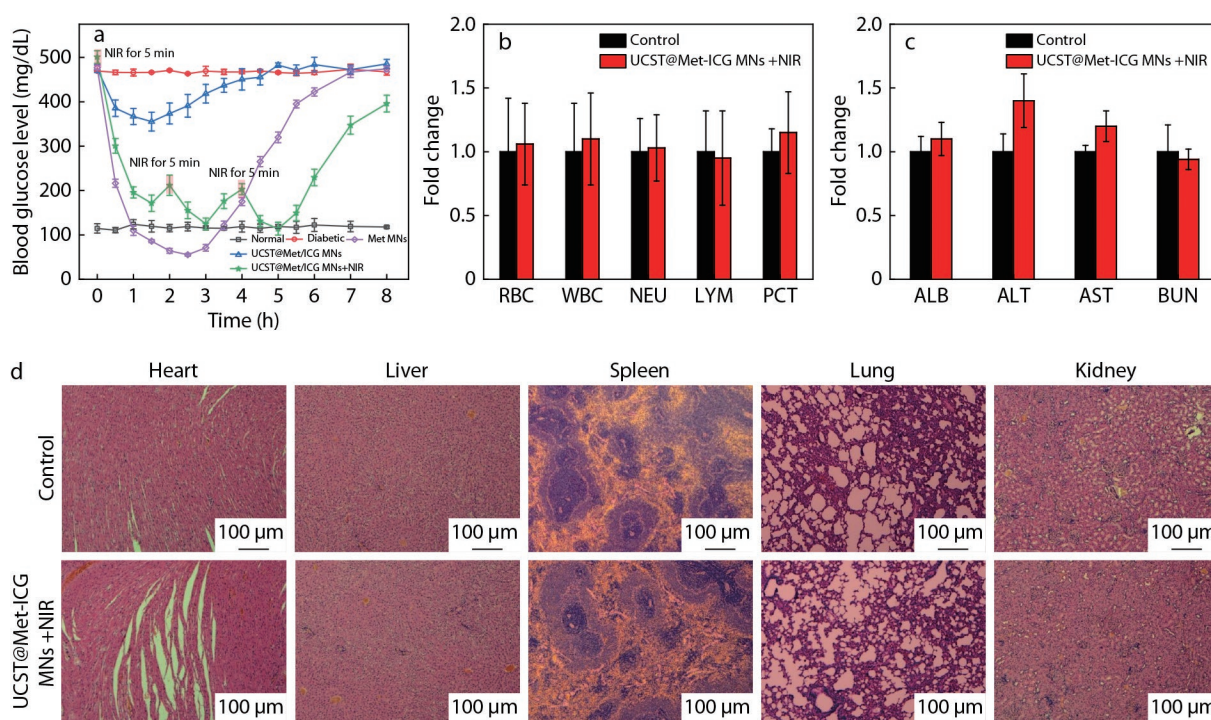


Fig. 5 (a) Blood glucose levels of rats with different treatments, the Group V of UCST@Met-ICG MNs+NIR was treated with NIR irradiation for 5 min (808 nm, 0.4 W/cm², 5 min) at beginning, the 2nd hour and 4th hour, respectively. (b) Blood routine examination indexes and (c) blood biochemistry indexes after application of UCST@Met-ICG MNs+NIR at the 7th day. (d) Microscopic images of H&E-stained tissue sections of rats in experimental group MNs loaded with UCST@Met-ICG+NIR.

without NIR irradiation, Group IV) is not well controlled, which may be caused by the limited leakage and the insufficient release of Met in carrier. On the contrary, experimental group (MNs loaded with UCST@Met-ICG + with NIR irradiation, Group V) received 5 min of NIR irradiation at the beginning of administration, which not only accelerate the dissolution of MNs in epidermis, but also accelerate the penetration and diffusion of the drugs. The blood glucose concentration quickly drop to the lowest value of 171 mg/dL at 1.5 h. The increased blood glucose concentration drop again to the lowest value of 125 mg/dL at 3 h after being irradiated for 5 min at 2 h. The subsequently increased blood glucose level drop again to the lowest value of 114 mg/dL at 5 h after the NIR irradiated for 5 min at 4 h. The controllable blood glucose level of the group with NIR may be attributed to the NIR-responsive release of Met in the UCST-type drug delivery system. And it was worth mentioning that compared to pure Met drug delivery, the UCST-type drug delivery system driven by NIR had blood glucose levels control for a longer time. Therefore, the application of UCST-type polymers in drug delivery made NIR-driven controlled release of drugs possible.

To further test the long-term potential toxicity of as-prepared MNs *in vivo*, the blood has been collected from the diabetic rats which were treated with UCST@Met-ICG MNs+NIR (Group V) and normal rats (Group I) for blood routine test. As shown in Fig. 5(b), after 7 days of administration, the blood indexes such as red blood cell (RBC), white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM) and albumin (ALB) do not change significantly compared with that of in control group (I), indicating that there was no syndrome caused by application of UCST@Met-ICG MNs+NIR (Group V). Moreover, the blood biochemistry indexes after UCST@Met-ICG MNs+NIR (Group V) shown in Fig. 5(c) including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and blood urea nitrogen (BUN) also had no obvious change compared to that of control group (I). Finally, the microscopic images of H&E-stained tissue sections of rats in experimental group (Group V) MNs loaded with UCST@Met-ICG + with NIR irradiation after 7 days of administration were shown in Fig. 5(c). Compared with the control group (Group I), no obvious tissue damage and inflammation were observed, which indicated that the NIR-driven drug delivery system had no potential acute toxicity as an on-demand drug release device.

CONCLUSIONS

In conclusion, a NIR-triggered photothermal MN path array device with on-demand drug supplement was successfully fabricated. The drug-loaded vesicles with a clearing point of 41 °C were successfully prepared through a self-assembly process. Meanwhile, the release behavior of Met from vesicles was controlled by NIR irradiation with the assistance of a photothermal conversion agent ICG *in vitro*. By integrating the drug-loaded vesicles with MNs for transdermal drug delivery, the drug-loaded MN device showed a significant effect on regulating the blood glucose level of diabetic rats to a normal level upon interval NIR irradiation. Additionally, the property of low cytotoxicity and negligible acute toxicity made it possible for clinical application.

NOTES

The authors declare no competing financial interest.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <http://doi.org/10.1007/s10118-021-2640-x>.

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