

## Supporting Information

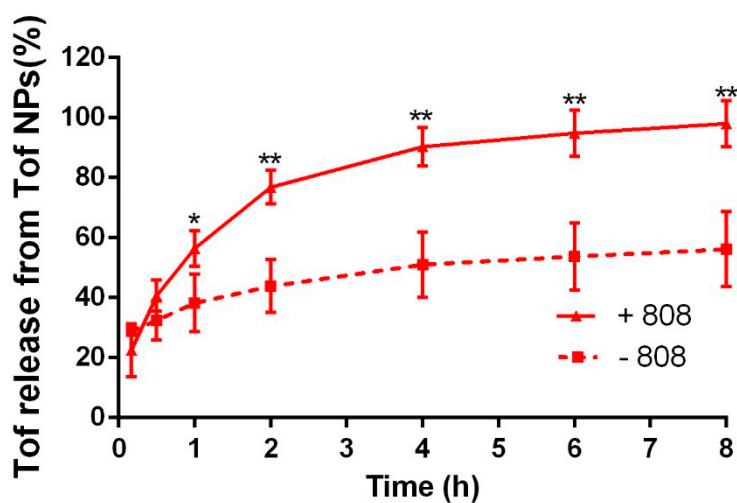


Figure S1. *In vitro* release of Tof from Tof NPs with or without light irradiation. The irradiation was performed with 808 nm near infra-red light at the power density of 1 W·cm<sup>-2</sup> for 5min prior to *in vitro* release. (\* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ ).

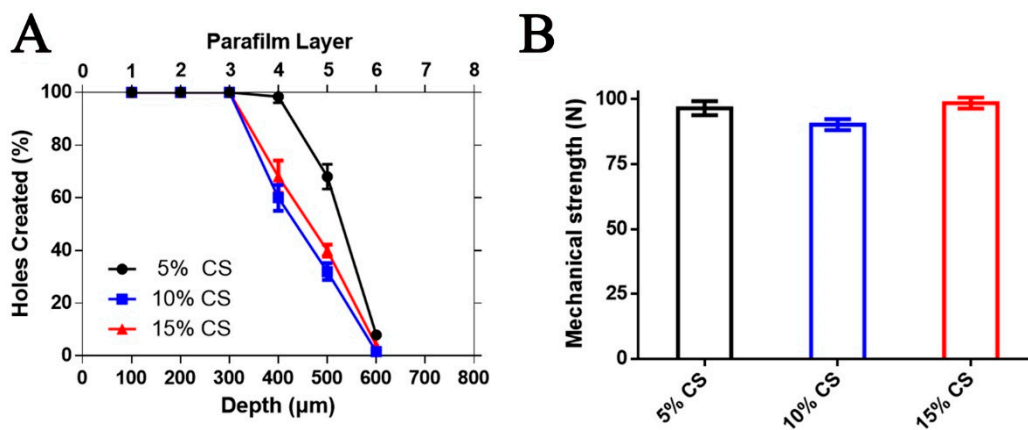


Figure S2. Screening the content of CS in MN formulation. The insertion depth (A), mechanical strength (B) of different (containing 5%,10%,15% of CS) MNs.

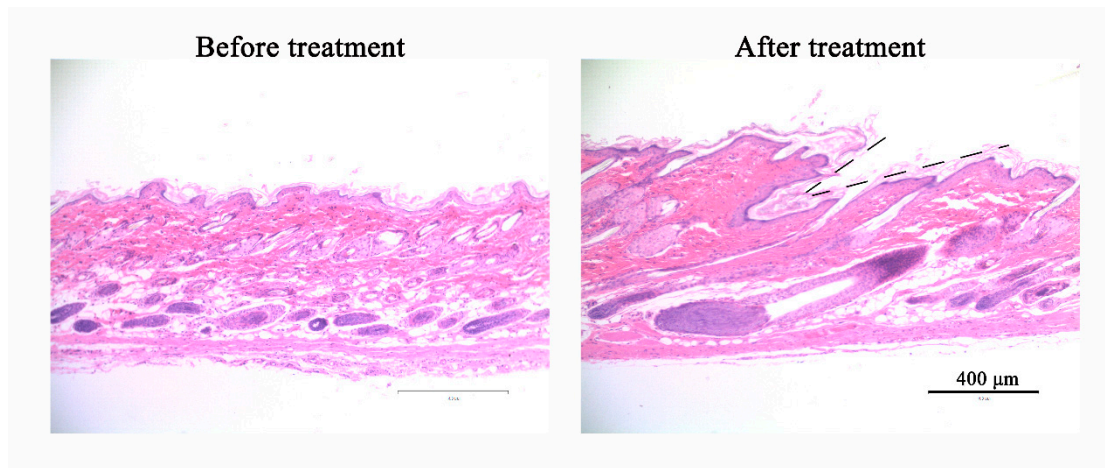


Figure S3. The HE stained sections before and after 808+Lox+Tof NPs@MN treatment.

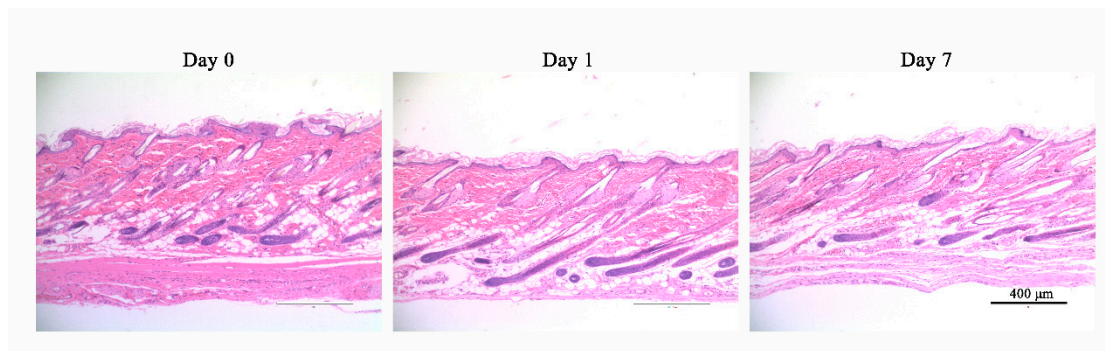


Figure S4. The HE stained sections before 808+Lox+Tof NPs@MN treatment (Day 0) and after 808+Lox+Tof NPs@MN treatment (Day 1 and Day 7).

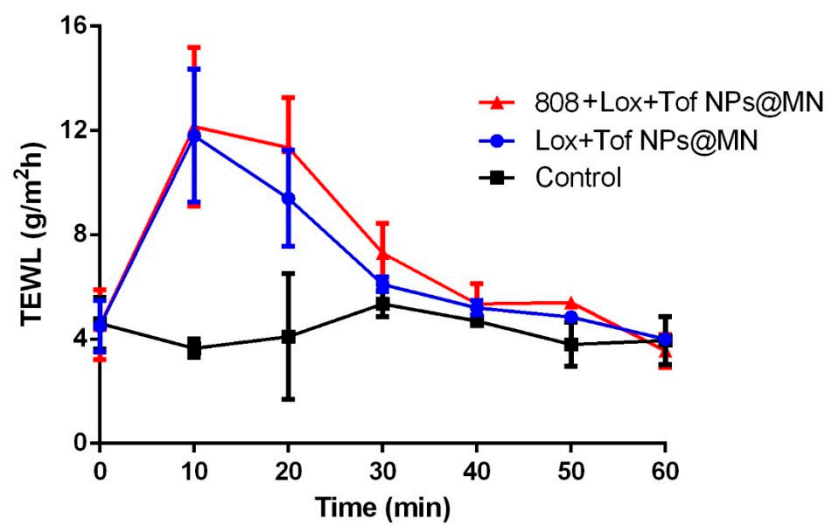


Figure S5. The TEWL after different treatment (Control, Lox+Tof NPs@MN, and 808+Lox+Tof NPs@MN).

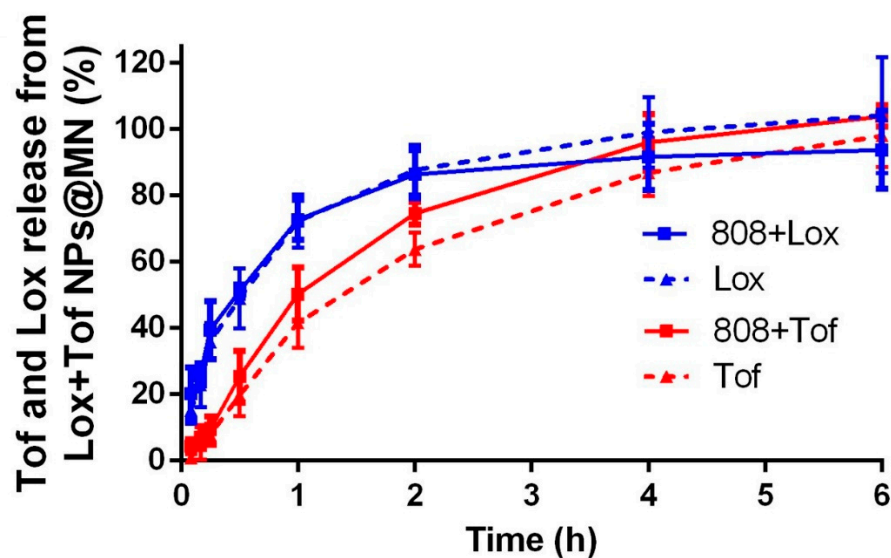


Figure S6. *In vitro* release of Tof and Lox from Lox+Tof NPs@MN. Cumulative release rate of Lox and Tof from Lox+Tof NPs@MNs with or without light irradiation. The irradiation was performed with 808 nm near infra-red light at the power density of 1 W·cm<sup>-2</sup> for 5min prior to *in vitro* release. (n=4, \**p* < 0.05, \*\**p* < 0.01, and \*\*\**p* < 0.001).

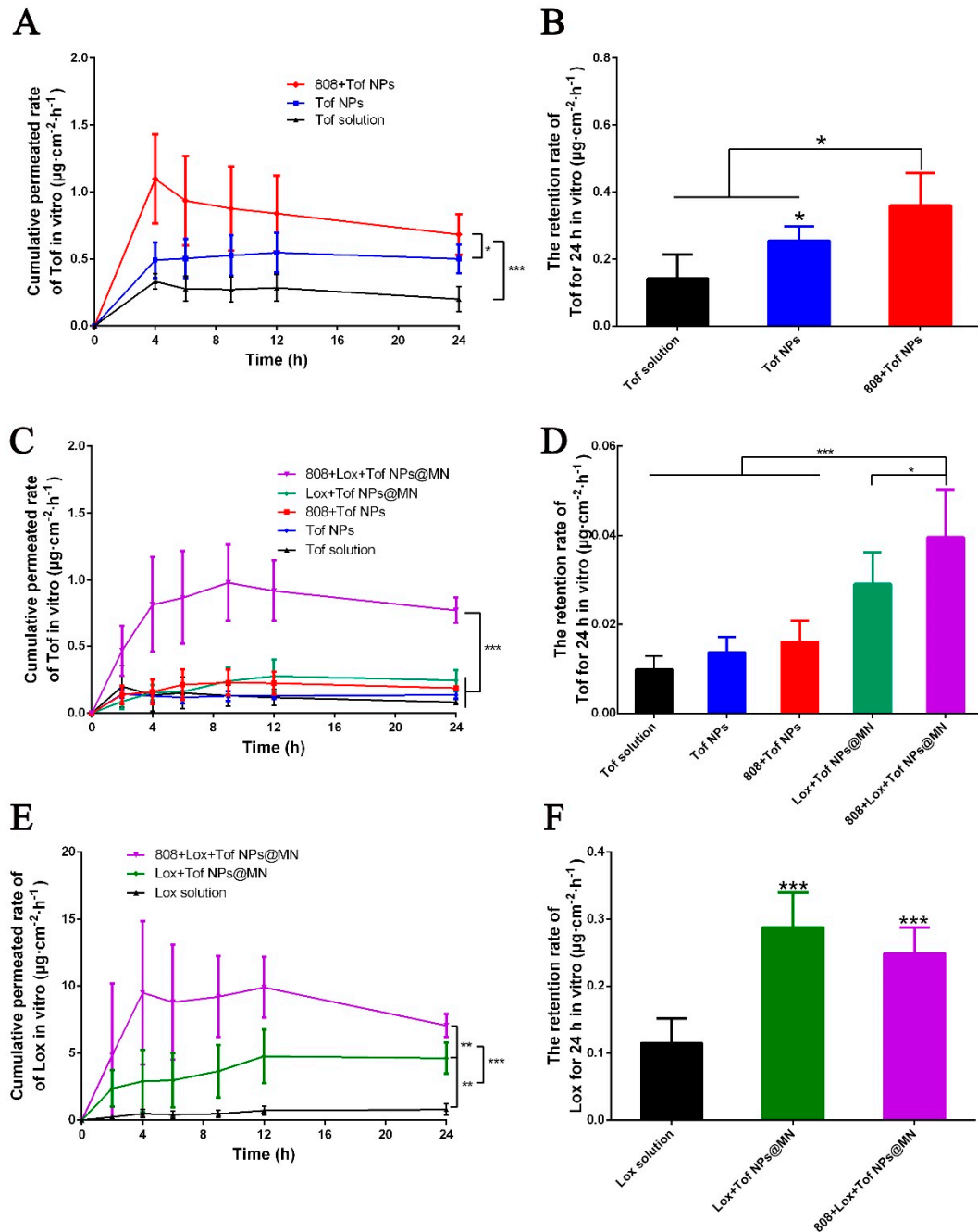


Figure S7. *In vitro* permeation of ToF NPs and Lox+ToF NPs@MN through rat skin for 24h.

Cumulative permeation rate (A) and skin retention rate (B) of ToF from ToF NPs with or without light irradiation. Cumulative permeation rate (C) and skin retention rate (D) of ToF from Lox+ToF NPs@MN with or without light irradiation. Cumulative permeation rate (E) and skin retention rate (F) of Lox from Lox+ToF NPs@MN with or without light irradiation.

(n=6, \* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ ).

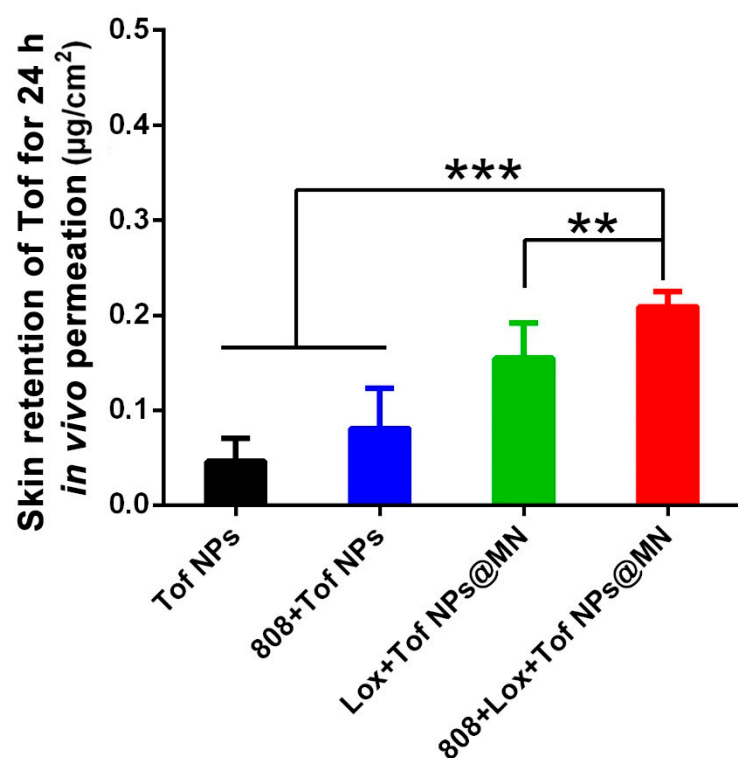


Figure S8. Skin retention of ToF for 24 h *in vivo* permeation from different formulations. (n=4,

\* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ )

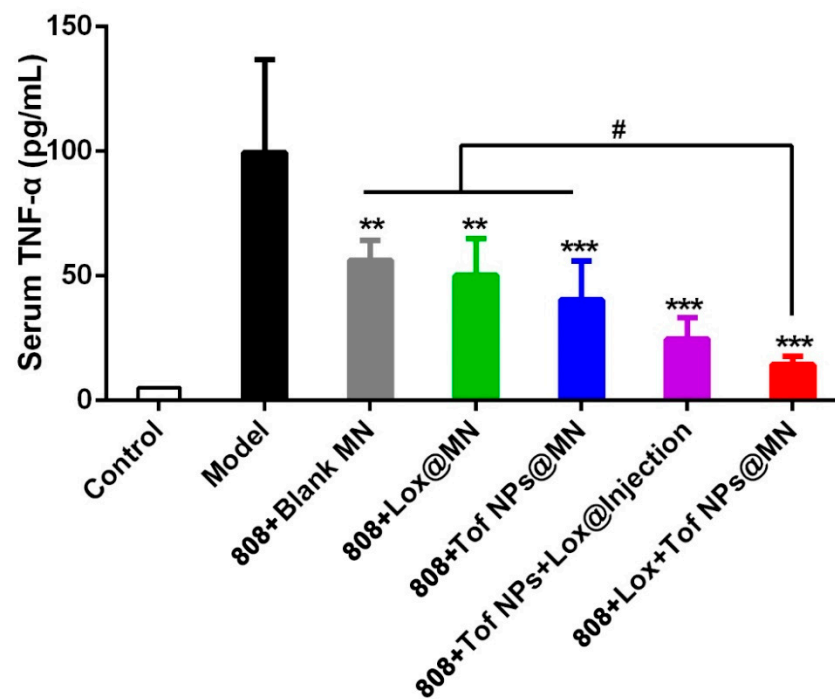


Figure S9. The serum TNF- $\alpha$  of arthritic rats. (n=4, <sup>#</sup>  $p < 0.05$ , \* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ )

**Table S1**

DNA sequence of primer pairs used for quantitative real time PCR in cells.

Primer	Base sequence (5'-3')
GAPDH (Forward primer)	AGAGGGAAATCGTGCGTGAC
GAPDH (Reverse primer)	CGATAGTGATGACCTGACCGT
iNOS (Forward primer)	CTTGGAGCGAGTTGTGGATTGTC
iNOS (Reverse primer)	TAGGTGAGGGCTTGGCTGAGTG
IL-1 $\beta$ (Forward primer)	ATTGTGGCTGTGGAGAAG
IL-1 $\beta$ (Reverse primer)	AAGATGAAGGAAAAGAAGGTG

**Table S2**

DNA sequence of primer pairs used for quantitative real time PCR in rats.

Primer	Base sequence (5'-3')
$\beta$ -actin (Forward primer)	CCCGCGAGTACAACCTTCT
$\beta$ -actin (Reverse primer)	CGTCATCCATGGCGAACT
STAT3 (Forward primer)	GTAGTGCTGCCCCTTACCTG
STAT3(Reverse primer)	TCCATGTCAAACGTGAGCGA
INOS (Forward primer)	TAGTCAACTACAAGCCCCACG
INOS (Reverse primer)	AGTCACATGCAGCTTGTCCA
TNF- $\alpha$ (Forward primer)	GGCTTTCGGAACCTCACTGGA
TNF- $\alpha$ (Reverse primer)	GGGAACAGTCTGGGAAGCTC
JAK2 (Forward primer)	TCCACCCAATCATGTCTTCCAC
JAK2 (Reverse primer)	GCTTCAGCCCCACGAGATAC
JAK3 (Forward primer)	CCTGGAGTGGCACGAGAATC
JAK3 (Reverse primer)	TCCACAACCTCCCGCCTAT
IL- $\beta$ (Forward primer)	TGCCACCTTTTGACAGTGATG
IL- $\beta$ (Reverse primer)	AAGGTCCACGGGAAAGACAC