Tackling Antibiotic Resistance Using Hydrogel-Forming Microneedle Technology to Deliver Antibiotics Transdermally

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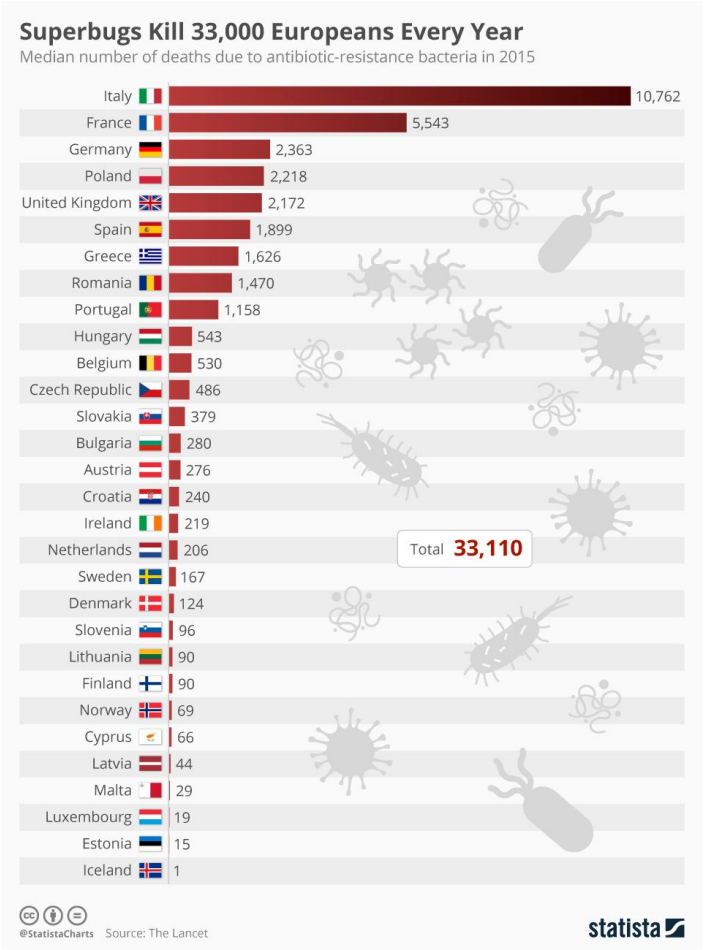
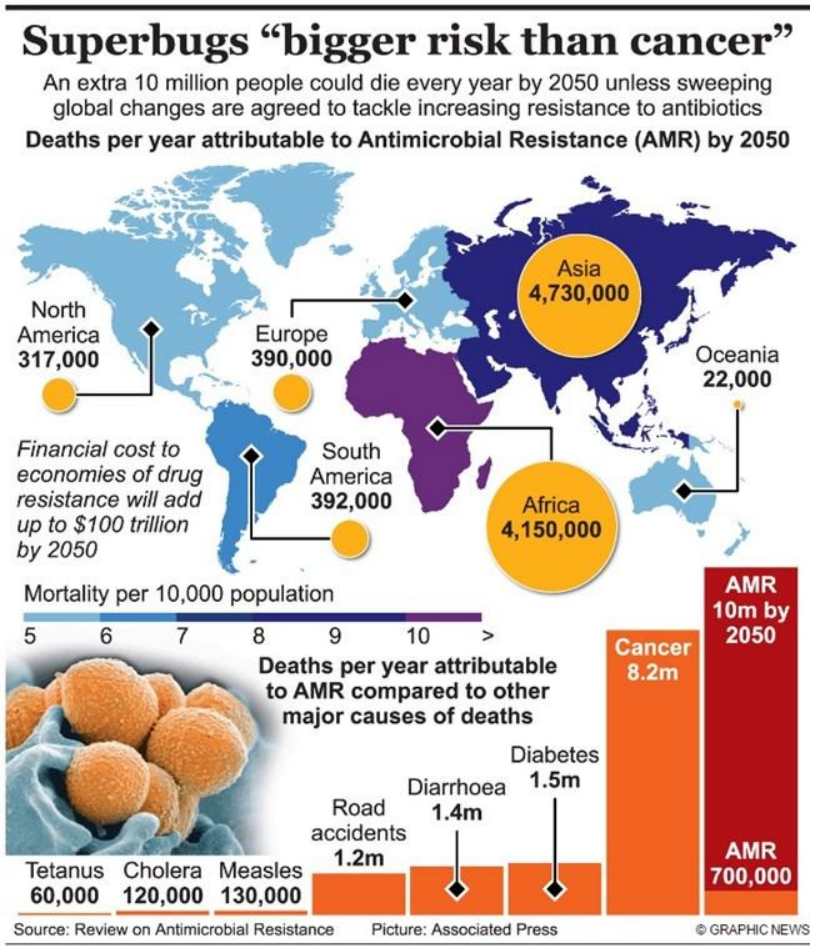
World Health Organization

Antibiotic resistance is currently one of the ten biggest health threats in the world.

Antibiotic resistance is a natural phenomenon, which can be dramatically accelerated by misuse of antibiotics.

- **Bad news: No new major antibiotic has been developed in the last 30 years!!!**





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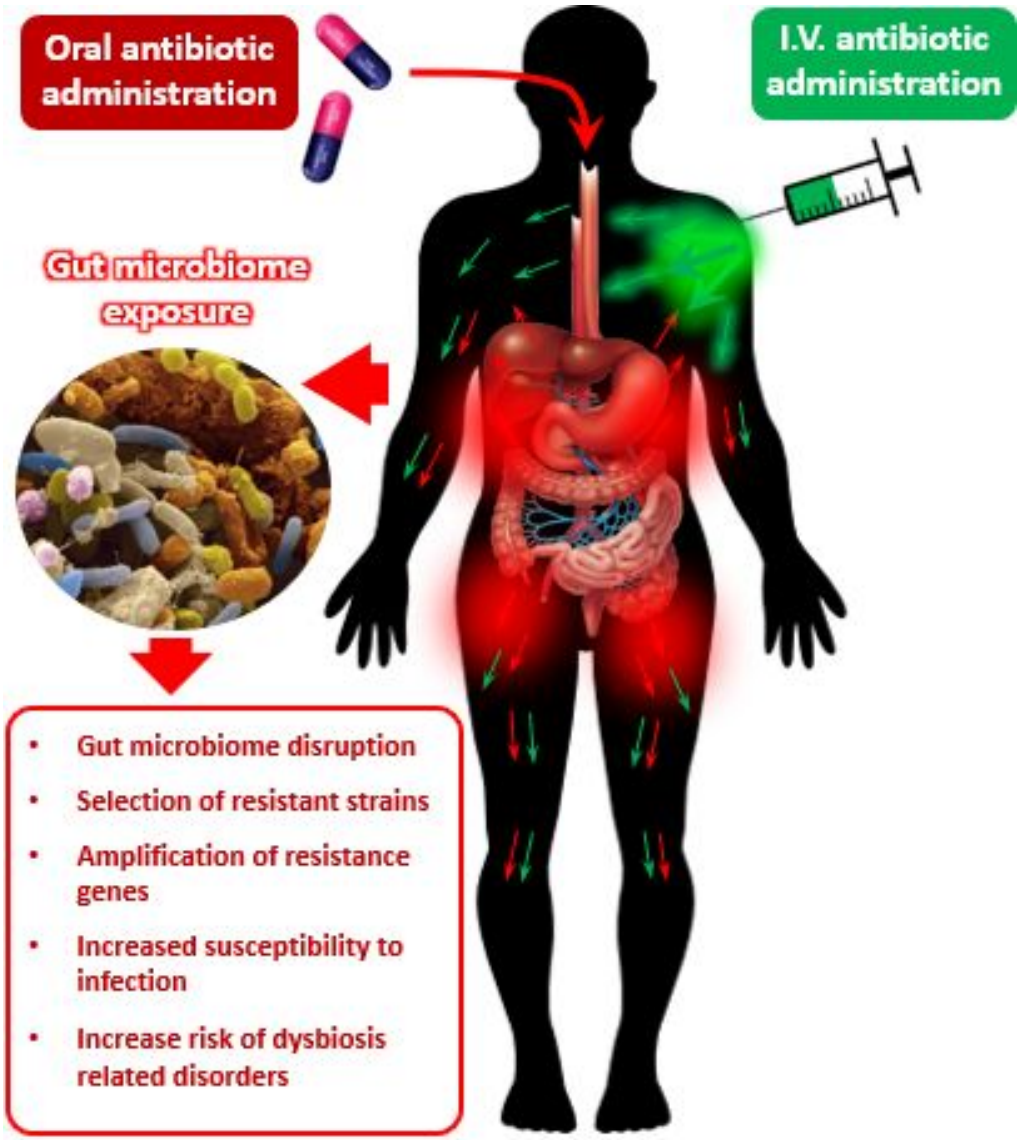
- Oral administration of antibiotics may significantly accelerate the development of antibiotic resistance because antibiotics will interact with bacteria inhabiting the human gut[1].

- Intravenous injection of antibiotics considerably reduces development of resistance amongst gut bacteria relative to oral administration, especially for antibiotics that are predominantly renally excreted[2].



Reference

1. Murray, B., Rensimer, E. and DuPont, *N Engl J Med* 306, 130-135 (1982).
2. Zhang L., Huang, Y., Zhou Y. Buckley, T. and Wang, H, Antimicrob Agents Chemother. 57(8), 3659-3666 (2013).

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- However, healthcare systems such as the NHS cannot afford such high cost if every antibiotic administration is carried out in hospital.

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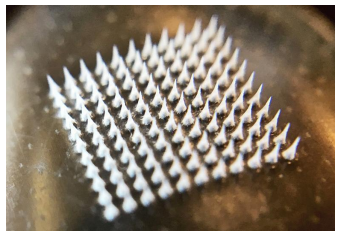
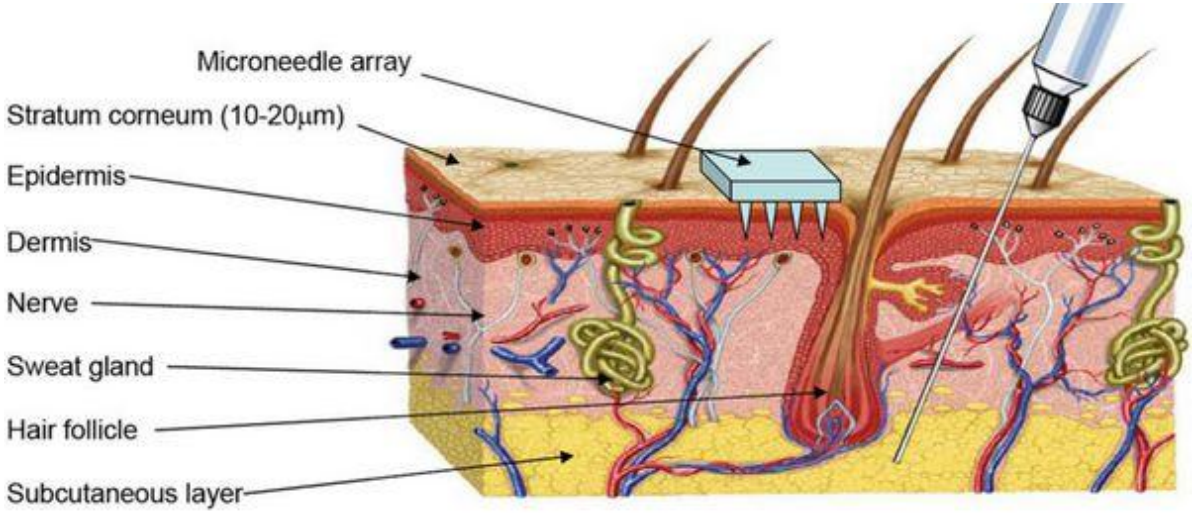
Why should we use microneedle (MN) technology?



A microneedle array patch (MAP) contains hundreds of small short needles which can deliver drug molecules into skin by painlessly penetrating *stratum corneum.* It can potentially allow patients to take antibiotics transdermally without the help of healthcare professionals.



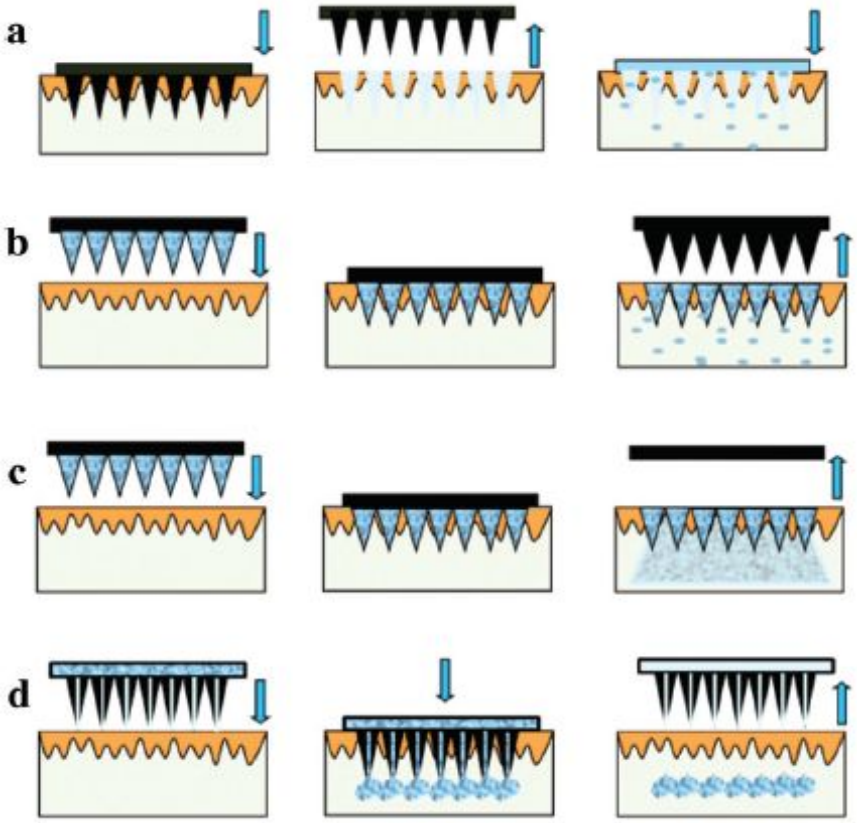


Figure 1. Schematic representation of different types of microneedles:
(a) Solid microneedle, (b) Coated microneedle
(c) Dissolving microneedle (d) Hollow microneedle

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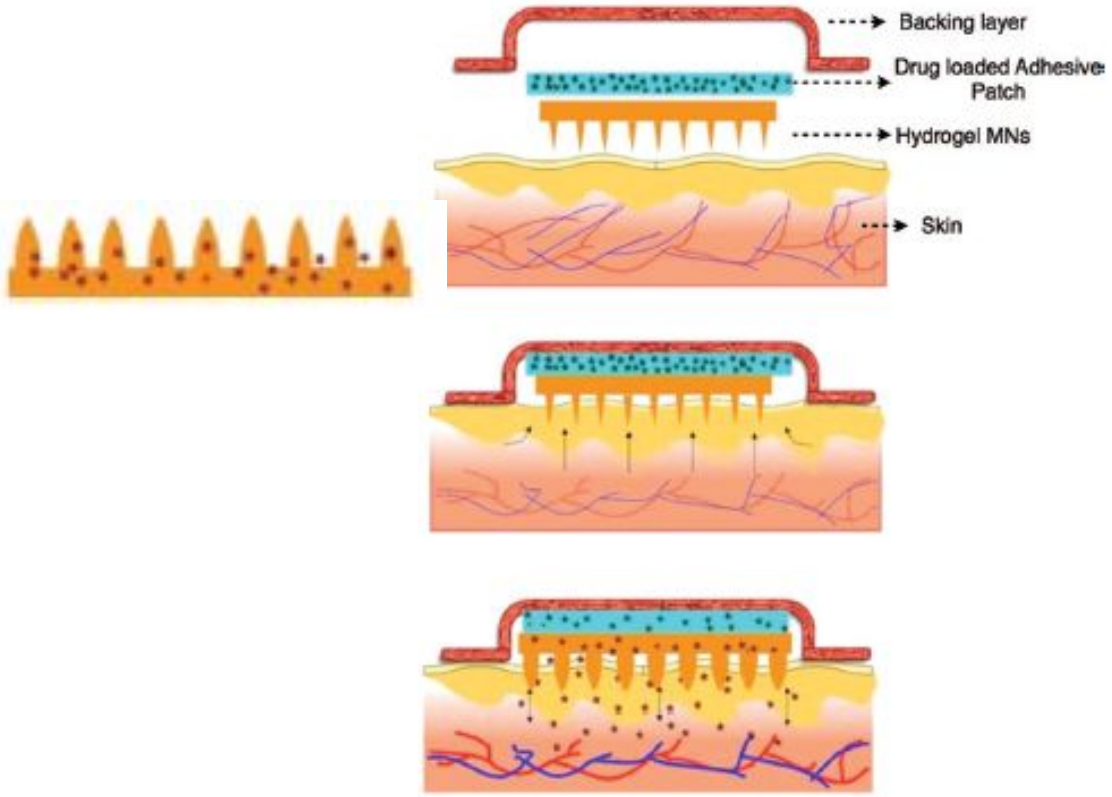
Hydrogel-forming microneedle,
which is able to deliver high dose drugs.



Aim:

To develop a high dose antibiotic patch using our hydrogel-forming microneedle technology, which allows antibiotics from a pre-prepared antibiotic 'tablet' that is attached to the microneedle patch to be delivered into the rich dermal microcirculation in the skin, thus bypassing the gut bacteria.

Drug candidates:

(1) Levofloxacin √
(2) Amoxicillin
(3) Tetracycline √
(4) Vancomycin

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Method of fabricating microneedle and drug tablet

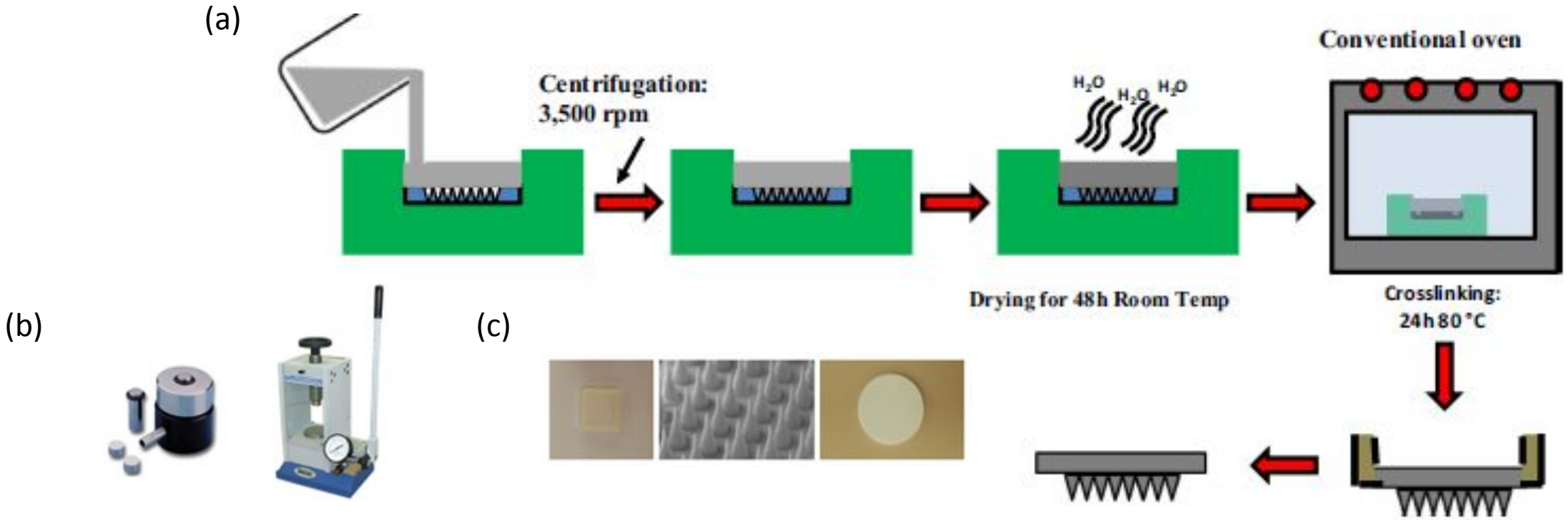

Figure 2. (a) Schematic diagram of microneedle fabrication procedure
(b) A FITR die and hydraulic press kit used to make the drug tablet by direct compression.
(c) Images of Gantrez™ hydrogel-forming microneedle patch (0.5 cm^2 each), SEM image of microneedles, drug tablet made by direct compression.

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Formulation of levofloxacin HCL drug tablet

Formulation No.	Levofloxacin HCl	Microcrystalline cellulose	Croscarmellose sodium	Mannitol	Tablet dissolution time in PBS (min)
1	60	20		20	5
2	60		20	20	3
3	60	30		10	4
4	60		10	30	4
5	60	10		30	4
6	80	15		5	6
7	80	10		10	5
8	80		10	10	2
9	80			20	3.5
10	80		20	0	2.5
11	90	5		5	3
12	90		5	5	3
13	90	10			3.5
14	90		10		3

Table 1. Levofloxacin HCl drug tablet formulation. Each tablet weighs 150mg.

In vitro drug permeation study

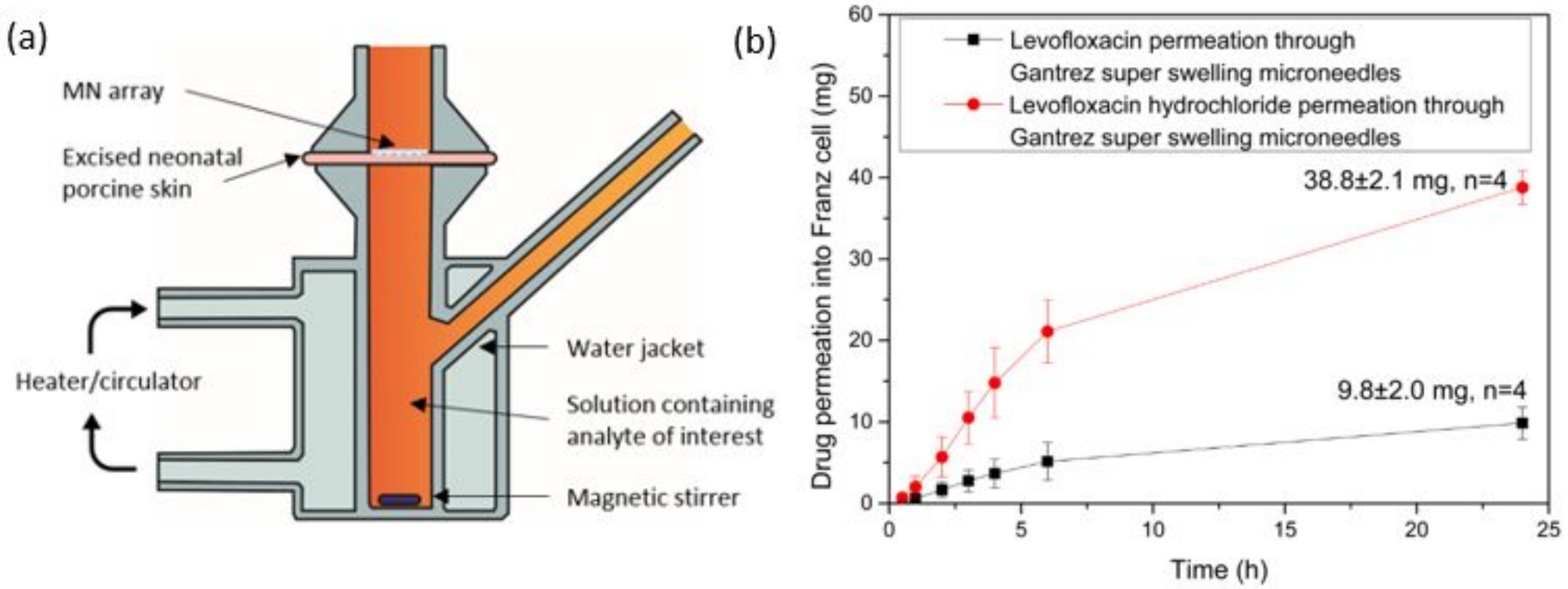

Figure 3. (a) An illustration of a typical Franz cell setup (b) *In vitro* levofloxacin drug permeation study using the Franz cell setup. Each drug tablet weighs 150 mg.

In vivo animal study

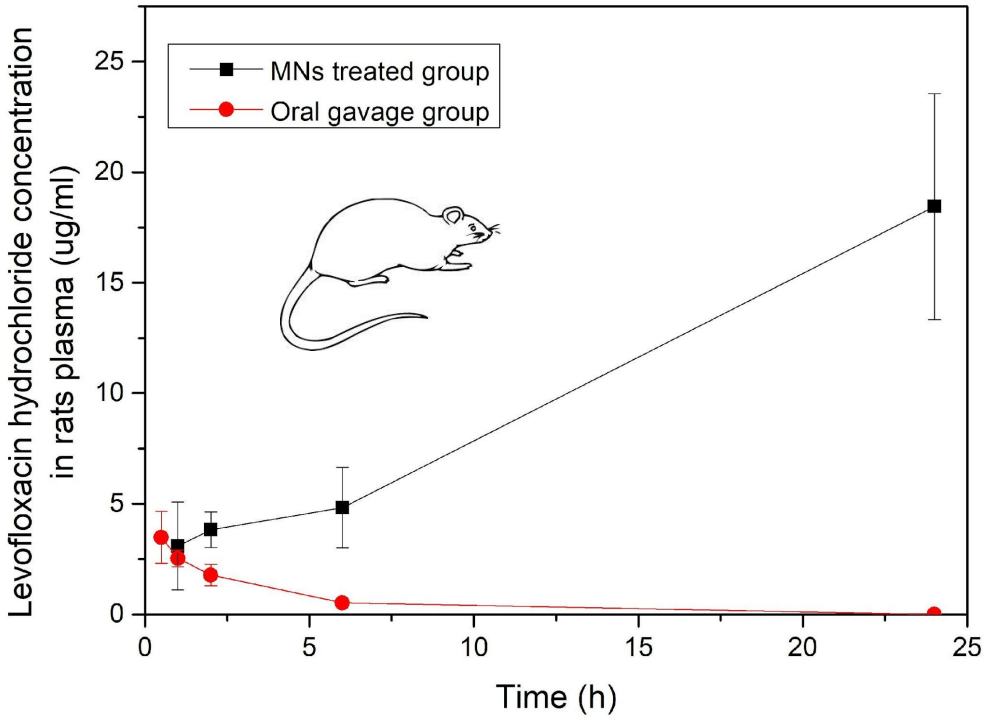

Figure 4. *In vivo* levofloxacin HCl delivery in rats.

4 MAPs containing 480 mg drug were applied to each rat, whereas 46 mg/kg levofloxacin HCl was given to each rat in oral group.

Max drug plasma concentration is 3.49 µg/mL (± 1.17) 0.5h after oral administration. It gradually decreased over time.

Min drug concentration for MN treated group is 3.09 µg/mL (± 1.99) 1 h after application, gradually increased to 18.45 µg/mL (± 5.11) at 24h.

$AUC_{MN}/AUC_{oral} = 27.8$

Based on a daily dose of 500 mg levofloxacin for common human infection treatment, a MAP of approx. 7.3 cm^2 is needed for daily human infection treatment.

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Formulation of tetracycline HCL drug tablet

Formulation No.	tetracycline HCl	Mannitol	Croscarmellose sodium	Mannitol	Tablet dissolution time in PBS (s)
1	90	5	5	20	<30
2	90	7.5	2.5	20	<30
3	90	2.5	7.5	10	<30
4	80	10	10	30	<60
5	80	15	5	30	<90
6	80	5	15	5	<30
7	70	15	15	10	<90
8	70	20	10	10	<90
9	70	10	20	20	<60

Table 2. Tetracycline HCl drug tablet formulation. Each tablet weighs 150mg.

In vitro permeation study

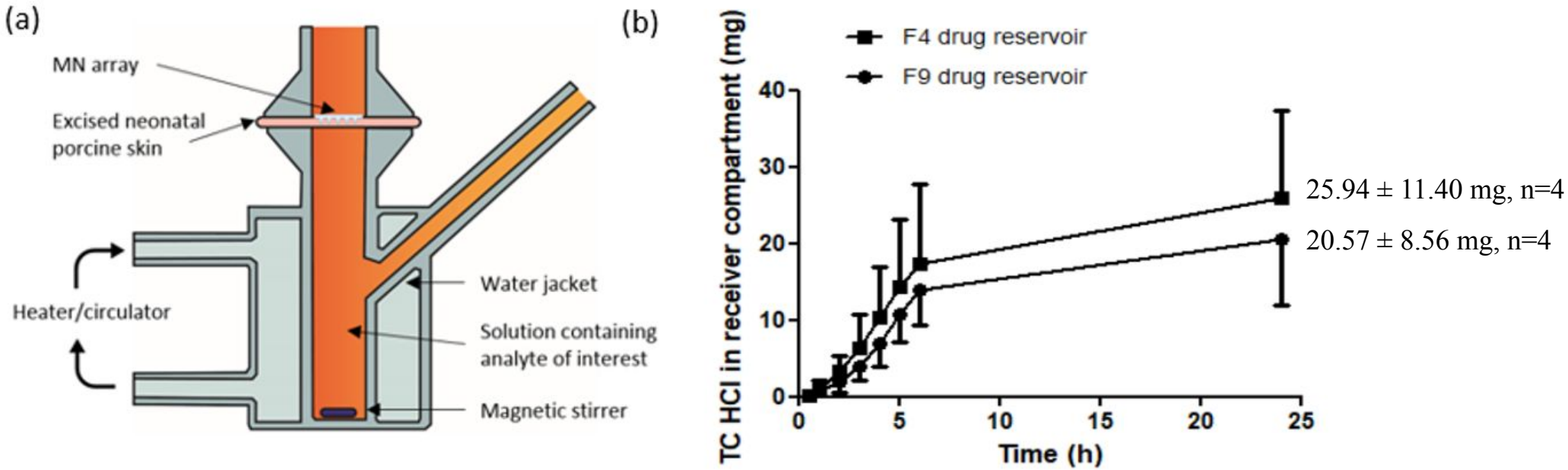

Figure 5. (a) An illustration of a typical Franz cell setup (b) *In vitro* tetracycline drug permeation study using the Franz cell setup. Each drug tablet weighs 150 mg.

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In vivo animal study

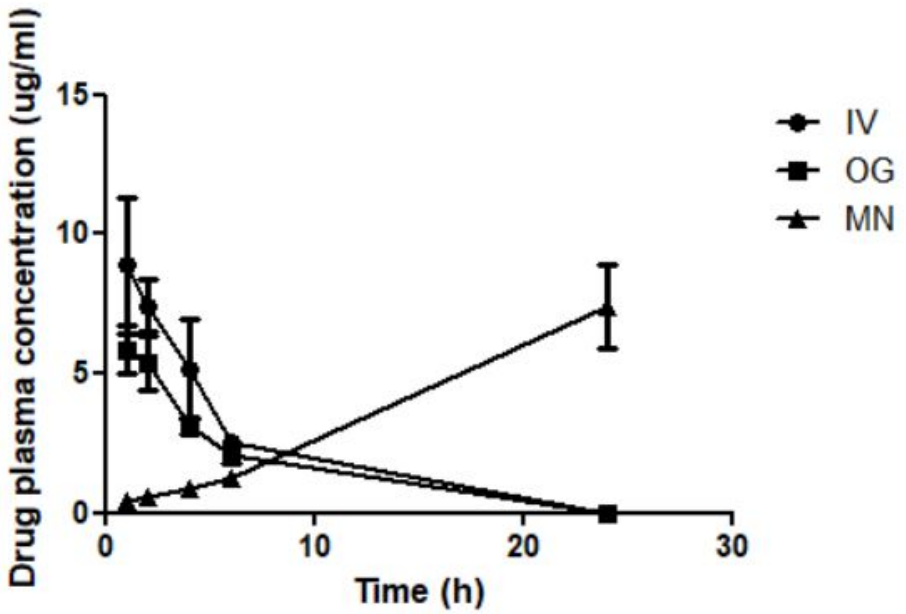

Figure 6. *In vivo* tetracycline HCl delivery in rats.

4 MAPs containing 160 mg drug were applied to each rat, whereas 50 mg/kg tetracycline HCl was given to each rat in oral group.

Max drug plasma concentration is 8.86 ± 4.19 µg/mL 1 h after IV administration. It gradually decreased over time.

Min drug concentration for MN treated group is 0.43 ± 0.11 µg/ml 1 h after application, gradually increased to 7.40 ± 4.74 µg/ml at 24h.

$AUC_{MN}/AUC_{IV} = 2.44$

Based on a daily dose of 500 mg tetracycline for human infection treatment, a MAP of approx. 32.8 cm^2 is needed for daily treatment.

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Key summaries

- A high dose antibiotic microneedle system that can potentially extend the lifespan of the existing antibiotics has been successfully developed.

Future work

- A repeated dosing animal study has been planned to mimic patients taking antibiotics repeatedly during a course of antibiotic treatment.

Future challenge

- Due to the relatively high cost of microneedle patch compared to oral tablets, we may need collaborations from a variety of stakeholders to help move the product towards commercialisation.

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Thank you for your attention!