Development of antibiotic hydrogel-forming microneedle array patches for improved tuberculosis treatment

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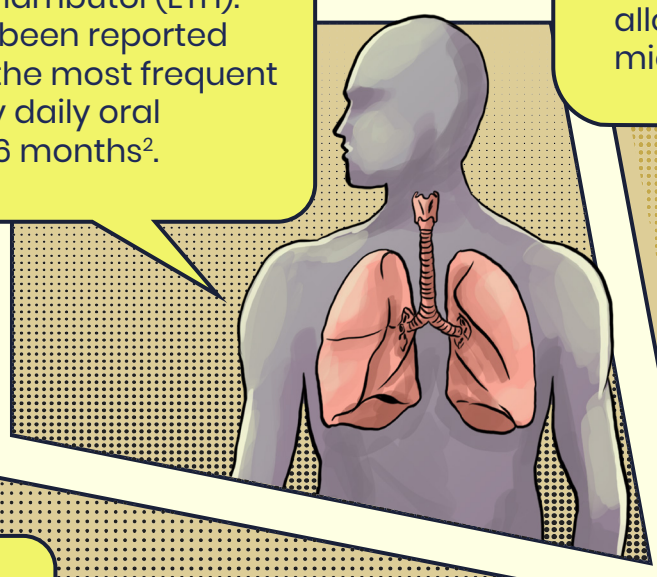
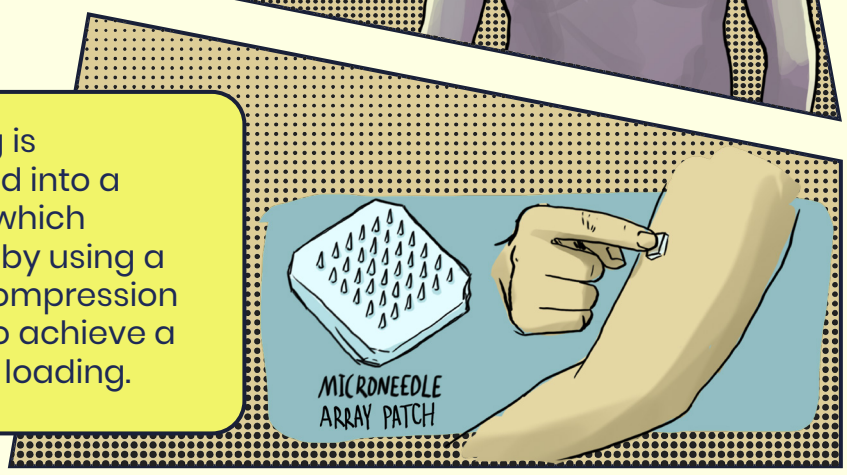
INTRODUCTION

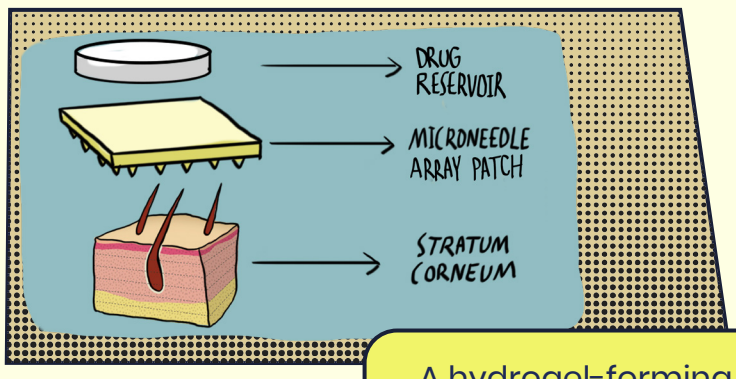
Almost 2 billion people in this planet has been infected by *Mycobacterium tuberculosis*[1]. The current available treatment for tuberculosis (TB) consists of rifampicin (RIF), isoniazid (INH), pyrazinamide (PYR) and ethambutol (ETH). However, this regimen has been reported causing hepatotoxicity as the most frequent adverse effect triggered by daily oral administration for at least 6 months[2].



Microneedle array patch (MAP) has a promising ability to penetrate deeper layers of skin by modifying the *stratum corneum barrier*[3]. This system consists of micron-sized needles that can be used to penetrate the deeper layer of skin, thus, allowing the drug permeated and reached the microcirculation for the systemic absorption.

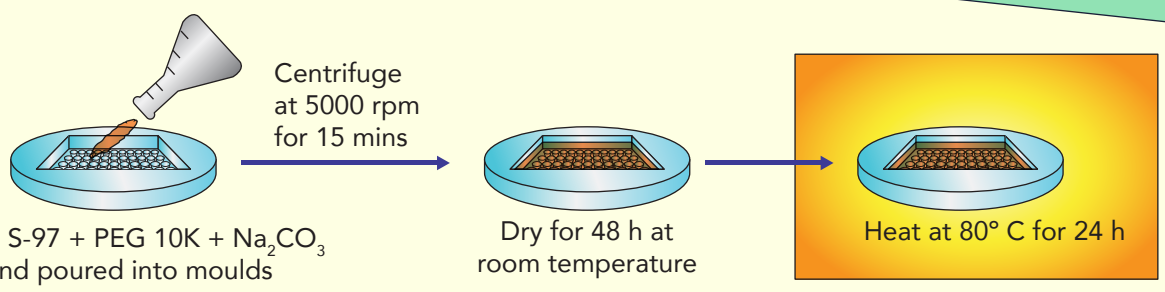
Each drug is formulated into a reservoir which prepared by using a directly compression method to achieve a high drug loading.



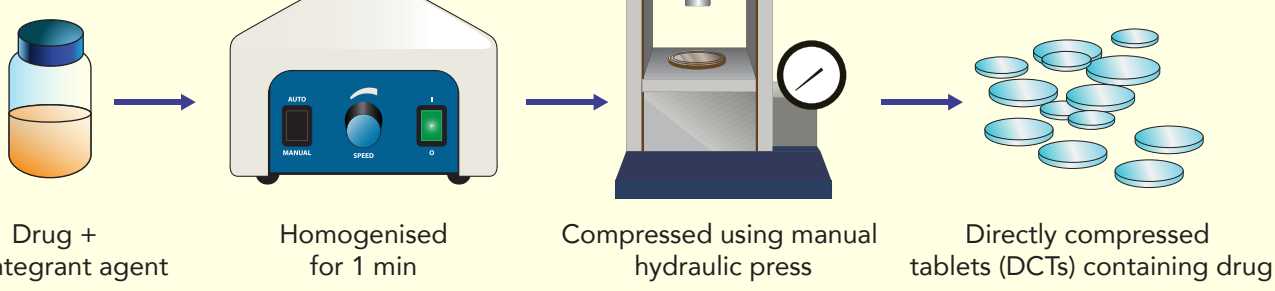


A hydrogel-forming MAP is combined with a drug-containing reservoir in the aim of delivering a high dose of TB drugs.

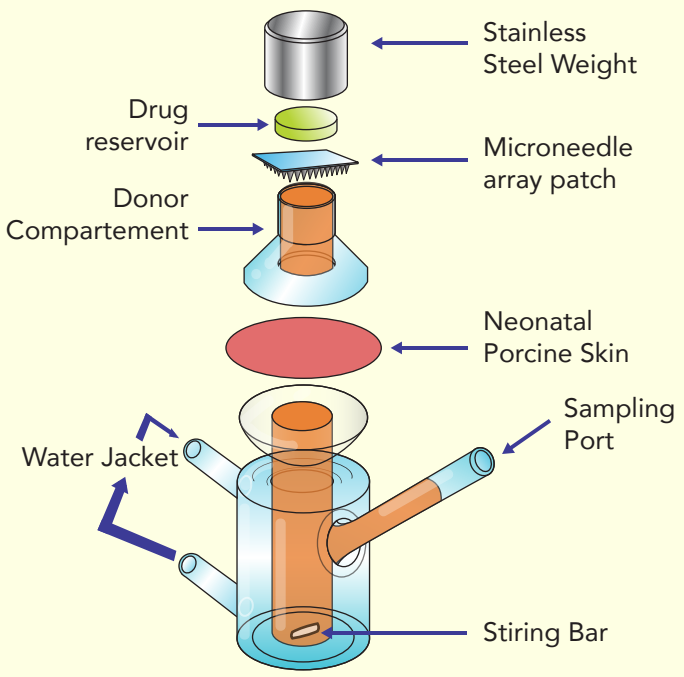
METHOD 1 Hydrogel-forming MAP fabrication



METHOD 2 Drug reservoir preparation

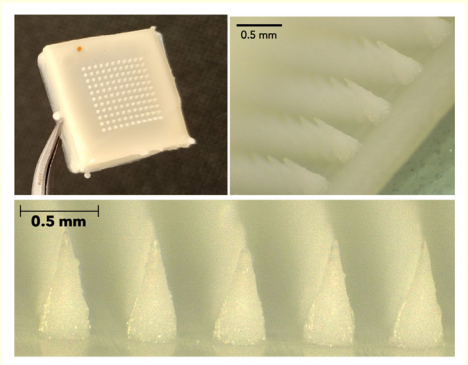


METHOD 3 *In vitro* permeation study



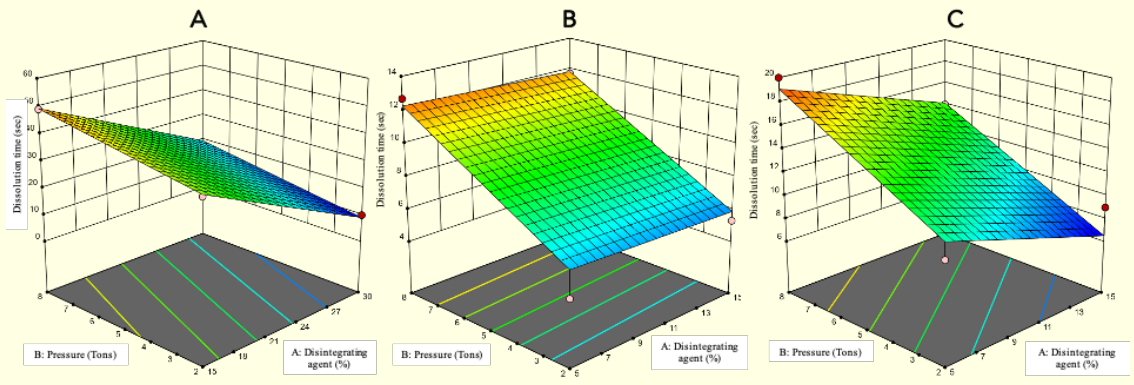
RESULTS

① Hydrogel-forming MAP formulation exhibited homogeneous and robust in term of physical appearance



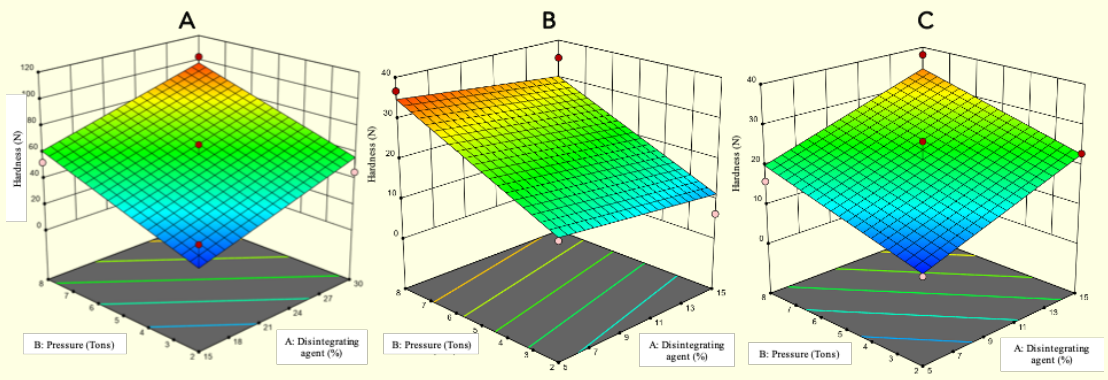
Images of hydrogel-forming MAP (Aqueous blend containing of 20% w/w Gantrez® S-97, 7.5% w/w PEG 10K, 3% w/w Na_2CO_3)

② The dissolution time was significantly affected by the disintegrating agent concentration and pressure compression ($p<0.05$). The dissolution time of the optimised formulations were in the range of 10-12 sec.



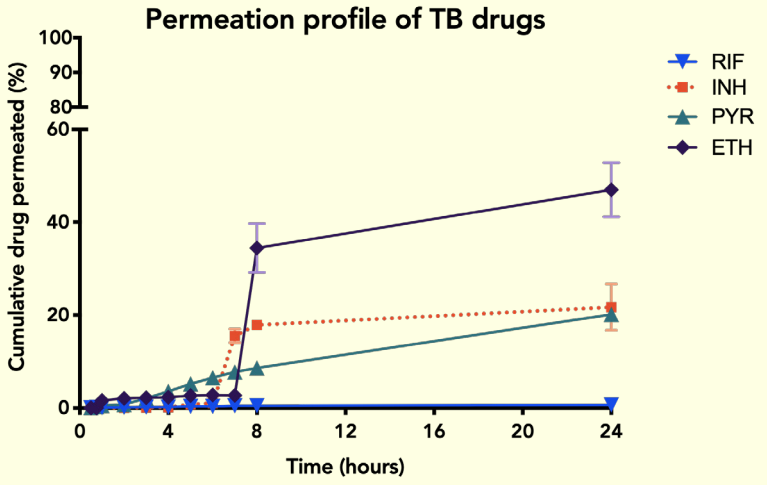
Response surface plots describing the effect of crospovidone concentration and compression pressure on the dissolution time of (A) RIF, (B) INH and (C) PYR loaded in DCT formulations.

③ The hardness parameter was also significantly affected by the disintegrating agent concentration and pressure compression ($p<0.05$). The hardness values of the optimised formulations were in the range of 33-58 N.



Response surface plots describing the effect of crospovidone concentration and compression pressure on the hardness parameter of (A) RIF, (B) INH and (C) PYR loaded in DCT formulations.

④ Each 0.5 cm^2 of hydrogel-forming MAP was capable to deliver approximately 0.66% (0.69 mg), 23.02% (30.96 mg), 20.16% (25.71 mg) and 46.99% (46.99 mg) in 24 h from individual drug reservoir for RIF, INH, PYR and ETH, respectively.



CONCLUSION

- The reservoir formulations of TB drug regimen combined with hydrogel-forming MAP were successfully developed.
- Based on the *in vitro* permeation studies, the developed MAP system was able to deliver the TB drugs across the dermatomed neonatal porcine skin.
- This approach could potentially contribute to the TB treatment improvement.

REFERENCES

1. WHO. (2020). *Global Tuberculosis Report* 2019.
2. Tostmann, A., Boeree, M. J., Aarnoutse, R. E., De Lange, W. C. M., Van Der Ven, A. J. A. M., & Dekhuijzen, R. (2008). Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review. *Journal of Gastroenterology and Hepatology* (Australia), 23(1), 192–202.
3. Donnelly, R. F., McCrudden, M. T. C., Alkilani, A. Z., Larrañeta, E., McAlister, E., Courtenay, A. J., Kearney, M. C., Thakur, R. R. S., McCarthy, H. O., Kett, V. L., Caffarel-Salvador, E., Al-Zahrani, S., & Woolfson, A. D. (2014). Hydrogel-forming microneedles prepared from "super swelling" polymers combined with lyophilised wafers for transdermal drug delivery. *PLoS ONE*, 9(10), 1–12.