The use of novel directly compressed tablets combined with hydrogel-forming microneedles for the transdermal delivery of a low molecular weight, high dose antibiotic

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Global health challenge

QUEEN'S UNIVERSITY BELFAST

DAILY NATION 2012

Neonatal sepsis: A leading cause of infant death

Neonatal sepsis is any infection in an infant during the first 28 days of life.

World Health Organization

Outpatient treatment guidelines:

- Oral amoxicillin (AMX)
- Intramuscular gentamicin

Limitations of recommended oral AMX treatment:

- Access to clean water
- Cold chain necessary
- Antibiotic resistance

EXPRESS 2017

Antibiotic resistance: Huge fears for 'end of modern medicine'

ENGLAND'S chief medical officer has warned of a "post-antibiotic apocalypse" as she issued a call to action urging global leaders to address the growing threat of antibiotic resistance.

Administration of oral antibiotic

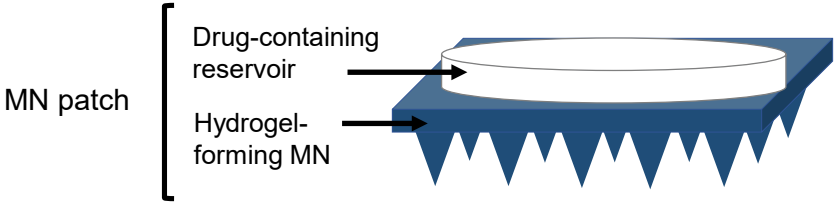
Exposure of gut microbiota to antibiotic

- Disturbance of gut microbiota
- Emergence of antibiotic-resistant genes
- Amplification of antibiotic-resistant genes
- Increased susceptibility to severe infection

AIM

To develop a unique system capable of **transdermally delivering** clinically effective doses of **AMX**; a low molecular weight, high dose antibiotic using **microneedle (MN) patches** for the potential treatment of **neonatal sepsis**

MN patch

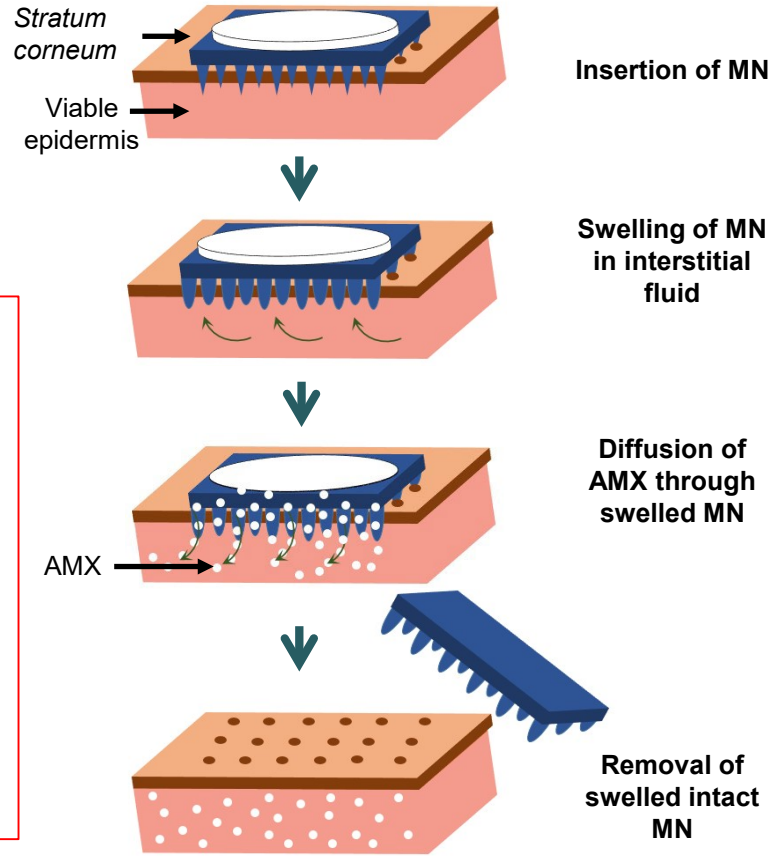


Hydrogel-forming MNs

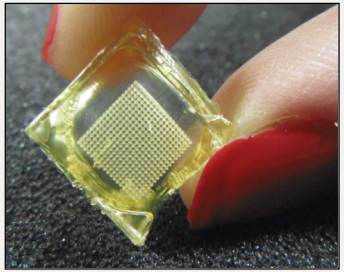
- Hard in the dry state
- Rapidly take up interstitial fluid, swell and triggers diffusion of drug from the attached drug-containing reservoir

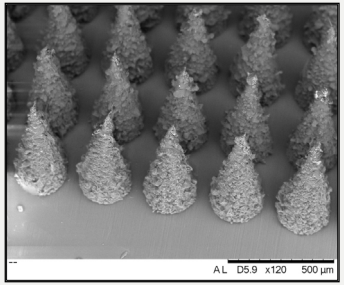
Benefits

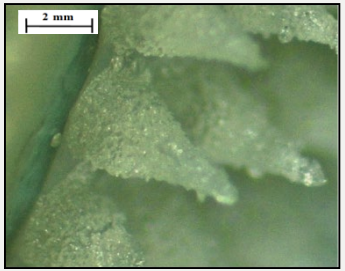
1. Removed from skin intact
2. Incapable of re-insertion
3. Loading capacity not linked to MN



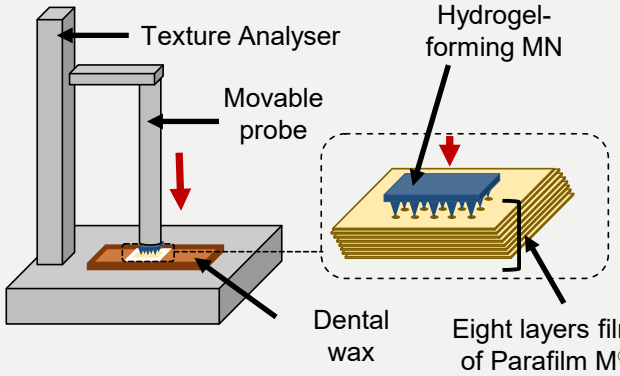
MN patch characterisation

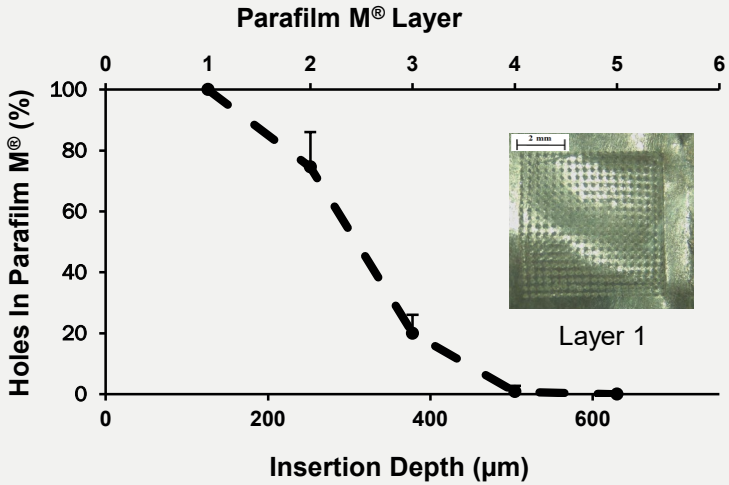


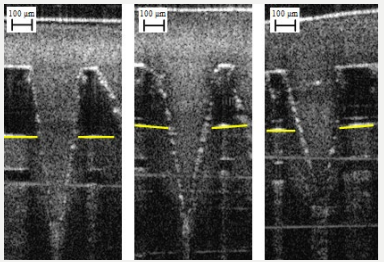




Hydrogel-forming MN fabrication and characterisation



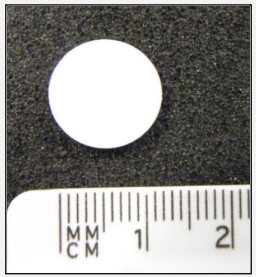


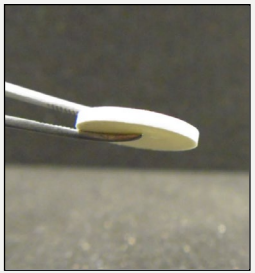


- These MNs consistently formed strong needles, with efficient insertion into at least the third layer of Parafilm M®

MN patch characterisation

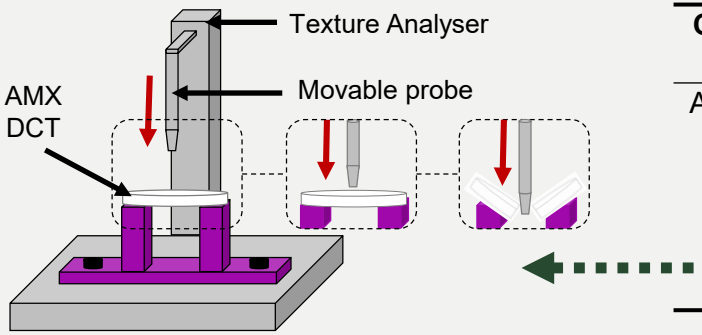
Novel AMX-containing directly compressed tablet (DCT) preparation and characterisation





Novel DCT preparation required – WHY?

- AMX is inherently unstable *via* hydrolysis
- Designed to minimise the degradation of AMX during the manufacturing process
- Two lead DCT formulations taken forward and physically characterised

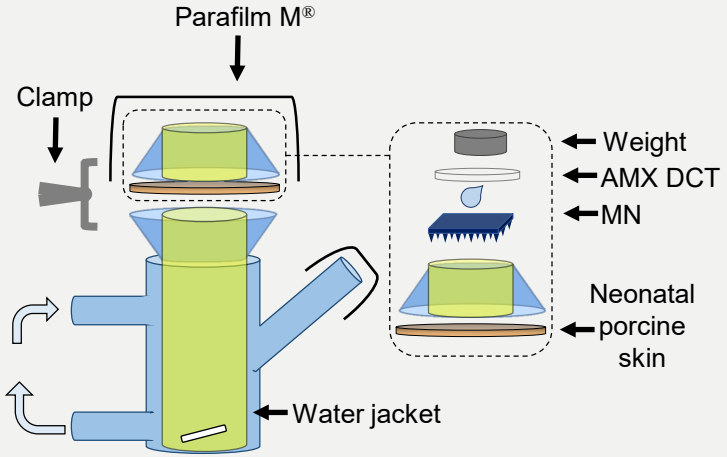


Break force measurement schematic

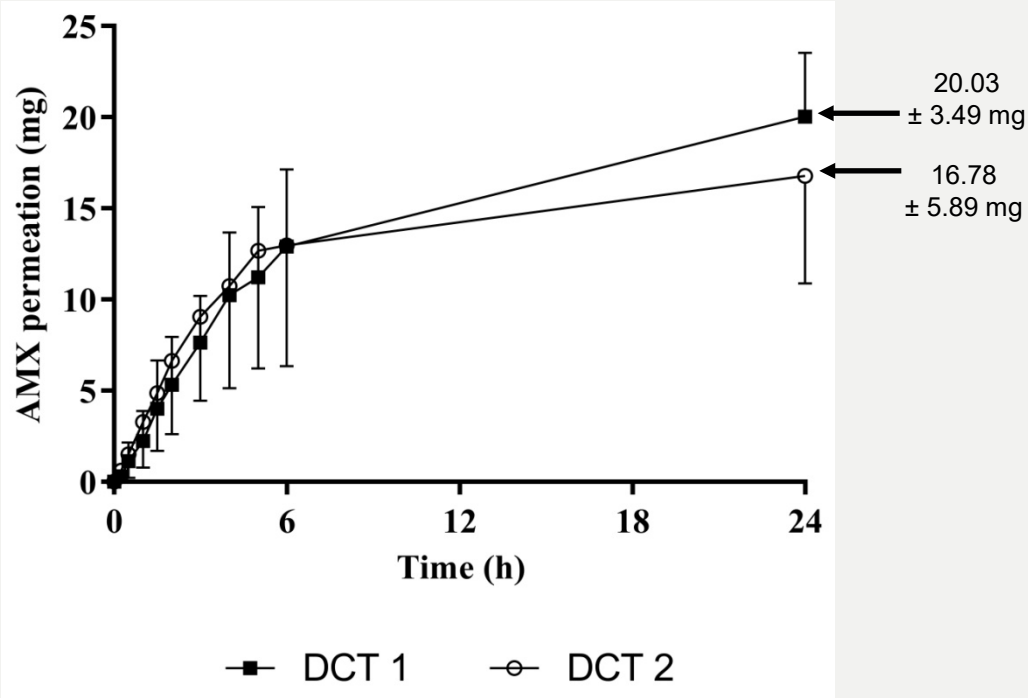
Characterisation parameter	DCT formulation code	
	DCT 1	DCT 2
AMX recovery (%)	100.78 ± 2.86	101.56 ± 3.34
Mass (mg)	199.64 ± 0.88	200.33 ± 0.97
Diameter (mm)	13.05 ± 0.02	13.02 ± 0.02
Thickness (mm)	1.32 ± 0.03	1.32 ± 0.04
Break force (N)	2.83 ± 0.56	5.06 ± 0.73
Hardness (N)	25.70 ± 6.95	64.20 ± 14.00

In vitro permeation of AMX

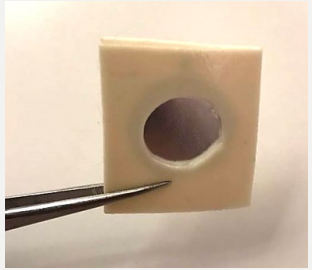
- *In vitro* permeation studies of AMX conducted on lead formulations
- Highest permeation of AMX at 24 h was achieved with MN patches consisting of DCT 1

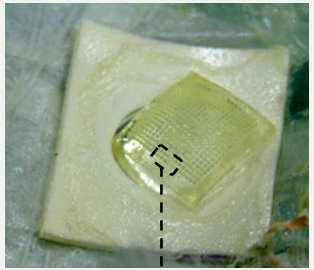


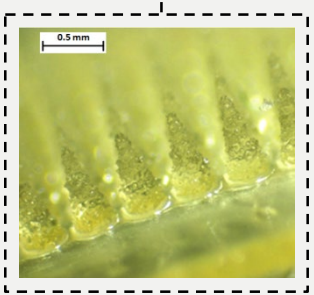
Modified Franz diffusion cell setup for *in vitro* permeation studies



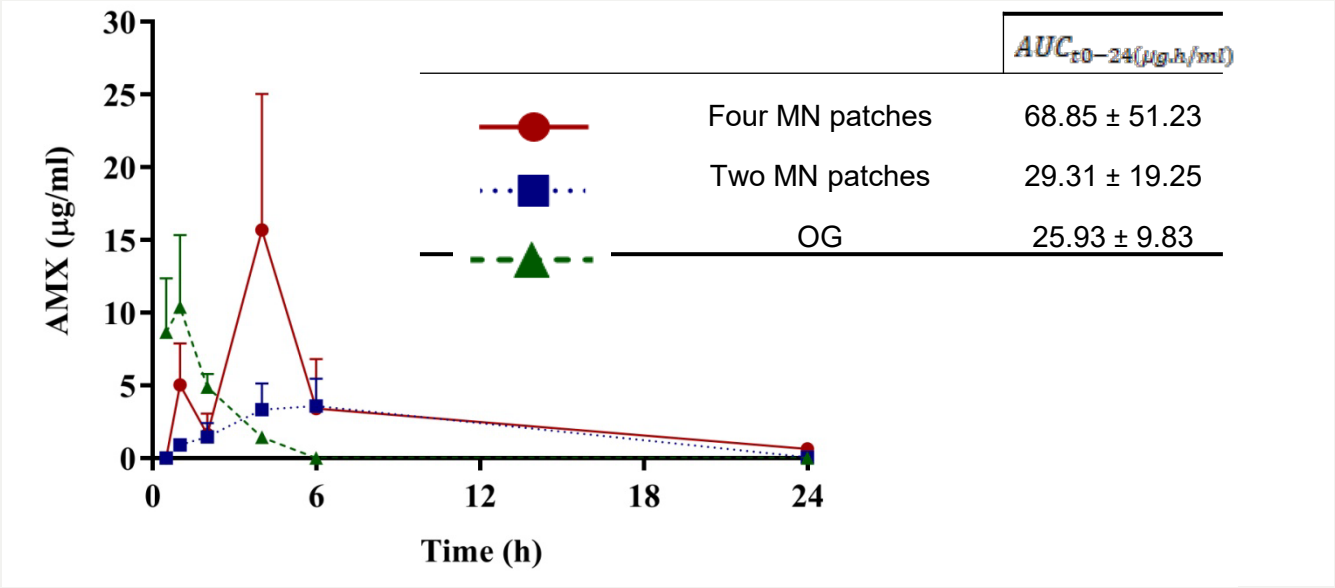
In vivo delivery of AMX



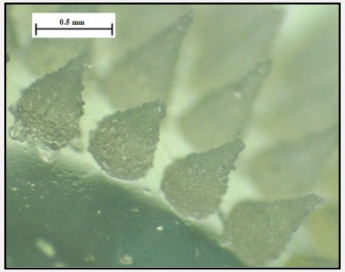


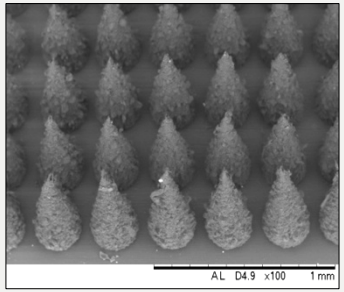


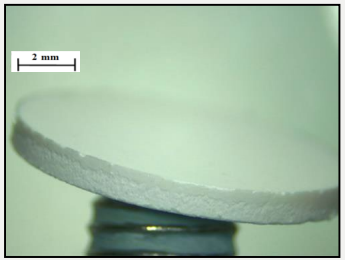
- Encouraging results facilitated an *in vivo* rat study to be performed with MN patches consisting of DCT 1
- Therapeutically relevant doses of AMX *delivered in vivo*
- Extrapolated MN patch size for therapeutic delivery in neonates = 18 cm^2



Conclusion







- Successful formulation and characterisation of novel AMX-containing MN patches
- Proof of concept evidence that AMX can be delivered at therapeutically relevant concentrations *in vivo* using novel MN patches
- Promising MN technology could simplify administration of AMX in low resource settings, thus expanding access to lifesaving outpatient antibiotic treatment

Future developments

1. Bacterial infection challenge studies
2. Stability studies
3. Usability studies

Acknowledgements

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  @ryanfdonnelly (Twitter)