Development of human milk for the delivery of poorly water-soluble drugs in neonatal and paediatric patients

Ellie Ponsonby-Thomas, Ben Boyd, Malinda Salim, Laura Klein

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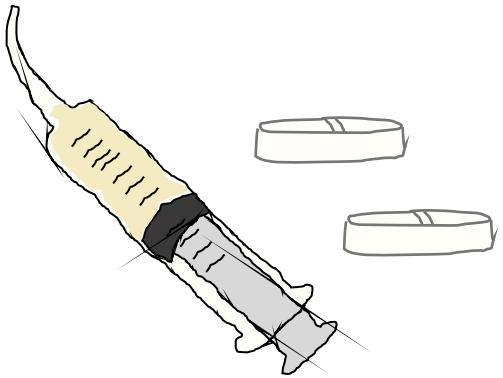
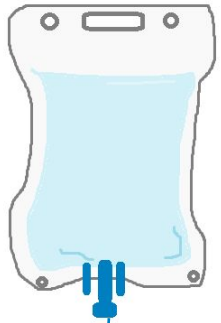
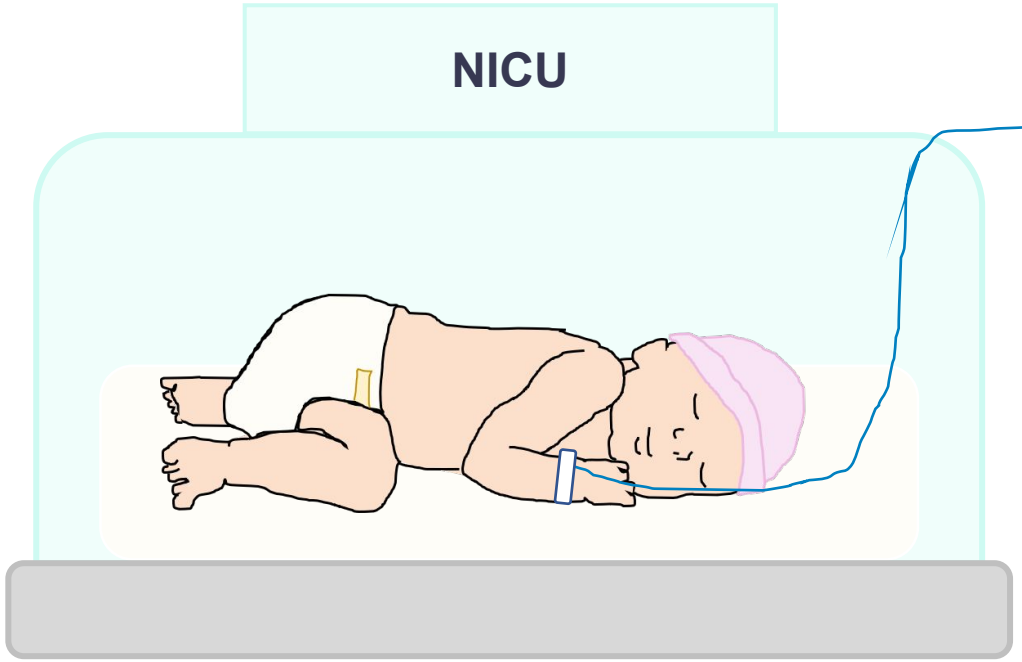
Advanced Delivery Science

Delivery of therapeutics to neonatal patients







Oral administration
- Preferred route of administration
- Designed for adult patients

Off-label use complications

IV administration
- Default option to oral delivery
- Invasive
- Large associated health care cost

Human milk as a patient friendly option

Human milk as a vehicle for poorly water-soluble drugs

Milk-based formulations

✔ Paediatric-friendly
✔ Lipid-based
✔ Orally delivered

Human milk

Advanced Drug Delivery Reviews 183 (2022) 114139

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

Opportunities for milk and milk-related systems as 'new' low-cost excipient drug delivery materials

Malinda Salim [a,*], Thomas Eason [a], Ben J. Boyd [a,b,*]

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

A nipple shield delivery system for oral drug delivery to breastfeeding infants: Microbicide delivery to inactivate HIV

Stephen E. Gerrard [a,b,c,+], Mary Lynn Baniecki [d], David C. Sokal [d], Mary K. Morris [b], Sandra Urdaneta-Hartmann [c,f], Fred C. Krebs [e], Brian Wigdahl [e], Barbara F. Abrams [c], Carl V. Hanson [b], Nigel K.H. Slater [a], Alexander D. Edwards [g,**]

Contents lists available at ScienceDirect

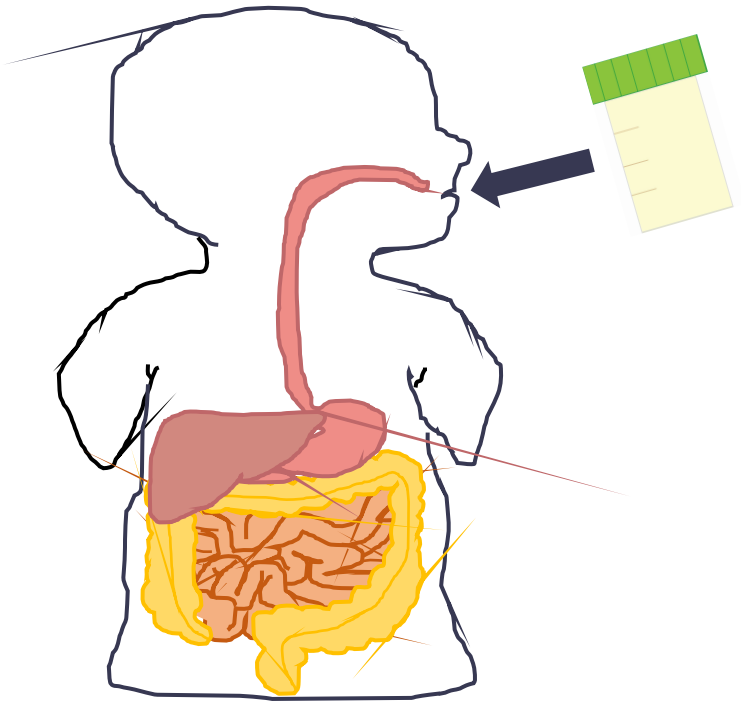
Journal of Neonatal Nursing

journal homepage: www.elsevier.com/locate/jnn

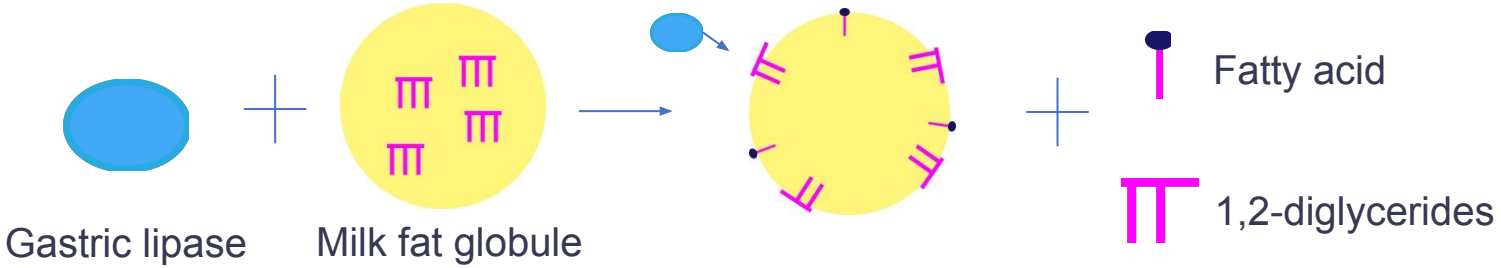
Drug and nutrient administration on the NICU – is delivery during breastfeeding an alternative to oral syringes?

Theresa Maier [a,b], Oliver Bonner [c], Paula Peirce [d], Nigel K.H. Slater [a], Kathryn Beardsall [b,d,+]

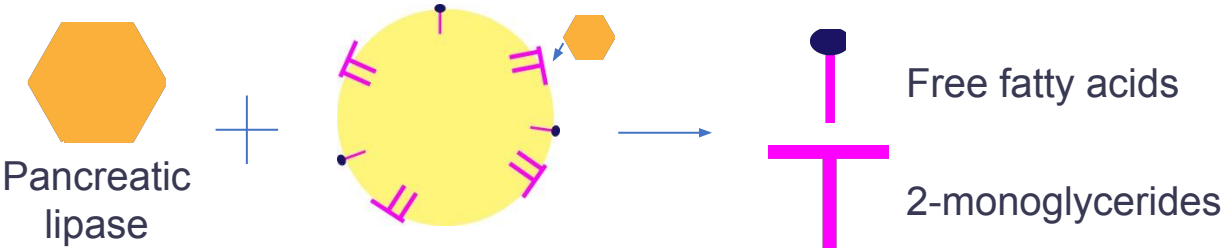
Digestion of lipid formulations in infants



Stomach



Small intestines



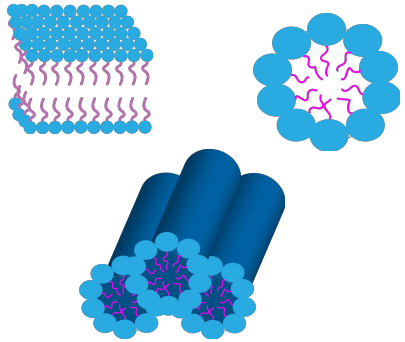
Digestion driven solubilisation of drugs

Digestion process

Free fatty acids

2-monoglycerides

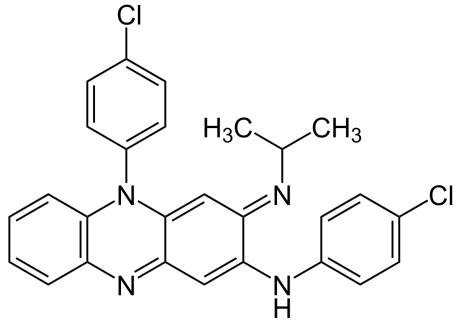
Colloidal structures



Poorly water-soluble drugs

Incorporation into lipid structures

Solubilisation of poorly water-soluble drugs in human milk



Clofazimine

Aqueous solubility of 1 µg/mL

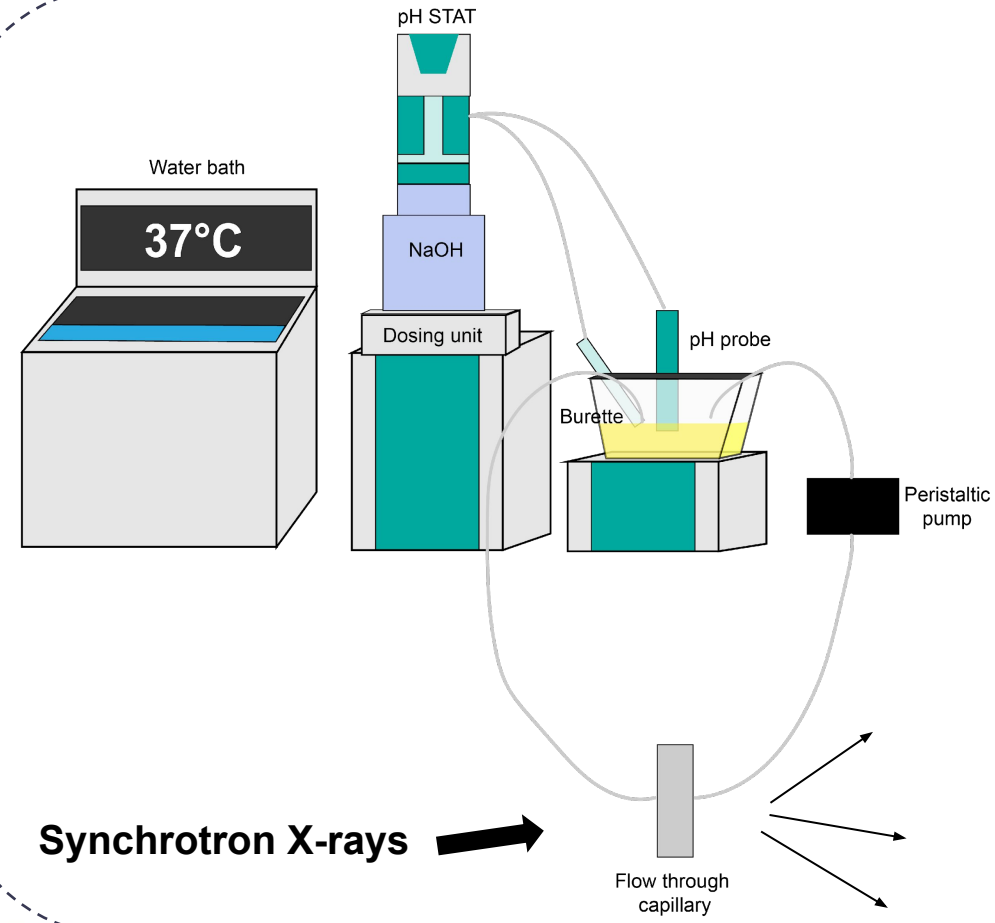
To understand the self-assembly behaviour of lipids during digestion with clofazimine present.

To measure the *in vitro* solubilisation of clofazimine in digesting human milk.

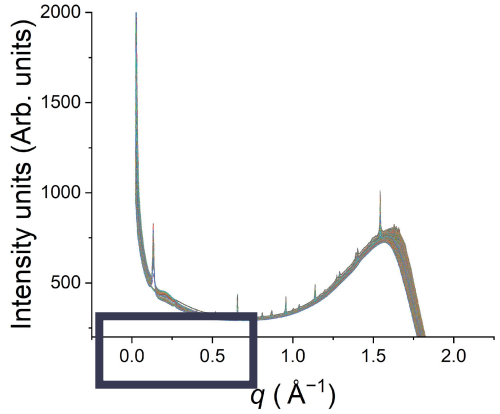
Determine the dose of clofazimine solubilised and compare to the clinical requirements for preterm infants.

Bevan, C., & Lloyd, R. (2000). A High-Throughput Screening Method for the Determination of Aqueous Drug Solubility Using Laser Nephelometry in Microtiter Plates. *Analytical Chemistry*, *72*(8), 1781-1787. doi: 10.1021/ac9912247

Research methods – *in vitro* digestion

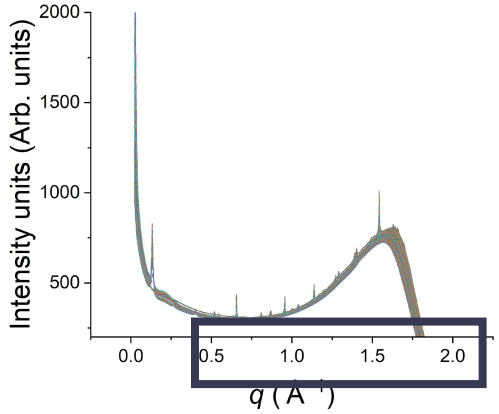


Colloidal lipid structures



Low *q*

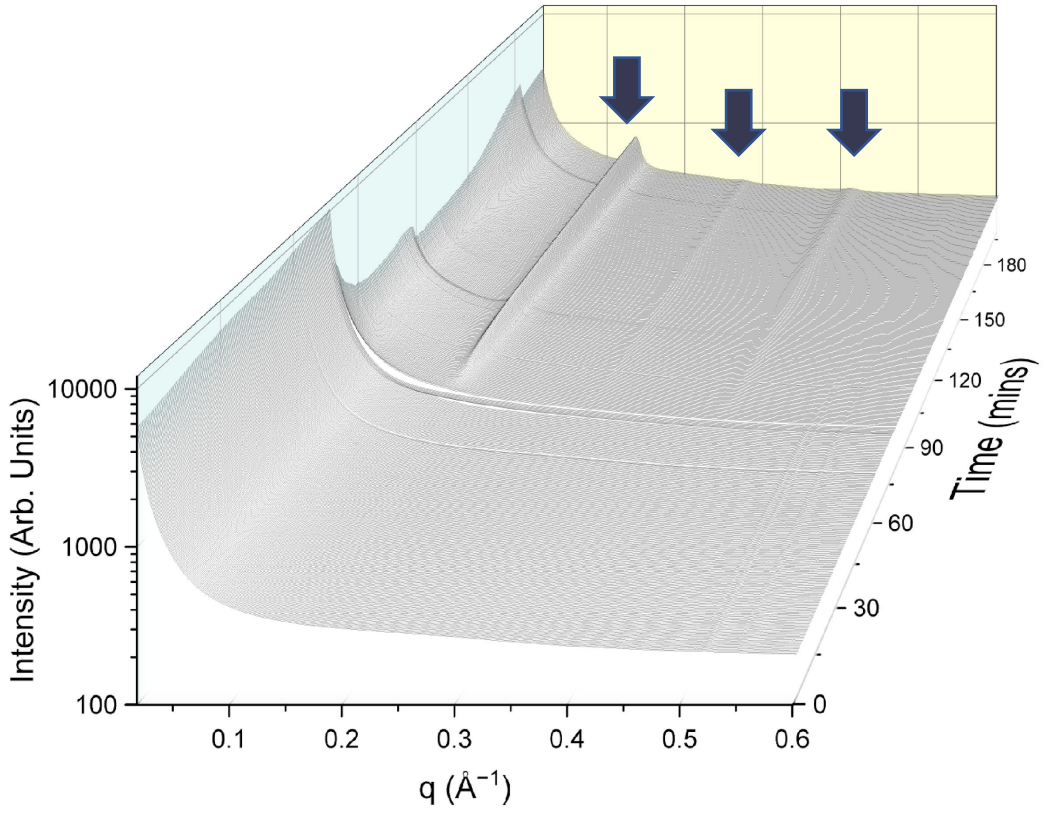
Presence of crystalline drug

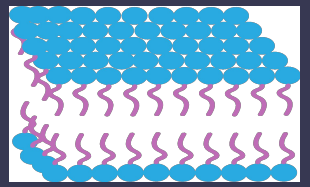


High *q*

Formation of liquid crystalline structures in digesting human milk

Digestion of human milk with clofazimine (50 mg)





Lamellar phase: consistent with previous findings

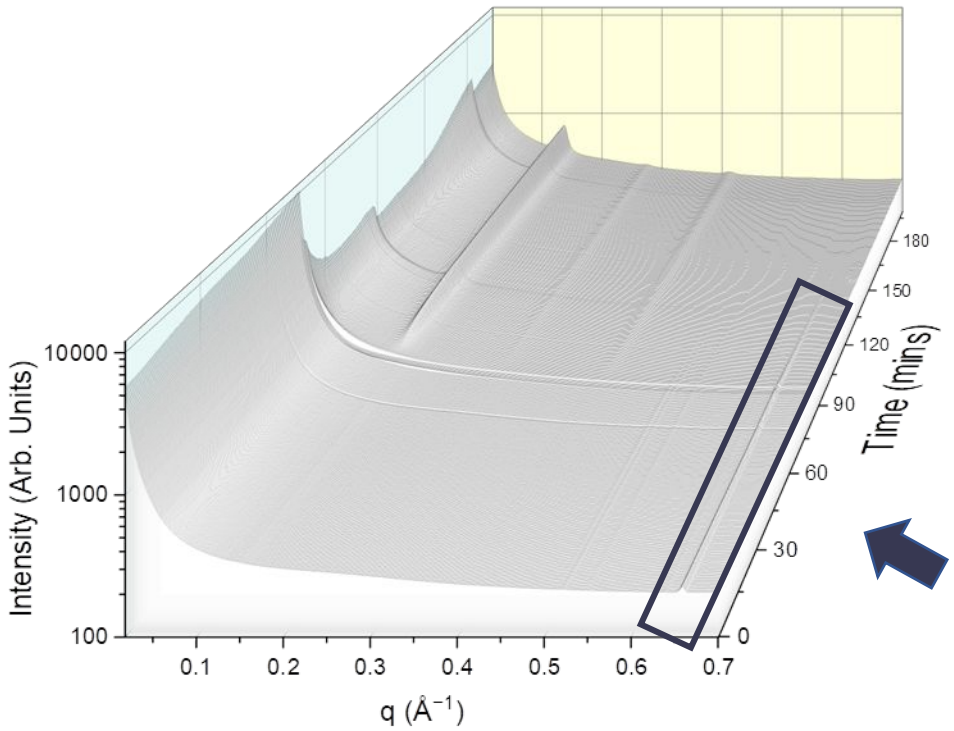
Self-Assembly Structure Formation during the Digestion of Human Breast Milk**

Stefan Salentinig, Stephanie Phan, Adrian Hawley, and Ben J. Boyd**

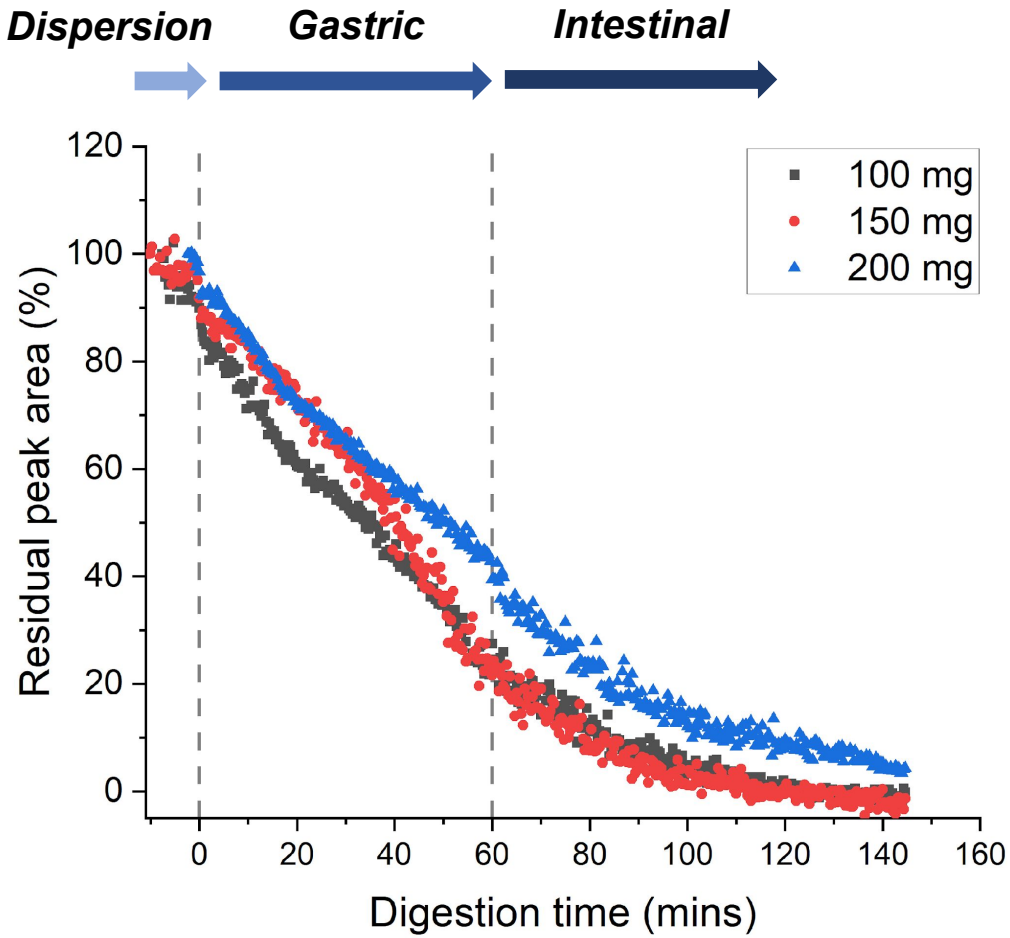
Correlating Digestion-Driven Self-Assembly in Milk and Infant Formulas with Changes in Lipid Composition

Anna C. Pham, Kang-Yu Peng, Malinda Salim, Gisela Ramirez, Adrian Hawley, Andrew J. Clulow, and Ben J. Boyd*

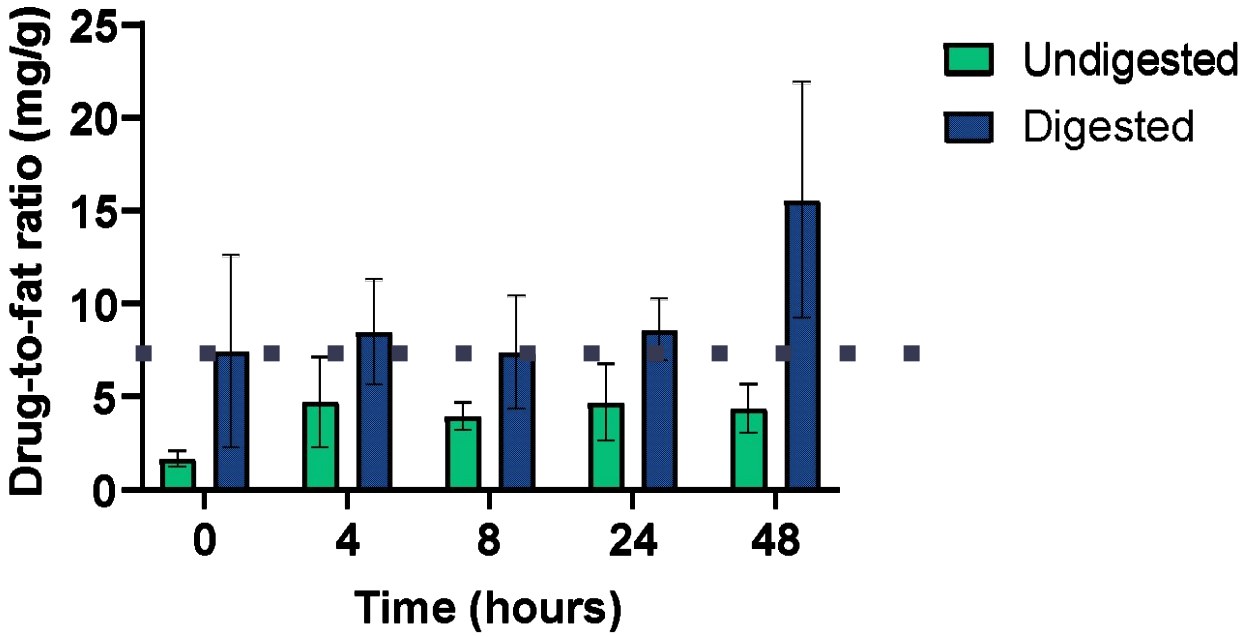
Digestion driven solubilisation of clofazimine



q = 0.66 Å^{-1}
Diffraction peak for crystalline clofazimine



Solubilisation of clofazimine in human milk



Greater drug-to-fat ratio exhibited in digested human milk

Theoretical drug-to-fat ratio exceeds the dose required for a preterm infant (2.5kg)

Determined

30 mg solubilised in 100 mL

Required

2.5 mg solubilised in 8.5 mL

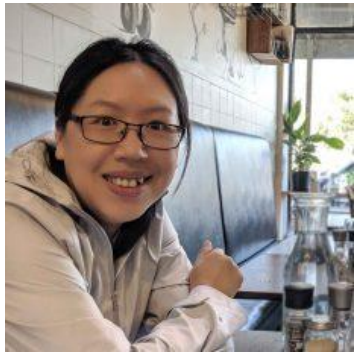
Conclusions

Digestion process is necessary for the formation of colloidal lipid structures and drug solubilisation.

Theoretical drug-to-fat ratio of clofazimine solubilised was 7 mg/g human milk fat. Represents 2.5 mg of clofazimine solubilised in 8.5 mL of human milk for a single dose for a preterm infant.

<u>Next steps:</u>
Expand the range of poorly water-soluble drugs investigated
 develop a framework for selection of drug candidates and infant friendly formulations

Acknowledgements



Ellie.Ponsonby-thomas1@monash.edu

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@group_boyd

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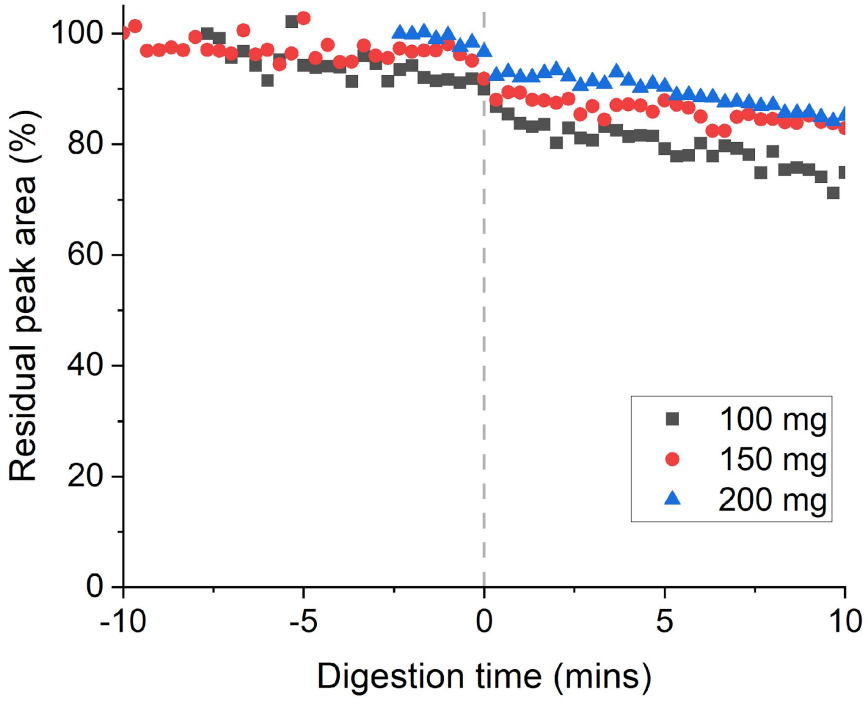
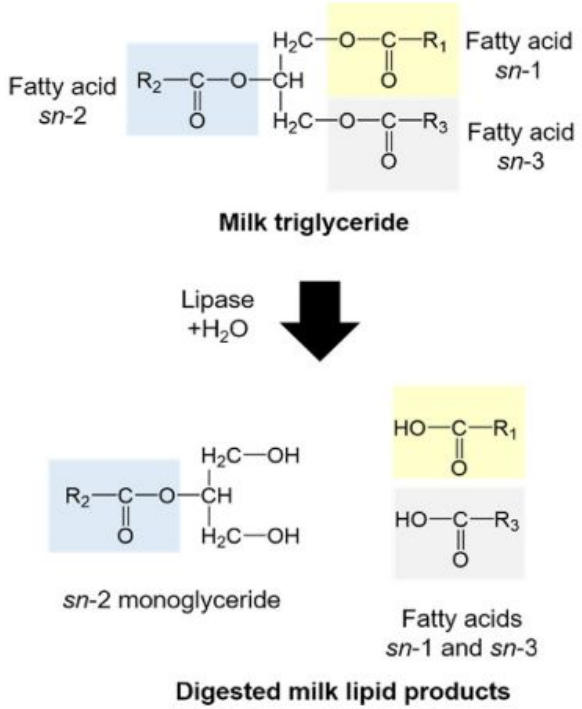
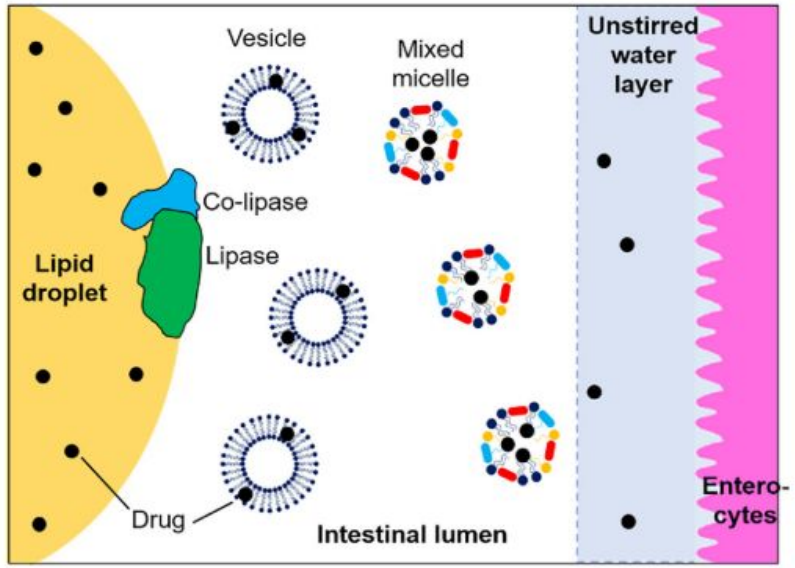
Dispersion stage for *in vitro* digestion of clofazimine



Solubilisation and absorption of poorly water-soluble drugs





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