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Formulation and Function of Food and Pharmaceuticals in a Continuous Culture Human Gut Model

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Introduction

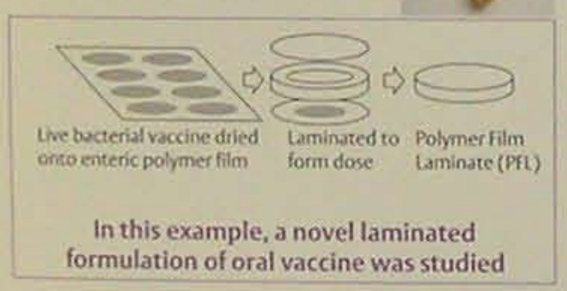
Understanding the fate of food and drugs after ingestion is vital both to achieve efficient delivery and uptake of pharmaceuticals, and to understand the impact of diet on gut health. Study of gut function in health and disease also underpins attempts to control chronic GI disease. The complexity of the human gut contents, especially the gut microbiome, makes accurate prediction of the in vivo fate of orally administered medicines, food, and nutritional supplements challenging.

At Reading, a complex continuous culture model has been used for decades to study gut biology in health and disease, . Recently, this was adapted for the study of the delivery of formulated pharmaceuticals such as oral vaccines.

Methods

The established human colon model was designed and validated to reproduce spatial, temporal, nutritional, and physicochemical characteristics of the microbiota in the human colon[1]. The colon model is a three-stage continuous culture system comprised of three fermenters simulating the proximal, transverse, and distal colon, and containing a complete microbiota inoculated from healthy faecal slurry and maintained at steady state. To this colon model, 3-4 gastric and small intestinal stages have now been added prior to entry to the validated colon stages to allow testing of formulated pharmaceuticals as well as food and nutraceuticals. All stages are kept anaerobic at 37°C, with controlled pH and composition to mimic physiological gut conditions.

1 Drug formulated into standard or novel formulation



In this example, a novel laminated formulation of oral vaccine was studied

2 PROBLEM: Conventional dissolution testing fails to accurately mimic *in vivo* conditions

3 A complete *in vitro gut* model is therefore needed that more accurately represents physiological gastrointestinal conditions. Here, the intestinal location of release is under examination using a dye.

4 Customised holders are used to rapidly move dose through stages

5 Complete model includes simulated intestinal plus validated microbially complete colon stages, and has been used both to study the fate of orally administered drugs, and also to determine the effect of drugs and nutritional supplements on gut microbiology

Case study: oral delivery of attenuated vaccines

Live bacterial cells are administered orally as attenuated vaccines, for in situ production of biopharmaceuticals, and as probiotics to improve gastrointestinal health. Live bacterial vaccines, such as attenuated *Salmonella* Typhoid Fever vaccines, are highly immunogenic after oral administration. Live attenuated strains can also be used as carriers of heterologous antigens. However, live baceteria represent a complex biological agent presenting unique formulation challenges, and after oral administration must survive antimicrobial defences including gastric acid and bile salts, so they can then be released alive in the small intestine. Initial studies using the Reading gut model rapidly demonstrated the value of *in vitro* modelling GI delivery for optimisation of oral delivery. We developed a new and simple oral delivery formulation concept, termed Polymer Film Laminate (PFL)[2], which completely protected bacterial cells from acid and released live cells into simple buffered dissolution solutions at intestinal pH. However, when tested in complete simulated intestinal fluid containing bile, dried cells were killed rapidly. To protect from bile toxicity, formulations incorporating a bile sequestrant resin[3] in addition to the enteric polymer film successfully protected dried live vaccine cells from both simulated gastric fluid and bile, and released all viable cells within 60min of transfer from acid into complete simulated intestinal fluid (data not shown).

Results and Conclusion

The validated colon model was established to study disease, and with the addition of intestinal stages can be additionally used be used to study drug fate. Significant differences in drug delivery kinetics, efficiency, and location were observed when experimental formulations were tested in the complete gut model, compared to conventional dissolution apparatus. This demonstrates that extending the colon model to the distal GI tract allows pharmaceutical testing, such as delivery of complex biologics and analysis of the fate of orally administered drugs. *In vitro* modeling remains the best way to understand and control both the effect of food and nutritional supplements on gut health, but also the fate of orally administered drugs in the GI tract.

References

1. Sannasiddappa, T. *et al.* (2011). PLoS ONE, 6 (8). **2.** Barros, J. *et al, J. Pharm. Sci.*, in press. **3.** Edwards, A. D. and Slater, N. K.H. (2009). Vaccine, 27 (29). pp. 3897-3903.

Acknowledgements

- We thank the University of Reading for funding JB.

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