TrabiORAL™ - Phase I

TrabiORAL™ – an exciting technology platform for oral delivery of protein/peptide drugs

The challenges of drug absorption/efficacy do not limit the barriers met in the gut, but they include the hepatic barriers after they enter the vessels under the intestinal epithelium as well. Although the oral route is the most desirable administration method for small therapeutic molecules, the challenges for large molecules such as monoclonal antibody drugs are even more harsh. (Figure 1)

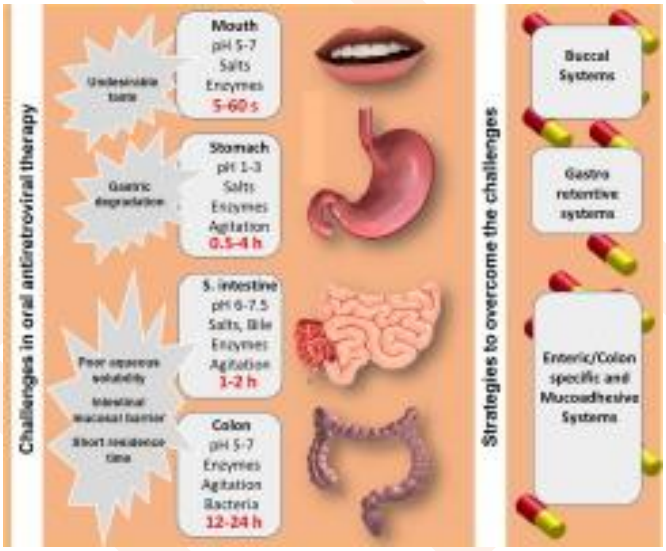

Figure I

A large absorption area and long residence time provides greater opportunities for drug absorption, which is one of the reasons why drug absorption mostly occurs in the small intestine.

In addition to the acidic and enzymatic degradation, the lumen of the GI tract can cause other damages to drug molecules. Osmotic stresses along the GI tract, peristalsis of the GI muscles, as well as the shear stresses by the flow rate of the gastric juice inside the lumen are other additional factors that may decrease drug efficiency.

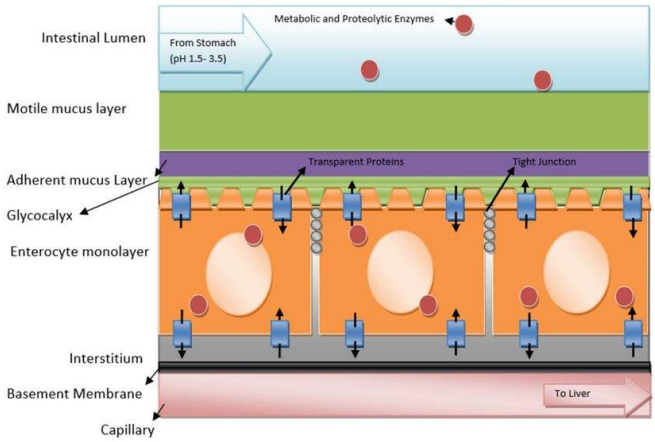

Figure 2

There is a need to design a technology not only to protect the chosen protein/peptide from enzymatic degradation but also in enhancing its absorption without altering its biological activity. Oral delivery of proteins and peptides has long been hailed as the 'Holy Grail' though attractive showing great potential but also presenting simultaneous problems in successfully developing such a technology.

Apart from the metabolic and biological barriers in developing oral delivery technology, challenges in attaining optimal bio-availability of the molecule poses another problem depending on its molecular mass.

One of the biological barriers is the harsh acidic conditions inside the stomach (pH 1–2.5), denaturing most of the administered molecules. Additional barriers include gastric and pancreatic enzymes that can degrade biopharmaceutical molecules.

Next set of barriers for a successful oral delivery of protein drugs are osmotic stresses along the GI tract, peristalsis of the GI muscles, as well as the shear stresses by the flow rate of the gastric juice inside the lumen of GI tract.

Mucus is the next barrier. The mucus itself is mainly composed of water and mucin protein molecules coated with proteoglycans, giving the mucus a negative charge. The thickness of mucus layer varies along the GI tract, as shown in the figure below:

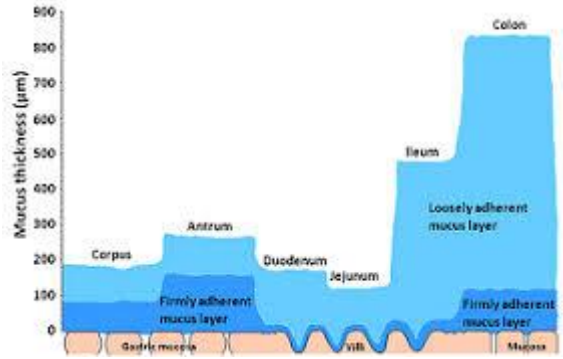

Figure 3

Other major obstacle after penetrating the mucus layer is to reach the apical side of the cells. Thereafter, there are two possibilities for the transport to the basal side. The first is a paracellular transport, which involves a loosening of tight junctions and a transport between epithelial cells without a cellular uptake. However, a paracellular transport is either toxic or simply not feasible due to size restrictions. The second possibility is transcytosis, which is the transport of a molecule through the interior of a cell. This process consists of an uptake, preferably endocytosis, a transport within the cell as well as a withdrawal from the interior of the cell, namely exocytosis.

Beyond the mentioned barriers, the drug carrier after leaving the stomach, it enters the small intestine and is transported along the duodenum, jejunum, and ileum. Here, either the cargo needs to be released for intestinal absorption or the carrier itself needs to be taken up within the small intestine before it reaches colon. Otherwise, it will inevitably be withdrawn from the human body, since the colon does not have the capacity to absorb solid materials. Following this uptake in the small intestine, the carrier needs to traverse the layer of epithelial cells to reach the lamina propria. However, a large absorption area and long residence time provides great opportunities for drug absorption, which is one of the reasons why drug absorption mostly occurs in the small intestine.

From there on, the next obstacle is a layer of endothelial cells of the blood vessel, which the carrier needs to transverse in order to reach the lumen of the blood vessel. Once the carrier enters the bloodstream, the drug can either be directly released into the blood stream or enters the target cell.

TrabiORAL™ - 2001 onwards Phase I

Realising the barriers one has to overcome, TrabiORAL™ embarked on the journey in the year 2001 for oral delivery of various protein or peptide molecules starting with Insulin using B12 as a carrier.

Transgene Biotek started work on oral delivery platform by developing nanoparticles based formulation but learning from those experiments it quickly shifted its focus on targeted delivery vehicles. One of the approaches Transgene explored earlier for oral insulin delivery was utilizing the uptake pathway for the water-soluble vitamin, vitamin B12 (cobalamin or cyanocobalamin). It has been shown that uptake of vitamin B12 is dependent upon binding of that vitamin to gastric intrinsic factor (IF), with subsequent recognition of the IF-VB12 complex by a membrane expressed receptor (IFCR) on the small intestinal epithelial cell (the enterocyte). Although Transgene's work on this transport system appeared to be successful, its commercial utility in the oral delivery of Insulin as well as other proteins is limited by a number of factors. Firstly, vitamin B12 needs to be chemically modified to provide a suitable site for conjugation which was found to be limited, secondly the uptake capacity of the vitamin B12 transport system is rather low (1 nmole per feed), and thirdly vitamin B12 is relatively large molecule with a molecular weight of 1355.38, when compared to other potential carriers.