Have existing pharmaceutical excipients failed to enable oral/nasal protein delivery?

Shireesh P. Apte*

Editorial Board, Journal of Excipients and Food Chemicals

Editorial

ABSTRACT

It seems evident that the ill-defined *weltanschauung* of the past decade of enabling oral, un-truncated permeability-dependent protein delivery carte-blanche, using existing excipients has produced sparse results. Existing excipients are better utilized for exploiting niches which do not require either permeation or a permeation enhancement that is incongruent with, and/or is, disproportionate to the existing excipient's ability.

KEY WORDS: Absorption, orally administered biologics, permeation enhancers, permeability, excipients, oral protein delivery

Oral therapies often seek to displace long existent, highly entrenched medications administered by the parenteral route. This is the case for conditions such as diabetes and hormone and enzyme replacement therapies. Unless biosimilars or oral small molecule APIs' emerge, it is not in the financial interest of the companies who make these parenteral medications to cannibalize them with in-house or competitor drug candidates administered via the oral route. Such may have been the impetus for Sanofi to develop an NCE orally administered small molecule for the treatment of Fabry disease due to the potential for increase in competition (notably from Protalix's plant derived 'biobetter', pegunigalcidase-alpha) with its currently manufactured enzyme, Fabrazyme®. This also appears to be the case with Novo-Nordisk's first of six phase IIIa trials with the oral peptide semiglutide, a glucagon-like-peptide, GLP-1 analog, that it is comparing against the oral dipeptidyl peptidase-4 inhibitor sitagliptin (Januvia®); and not against parenteral insulin or parenteral insulin analogs. Oramed Pharmaceuticals, whose technology relies on encapsulating the peptide or protein and delivering it alongside enzyme inhibitors and permeation enhancers, has an oral GLP-1 agonist candidate in clinical trials.

Furthermore, in general ADME terms, an oral or nasal delivery system requires approximately 5-10 times more protein-API on a per-dose basis due to the low bioavailability (usually <10%, even with the most promising absorption enhancers or technology) via these routes. This is particularly difficult to justify to

*Corresponding address: 5204 Coventry Court, Colleyville, TX 76034, Tel: 817 501 2984, e-mail: **shireeshpapte@msn.com**

insurance companies, especially when cheaper parenteral alternatives already exist, or where the API is cheap, and consequently, megadoses can be administered (as is done for OTC vitamin B12). Since the developed countries contribute the most to the revenue stream of parenteral medications for chronic diseases, it is not financially prudent to embark on an oral replacement for a parenteral drug, unless such a replacement was designed to reduce the frequency of parenteral dosing, thereby still necessitating and retaining a market for the parenteral form (an analogy can be made with the failed phase II trial of Ohr Pharmaceuticals' topically administered squalamine eye drops for age related macular degeneration that was designed to reduce the frequency of intraocular Lucentis® injections), or to obtain market share from an existing oral non-peptide drug with a mechanism of action in the same signal cascade (Januvia® acts upstream to increase GLP-1 levels while semiglutide is itself an analog of GLP-1).

Several companies have tried (and are trying) to deliver proteins orally using specialized platforms containing combinations of existing excipients, without much success. Enteris Pharma is testing its (pre phase II) once daily oral leuprolide acetate for endometriosis to replace monthly depot injections using its Peptelligence™ platform consisting of surfactants and citric acid. Its platform is licensed to Cara Therapeutics for its oral kappa opioid receptor CR845 phase II osteroarthritis trial and to Nordic biosciences for the delivery of oral DACRA peptides. Merrion Pharmaceuticals sold its GIPET™ IP assets (using fatty acid salts or derivatives as absorption enhancers) to Novo-Nordisk, liquidated its material assets and transitioned to an investing company. Tarsa Therapeutics sponsored a phase III clinical trial in post-menopausal women with osteoporosis using Enteris Pharma technology that demonstrated a marginal improvement (orally administered recombinant serum calcitonin was not less than one-half as effective) versus the nasal spray. It is seeking NDA approval. Diabetology's Capsulin® oral insulin based on Proxima Concepts' Axcess aromatic alcohol-based absorption enhancer technology seems to have stalled after it achieved half the circulating insulin levels obtained via subcutaneous insulin using as much as 25 times the subcutaneous dose in a phase II, 2009 clinical study.

Sanofi withdrew its stake in Mannkind's approved inhaled insulin, Afrezza®, reportedly due to disappointing sales. The FDA application for Chiasma Pharma's oral octreotide capsules (after Roche handed back the rights to develop) was not approved (April, 2016) reportedly due to the percent responders being less than those responding to injectable somatotropin in a phase III trial for control of acromegaly symptoms. While waiting for long term phase III results from its licensing partner Novo-Nordisk, Emisphere Technologies has obtained approval of low-hanging fruit; the EligenB12® prescription oral medicine, utilizing the excipient salcaprozoate sodium (SNAC) to chaperone vitamin B12 through the gastric lining and increase its absorption.

The failure of existing excipients to enable oral protein delivery has led to innovation in medical devices, in covalently attached chaperones as a platform to deliver oral peptides, or in a shift toward orally administered small molecule non-biologics with different mechanism(s) of action. Rani Therapeutics has designed a 'robotic pill' that may deliver proteins by gas enabled abrasive indentation of the intestinal wall with drug loaded sugar crystals. A publication associated with Entrega Biologics, that utilizes bioadhesive drug loaded wafers packaged in a capsule to deliver proteins to the intestinal epithelium , states that "… a reduction in blood glucose levels comparable to that induced by subcutaneous injections can be achieved via enteral insulin absorption with doses only 2-10-fold higher than subcutaneous doses". Applied Molecular Transport's platform uses a cytotoxic incompetent truncated form of the

cholix protein that contains the part required for epithelial transport. The truncated toxin is covalently bound to the therapeutic cargo protein. The shift toward orally administered non-biologics is exemplified by Xeljanz®, the first oral, non-biologic disease modifying anti-rheumatic drug (DMARD), belonging to the janus kinase (JAK) inhibitors drug class, that provides an alternative to the biologic DMARDs including tumor necrosis factor (TNF) inhibitors, such as Humira®, Enbrel® and Remicade®. Isocitrate dehydrogenase inhibitors, sigma2/PGRMC1 blockers, α1β4 antagonists represent more of such transitions toward orally administered targeted non-biologics.

More than a decade of research into (mostly existing utilizable) excipients to deliver proteins to their therapeutic targets via the oral/nasal route has not yet produced results. The relatively small increases in bioavailability achieved are not enough to counter the high cost of goods of proteins, even for orphan indications, and not enough to convince insurance payers. The cannibalizing of parenteral medications that contribute substantially to existing revenue streams dampens financial and innovative interest. The regulatory burden and the absence of independent new excipient regulatory approvable mechanisms limits the molecules that can be used as excipients hence hindering the research into and exploitation of new permeability and/or transport mechanisms; such as alteration of gut microbiota to modulate permeability. Given these caveats, it is perhaps not surprising that conventional excipient enabled oral protein delivery has not made much progress.

On the other hand, oral/nasal peptide delivery using existing excipients seems well suited to local delivery that does not require the protein to permeate cellular barriers, and therefore does not require excipients that are classified as permeability enhancers, merely those that can deliver the drug to the lungs/intestine, a task for which existing excipients are well qualified. For example, Pulmozyme® is designed to act locally in the lungs to reduce the viscosity of sputum in cystic fibrosis patients. Peptides that are designed to act in the gut itself, such as those that may alleviate symptoms of inflammatory bowel diseases including ulcerative colitis and Crohn's disease, again, do not need to be permeable. For example, the orally administered peptide drugs, Linzess® (linaclotide) and Trulance® (plecanatide) are both guanylate cyclase-C (GC-C) agonists approved for chronic idiopathic constipation and do not need to be absorbed. Enzymes that prevent absorption of terminal metabolites/ dietary components can be administered orally. Orally administered recombinant oxalate decarboxylase enzyme obtained from *Bacillus subtilis* is undergoing phase II trials to reduce the absorption of oxalate from the gut thereby reducing hyperoxaluria mediated neuropathy and kidney disease. An intriguing application of gut localized orally administered proteins is to inactivate parenterally administered molecules that permeate into the gut thus creating opportunistic colonization of pathogenic bacteria. For example, the oral protein beta-lactamase inhibiting enzyme, ribaxamase by Synthetic Biologics Inc., is in phase II trials to protect the gut microbiome from parenterally administered antibiotic-mediated damage and prevent *Clostridium difficile* infection.

Oral/nasal peptide delivery is also feasible with low cost of goods, relatively small molecular weight (or truncated forms of the biologically existent proteins that can be manufactured using non-recombinant methods) peptides that can obtain market share from oral non-peptidyl molecules acting on the same signal cascade (kappa opioid or GLP-1 receptor agonists as examples) by virtue of their lesser side effects. In addition, peptides that are resistant to enzymatic degradation in the gut, such as D-enantiomeric peptides, are also candidates for oral delivery. Phase I trials are planned for such orally administered peptides that can cross the blood brain barrier and reduce Aβ plaque load and brain inflammation in Alzheimer's disease. These opportunistic niches may expand

as more of such small and/or enantiomeric peptides are discovered.

A small, but growing number of peptides that populate these niches indicate that the pharmaceutical industry has realized that oral peptide delivery using existing excipients is suitable only under certain, well defined delivery, clinical and market conditions, for select proteins, and patient populations. Existing excipients are better utilized at exploiting the niches mentioned above, which do not require either permeation or permeation enhancement incongruent with and/or disproportionate to the existing excipient molecules' ability, instead of the ill-defined weltanschauung of the past decade of enabling oral un-truncated permeability-dependent protein delivery *carte blanche*.