Perspective: Oral Drug Delivery Research in Europe

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ABSTRACT
The oral delivery of drugs is considered by decision-makers in the pharmaceutical industry to be the most appealing route of administration. This belief has led to the identification of many very successful drugs, but also to the downfall of some promising therapeutics that failed to meet criteria required for sufficient oral bioavailability. Efforts to correct these deficiencies have led to a plethora of creative strategies to overcome the physical, chemical, and biological barriers that limit the efficient and consistent delivery of drugs that are not readily absorbed following oral administration. The goal of this perspective is to describe these barriers to oral drug delivery in relation to some of the work currently being undertaken by the community of European scientists. This perspective is not intended to be inclusive and the author apologizes in advance to the many scientists working in Europe whose recent work was not included.

BACKGROUND
It is unclear why people prefer taking a drug by the oral route over just about every other method; commonly these drugs are administered in a small- to moderate-sized pill or capsule form. Thinking about it, swallowing an object without mastication is contrary to all our default mechanisms for items that enter our mouth. Most mammals, other than canines that wolf their food, will examine a pill or capsule in their mouth and then reject it as something foreign and unacceptable. Indeed, pilling a cat can lead to a rather stressful outcome for the pet and lacerations for the owner. The cat, however, is merely following its natural survival instinct of first examining any material that enters its mouth prior to mastication and swallowing. While the reason(s) behind man’s willingness to so readily swallow unknown materials remain obscure and quite debatable, it leaves the pharmaceutical industry with a huge challenge of finding new therapeutic entities that can be delivered by this preferred route of administration.

Successful oral delivery requires the selection of a drug that selectively hits a pharmaceutical target as well as the identification of a formulation for that drug which provides the required pharmacokinetic (PK) profile to result in a desired pharmacodynamic (PD) outcome. I have heard it said by several individuals associated
with the pharmaceutical industry that all the “low hanging fruit” of drug discovery is gone. What I believe these individuals are really saying is that most of the therapeutic targets where compound could be readily found with the required properties of high bioavailability, PK profile and safety window following oral administration have been identified and drugged (a term used by pharmaceutical executives to describe a commercially successful program). While the technologies that were used to prepare these successful oral formulations should not be trivialized, it has become clear that these previous technologies are insufficient to meet the challenges of potential drugs that are not readily absorbed following oral administration. Some of the challenges that must be addressed include instability in the gastrointestinal (GI) tract, poor uptake leading to low bioavailability, poor PK characteristics, insufficient target access, and off-target effects.

I cannot definitively say whether those individuals predicting limited future opportunities for identifying promising oral drug candidates are right or wrong. There are some facts, however, that support their pessimism. Cumulatively, the pharmaceutical industry has spent billions searching for compounds with same properties of successful oral drugs [1]. Multiple, extensive, high-throughput screens (HTS) performed by the major pharmaceutical companies have looked at natural products as well as herbal and even traditional medicines [2]. Further, some of these HTS efforts were performed in combination with genomic, proteomic, kinomic, and metabalomic data [3-5]. These efforts have yielded a few molecules for the pharmaceutical industry to develop; the factor Xa inhibitor rivaroxaban being one of these few success stories [6]. There certainly has not been a tidal wave of new oral blockbusters, however, that some analysts had predicted when these new HTS technologies first identified [7].

With the continued desire for new (and old) therapeutic agents to be administered by the oral route and the likelihood that HTS efforts and elaborate search methods will not identify as many new lead compounds as hoped [8], pharmaceutical scientists have logically focused on ways to improve the bioavailability of therapeutic agents that would not be otherwise considered appropriate for oral drug delivery. Previous studies to optimize the delivery of currently approved drugs have identified a wide range of creative methods to stabilize labile compounds that can deliver these materials to a specific segment of the GI tract. Building upon that previous knowledge base, more
Recent efforts have focused on stability approaches and on strategies to improve the uptake of drugs that would otherwise not be absorbed following oral administration. Approaches currently being taken by European research groups to address some of these issues are the focus of this perspective.

**DRUGS DELIVERED BY THE ORAL ROUTE CONFRONT MULTIPLE CHALLENGES**

The complex digestive mechanisms of the GI tract are designed to safely, selectively, and effectively absorb as many nutrients as possible from our diet. Materials administered orally experience a very harsh environment in the stomach that is strongly acidic (pH 2-3) and contains a variety of enzymes that include lipases and proteases which normally function to initiate foodstuff digestion and destroy unwanted pathogens and toxins. Partly digested material (chyme) is then passed to the first segment of the small intestine (duodenum) where pancreatic enzymes, bicarbonate buffer, and bile salts are released from the common bile duct in coordination with the presence of chyme. This bolus of partly digested material then proceeds along the jejunum and ileum segments of the small intestine. During this transit the pH of the GI tract lumen rises from the acidic level in the stomach, to 5-6 in the duodenum, to neutrality (~pH 7) in the mid-to-distal jejunum; along the way large protein fragments are cut into small peptides, then processed further by peptidases at the apical surface of intestinal epithelial cells prior to selected uptake as amino acids as well as di- and tri-peptides [9]. Simultaneously, lipids in the GI tract have been solubilized by bile salts, broken down into free fatty acids and di- and tri-glycerides, and absorbed. Complex carbohydrates are cut into mono- and di-saccharides that are selectively taken in through specific transporters; similarly, vitamins and co-factors are also absorbed via specific uptake mechanisms. Poly-nucleic acids are extensively digested and taken up as nucleosides. Thus, the digestive processes of the GI tract are coordinated to sequentially breakdown complex nutrients into their elemental building blocks and then selectively absorb these nutritional elements in an organized fashion.

In consideration of the many aspects of GI-mediated catabolic processes a variety of methods, such as those described above, can limit direct exposure of labile molecules to the most damaging aspects of these digestive events. Since the stomach, duodenum, and early jejunum are particularly harsh environments, many efforts have
focused on by-passing these regions and deliver poorly-absorbed drugs to the late jejunum and ileum. In essence, the goal is to allow passage of labile drugs through the stomach in a protective structure and then release them later in the GI tract to allow their absorption. Many poorly-absorbed drugs are not only labile but also are not readily transported across the intestinal epithelia once they reach the latter jejunum and ileum. Thus, acceptable methods to improve their uptake must also be identified [10]. In this perspective, some of the recent efforts taken by European scientists in these two areas of research are discussed. Additionally, I have tried to highlight some of the exceptional European expertise related to principles of oral drug delivery design and evaluation. I apologize in advance for omissions in this non-exhaustive and personal selection of recently published work.

PROTECTION FROM THE HIGHLY ACIDIC ENVIRONMENT OF THE STOMACH

It is not surprising that many drug candidate molecules can be altered or destroyed in the harsh, acidic, and enzymatically rich environments of the stomach, duodenum, and early jejunum. If these actions do not completely destroy the drug, its partial destruction or modification can lead to unacceptably low or inconsistent delivery profiles. The likelihood of destructive outcomes is further enhanced when the drug entity is retained in the stomach for extended periods of time which can occur due to diet and individual variations. One obvious way to address this situation is to isolate the drug from these harsh GI tract digestive environments as much as possible. There are well-established methods of coating capsules and tablets with polymers that are stable at the low pH of the stomach but dissolve in the more neutral pH experienced in the lumen of the late jejunum or ileum. Clearly, understanding the physiological characteristics of stomach retention and transit would be benefited by studies that examine parameters of how and why materials are retained by or pass through the stomach [11].

Eudragit® (poly(meth)acrylate) polymers are an example of an acid-stable material that has been used to coat tablets and capsules to protect a drug compound against the low pH and enzymatic burden of the stomach and proximal small intestine. Hot-melt extrusion technology has been applied to Eudragit 4155F and polyvinylpyrrolidone for the preparation of amorphous solid dispersions of drug/polymer systems with good
drug stability under conditions experienced in the stomach and characteristics that would target drug release in the colon [12]. Tannic acid combined with poly(N-isopropylacrylamide) and poly(2-isopropyl-2-oxazoline) has been examined to provide hydrogen-bonded coating films with the promise of biocompatibility and lower critical solution temperature while still being pH-responsive at physiological temperatures [13]. Additionally, a food-grade lyotropic liquid crystal system composed of monolinolein and linoleic acid has been described that responds to pH variations as a reversible switch which results in changes of both structure and physical properties; characteristics that could facilitate targeted delivery to the small intestine or colon [14].

Rather than a single capsule or tablet dosage form being protected during passage through the stomach, one could envisage coating individual particles. Solid pH-dependent drug-releasing nanoparticles, prepared using hydroxypropyl-Β-cyclodextrin and/or Eudragit® L100, have been described [15]. Evaluation of cationic liposomes coated with the pH-responsive anionic polymer Eudragit S100 suggests these materials could be used for delivery to the distal regions of the small intestine or to the colon [16]. With respect to colon targeting, Eudragit®-based drug delivery systems, prepared via hot melt extrusion, appear to work quite well for this task [17]. Another recently-described effort to produce enteric-coated microparticles for oral administration employed a water-in-oil-in-water solvent evaporation technique and used the pH-sensitive polymer cellulose acetate phthalate or poly(methyl methacrylate-acrylic acid) copolymer with varying amounts of polyvinyl alcohol as an emulsion stabilizer [18].

Due to the heterogeneity within some solid oral dosage systems it is difficult to obtain a precise prediction of the actual pH within the matrix microenvironment. Several strategies have been investigated to provide a more cohesive picture of conditions within such as system: integration of data from a pH indicator dye, fluorescence imaging and electron paramagnetic resonance (EPR) imaging [19]. While understanding pH changes that might be occurring within the dosage system is important, it is equally important to tune pH-regulated polymer coating systems for drug release with pH events occurring in the GI tract. Laboratory animals are the mainstay of preclinical testing for such oral drug delivery strategies with guinea pigs, rabbits, and pigs being commonly used species; each species has similarities and unique differences to man. A
recent evaluation of pH in the stomach, small intestine, and colon as well as water content in the same areas of these species has better defined some of these similarities and differences [20]. And finally, once a protective polymeric coating begins to dissolve, the material inside a coated capsule or tablet must leave the system quickly or it will be digested without ever reaching the epithelial surface for transmucosal uptake. Ordered mesoporous silica materials have been described as a promising material to produce immediate-release oral-dosage formulations [21].

IMPROVING DRUG STABILITY IN THE GI TRACT

Safe passage of labile therapeutic agents through the low pH environment of the stomach and duodenum does not ensure their stability against the exhaustive enzymatic burden of the small intestine. Polymeric structures offer one approach to shield labile materials until they can reach the mucosal surface (discussed below). A protective matrix, however, does not have to be in the nanoscale. For example, a biocompatible polymer such as ethylcellulose can be used to microencapsulate formulations to produce a liquid, sustained-release pharmaceutical for oral administration [22]. Similarly, a hydrogel system composed of methacrylic acid and poly(ethylene glycol) that releases entrapped drug with zero-order kinetics can be used [23]. Microparticles can also be produced by a spray congealing technology using Gelucire® 50/13 that would function as a hydrophilic carrier; data showed a significant improvement in the oral bioavailability of flavolignans found in Silybum Marianum dry extract [24].

Alginate/chitosan microparticles containing a biopharmaceutical have been prepared by spray-drying an aqueous drug/alginate solution and subsequent cross-linking with Ca²⁺ and chitosan. These particles protect the incorporated biopharmaceutical until they are taken up by both M cells in Peyer’s patches and into enterocytes; only M cell endocytosis appears to provide microparticle transport from the epithelium toward deeper sub-epithelial regions [25]. Promising gel-based emulsions for the preparation of self-microemulsifying drug delivery system (SMEDDS) were identified using molecular modeling and empirical force field calculations; the Flory-Huggins theory was used to study paired interactions of cyclosporine A with various types of surfactants to select a most promising candidate formulation for the oral delivery of
cyclosporine A [26]. Similarly, a system composed of poly(acrylic acid)-cysteine and reduced glutathione has been examined in vitro and in vivo as an oral drug delivery system and shown to improve the bioavailability of compounds that are P-gp and CYP450 substrates [27].

All formulation excipients must be vetted by a variety of criteria to assess purity, stability, extent of systemic exposure, bio-distribution, elimination, etc. Excipients for oral drug formulations are typically selected from list of agents that have a long history of oral exposure, such as through food substances, and categorized as generally regarded as safe or GRAS. Some new stabilizing agents that are being examined as excipients to protect labile drugs fall into this GRAS list, others do not. Even GRAS molecules, however, might need further examination if they are delivered to a segment of the GI tract they normally would not reach. For example, gelatin would be considered as a GRAS material as it is found extensively in our diet where it is broken down in the upper GI tract. It is also the material used to make many capsules. Use of gelatin as an excipient in an oral delivery system that opens in the colon would place undigested gelatin in a segment of the GI tract inconsistent with its normal fate as a food substance or from a gelatin capsule. Here one might need to consider the potential actions of this GRAS excipient on the bacterial flora of the gut as well as its potential uptake into the systemic circulation at low levels. In this regard, a recent study has examined the uptake and distribution of a dextran derivative termed OTR4120 following oral administration and shown that this material is absorbed and metabolized with some accumulation in the spleen and kidney [28].

Many new targets for specific cellular events are being validated by peptides that function to selectively disrupt protein/protein interfacial contacts. While peptides can be exquisitely specific and effective for in silico validation, their instability and poor bioavailability in the GI tract have limited their translation as drug candidates. Recent work to identify stable peptide forms as well as peptidomimetic approaches may allow for the oral delivery of peptide candidates that target selected protein-protein interactions implicated in disease pathogenesis [29]. Peptide modifications such as PEGylation, lipidisation, and multimerisation may help bring about these new peptide-based therapeutic opportunities [30]. Another approach to protect peptides may come through an improved capacity to selectively inhibit specific intestinal peptidases. For example, studies examining high-resolution X-ray diffraction data of a
carboxypeptidase-Zn$^{2+}$-citrate complex now provide an opportunity to design novel agents to regulate this enzyme [31].

**IMPROVING DRUG SOLUBILITY IN THE UPPER GI TRACT**

In other cases, poor solubility rather than poor stability is the cause of low oral bioavailability. The absorptive fate of lipophilic materials is dominated by entry into lacteals of the intestinal villi that drain into the lymphatic duct before entering into the systemic circulation. This route of entry avoids first-pass elimination events that can occur for drugs absorbed via the portal venous system that directly shunts to the liver and its extensive array of metabolic enzymes. Liposomes, a logical choice for the delivery of lipophilic drugs, were the first nanoparticles to be examined for oral drug delivery. Unfortunately, the instability of liposomes in the GI tract has been a serious problem for this application.

Poorly soluble compounds identified in drug discovery are no longer immediately discarded and ways to solve the problems of delivery associated with these materials are being studied. Some of these efforts focus on identifying formulations that can enhance bioavailability and decrease variability typically that is frequently a concern of these materials. Lipid- and surfactant-based oral drug delivery systems can produce the desired formulations for the development of these compounds. A recent review of these approaches has provided a more cohesive picture of the physicochemical nature of suitable detergents and lipid excipients in relation to gastrointestinal digestion [32]. A thorough understanding of the physiological features of lymphatic-based uptake and metabolism is also critical in the design of successful lipid- or pro-drug-based drug delivery systems that could enhance lymphatic drug transport [33].

Cyclodextrins have been described as “an important tool in the formulator’s armamentarium to improve drug solubility and dissolution rate for poorly water-soluble drug candidates” and efforts have been made to predict whether cyclodextrins will be of benefit in creating a dosage form for a particular drug candidate [34]. Multiparticulate systems composed of α-cyclodextrin and soybean oil have also been described for the oral delivery of lipophilic drugs [35]. Such a system might also be used to target lymphatic uptake. Some nanomaterials, such as mesoporous silicon particles, function to improve the solubility of an otherwise poorly soluble drug as a
means to improve its uptake following oral delivery [36]. In this case, the particle itself does not appear to transport across epithelial barriers, but instead increased the permeation of the loaded poorly soluble drug.

Other methods have been described to improve the oral delivery of lipophilic materials. Addition of the tetraether lipid glycerylcaldityl tetraether to liposomes prepared from egg phosphatidylcholine and cholesterol can stabilize these structures against the actions of bile salts; making them more promising carriers for oral drug delivery [37]. Nanostructured lipid carriers produced using a high pressure homogenization method and which can be loaded up to ~30% with drug have been shown to improve the oral delivery of testosterone undecanoate [38]. Tween 80-coated polylactide-co-glycolide (PLGA) nanoparticles have been shown to effectively deliver the hydrophobic drug estradiol after an oral administration in a manner that was comparable to the injection of this hormone [39].

The ability of liposomes to facilitate hydrophilic macromolecule delivery across polarized epithelial barriers can be improved by the incorporation of enhancing agents such as cholylsarcosine, cetylpyridinium chloride, and stearylamine [40]. Nanoparticles formed by Ca$^{2+}$ nucleation of alginate and dextran sulfate bound to poloxamer were stabilized by chitosan and subsequently coated with albumin. These negatively charged nanoparticles improved the delivery of an incorporate macromolecule following oral administration [41]. A novel pulsatile release system for oral drug delivery has also been described that employs an enteric subcoating that eliminates drug diffusion through the gelled polymer coating layer prior to its erosion; the system incorporates varying ratios of a drug in the compression-coating layers in addition to the tablet core [42]. Thus, combinations of these new methodologies may offer novel approaches to facilitate the oral delivery of poorly soluble drug candidates that previously might have been rejected from oral screening.

**USING NANOSTRUCTURES IN ORAL DOSAGE FORMS**

While still unproven in clinical settings, nanostructures have been proposed to improve oral drug delivery efforts in several ways. One way is to protect labile materials prior to their presentation to the intestinal epithelial surface where they can then be absorbed. Since some animal data suggest nanostructure can are absorbed from the
intestinal lumen, these materials may help in the oral delivery of poorly-absorbed drugs. Such studies have shown that incorporated drugs have greater oral bioavailability compared to a solution form of the same drug. Finally, nanostructures are anticipated to provide a greater drug distribution at the apical surface of the intestinal epithelium when compared to other solid dosage forms; potentially improving the uptake outcome and/or absorption profile of the drug.

A variety of new approaches to produce nanomaterials for the delivery of labile molecules have recently been described. Mannan is a plant polysaccharide composed of the sugar mannose. Nanogels made using an amphiphilic form of mannan can spontaneously incorporate proteins and other agents, potentially providing a new nanostructure oral delivery system [43]. Amphiphilic polyelectrolyte nanocomplexes prepared from polyallylamine grafted with palmitoyl chains and subsequently modified with quaternary ammonium moieties was shown to improve the uptake of incorporated insulin across Caco-2 cell monolayers in vitro [44]. The mechanism(s) by which these systems facilitate oral insulin uptake appear to be particularly complex as both active transport and reversible opening of tight junctions appeared to be involved [44].

Nanoparticles, by themselves, are not necessarily prone to efficient transcytosis after contacting the apical surface of intestinal epithelial cells. It is therefore not surprising that recent studies with nanoparticles have demonstrated inclusion of hydroxypropyl-β-cyclodextrin, an agent capable of modifying epithelial barrier function, can improve drug permeation across colonic pig mucosa. Nanoparticles made by coacervation of chitosan and DNA complexes which have a net positive zeta potential can protect an intercalated plasmid against nuclease degradation and improve transfection of M cells [45]. Importantly, these nanomaterials provided transfection with efficiency similar to polyethyleneimine-DNA complexes but without the cytotoxicity associated with this polymer. Related to delivery for oral immunization, targeting ligands have been described that increase antigen-particle uptake to intestinal antigen-presenting cells, including dendritic cells [46]. Silk fibroin matrices are biocompatible, slowly biodegradable, and endowed with excellent mechanical properties; they have been suggested for applications in oral drug delivery. In this regard, a recent review has examined the potential of using silk fibroin matrices to aid in the delivery of micro- or nanoparticles as a carrier or coating [47].
Nanoparticles, even in the absence of enhancing agents, have been touted as having the capacity to move across epithelial surfaces following oral delivery; some have even been described that can subsequently target selective sites within the body following mucosal transport. Recent studies using gold nanoparticles have suggested that particle size and surface properties can control the nature and extent of tissue distribution following oral uptake [48]. Another issue of using nanoparticles involves incorporation of a drug material, which can be an issue since some nanoparticle preparation techniques can damage labile drugs. Elements of two different techniques were used to prepare nanoparticles under less harsh conditions: hydrophobic ion pairing followed by encapsulation of an inter-polymer complex involving polyacrylic acid and a detergent. These particles were shown to increased oral bioavailability of leuprolide [49]. There are still many uncertainties regarding the production, fate, and safety of nanoparticles used for oral drug delivery with successful clinical applications likely requiring matching this technology with the right drug for the right indication. A study examining nanoparticle-mediated oral delivery of cyclosporine may have hit on one promising combination [50].

INCREASING MUCOSAL ADHERANCE OF ORAL DOSAGE FORMS

Efforts to orally deliver labile, poorly-absorbed drugs should benefit from bringing protective drug carriers into close proximity with the intestinal mucosa such that released drug can reach the epithelial cell surface before being destroyed in the intestinal lumen. Carriers with mucoadhesive properties could function to achieve this outcome. While the focus of this perspective is on drug delivery in the small intestine and colon, important advances in bioadhesive strategies for buccal administration [51, 52] may provide important principles that could be applied to adhesion of materials to mucosal surfaces of the small intestine and colon. In this regard, β-limit dextrin (a starch derivative) was found to have significant mucoadhesive properties; similar to carbopol but superior to chitosan strategies [53].

Chitosan is an important polymer for oral drug delivery because of its properties, safety, and availability; chitosan nanocapsules have shown promising results as carriers for oral peptide delivery. A recent study has examined the impact of molecular weight and degree of acetylation on chitosan nanocapsule production and
characteristics [54]. Further, chitosan treated Ca\textsuperscript{2+}-alginate microparticles were screened to identify those having characteristics that would be consistent with improved delivery of naproxen to lower parts of GI tract [55]. Nanoparticles prepared from thiolated chitosan have mucoadhesive properties that can facilitate the oral delivery of labile drugs [56]. Modifications to chitosan, such a conjugation with mercaptonicotinic acid, can produce nanoparticles having strong mucoadhesive properties that make them useful for as vehicles for oral delivery of peptide drugs [57].

Incorporation of cyclodextrins in poly(anhydride) nanoparticles provides desirable bioadhesive properties and sufficient lipophilic drug loading to promote the oral bioavailability of (Class IV of the BCS) drugs displaying poor aqueous solubility and specific permeability characteristics [58]. Cyclodextrin-poly(anhydride) nanoparticles having bioadhesive properties can improve oral delivery of the lipophilic drug atovaquone [59]. Another approach to improve the proximity of an orally delivered drug to the mucosal surface is to place the drug in a patch that can be prepared using traditional microfabrication techniques and delivered by an orally-administered system [60, 61]. Overall, a variety of mucoadhesive materials are being studied to identify methods to bring labile, poorly-absorbed drugs to the epithelial surface where they have a greater chance of being absorbed than if they were released in the intestinal lumen.

**IMPROVING THE BIOAVAILABILITY OF POORLY ABSORBED DRUGS**

It is critical that the intestine functions as a selective barrier for it to function effectively in the absorption of nutrients in a safe manner. Non-self proteins in our diet cannot simply flood into our bodies for later catabolism or we would have massive immune responses to these dietary components and could not repeatedly eat the same food. The delicate but formidable permeability barrier established by intestinal epithelial cells limits uptake until these dietary elements are reduced to structures that are too small to load into major histocompatibility complex proteins involved in antigen presentation. Thus, despite excellent methods to safely guide materials through the stomach and early segments of the small intestine and deliver them to the apical surface of epithelial cells in the jejunum or ileum, these biotherapeutics cannot
be effectively absorbed at these distal sites until they are digested locally. This problem has been well-recognized and a large number of methods have been tested to improve epithelial permeability either through transcellular or paracellular routes.

Enhancing agents used to date fall into several chemical categories: detergents, fatty acids, novel amino acids, lipid complexes, etc. While substantial uptake of protein and peptide therapeutics can be observed in animal models, only a few approaches have been translated to human clinical studies. The enhancing agents shown to be most successful to date for this clinical translation have been selected from a list of agents that are generally regarded as safe (GRAS). Since many poorly-absorbed compounds could be damaged by high concentrations of some GRAS agents, it is important to use enhancing agents that do not compromise these labile materials. For example, microemulsions composed of the surfactant didocetyl(dimethyl)ammonium bromide, the co-surfactant propylene glycol, and triacetin have been shown to enhance the oral bioavailability of incorporated insulin [62].

Salmon calcitonin, approved for the treatment of osteoporosis, has been examined in clinical studies as an oral dosage form that incorporates the permeation enhancer N-(5-chlorosalicyloyl)-8-aminocaprylic acid [63]. Analysis of Phase III clinical trials have suggested that a tablet configuration of these materials can safely delivery, albeit at low levels of bioavailability, bioactive peptide [64]. Ways to improve the low bioavailability have been examined. Nanoparticles containing salmon calcitonin can be prepared by complexation of the peptide with the cationic amphiphilic polyelectrolyte poly(allyl)amine grafted with palmitoyl and quaternary ammonium moieties. The resulting positively-charged particle complexes can reduce free and serum calcium over 240 min following intra-jejunal administration demonstrating the oral delivery of biologically-active calcitonin [65].

The permeation enhancer N-[8-(2-hydroxybenzoyl) amino] caprylate, distinct from the enhancer described above, can increase the oral bioavailability of biologically-active glucagon-like peptide 1 or peptide YY 3-36 in healthy adults [66]. Thus, use of an enhancing agent can improve the oral delivery of poorly-absorbed drugs if they are kept sufficiently stable in the intestinal lumen prior to uptake. In some ways, the complete strategy for a successful oral drug delivery would involve a system to deliver a labile drug in the presence of materials that inhibit destructive enzymes along with an absorption enhancer to facilitate uptake. This approach has been described using a
two-pulse colonic release system for insulin delivered with the protease inhibitor camostat mesilate and the absorption enhancer sodium glycocholate [67].

For most individuals, oral drug delivery connotes systemic bioavailability. There are, however, important pharmaceutical targets associated with various cells of the GI tract itself and methods have been described to stabilize, protect, and deliver labile drugs locally in the intestine. One such example as been described in a study using mesoporous silica nanoparticles as a drug delivery system for the targeted inhibition of notch signaling in intestinal stem cells [68]. Another approach has been described where covalent modification of a therapeutic protein with glycosylphosphatidylinositol to would allow its association with lipid structures, allowing it to transfer from these structures to the membranes of target cells. It is proposed that these materials could also enable the transport of therapeutic proteins across the intestinal barrier and into the circulation [69].

**OPTIMIZATION OF ORAL DRUG DELIVERY SYSTEMS FOR THE FUTURE**

This perspective has focused on how European scientists are addressing the challenges of stabilizing labile drugs and finding ways to improve the oral bioavailability of poorly-absorbed drugs. The clinical impact of such work, however, may be optimized by methods that provide a defined pattern of drug delivery. These patterns could involve pulsatile/delayed delivery systems designed to elicit programmable lag phases preceding a prompt and quantitative, repeated or prolonged drug release. Formulation strategies behind delayed-release and pulsatile dosage forms intended for the pharmacological treatment of chronopathologies have recently been discussed [70].

Personalized medicine has been discussed for several years now as the way to optimally treat patients. Bringing that concept to a realistic outcome has many challenges. One such issue is being addressed by research examining the feasibility of solid systems that can enable flexible dosing such as dispensers for multiparticulate drug formulations, a solid dosage pen, and drug-loaded oral films which can be cut in individual sections [71]. Additionally, a device has been developed that allows for dose adjustment by the selected cutting of a monolithic drug carrier into defined individual doses [72].
Understanding the nature and characteristics of drug release from an oral delivery system is essential to predict the use of that system in that application and to project its potential use for other applications. A mathematical modeling approach to describe drug release and in vivo absorption has been described [73]. Such a study falls in line with research performed to identify dissolution methods that can be applied to correlate in vivo outcomes with in vitro performance assessments of oral drug delivery systems [74] with hydrodynamic events experienced by an extended release formulation being one parameter for consideration [75]. Similarly, simulations which includes pressure force exerted by GI motility, shear stress force generated during phases of GI transport and intermittent contact with intestinal fluids due to occasional encounters with intestinal air pockets have been described [76].

Efforts have also been made to improve our understanding of the fate of oral delivery systems following their administration. European scientists have been at the forefront of establishing non-invasive methodologies of scintigraphy, magnetic tracking techniques like magnetic marker monitoring, magnetic moment imaging, AC biosusceptometry, and magnetic resonance imaging for this assessment [77]. Identification of optimal regions of the intestine for the delivery of a specific drug formulation can be determined using a remote-controlled capsule device that provides targeted drug delivery and is monitored for its location in the GI tract by scintigraphy [78]. Drugs designed to treat ulcerative colitis would obviously benefit from a delivery format directed to the colon. A pharmacoscintigraphic study in healthy volunteers using the MMX Multi Matrix System(®) (MMX™) to deliver propionyl-l-carnitine (PLC), a naturally occurring analogue of l-carnitine, demonstrated the colon to be the main site of PLC release and absorption [79].

An issue that is not often appreciated early enough in oral formulation design is the potential impact that specific excipients used might have on the complex intestinal flora present in the GI tract. Thus, studies using the Simulator of the Human Intestinal Microbial Ecosystem (SHIME) to examine the impact of different ethylene vinyl acetate grades on the GI ecosystem following oral administration can anticipate and potentially mitigate expensive formulation changes at later stages of development [80]. Additionally, both regulatory agencies and pharmaceutical companies have become more appreciative that pediatric dosage forms must be designed to match unique issues associated with this patient population. Such concerns must be equally
considered when it comes to the identification of pediatric oral drug delivery strategies [81].

OUTLOOK

While the studies described in this perspective were authored by established European scientists, I cannot verify that that all of this work was performed in European laboratories. Clearly, scientific efforts have become more and more collaborative and many of these established European scientists work within international networks. One point that can be definitively stated, however, is that European pharmaceutical scientists have had tremendous impact on the successful development of therapeutics currently being administered by the oral route. Their ability to find innovative, elegant, and practical solutions to overcome the challenges to deliver materials to the GI tract has been impressive. With the inability of HTS efforts to find large numbers of obvious candidates that would be defined by current industry standards as promising lead compounds, new types of challenges now confront European pharmaceutical scientists. Unlike some other areas of the world, the European pharmaceutical community has enjoyed a fruitful collaborative arrangement between industrial and academic colleagues. I feel that continuation of this mutually-beneficial relationship will be critical to meet current challenges now faced by pharmaceutical companies to bring labile and/or poorly absorbed drug candidates through successful clinical development. With the ever-shrinking research budgets available to both academic and industrial scientists, success in the future for these programs may require not just creativity in the lab, but also new mechanisms and strategies to fund these essential studies. Some of these creative new mechanisms to bring academic and industrial groups together in multi-disciplinary, multi-regional efforts have included the FP-7 and IMI funding schemes. It is hoped that these approaches will prove fruitful and provide funding templates that can be expanded in the future.

REFERENCES
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