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Review Article

Theme: Established Drug Delivery Technologies-Successes and Challenges
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Absorption Enhancers: Applications and Advances

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Abstract. Absorption enhancers are functional excipients included in formulations to improve the absorption of a pharmacologically active drug. The term absorption enhancer usually refers to an agent whose function is to increase absorption by enhancing membrane permeation, rather than increasing solubility, so such agents are sometimes more specifically termed permeation enhancers. Absorption enhancers have been investigated for at least two decades, particularly in efforts to develop non-injection formulations for peptides, proteins, and other pharmacologically active compounds that have poor membrane permeability. While at least one product utilizing an absorption enhancer for transdermal use has reached the market, quite a few more appear to be at the threshold of becoming products, and these include oral and transmucosal applications. This paper will review some of the most advanced absorption enhancers currently in development and the formulation technologies employed that have led to their success. In addition, a more basic review of the barriers to absorption and the mechanisms by which those barriers can be surmounted is presented. Factors influencing the success of absorption-enhancing formulations are discussed. If ultimately successful, the products now in development should offer non-injection alternatives for several peptide or protein drugs currently only administered by injection. The introduction of new absorption enhancers as accepted pharmaceutical excipients, and the development of formulation technologies that afford the greatest benefit/risk ratio for their use, may create opportunities to apply these enabling technologies more broadly to existing drugs with non-optimal delivery properties.

KEY WORDS: absorption; bioavailability; enhancer; permeability.

INTRODUCTION

Oral dosing is generally considered to be the most patient-friendly and convenient route of drug administration. However, many pharmacologically active compounds cannot be administered orally because of inadequate oral bioavailability, and this may limit the usefulness of these compounds. Poor oral bioavailability can be caused by poor aqueous solubility, degradation within the gastrointestinal contents, poor membrane permeability, or presystemic metabolism. Compounds can have poor membrane permeation due to large-molecular weight, as is the case with proteins and other macromolecules, or insufficient lipophilicity to partition into biological membranes, as with many hydrophilic, low-molecular weight compounds. There are numerous pharmacologically effective compounds currently used that must be administered by injection because of inadequate bioavailability by non-injection routes. Others are used orally even though their oral bioavailability is low, and inter-individual variability in systemic exposure is high, making therapy with these drugs less than optimal. Absorption enhancement is the technology aimed at enabling non-injection delivery of poorly membrane-permeable compounds.

This review provides a summary of the current status of various absorption enhancement technologies, particularly focusing on those that are currently in clinical trials or are already used in marketed products. Much of the discussion is on gastrointestinal absorption enhancement, which if successful, could have the greatest impact on drug therapy. However, absorption enhancement has also been applied to delivery by the transmucosal and transdermal routes, and these will also be discussed to some extent. The agents and technologies reviewed are mainly those that alter drug permeation through the biological membrane that acts as the barrier to absorption. While one approach to improve membrane permeability and absorption is to chemically modify the structure of the active compound, this review will be restricted to those technologies in which the active ingredient is not chemically altered, but is combined with an another agent or a specific formulation composition to increase permeability. Technologies that enhance absorption by increasing dissolution or solubility are not the subject of this review. Technologies intended for reducing presystemic metabolism are only considered here for those compounds that require membrane permeability enhancement and stabilization on the way to or at the absorption site.

This review focuses on the progress that has been made in this field in the last decade toward marketed products. For

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a more thorough and fundamental discussion of absorption enhancement and the earlier literature, the reader is referred to previous reviews of this subject (1–4). Since the impact of absorption-enhancing technologies will be determined by the benefits and successes of the commercially available products, now or in the near future, a component of this review is the absorption enhancers that are currently in development, and the companies pursuing them.

THE NEED

A number of advantages may be gained by maximizing systemic bioavailability after oral administration or administration via a transmucosal (i.e., nasal, buccal, sublingual, and rectal) absorption site. First, these routes offer needle-free delivery, which is usually considered to be more acceptable than injections for patients taking a medicine chronically. Increased patient acceptance should result in improved compliance. Low bioavailability has been shown to be associated with large inter-subject variability in systemic exposure. The second advantage of increasing bioavailability is the reduction of intra- and inter-patient variability, thus improving the control of the drug's intended and unintended actions. Finally, if an active drug substance is costly to manufacture, there is the economic advantage of reducing the waste of the drug material due to its lack of systemic absorption.

Consider the types of compounds that could benefit from an absorption-enhancing technology. Table I lists some of the compounds for which absorption enhancement technologies have been proposed and tested, clinically in many cases. For the purpose of this discussion, these compounds are divided into three categories: (1) proteins, polypeptides, and peptides, (2) non-peptide macromolecules, and (3) hydrophilic small molecules.

Many proteins and peptides have demonstrated highly potent and selective pharmacologic activities toward various therapeutic targets. While some of these have been developed into marketed injectable products, there is clearly a need for non-injection alternatives, especially for compounds that are used chronically and require frequent dose administration. Insulin is an example of a protein that is administered by injection, and which is administered chronically to insulin-dependent diabetics. The term "insulin-dependent" indicates how beneficial this drug is for those in the growing diabetic population. The quest for non-injection insulin dosage forms has been ongoing for much of the nearly 100 years since the discovery of insulin. In addition to benefiting patient convenience, the oral route of insulin delivery could also have pharmacologic benefits, since it represents a more physiologic route of delivery. Insulin is normally secreted from the pancreas into the portal vein and is then highly extracted by the liver, binding to insulin receptors there. The potential clinical benefits of liver targeting of insulin via oral delivery

Table I. Candidate Compounds for Oral and Transmucosal Absorption Enhancement Technologies

Compound or compound family	Uses	Chemical properties	Comments
Peptides, proteins			
Calcitonin	Postmenopausal osteoporosis	32 amino acid peptide, MW ~3,455	Injection and nasal (F=3–5%) products are available
Desmopressin (DDAVP)	Diabetes insipidus, nocturnal enuresis	9 amino acid peptide, MW 1,183	Oral (F=0.16%) and nasal (F=5–10%) products
Insulin	Diabetes	51 amino acid peptide, MW ~5,800, hexamer form	Various injection products and one inhaled form available
Leuprolide	Endometriosis, prostate cancer	9 amino acid peptide analog, MW ~1,200	Solution and depot injections and implant forms available
Octreotide	Acromegaly, carcinoid tumors	Cyclic octapeptide, MW ~1,000	IV and SC injection use only (50–500 μg tid dose)
Non-peptide macromolecules			
Heparin	Anticoagulant	Highly sulfated polymer, MW 12,000–15,000	IV and SC use only
Low-molecular weight heparin (enoxaparin)	Prevention and treatment of thrombosis	MW ~4,500, sulfonate and carboxylate groups	IV and SC use only, usually 30–40 mg/day
Fondaparinux	Factor Xa inhibitor, anticoagulant	Pentasaccharide, MW ~1,727, sulfonate and carboxylate groups	SC injection only, usually 2.5–10 mg/day
Oligonucleotides	Modulate various biological pathways	Hydrophilic, high MW	Emerging as potential parenteral products
Vancomycin	Antibiotic	Glycopeptide, MW 1,449	IV use, high doses, oral product for colitis only
Hydrophilic small molecules			
Aminoglycosides (e.g., amikacin, gentamycin)	Antibiotics	MW ≥500	IV and IM use, high doses, some topical products
Amphotericin B	Antifungal	MW 924, low log P, high-polar surface area	IV use
Bisphosphonates	Osteoporosis	Strongly acidic phosphonate groups, MW approx. 250–325	Oral bioavailability <1% for many in class

may include reduced hyperinsulinemia and risk of hypoglycemia and improved weight control (5).

In contrast to insulin, calcitonin is a peptide drug used to treat a condition, postmenopausal osteoporosis, for which there are already alternative therapeutic options not requiring injection. Calcitonin is available as a nasal spray, but the bioavailability when administered by that route is quite low, roughly 3–5%. In the case of calcitonin, the need is for a product that can be administered as conveniently as other available osteoporosis therapies, with adequate bioavailability, and with safety and effectiveness comparable to injectable calcitonin. The development of bioavailable, non-injection formulations of calcitonin could expand its use in the treatment and prevention of osteoporosis, as well as other potential indications.

Absorption enhancement technologies have also been investigated for non-peptide macromolecules (MW>1,000) including heparin, low-molecular weight heparins, and some oligonucleotide drugs. Oligonucleotides as a structural class may see increased applications in the future, especially if the delivery issues associated with their use can be resolved. Also listed in Table I are a few groups of structurally related hydrophilic small molecules, in which one or more functional groups associated with pharmacologic activity also contributes significantly to poor membrane permeability characteristics. Examples include the aminoglycoside antibiotics and bisphosphonates.

The compounds listed in Table I are, for the most part, approved drugs. The efficacy of each of these marketed agents has been proven, and a technology that enhances absorption may enable the development of a product that provides an alternative to the mainly injectable products already available. There are certainly many other pharmacologically active compounds which have not been developed as injectable products and for which inadequate bioavailability prevented their development into non-injection products. An example of a small molecule new chemical entity for which absorption enhancement was investigated during its development is DMP728, a cyclic peptide antagonist of the glycoprotein IIb/IIIa receptor (6,7). For compounds like this, with unproven human efficacy and safety, the development or application of an absorption-enhancing technology surely increases the risks involved in developing the compound. However, once absorption-enhancing technologies have been proven and accepted into the market, it seems quite likely that an existing technology would be applied readily in the development of new chemical entities with less than optimal absorption properties.

THE BARRIERS

Potential routes of administration that have been considered as alternatives to the injection route of drug delivery include oral, transmucosal, and transdermal. In this section, the nature of the barriers to drug delivery by the oral, transmucosal, and transdermal routes is briefly reviewed. Pulmonary delivery for systemic absorption has also been shown to represent an alternative to injection, and inhaled insulin has been introduced to the market. However, there is scarce literature on the need for, or the benefits of pulmonary absorption enhancers. So, pulmonary absorption enhancement will not be discussed further in this review.

The first requirement for drug absorption is for the active ingredient to reach the absorbing membrane, which can occur by direct dermal or mucosal application, or in the case of intestinal absorption, the drug has to be delivered to the intestinal membrane surface intact. This may require controlling the release of the drug and the absorption-enhancing excipient as they pass through the acidic contents of the stomach and the digestive enzymes in the contents of the stomach and small intestine. As will be described later, special formulations have been designed to protect unstable drugs and to release drug and excipient simultaneous or in sequence within specific regions of the gastrointestinal tract.

The intestinal epithelial membrane, which functions as the barrier to intestinal absorption, is comprised of a layer of columnar cells interconnected via tight junctions. The luminal surface of the intestinal membrane is covered by a layer of mucus, which is generally not a rate-limiting barrier to absorption. Most drugs are primarily absorbed transcellularly, permeating through the lipid bilayer that comprises the apical cell membrane. Transporters on the apical and basolateral cell membranes may move drug molecules either toward the cell interior or in a direction from the inside of the cell to the outside. Approaches to increasing absorption have included using excipients that inhibit secretory (efflux) drug transporters on the apical surface. For example, the common excipient polysorbate 80 increased the oral bioavailability of digoxin in rats (8). Also, there have been successes in linking drugs to compounds that utilize transporters for active drug absorption and in designing drugs to be substrates for these transporters. An example of success of this approach is the prodrug valacyclovir, which is a substrate for the proton-linked intestinal peptide transporter and has three- to fivefold improved bioavailability relative to acyclovir in humans (9). However, transporters are not considered further in this review. In addition to transcellular permeation, drugs can be absorbed by a paracellular mechanism, and the tight junction structure represents the barrier to paracellular absorption. Once a drug molecule has passed through to the basolateral side of the intestinal epithelium, absorption into the blood is generally not restricted. Of course, peptides, polypeptides, and proteins may be subject to metabolism before reaching the intestinal epithelium or during permeation of the intestinal membrane.

Insulin, calcitonin, and other polypeptides and proteins have poor intestinal membrane permeability due to their large molecular weight relative to most orally administered drugs and due to the tendency of compounds with many hydrogen-bonding groups to permeate epithelial membranes poorly. The molecular size of non-peptide macromolecules, such as low-molecular weight heparins, is also not within the range usually associated with reasonable membrane permeability. In addition, many of these agents are very hydrophilic due to the presence of numerous functional groups that are charged at physiological pH, such as the sulfonates of heparin and its analogs. Strongly ionized, small molecule drugs, such as the bisphosphonates, are poorly permeable due to their inability to partition into the intestinal cell membrane, and paracellular absorption is also restricted when the molecular size is greater than the effective pore size of the paracellular channels.

The membrane lining the nasal cavity consists of several different types of cells, but in general, the nasal epithelium is similar to the gastrointestinal epithelium in that it is a pseudostratified columnar epithelium, with a single layer of cells and interconnecting tight junctions presenting the main

barriers to absorption. For nasal absorption, a drug formulation can be sprayed into the nasal cavity delivering the drug to the membrane surface. But ciliary movement at the membrane surface steadily moves materials from the anterior to the posterior portion of the nasal cavity where the materials are swallowed. Because ciliary action removes drug from the absorption site, nasal membrane permeation must be fairly rapid for bioavailability to be complete. Another limitation for nasal drug delivery is that generally only low volumes (a fraction of a milliliter) can be administered by this route; a larger volume will run out or be swallowed. So, the nasal route is useful only for potent compounds with good solubility in the dosing vehicle. An advantage *versus* oral delivery is that drugs absorbed by the nasal route are not subject to hepatic first-pass metabolism.

The skin is a stratified squamous epithelium. The barrier to delivery through the skin is the stratum corneum, a layer of dead skin cells compressed into a matrix of intercellular lipids. The stratum corneum has been likened to a brick and mortar structure in which the cells are compactly stacked like bricks, and the intercellular spaces are filled with lipids, representing the mortar. Inside the stratified cells are keratin and other proteins that give the outer layer of skin its durability. The pathways for permeation of the stratum corneum are either through the multiple cell layers, the bricks, or through the intercellular lipids, the tortuous pathway through the mortar. The thickness of the stratum corneum barrier varies with location on the body, and skin permeability depends on the stratum corneum thickness.

The buccal and sublingual membranes lining the mouth are similar to skin in being stratified squamous epithelia. The extent of keratinization varies within the region of the mouth, being greatest in the masticatory regions and hard palate. As with delivery via the nasal mucosa and skin, a drug formulation can be applied directly onto the membrane, and a drug that is absorbed from the mouth is not subject to hepatic first-pass metabolism.

MECHANISMS OF ABSORPTION ENHANCEMENT

Formulating a solution to an absorption problem requires defining the barriers to absorption for that compound as well as understanding the mechanisms by which absorption might be improved. An outline of the possible mechanisms of absorption enhancement is given in Table II. For many peptides and protein drugs, degradation and/or metabolism could occur at the absorption site or during delivery to the absorption site in the case of oral delivery. For these compounds, one mechanism to improve bioavailability that may be applicable is the reduction of their degradation or metabolism. As examples described later will illustrate, this might be accomplished by encapsulation of the drug to protect it, by including a protease-inhibiting excipient in the formulation, or by controlling the pH of the environment where the drug is released.

Table II. Mechanisms of Absorption Enhancement

A. Preventing degradation/metabolism
B. Enhancing membrane permeability
Gastrointestinal and nasal membranes
Transient opening of tight junction
Disruption of lipid bilayer packing
Complexation/carrier/ion pairing
Skin, buccal, sublingual membranes
Disruption of lipid packing in intercellular spaces
Disruption of cellular protein structure
Complexation/carrier/ion pairing
Solvent drag

Compounds with poor membrane permeability may require the use of an excipient that modulates membrane permeability. The mechanism by which increased permeability is accomplished is likely to determine whether the increase in permeability is transient and non-cytotoxic. These factors are critical for the ultimate success of utilizing a permeation-enhancing excipient. Therefore, the most advanced permeation enhancers have been the subject of in-depth studies of the mechanisms of their effects on epithelial membranes.

For gastrointestinal and nasal epithelial membranes, the movement of water and low-molecular weight solutes is physiologically regulated through the distension and constriction of the tight junctions, which alter paracellular porosity. Since the tight junctions open and close in response to physiological stimuli, regulating the permeabilities of at least some low-molecular weight compounds, it would seem possible that this mechanism might afford a relatively safe and reversible means of permeation enhancement. In their review of this subject, Hochman and Artursson (3) listed various types of tight junction modulators, including calcium chelators, protein kinase C activators, cytochalasins B or D, and *Clostridium difficile* toxin. More recently, some investigators have targeted specific proteins comprising the tight junction, such as claudin and occludin, and have described agents with potent and specific effects on these proteins and on tight junction permeability (10). Several companies have focused their research on the identification and design of tight junction modulators that could be used to enable drug delivery. Nastech scientists reported on the *in vitro* effects of tight junction-modulating lipids as well as a tight junction-modulating peptide (11). The drug delivery technology developed at Nastech has been acquired by Marina Biotech. An approach being pursued at Alba Therapeutics is based on the identification of a zonula occludens toxin protein, and subsequently a peptide fragment thereof, that increased the intestinal absorption of several poorly absorbed compounds in rats through a mechanism targeting tight junction modulation (12). However, the selective targeting of tight junction elements is at an early stage relative to other absorption-enhancing technologies, and less evidence of *in vivo* effects is available.

The alternative mechanism of permeation enhancement involves promoting the transcellular permeation of drugs. This requires disrupting the structure of the cellular membrane. As reviewed by Swenson and Curatolo (2), surfactants can act as permeability enhancers by partitioning into the epithelial cell membrane and disrupting the packing of membrane lipids, forming structural defects that reduce membrane integrity. Surfactants can also extract proteins from the cellular membrane. Agents that alter cell membrane permeability in a way that disrupts the normal extracellular–intracellular ion gradients could be cytotoxic, since various cellular functions depend on maintaining transmembrane ion gradients. The important issues then are whether the permeabilization is transient, and if cytotoxicity occurs, whether the tissue can readily rejuvenate areas where cytotoxicity has occurred.

As will be described later in this paper, some of the absorption-enhancing agents in advanced clinical trials are comprised of medium chain fatty acids or contain a medium chain alkyl functional group as part of their structure. For example, sodium caprate is already in use in a suppository product available in Japan and is currently being evaluated as an oral absorption enhancer. A consideration of the putative mechanisms by which this agent can enhance absorption may be useful. Sodium caprate was shown by microscopy to both dilate the tight junction (paracellular permeation enhancement) and to increase cell membrane penetration (transcellular permeation enhancement) of a fluorescent marker (3). The *in vitro* effects on drug permeation were more closely aligned with the effects on the tight junctions, suggesting that paracellular permeation enhancement may be more significant. However, sodium caprate can cause the release of membrane phospholipids *in situ* and can cause cytotoxicity *in vitro* (1), so it would seem that both paracellular and transcellular mechanisms of permeation enhancement may occur, depending on the caprate concentration, whether *in vitro* or *in vivo*, and other factors. Furthermore, the cytotoxicity associated with exposure to the structurally related enhancer, sodium laurate, was reduced by the presence of the amino acids taurine and L-glutamine (13). The cytotoxicity seen with sodium laurate exposure was associated with increased intracellular calcium resulting in apoptosis, and these effects were reduced by the amino acids. These studies are examples illustrating why it is important to understand the mechanisms of altered absorption and how this information might be used to optimize safety and efficacy.

Another mechanism that has been proposed for enhancing absorption is the formation of a membrane permeable complex, with one type of complex being an ion pair. The distinction must be made between using complexation to increase aqueous solubility, which is quite common, and to increase membrane permeability. A recently reported example designed to utilize ion pairing is the enhanced intestinal membrane permeability of two poorly permeable antivirals, zanamivir heptyl ester and guanidino oseltamivir, by inclusion of 1-hydroxy-2-naphthoic acid as a counter-ion (14). Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (also referred to as SNAC) is an absorption enhancer in late-stage clinical trials. As will be discussed in more depth later, several publications have provided evidence that this agent may act by forming an association with the drug in a way that increases the membrane permeation of the drug, but without permeabilizing the membrane.

A hypothesis to generally describe the mechanisms of skin permeability enhancement referred to as the lipid–protein–partitioning (LPP) concept was proposed (15). This hypothesis proposes that skin permeation enhancers usually work by one or more of three mechanisms: by altering the stratum corneum lipids, proteins, or by increasing partitioning of the drug or another applied excipient into the stratum corneum. Lipids packed into well-organized structures constitute the intercellular spaces of the stratum corneum. Some skin permeation enhancers have been shown to disrupt the packed structure of stratum corneum lipids. An example is oleic acid, which was shown by differential scanning calorimetry to alter the transition temperatures of stratum corneum lipids, with proportional effects on permeability (16). Other agents, such as non-ionic surfactants, cause changes in the intracellular proteins of stratum corneum and increase permeability by this mechanism. Increased partitioning can involve the formation of a drug–excipient association or increased penetration of the vehicle into skin with increased drug permeation by solvent drag (17).

The available mechanisms for enhancing permeability of the buccal and sublingual membranes may be similar to those for skin, as summarized in the LPP concept. However, it has also been suggested that the lipids of the buccal mucosa are chemically and structurally different from those of the stratum corneum, and the mechanism of a particular permeation enhancer may differ between the skin and the buccal mucosa (18).

THE DEVELOPMENT PROCESS AND REQUIREMENTS FOR SUCCESS

Much of the published literature on permeation enhancers represent work that was performed at an early research stage. Typically, the initial work on absorption enhancement utilizes *in vitro* permeation studies with cell culture models or excised tissue membranes to identify agents that are effective in increasing permeation of the drug through the membrane targeted as the delivery route (e.g., intestine, skin, etc.). Important components of the early *in vitro* evaluation are to define the effective concentration range of the enhancer, and the concentration range where membrane damage occurs, to identify a safety margin. In the case of intestinal delivery, it is also important to develop an understanding of how the effects of the enhancer vary in different locations of the intestinal tract. In addition, *in vitro* studies often provide useful information regarding the mechanism of permeation enhancement.

As an absorption enhancement concept moves to the preclinical stage, the goal is to take what is known from the *in vitro* studies and apply it in a much more complex, whole animal system. One of the main challenges in establishing *in vitro*/*in vivo* correlations is that in a diffusion experiment conducted *in vitro*, the concentrations and environment of drug and enhancer can be precisely controlled, but in an animal, this may be difficult to accomplish. Formulations applied directly to an absorption site such as the nasal cavity or buccal mucosa will be diluted by the fluids present there and are subject to processes that tend to remove it from the application site. For intestinal delivery, the dilution effect can be tremendous and will be a function of gastric emptying and intestinal transit times. However, the aim is to deliver the drug and enhancer together to the surface of the absorbing membrane. This review will later describe some products that are in development and have used coatings, encapsulation, or other means of modifying the release of drug and enhancer for oral delivery. It is not surprising that the *in vivo* effects of absorption enhancers may not be as great as their *in vitro* effects on isolated membranes. Not only is this due to the dilution effect discussed above, but intact membranes may be more resilient to the insult of permeation enhancement than excised membranes or cultured cells.

Preclinical development should include an evaluation of the safety of the permeation-enhancing technology. In addition to general safety indices, particular attention should be given to the targeted membrane or tissue. It is important to assess how long the state of enhanced permeability lasts;

ideally the effect is transient and the tissue recovers quickly and completely. One might also question whether enhanced permeability allows unwanted foreign substances to be absorbed and what might be the consequences of that event. Finally, it is important to assess whether the extent of drug absorption is acceptable, with regard to average bioavailability as well as inter-subject variability. A successful permeation-enhancing formulation may increase bioavailability from negligible or very low levels to low or moderate levels. When bioavailability is incomplete, inter-subject variability can be expected. The question then is whether the drug safety margin can tolerate the level of inter-subject variability that might be seen with the absorption-enhancing formulation.

PRODUCTS IN DEVELOPMENT

This section will provide an update on some of the more advanced products in development that employ an absorption-enhancing technology. This is not meant to be inclusive of all the technologies or products in development, especially since the most current information on development pipelines is not necessarily made available to the public. Table III provides a list of some of the companies utilizing absorption enhancers and their technologies and development candidates. Most commonly these companies control some form of intellectual property around a specific technology, and the technology is being applied to non-proprietary compounds, in addition to the possibility of licensing the technology or the products in development to partners. There may also be companies that recognized a need or potential application of an absorption-enhancing technology for their proprietary compounds or for a therapeutic area of particular interest and have initiated product development with non-proprietary absorption-enhancing excipients. The information presented covers only what is publically available. For some products in development, the developer has not disclosed specific information on the enabling technology used, and pharmacokinetic data with the potential new product are not yet published. Therefore, in some of the cases presented, information from the patent literature has been used to help envisage the absorption-enhancing approach used.

One of the few absorption enhancers to have advanced to a marketed product is cyclopentadecalactone, also referred to as pentadecalactone. This agent was proprietary to Bentley Pharmaceuticals, Inc. and is now being promoted as CPE-215 by CPEX Pharmaceuticals, a spin-off of Bentley. This absorption enhancer is currently used in a transdermal testosterone product Testim, marketed by Auxillium. The formulation contains up to 8% pentadecalactone in a gel formulation primarily comprised of ethanol. CPEX Pharmaceuticals is also currently pursuing a nasal insulin delivery product utilizing CPE-215 as an absorption promoter, which is in early clinical trials. Nasal bioavailability of insulin, relative to subcutaneous injection, was reported to be 10–20%, and the formulation was well tolerated (19).

Emisphere Technologies, Inc. is developing products utilizing its proprietary Eligen technology, a library of absorption-enhancing compounds of which sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (also referred to as SNAC and salcaprozate sodium) is the lead. Emisphere contends that SNAC enhances absorption by forming a noncovalent complex with the active compound that enables transcellular absorption, without altering tight junctions (20). For proteins, the mechanism may involve a reversible change in protein

Table III. Pipeline of Permeation Enhancement Technologies

Company	Enhancer/technology	Pipeline[a]
CPEX Pharmaceuticals	Cyclopentadecalactone	Transdermal testosterone (Market); nasal insulin (phase 2)
Emisphere Technologies	Sodium N-[8-(2-hydroxylbenzoyl)amino] caprylate (SNAC)	Calcitonin (phase 3), vitamin B_{12}, GLP-1, peptide Y
Nordic Biosciences	8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid (5-CNAC)	Calcitonin (phase 3)
Merrion Pharmaceuticals	Medium chain fatty acids, salts, and derivatives	Alendronate (phase 2/3), zoledronic acid (phase 3), gonadotropin-releasing hormone antagonist (phase 1/2), fondaparinux (phase 1)
Isis Pharmaceuticals	Sodium caprate, modified release formulation	Antisense oligonucleotide (phase 1)
Chiasma	Sodium caprylate suspension in hydrophobic medium with matrix forming polymer	Octreotide (phase 2)
Oramed Pharmaceuticals	Protease inhibitor and omega 3 fatty acid	Insulin (phase 2), glucagon-like peptide 1 analog
Diabetology Ltd.	Unknown GRAS excipients	Insulin (phase 2)
Generex	Liquid mixed-micelle spray	Insulin (approved in some countries, treatment IND in USA)
Unigene/Tarsa	Combo of protease inhibitor, permeation enhancer, pH modifier, enteric coating	Calcitonin (phase 3)
Soligenix (Dor)	Lipid polymer micelle	Leuprolide (preclinical)
Aegis Therapeutics	Alkylglycosides	Feasibility claimed for various intranasal peptides
Archimedes Pharma	Chitosan	Intranasal morphine (phase 3), intranasal granisetron (phase 1)
NexMed/Apricus Bio	Dodecyl-2-N,N-dimethylamino propionate (DDAIP)	Topical alprostadil (NDA) and possibly other topical agents

GLP-1 glucagon-like peptide-1, *GRAS* generally recognized as safe
[a] Intended route of administration is oral unless indicated otherwise

conformation and protection against degradation prior to absorption. SNAC was found to increase the absorption of cromolyn approximately eightfold, and the mechanism appeared to be related to an increase in membrane fluidity, since SNAC had no effect on cromolyn lipophilicity (21). A subchronic toxicity study in rats indicated a no observable adverse effect level of 1,000 mg/kg/day or greater (22). It is interesting to also note that Caco-2 cells exposed to SNAC showed evidence of cell damage using various cytotoxicity assays, including lactate dehydrogenase, mitochondrial dehydrogenase activity, trypan blue exclusion, and neutral red binding (21). The current lead products in development utilizing SNAC are calcitonin, which is in phase 3 trials in partnership with Novartis, and vitamin B_{12}. Earlier in development are products intended to deliver glucagon-like peptide-1 and peptide Y via the oral route. Previous efforts by Emisphere to deliver heparin and insulin orally may not have achieved the level of clinical success required to invest in their continued development.

A structurally related absorption enhancer also originating from Emisphere is 8-(N-2-hydroxy-5-chloro-benzyl)-amino-caprylic acid, or 5-CNAC, which is in the clinical trial phase of development in an oral calcitonin formulation being developed by Nordic Biosciences in partnership with Novartis. A tablet containing 200 mg 5-CNAC and 0.8 mg calcitonin provided greater calcitonin absorption and greater effects on a biomarker of bone resorption than nasal calcitonin, but absorption was influenced by fed state and the volume of water taken with the tablet (23). A 14-day clinical trial of twice daily oral calcitonin with 5-CNAC suggested potentially useful reductions in biomarkers of bone resorption and cartilage degradation (24).

Another drug delivery specialty company focused on improving the oral delivery of existing drugs with poor absorption is Merrion Pharmaceuticals. Their proprietary formulations, collectively referred to as gastrointestinal permeation enhancement technology (GIPET), are based on the use of medium chain fatty acids and salts and derivatives of medium chain fatty acids. The products in development include two bisphosphonates, alendronate and zoledronic acid, a gonadotropin-releasing hormone antagonist, and fondaparinux, a pentasaccharide factor Xa antagonist. The Merrion absorption-enhancing excipients and active drug are preferably delivered using an enteric-coated dosage form. The excipients, the main enhancer being sodium caprate, are claimed to have generally recognized as safe (GRAS) status based on prior use as food additives. Using the GIPET formulation approach, it was possible to achieve 5–9% oral bioavailability of low-molecular weight heparin and to increase alendronate oral bioavailability 12-fold relative to the existing marketed product, to approximately 7% (25). In clinical phase 1 and 2 studies conducted so far, GIPET formulations appear to have been well tolerated.

Sodium caprate has also been utilized as an excipient to improve the oral absorption of an antisense oligonucleotide of molecular weight 7701 (ISIS 104838) in preclinical and clinical studies conducted by Isis Pharmaceuticals. In the absence of an absorption enhancer, ISIS 104838 had undetectable oral bioavailability in rats, dogs, and pigs. But in dogs administered an enteric-coated tablet formulation containing sodium caprate and ISIS 104838, systemic oral bioavailability averaged 1.4% compared to IV administration (26). Tissue histology of the small intestine and large intestine indicated no changes after once daily dosing of tablets containing approximately 1 g of sodium caprate for seven consecutive days. Oral ISIS 104838 was also evaluated in humans using solid formulations designed to combine immediate release and delayed release sodium caprate (660 mg total) in an enteric-coated capsule (27). The formulation providing the greatest average oral bioavailability resulted in 12.0% average bioavailability relative to subcutaneous injection and ranging from approximately 2% to 27.5% in ten fasted subjects. Average bioavailability and inter-subject variability were similar in the fed state. Modifying the release of sodium caprate was thought to have prolonged the duration of exposure of the intestinal membrane to the enhancer, as well as expanding the surface area exposed. Oral dosing of this antisense oligonucleotide in specifically designed formulations with sodium caprate could feasibly result in systemic exposure at levels required for therapeutic efficacy.

Formulation technology is also apparently key to the effectiveness of an absorption-enhancing approach being pursued by Chiasma, who refer to their proprietary technology as a transient permeability enhancer (TPE) system. While the Chiasma TPE technology has not been disclosed, intellectual property covering absorption-enhancing formulations has been described by scientists affiliated with Chiasma (28). These formulations consist of a suspension of a medium chain fatty acid salt, exemplified by sodium caprylate, and a matrix-forming polymer in a hydrophobic medium, such as glyceryl triglyceride, and their utility in improving the oral bioavailability of octreoride, exenatide, and other macromolecules was demonstrated. Using the TPE system, Chiasma is in early clinical studies with an oral form of octreotide acetate.

Scientists have long sought for an oral dosage form for insulin delivery. In addition to offering an alternative to daily injections for the millions of diabetic patients requiring insulin therapy, the oral route of insulin delivery could have a physiological advantage of mimicking insulin secretion from the pancreas via the portal circulation to the liver (5). Oral insulin delivery requires protection from degradation in the stomach and intestinal lumen, as well as enhancement of its permeation across the intestinal membrane. One of the companies developing an oral insulin product is Oramed Pharmaceuticals. In a formulation comparison study in healthy subjects, one orally administered Oramed insulin formulation exhibited pharmacologic response (glucose and c-peptide lowering) and was well tolerated (29). The formulation composition is not known, but the patent literature suggests that the formulation may include one or more protease inhibitors (such as aprotinin and soybean trypsin inhibitor), EDTA or a bile acid or bile salt as a permeation enhancer, and an omega-3 fatty acid in an enteric-coated formulation (30). The extent of insulin oral bioavailability afforded with this approach is not known.

Diabetology Ltd. has also performed clinical trials with an oral insulin formulation referred to as Capsulin, which employs unknown GRAS excipients for absorption enhancement. Oral 150 and 300 U insulin doses produced hypoglycemic effects with modest increases of plasma insulin concentration (31).

An alternative approach to achieving systemic insulin exposure and effects, which is under continuing clinical investigation, is the buccal delivery technology of Generex Biotechnology. This employs a combination of several proprietary excipients, which may include sodium lauryl sulfate, fatty acids, bile acids, and other excipients in a liquid mixed-micellar spray (32). The permeation-enhancing excipients are claimed to be GRAS, and the system was said to provide 10% absorption (33). This has already been marketed in some countries outside the USA and is being studied in the USA under a treatment IND.

A formulation strategy has been described by Unigene scientists combining a permeation-enhancing excipient with an acid to lower the local pH of the intestinal fluids to a pH where protease activity is reduced (34). This is preferably formulated as an enteric-coated tablet, and for the oral delivery of salmon calcitonin, the preferred permeation enhancer is lauroyl L-carnitine. Unigene has licensed the oral calcitonin delivery technology to Tarsa, and a product is in late-stage clinical trials for the treatment and prevention of postmenopausal osteoporosis in collaboration with Novartis.

Another strategy that has been utilized for protecting a peptide drug from degradation in the stomach and small intestinal lumen is encapsulation of the drug within the inner aqueous phase of a reverse micelle stabilized by polymers. The components of the reverse micelle may also increase intestinal permeability. This is the formulation approach Solgenix (formerly DorBiopharma) expects to use to deliver leuprolide in clinical trials. Solgenix claims that with this lipid polymer micelle formulation, oral bioavailability in rats and dogs was improved from 2.2% to 20–40%. This technology is early in development.

While many of the absorption-enhancing technologies discussed so far have centered on oral drug delivery, there have also been advances made in transmucosal absorption enhancement. One of the companies focusing on nasal drug absorption enhancement is Aegis Therapeutics, with their group of proprietary enhancers referred to as Intravail. These agents, which were initially developed at the University of Alabama at Birmingham, are a group of medium chain alkylglycosides including dodecylmaltoside and tetradecylmaltoside. Enhanced nasal bioavailabilities of calcitonin, insulin, and human growth hormone were demonstrated in rats (35), and the enabling excipients are said to be well tolerated (36). In a study in healthy human subjects, nasal bioavailability of calcitonin was improved from 6.6% with a control formulation to 35.9% with dodecylmaltoside (37). Aegis seems to be positioning its technology more for out-licensing, rather than developing products internally.

Another company with proprietary technology being applied toward nasal drug delivery enhancement is Archimedes Pharma, which is using chitosan to develop nasal formulations with increased bioavailability. Archimedes technology is being used in clinical development candidates for the nasal delivery of morphine, granisetron, and vaccines. While chitosan has both mucoadhesive and permeation-enhancing properties, some chitosan derivatives such as N-trimethyl chitosan, have been shown to have greater permeation enhancement, especially at neutral pH (38). Thiolated polycarbophil is another structurally modified pharmaceutical excipient designed to maximize its effects as an absorption promoter (39).

Finally, the permeation enhancer dodecyl-2-N,N-dimethylamino propionate (DDAIP) has been used in topical alprostadil products which are approved in some countries and is in late-stage clinical studies for US registration. This technology referred to as NexACT was developed by Apricus Bio (formerly NexMed) and is claimed to enhance the absorption of various types of compounds through skin, buccal, or intestinal absorption sites. Other potential products are at earlier stages of development. DDAIP has been investigated for more than 20 years, since the first descriptions of its permeation-enhancing actions (40).

CONCLUSIONS

Several technologies for enhancing absorption of poorly bioavailable compounds have progressed from the early studies demonstrating permeation enhancement in an isolated membrane model, and a number of absorption-enhancing technologies are now in clinical trials. Some of these utilize GRAS excipients in a new way or in different concentrations or combinations than have been used in existing products. Others utilize new excipients for their permeation-enhancing function. These new excipients and formulations increase systemic exposure after oral, transmucosal, or transdermal dosing, as indicated by improved bioavailability or bioactivity, and appear to represent feasible alternatives to existing products, which afford non-optimal bioavailability or must be administered by injection. It seems likely that gradually absorption-enhancing formulations will be more broadly accepted into the US market. One of the barriers to regulatory approval may be the requirement for demonstrating safety of a new excipient, which itself has biological activity. Understanding the mechanism of absorption enhancement may be very useful toward registration. However, it seems reasonable that once a delivery technology is proven to be successful for one particular drug, that technology might be readily adapted to improving the delivery of other poorly absorbed drugs. New absorption enhancers that are designed to function through specific mechanisms and are more potent and specific than those currently in clinical trials may follow. These technologies may afford alternatives for proteins and peptides currently only administered by injection. In addition, and as important, these technologies may enable the development of new chemical entities with good pharmacologic activity, but poor biopharmaceutical properties, that otherwise would not be developed into drugs.

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