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Strategies to improve oral drug bioavailability

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Efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies have been required to develop orally active therapeutics. The past two decades have been characterised by an increased understanding of the causes of low bioavailability and a great deal of innovation in oral drug delivery technologies, marked by an unprecedented growth of the drug delivery industry. The advent of biotechnology and consequent proliferation of biopharmaceuticals have brought new challenges to the drug delivery field. In spite of the difficulties associated with developing oral forms of this type of therapeutics, significant progress has been made in the past few years, with some oral proteins, peptides and other macromolecules currently advancing through clinical trials. This article reviews the approaches that have been successfully applied to improve oral drug bioavailability, primarily, prodrug strategies, lead optimisation through medicinal chemistry and formulation design. Specific strategies to improve the oral bioavailability of biopharmaceuticals are also discussed.

Keywords: biopharmaceuticals, formulation, macromolecules, medicinal chemistry, oral bioavailability, prodrugs

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1. Introduction

Oral administration is regarded as the preferred route of drug intake, offering numerous advantages, including convenience, ease of compliance, potential for availability to large patient populations and cost-effectiveness. Not surprisingly, oral bioavailability plays an important role in lead selection at the discovery stage and is a key factor in many go/no-go decisions for the development of new drugs [1-7].

Understanding the causes of low oral absorption and the approaches to improve it is critical for decreasing attrition rates in drug development and successfully bringing new drugs to market. Poor oral bioavailability affects drug performance and leads to high intra- and interpatient variability. The recourse to parenteral administration in these cases faces limitations of cost, patient compliance, especially in chronic therapies, and weak competitive positions compared with alternative oral therapies.

Oral bioavailability depends on a number of factors, primarily drug permeability, aqueous solubility, dissolution rate, presystemic metabolism, first-pass metabolism and susceptibility to efflux mechanisms. Among these factors, low permeability and poor solubility stand as the most frequent causes of low oral bioavailability [8-11]. In 1997, Lipinski and colleagues introduced the so-called 'rule of 5', which became a reference to estimate oral drug absorption [12]. The rule incorporates parameters such as molecular size, hydrogen bonding capability and water/octanol partition coefficient, which determine the hydrophilicity/lipophicicity balance required for appropriate solubility and permeability. Since then, numerous other approaches to estimate oral bioavailability have been proposed. The development of *in vitro* and *in silico* prediction methods is still a very active field and has contributed to a better understanding of the factors influencing systemic drug absorption following oral

administration [13-15]. Initially, predictive methods focused exclusively on passive absorption, giving primary importance to the drug characteristics that determine solubility and permeability through lipid membranes. This was useful for a number of drugs, but often failed with drugs that are absorbed through transporter proteins, as is the case of β-lactam antibiotics, angiotensin-converting enzyme inhibitors and nucleoside antivirals [16-21]. In addition, these early methods overlooked factors such as potential high presystemic and/or first-pass metabolism and susceptibility to efflux pumps, including P-glycoprotein (Pgp) or multi-drug resistance proteins (MRPs), which are known to have a significant impact on the bioavailability of certain drug types [22-26]. Recent approaches recognise that predictive methods are, to a certain extent, drug-class-specific and that it is important to understand the pathway of absorption of a particular drug or drug class in order to select the appropriate *in vitro* and/or *in silico* methods to assess oral bioavailability [27-32].

The advances in the understanding of the causes of low oral bioavailability have led to significant improvements in the design of technologies to address these deficiencies. The past two decades have witnessed a great deal of innovation in oral drug delivery, marked by an unprecedented growth of the drug delivery industry. Overall, the strategies developed to improve oral bioavailability can be grouped into three main categories:

- prodrugs and drug conjugates
- medicinal chemistry
- formulation design

These strategies are not mutually exclusive; on the contrary, they are often applied in combination. For instance, a prodrug designed to improve drug absorption can, in addition, use a formulation approach to enable rapid onset or to target absorption from a particular site in the gastrointestinal tract. Choosing a suitable approach among the vast number of options is often not an easy task. Good knowledge of the causes of low bioavailability and preferred absorption pathways, as well as the impact of the different approaches on drug metabolism and desired pharmacokinetic profile is key to the successful selection of an appropriate strategy for a particular drug or drug candidate.

2. Prodrugs

Prodrugs are inactive drug derivatives that are transformed into the active drug inside the body through chemical hydrolysis or enzymatic reaction. Typically, prodrugs are formed by covalent attachment to a drug of a chemical moiety that alters the physicochemical properties of the drug, to improve bioavailability. This covalent link should be relatively labile and designed to be cleaved, liberating the active drug, once the prodrug is absorbed into the systemic circulation (**Figure 1**), this strategy has worked successfully for a number of drugs [33]. The potential downsides are the reduced solubility of the prodrug, particularly when all the ionisable groups are masked with non-polar moieties, and the risk of entrapment or drug accumulation inside cells where the biotransformation of the prodrug into active drug often occurs.

A well-known prodrug approach relies on the attachment of a non-polar group through an ester bond as a way of masking highly polar or charged moieties, such as phosphates and carboxyl groups. This increases the lipophilicity of the drug molecule and, consequently, its permeability. The ester bond is readily cleaved by esterases in the plasma and liver. Some examples of this approach are etilevodopa, the ethyl ester of Parkinson's disease drug levodopa [34], antivirals such as adefovir dipivoxil [35,36], capecitabine, an oral prodrug of 5-fluorouracil [37,38], oseltamivir [39], docarpamine [40] and tenofovir disoproxil fumarate [41-43].

Other prodrug strategies rely on modified chemical groups that confer appropriate permeability properties and are biotransformed after absorption, to liberate the active drug. This is the case, for example, for sibrafiban and ximelagatran, in which amidoxime groups (neutral) of the inactive prodrug form are transformed after absorption into amidines (charged), to yield the active drug. Following a similar strategy, thioesters have recently been used in a novel approach to design oral prodrugs of promising antimalarial agents [44]. Lactone prodrugs such as simvastatin and lovastatin are also examples of this approach [45-47].

Prodrugs in which the role of the attached moiety is not to mask charged or highly polar groups but rather to promote or enhance transporter-mediated absorption are a growing class. In these cases the attached moiety acts as a recognition site for transporter proteins that can shuttle the molecule across the intestinal epithelium. Oligopeptide transporters, such as peptide transporter 1 (PEPT1) and human intestinal peptide transporter 1 (HPT1), are abundant in the small intestine, have a broad specificity, and are capable of transporting a variety of chemically diverse substrates into the systemic circulation, provided that they contain a minimum of recognition features [48-50]. These transporters have been exploited, for example, to increase the bioavailability of acyclovir and ganciclovir in their respective valine esters, valacyclovir and valganciclovir [51-55]. Another interesting example is the recently proposed valquinidine. This prodrug approach was designed to target absorption via oligopeptide transporters and at the same time avoid Pgp-mediated efflux [56].

Bile acid transporters have also been explored to improve oral bioavailability through the attachment of cholic acid or other bile acids. The attachment site and drug size play an important role in determining affinity for the transporter and, thus, the efficiency of this approach [57,58]. Absorption through bile acid transporters has particular interest for drugs targeting the liver and hepatobiliary system but presents limitations for systemic drug absorption due to the rapid biliary uptake by the liver. Successful systemic absorption requires release of the free drug from the conjugate before reaching the liver. Recent applications of this approach include the

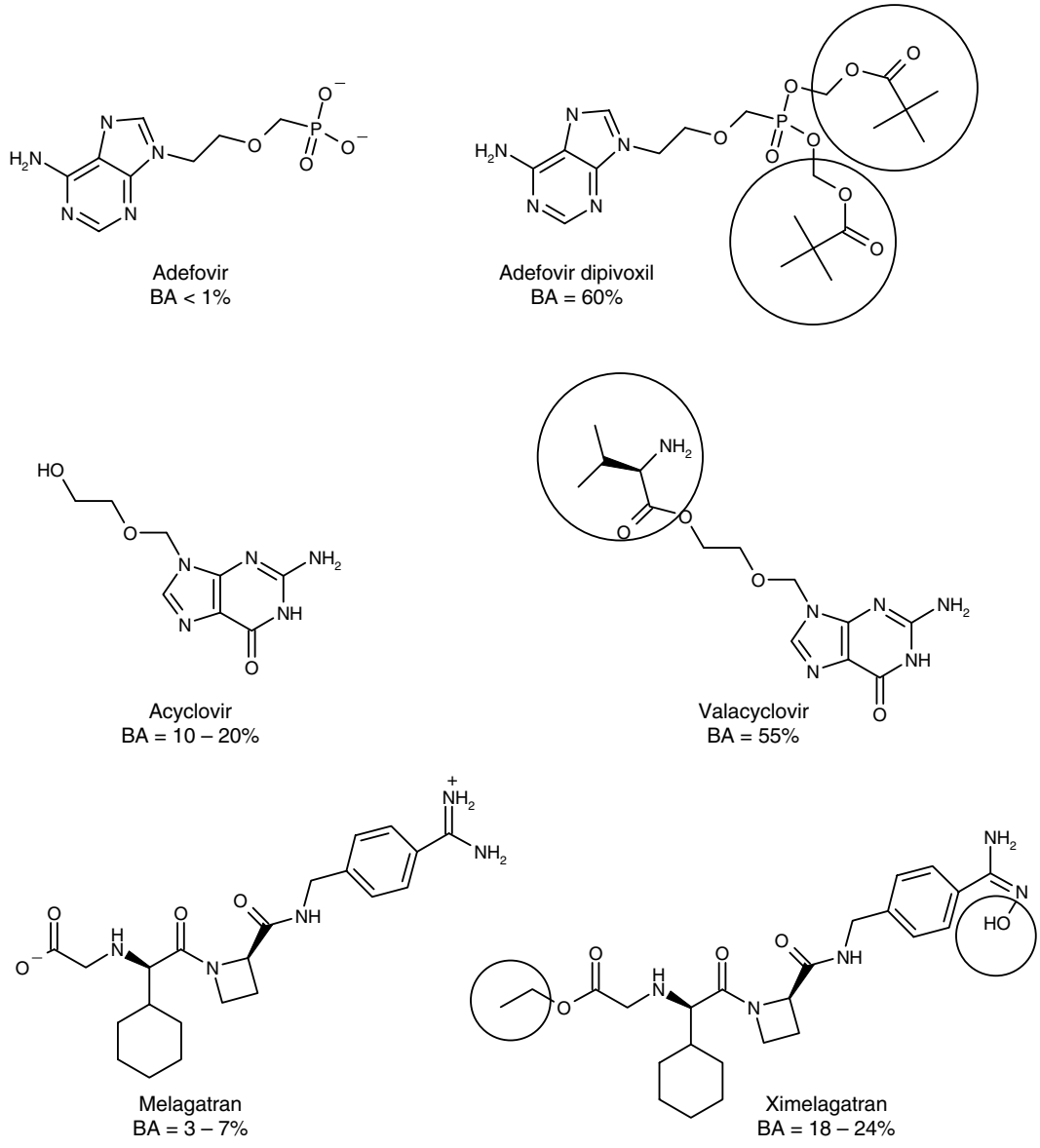

Figure 1. Examples of prodrugs and their impact on the oral bioavailability of the active drug. The attached moieties are marked with a circle and the active drug is shown next to each prodrug. In the case of adefovir dipivoxil and ximelagatran, the attached moieties mask charged groups, to increase the hydrophobicity and permeability of the molecule. In the case of valacyclovir, the attached moiety acts as a recognition site for oligopeptide transporters that transfer the drug across the intestinal epithelium.
BA: Oral bioavailability.

development of oral cisplatin–bile acid conjugates to treat liver tumours [59,60] and conjugates of deoxycholic acid and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors aimed at improving the efficiency of cholesterol-lowering agents [61,62].

XP-13512, a gabapentin prodrug engineered to be absorbed by various nutrient transporters, including the sodium-dependent multivitamin transporter and monocarboxylate transporters, has been shown to improve bioavailability and reduced interpatient variability [63,64]. Mono- and disaccharide conjugates have also been shown to be a potential strategy to target drug absorption through intestinal glucose transporters [65-71]. Other transporter proteins present in the gastrointestinal tract, such as organic anion transporters, nucleoside transporters, vitamin transporters and organic cation transporters, are known to contribute to drug absorption and are being explored in prodrug strategies [72]. The successful application of these strategies requires a good understanding of the transporter recognition characteristics [73-75], gastrointestinal tract distribution [76,77], transport capacity, as well as potential inhibitors, agonists [78-81] and drug–drug interactions [82,83]. It is also important to take into consideration the tissue distribution of these transporters

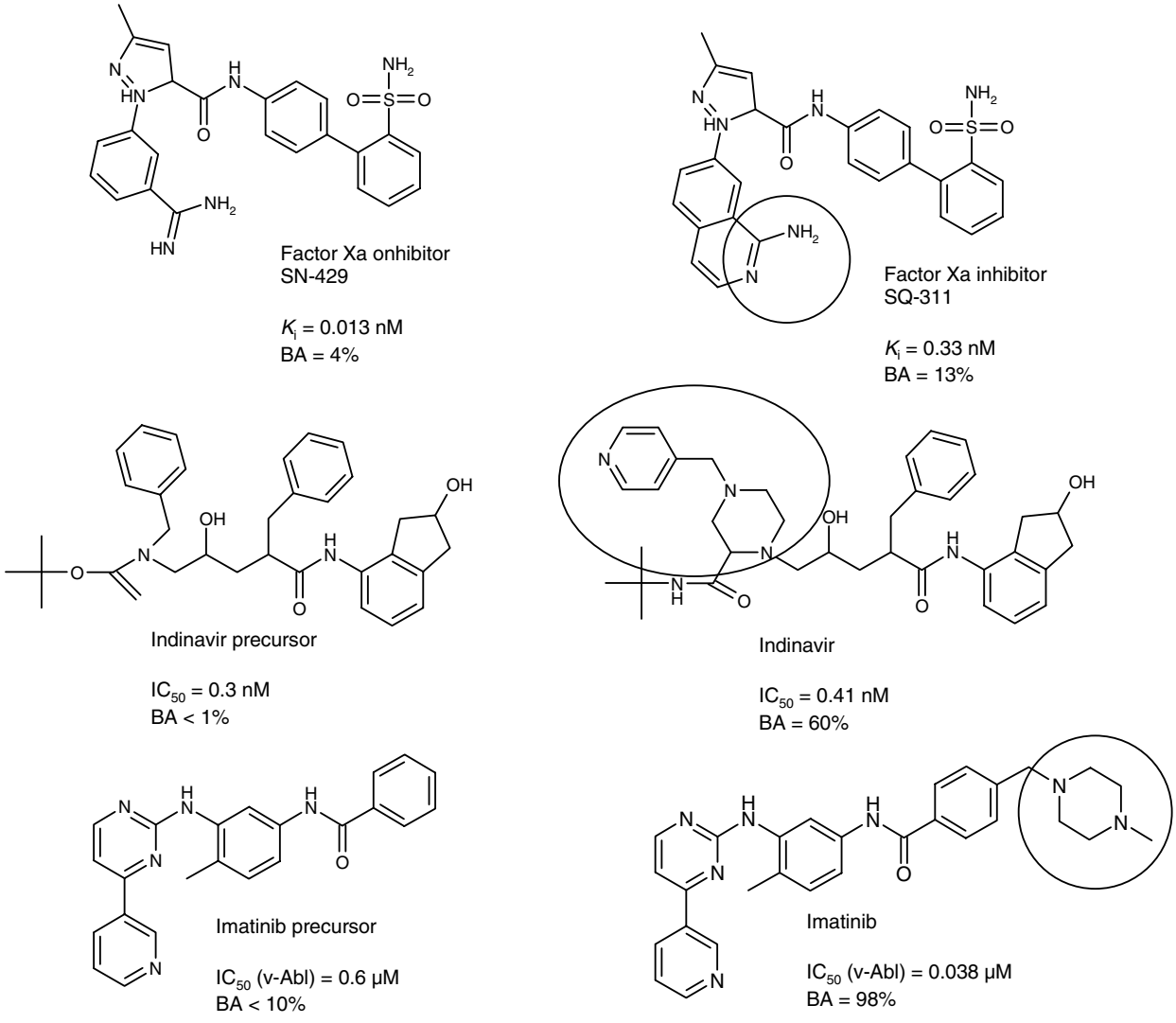

Figure 2. Examples of improved oral bioavailability through medicinal chemistry approaches. The strategy followed in the case of Factor Xa inhibitor SQ-311 was to lower the pK_a of benzamidine by incorporating it into an aromatic ring. This decreased the hydrophilicity and solubility at physiological conditions, thus increasing the permeability. The potency of Factor Xa inhibitor was reduced by an order of magnitude, which was considered a reasonable trade-off in this case [105]. In the case of indinavir and imatinib, the precursors had limited bioavailability due to their poor aqueous solubility. This was addressed by introducing ionisable groups (marked with circles) that increased the overall solubility of the molecule. The impact on activity (IC_{50}) was moderate for indinavir. Interestingly, for imatinib this strategy had a positive impact on activity, improving specificity towards target tyrosine kinases.
BA: Oral bioavailability; IC_{50}: Median inhibitory concentration; K_i: Inhibition constant; pK_a: -Log_{10} dissociation constant for an acid.

and their potential effect on clearance. Many transporters present in the gastrointestinal tract are also abundant in the kidneys and liver, and can contribute to rapid elimination, thus offsetting the absorption advantages [84,85].

Prodrugs have proven to be an effective approach to increase oral bioavailability. In addition, they can provide long-acting pharmacokinetic profiles and increased drug half-lifes by targeting appropriate mechanisms of active drug release and/or slowing down metabolism and clearance. In these cases, prodrugs offer advantages of both lower dosing frequency and improved absorption. Valacyclovir, for example, enables the reduction of dosing regimen from five- to three-times a day because its gradual biotransformation into acyclovir creates a sustained release of active drug into the systemic circulation. Bambuterol and docarpamine are other examples of prodrugs that provide prolonged half-lifes through slow biotransformation and metabolism rates [40]. Bambuterol, a prodrug of terbutalin, has comparable bioavailability to the active drug. Its advantage lies primarily on its relatively slow biotransformation that enables a sustained release of terbutalin into the blood, enabling once-daily dosing regimens instead of three-times a day.

Table 1. Examples of substrates of membrane transporter proteins.

Transporter protein	Substrate
Amino acid transporters	Gabapentin, levodopa, baclofen
Oligopeptide transporters	ACE inhibitors, β-lactam antibiotics, cephalosporins, renin inhibitors, bestatin
Nucleoside transporters	Zidovudine, acyclovir, zalcitabine, gemcitabine
Organic anion transporters	Pravastin, methotrexate

ACE: Angiotensin-converting enzyme.

3. Medicinal chemistry

Medicinal chemistry encompasses the design of drugs with appropriate bioactivity and bioavailability characteristics [7]. Incorporating good oral absorption features into the drug design process entails managing a delicate balance between activity and bioavailability goals (**Figure 2**). Designing for optimal bioavailability profiles often requires compromising on activity; nevertheless, in many instances the advantages of oral absorption compensate for small activity trade-offs [2,86,87].

Drug design efforts targeting good oral bioavailability normally take place at the early stages of lead selection and optimisation, although sometimes this strategy is applied to the development of second-generation drugs, providing novel and competitive proprietary positions [88]. Lead optimisation often involves a significant investment of resources in design, synthesis and testing. The availability of reliable computational methods and high-throughput assays to estimate both activity and bioavailability is critical for the efficiency of this process [31,89-98]. Successful drug design strategies require a good understanding of the specific drug absorption pathways and causes of poor bioavailability, including efflux mechanisms, liver first-pass metabolism and presystemic degradation [99-101]. Typically, lead optimisation strategies targeting oral bioavailability focus on chemistries that confer solubility and permeability characteristics required for passive absorption [102-106]. When transporter proteins are known to be involved in the absorption process, medicinal chemistry strategies concentrate transporter affinity features (**Table 1**). A good understanding of the factors that determine recognition and affinity is key for successful lead optimisation in these cases [73,74,107-113].

4. Formulation strategies

Improving oral bioavailability through formulation design is often the approach of choice, particularly for drugs that are already in development stages or on the market. Formulation strategies offer relatively low-cost opportunities to improve oral bioavailability of new drugs and manage the life cycle of existing ones. As opposed to prodrug and medicinal chemistry approaches, they do not require chemical modification of the drug or creation of new chemical entities. This provides considerable advantages in terms of reduced cost and development time. The use of already approved excipients and generally recognised as safe materials is often preferred due to their reduced risk and development requirements. Nevertheless, the need for innovation in the development of new classes of excipients that can address unmet formulation needs has long been recognised, and substantial efforts are being invested in this direction. Solubility enhancing agents such as cyclodextrins, or permeability increasing agents such as chitosans or medium chain fatty acids, are some examples of these ongoing efforts. Efflux problems are also being addressed through the use of excipients that have properties as efflux pump inhibitors. Examples of reported Pgp inhibitors are grapefruit juice, tocopheryl polyethylene glycol 1000 succinate, polyethylene glycol 400, Tween 80 and Cremophor EL [114-118].

4.1 Solubility and dissolution rate

Formulation approaches vary depending on the unfavourable drug properties that limit bioavailability and the desired pharmacokinetic profiles. Poor aqueous solubility is one factor that frequently affects the oral performance of drugs. It has been successfully tackled with the use of co-solvents, solid dispersions [119], microemulsions, self-emulsifying systems [120,121], nanosuspensions [122-125] and inclusion compounds [126,127]. Solid-state strategies, such as freeze-drying, micronisation and nanocrystals [128,129] have been successfully applied to increase dissolution rates by optimising particle size and surface area. Stabilisation of polymorphs or the development of specific solvates are other solid-state approaches commonly applied to improve dissolution profiles and solubility [130].

Fast-dissolving and orally disintegrating technologies that target rapid dissolution in the mouth and pregastric absorption from the oral cavity have rapidly grown in recent years. They address poor dissolution profiles, are an appropriate strategy for drugs subject to high presystemic or first-pass metabolism, and are suitable for drugs that require a rapid onset and/or present gastrointestinal compatibility or food interaction issues. In addition, this approach offers a dosage form alternative for patient populations with swallowing difficulties. Fast-dissolving technologies targeting absorption from the mouth rely on freeze-drying, effervescence or direct compression (**Table 2**). A good number of medications currently benefit from these types of drug delivery approaches [131-141]. The main requirements for the successful application of orally disintegrating technologies are adequate taste and loading capacity.

4.2 Hydrophilic drugs

The oral bioavailability challenges of drugs with poor permeability, which are normally highly polar or charged, have been addressed primarily through the use of absorption

Table 2. Examples of rapid-disintegration technologies that enable absorption from the oral cavity.

Trade name	Base technology	Example products
Zydis®	Freeze drying	Zyprexa® Zydis®, Zydis® Selegiline, Claritin® RediTabs®, Zofran ODT®
DuraSolv®	Direct compression and mild effervescence	Zomig ZMT®/ Rapidmelt, Nulev™, Parpoca™, Alavert™, Loratadine ODT
OraSolv®	Direct compression and mild effervescence	Remeron®, SolTabs™, FazaClo™, Triaminic®, SoftChews®, Tempra® FirstTabs
Flashtab®	Direct compression	Excedrin®, QuickTabs™
WOWTAB®	Direct compression	Benadryl®, Fastmelt™

enhancers such as medium chain fatty acids, bile salts, surfactants, liposaccharides and chitosans [142-149]. Typically, enhancers facilitate absorption by increasing the permeability of cell membranes and/or opening the tight junctions between adjacent cells to facilitate paracellular absorption, which has sometimes raised safety concerns. Alternative approaches rely on the co-administration with specific delivery agents capable of forming transient, non-covalent complexes with the drugs, which facilitate or enable their transcellular absorption [150,151].

4.3 Sustained-release and gastroretentive approaches

Sustained-release formulations have been applied successfully to improve the oral bioavailability of drugs with inappropriate solubility or dissolution profiles and/or high presystemic metabolism [152]. The added benefits of reduced dosage frequency and improved performance of therapeutics that require sustained blood levels are the clear advantages of this approach [153]. Numerous sustained-release technologies have been developed in recent years, and today, there are close to 100 drugs on the market in sustained-release formulations. Most sustained-release technologies are based on polymeric systems that release the drug through gradual erosion, swelling or diffusion. These different release processes are typically controlled by pH [154,155], osmotic pressure [156], or enzymatic or chemical reaction [157,158]. Some key factors to consider in the selection of the appropriate technology are drug compatibility, loading capacity and manufacturing costs.

Gastroretentive systems are a particular case of sustained-release technologies designed to ensure that the drug is released in the stomach. They aim at avoiding the variability associated with the randomness of intestinal transit times and target drug release into the upper gastrointestinal tract where absorption is high for many drugs. Gastroretentive technologies are based on polymeric materials that swell or expand in the stomach creating a large size matrix unable to escape through the pylorus [159]. Eventually, these polymeric matrices disintegrate and are eliminated or biodegraded. These technologies have found applications in drugs targeting the stomach, as well as in drugs requiring systemic absorption. They are applicable primarily to drugs that are preferentially absorbed in the upper gastrointestinal tract, and are stable and have good solubility and dissolution profiles under the acidic pH conditions typical of the stomach [160-168].

A potential alternative for drugs that are sensitive to the low pH and high enzymatic activity of the upper gastrointestinal tract would be to target absorption from the ileum and/or colon where the pH is close to neutral and enzymatic activity is reduced. This can be achieved by using enteric coatings, time-dependent systems, polymers that disintegrate at neutral or near neutral pH, or polymeric materials that are specifically metabolised by bacteria residing in the colon. pH-dependent polymers are susceptible to the variability of gastrointestinal pHs, whereas bacteria-metabolised polymers can ensure specific release in the colon. Nevertheless, all of these approaches are limited by the variability of transit times. They are applicable to drugs that do not require rapid onset or timely absorption and are stable at body temperature for several hours. So far, these approaches have been more successful in the development of drug products that target local gastrointestinal conditions, such as ulcerative colitis or Crohn's disease, than for systemic drug absorption.

5. Macromolecules and biopharmaceuticals

Macromolecules comprise a particular drug class characterised by their large molecular size (typically > 1000 Da). Most biopharmaceuticals, including proteins, peptides, vaccines, antisense oligonucleotides and heparins, fall within this category. Their oral bioavailability is almost negligible due to their size and high presystemic degradation [8-10]. In addition, most of biopharmaceuticals are very hydrophilic, a property that further limits their oral absorption [169]. Today, most biopharmaceuticals are available only in injections. Exceptions are calcitonin and GnRH analogues, which are available as nasal solutions or sprays, cyclosporin, which is available in oral forms, and desmopressin, which is available in both oral and nasal administration forms. Cyclosporin, desmopressin and GnRH analogues are relatively small peptides subject to low presystemic degradation in the gastrointestinal tract, two characteristics that have greatly facilitated the development of their oral forms. Unfortunately, the formulation approaches pursued with these two peptides are not applicable to most biopharmaceuticals, which have larger molecular sizes and are susceptible to substantial presystemic metabolism.

In spite of the inherent difficulties associated with developing oral biopharmaceuticals, significant progress has been made in recent years; a number of different technologies and approaches have been generated [170-176], and some oral biopharmaceuticals have already advanced into clinical development. The main strategies applied to date to improve the oral bioavailability of macromolecules fall within four main categories:

- drug conjugates
- formulation with permeation enhancers
- co-administration with delivery agents
- micro- and nanoparticle formulations

Drug conjugates aim at increasing oral bioavailability through the attachment of a chemical moiety that either increases the lipophilicity and permeability of the macromolecule [177-179] or enables its absorption via transporter proteins or receptor-mediated endocytosis [180-183]. Conjugates must retain biological activity or release the attached molecule after absorption. Permeation enhancers open tight junctions between adjacent cells, to enable paracellular absorption, and/or to alter the permeability of cell membranes, to increase absorption across the intestinal epithelium [184-189]. Technologies based on co-administration with drug delivery agents rely on specific low molecular weight compounds that interact weakly and reversibly with macromolecules, thus increasing their lipophilicity and enabling their transcellular absorption [190-193]. Micro- and nanoparticle formulation approaches target absorption through the gut-associated lymphoid tissue and are being investigated primarily for the development of oral vaccines [194,195]. These four basic approaches are often combined with other strategies, primarily, co-administration with enzyme inhibitors capable of reducing presystemic degradation [196-199] and/or formulation with mucoadhesive polymers that can improve absorption by increasing the residence time of the formulation on the gastrointestinal epithelium [200-203].

Many of these strategies have been tested *in vitro* and in animal models but, to date, only a few have advanced into clinical development. Among the latter are hexyl–insulin monoconjugate 2; a modified insulin with improved oral permeability due to its conjugation to an amphililic polymer, which has shown efficacy in Type I and II diabetic patients [204-207]. A similar approach has been successfully applied to the oral delivery of calcitonin [208]. Absorption enhancer approaches have been applied to the development of oral forms of an antisense therapeutic [209,210] and heparin [211], and both have initiated Phase I clinical studies. The eligen® technology, which relies on co-administration with drug delivery agents that enable transcellular drug absorption, has been successfully applied to the development of oral forms of several biopharmaceuticals, including heparin, insulin, calcitonin, parathyroid hormone and growth hormone, all of which are advancing through clinical trials [176,212-222]. Oral formulations of calcitonin and parathyroid hormone consisting of a combination of enzyme inhibitors, absorption enhancers and enteric coating also have been evaluated in humans [223]. Technologies based on oral sprays and sublingual tablets that target absorption from the buccal cavity have also advanced into clinical studies with insulin [224,225] and glucagon-like peptide-1 [226,227].

6. Expert opinion

Efforts to improve oral drug bioavailability have led to a great deal of innovation in drug delivery, which has been demonstrated in a good number of breakthroughs and success stories, particularly in the past two decades. It remains a very active field and one that is critical for the successful development of new drugs.

To date, formulation strategies have been far more successful in improving the bioavailability of hydrophobic drugs, with poor solubility, than with hydrophilic, polar drugs, which have good solubility but rather impaired permeability; prodrug and medicinal chemistry approaches have been more successful with the latter. Oral delivery remains a challenge for biopharmaceuticals. Nevertheless, significant progress has been made in the past few years, with some oral proteins, peptides and other macromolecules currently advancing through clinical trials. The first oral macromolecules to reach the market will open the doors to further advances and confidence in this field.

It is important to note that the approaches to improve bioavailability often have a significant impact on pharmacokinetic profiles. This can be exploited to improve drug performance; for example, in the case of fast-dissolving technologies to achieve a rapid onset, or in the case of some prodrugs and sustained-release formulations to reduce dosing frequency. The selection of an appropriate approach for a particular drug is a case-dependent process. It is important to take into consideration not only the compatibility of the approach and the causes of low absorption of the drug, but also the impact on the pharmacokinetic profile, drug distribution, elimination, metabolism, onset, blood levels and duration. All of these factors must be evaluated in order to determine the appropriate strategy for each drug. All approaches have, in principle, a tremendous potential. Their success depends to a large extent on their application to the appropriate drugs. For example, fast-dissolving technologies that target absorption from the mouth may be a good strategy for migraine drugs, but would be inappropriate for a drug such as valacyclovir that targets absorption via oligopeptide transporters, which are not abundant in the buccal cavity.

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