Oral Delivery of Macromolecular Drugs
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Barriers, Strategies and Future Trends
Preface

Due to a rapid development in biotechnology more and more macromolecular drugs such as therapeutic peptides, oligosaccharides and nucleic acids are entering the pharmaceutical arena representing unprecedented challenges from the drug delivery point of view. One of the likely greatest challenges is their oral administration presenting a series of attractive advantages. These advantages are in particular of high relevance for the treatment of pediatric patients and include the avoidance of additional risks, pain and discomfort associated with injections. Furthermore, oral formulations are less expensive to produce, as they do not need to be manufactured under sterile conditions.

The oral administration is by far the most favored one. The majority (84%) of 50 most-sold pharmaceutical products in US and Europe markets are given orally. Although there have been major advances in delivering macromolecular drugs in humans by other non-invasive routes, including the pulmonary delivery of insulin, we did so far not succeed in the development of oral delivery systems for these therapeutic agents. Apart from a few exceptions such as ciclosporin, desmopressin, chondroitin sulphate and bromelain macromolecular drugs cannot be administered orally. The development of oral formulations for macromolecular drugs is therefore highly on demand. Due to the scientific progress having been made within the 1990s and this decade numerous novel oral delivery systems for macromolecular drugs are meanwhile subject of clinical trials. This book addresses the most critical issues for a successful oral delivery of macromolecular drugs by a detailed characterisation of the ‘enemy’s strength’. Furthermore, an overview on the likely most promising strategies to overcome barriers encountered with the gastrointestinal (GI) tract is provided. These barriers are mainly the enzymatic barrier (Chapter 1), the mucus gel layer barrier (Chapter 2) and the absorption barrier (Chapter 3).

The enzymatic barrier is based on various classes of enzymes including proteases/peptidases, nucleases, glycosidases and lipases. Taking the most important macromolecular drugs into consideration, which are likely candidates for oral administration, the enzymatic barrier is primarily represented by proteases/peptidases and nucleases. Proteases/peptidases are on the one hand based on luminally secreted proteases including pepsin,
trypsin, chymotrypsin, elastase and carboxypeptidases A and B and on the other hand based on membrane-bound peptidases including various endo- as well as amino- and carboxypeptidases. In the colon numerous additional enzymes originating from the local microflora have to be taken into consideration. In terms of nucleases the enzymatic barrier is much less characterized.

The mucus gel layer barrier is based on mucus glycoproteins being crosslinked via disulphide bonds. Macromolecular drugs have to diffuse through this 50–200 μm thick three-dimensional network in order to reach the absorption membrane. In addition, due to its negative net charge being based on sialic acid and sulphonic acid substructures therapeutic macromolecules exhibiting a positive charge can be immobilized on the mucus gel barrier because of ionic interactions.

As the GI mucosa is highly vascularized, macromolecular drugs have to ‘merely’ permeate the epithelial cell layer in order to reach the systemic circulation. More lipophilic and relatively small drugs are primarily absorbed via the transeellular route, whereas more hydrophilic and relatively bigger drugs enter the systemic circulation via the paracellular route. In addition, efflux pumps can significantly further reduce the absorption of macromolecular drugs such as the case for ciclosporin. Because of this absorption barrier the size of orally administered macromolecular drugs is more or less limited to up to 10 kDa in maximum. Macromolecules greater than that are still absorbed to a certain extent; however, gained oral bioavailabilities are in most cases not anymore of therapeutic and/or commercial relevance.

Strategies to overcome the enzymatic barrier (Chapter 4) include the design of macromolecular drugs remaining more stable in the GI environment. From the drug delivery point of view, a protective effect towards enzymatic degradation can be achieved by using auxiliary agents such as enzyme inhibitors and/or polymers displaying enzyme inhibitory properties. In particular in combination with appropriate dosage forms shielding towards enzymatic attack such as micro- and nanoparticulate delivery systems and patch systems sufficient protection towards this barrier can be achieved.

Strategies to overcome the absorption barrier focus on the other hand on low molecular mass permeation enhancers (Chapter 5) such as medium chain fatty acids, which can still be regarded as a kind of gold standard. As low molecular mass permeation enhancers are per se rapidly uptaken from the gastrointestinal mucosa, however, the macromolecular drug is to a considerable high extent left alone behind in the gastrointestinal tract. In addition, local and systemic toxic side effects of low molecular mass permeation enhancers cannot be excluded. In contrast, polymeric permeation enhancers (Chapter 6) are simply too big to be absorbed from the GI tract. Consequently, systemic toxic side effects can be excluded. More recently various excipients could be identified as potent efflux pump inhibitors which can be subdivided into low molecular mass efflux pump inhibitors and polymeric efflux pump inhibitors (Chapter 7). Certain polymeric
excipients exhibit various favourable properties for oral macromolecular delivery such as high mucoadhesive, enzyme inhibitory, permeation enhancing and efflux pump inhibitory properties. Among them thiolated polymers – designated thiomers – showed most encouraging results (Chapter 8). From the drug delivery point of view certain formulations could be identified to show beneficial properties in order to improve the oral uptake of macromolecular drugs. Matrix tablets, patch systems, micro- and nanoparticulate delivery systems and liposomes seem to be most promising. Micro- and nanoparticles (Chapter 9) offer the advantage to penetrate into the mucus gel layer. Consequently, their gastrointestinal residence time is strongly prolonged resulting in a prolonged period of time for drug absorption. Furthermore, a presystemic degradation, for instance, of therapeutic peptides or oligonucleotides by luminally secreted enzymes can be avoided. The likely best protection towards enzymatic degradation in the GI tract is provided by liposomal formulations (Chapter 10), which can also guarantee an intimate contact with the mucosa when being coated with a mucoadhesive polymer.

Special and to some extent different approaches are needed for oral immunization utilizing various types of antigens and immunostimulating auxiliary agents (Chapter 11). Particulate delivery systems such as nanoparticles and liposomes accumulating in the region of Peyer’s patches seem to be highly beneficial. Oral nucleic acid delivery systems are designed for local and systemic treatment (Chapter 12). The systemic delivery of nucleic acids via the oral route is likely the most challenging aim in oral macromolecular delivery.

The combination of suitable and comparatively more stable macromolecular drugs (I), highly efficient, multifunctional and non-toxic excipients (II) and appropriate formulations (III) is certainly the key for success in oral macromolecular delivery. On the one hand macromolecular drugs can be produced more and more effectively making also low oral bioavailabilities in the range of 0.5–5% commercially interesting. The oral bioavailability of desmopressin tablets, which are for almost 20 years on the market, for instance, is just 0.5%. On the other hand, oral macromolecular drug formulations are becoming more and more efficient. Taking these developments into consideration, the number of oral macromolecular delivery systems entering the market will increase considerably over the years. ‘Invasive-to-oral-conversions’ promise great rewards for those investing in this market. This book should encourage and motivate scientists in academia and industry to move on or intensify their activities in this challenging research field of great future.

Finally, I wish to thank all the contributing authors for their excellent chapters, which were certainly not easy to write in such a complex and challenging field. Moreover, I wish to thank the Editorial Director Andrea Macaluso from Springer Science and Business Media for inviting me to edit this book.

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