Micro- and nanoparticles for intestinal drug delivery

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Abstract

Smart dosage form design allows for distinct progresses in selectivity of delivery to the site of action as well as in enhanced transport of the drug across biological membranes. By an optimal choice of carrier type and excipients such systems may offer new therapeutic options such as oral administration of insulin or heparin, where currently no absorption is possible and, on the other hand, local and selective drug delivery to inflamed tissues of the gastrointestinal tract where currently major amounts the drugs are undesirably available for systemic absorption and only a limited dose is actually providing the therapeutic effect.

Key words: drug targeting, colitis targeting, oral drug delivery, heparin absorption, nanoparticles

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Multiparticulates in the size of millimetres down to the size range of colloids have proven their usefulness in the field of drug delivery. In the context of oral drug administration they can fulfil various duties, such as controlled drug release during the gastrointestinal passage, especially interesting for selective drug delivery to certain intestinal regions, and also providing protective properties for fragile actives in the hostile environment of the intestinal lumen. Besides, in the case of colloids, their small size permits alternative therapeutic strategies such as selective or targeted drug delivery towards a specific tissue or enhanced drug transport across biological barriers (leading to an increased bioavailability of the entrapped drug).

1. Oral delivery for systemic drug availability

A major challenge is the oral delivery of the so-called 'undeliverables', which regroup unstable macromolecular drugs with high therapeutic specificity, namely peptides, proteins, and glycoproteins or polysaccharides. While the encapsulation can also provide protection against early degradation in the luminal content, its main focus is directed towards the potential absorption enhancing effect. For example, oral bioavailability of low molecular weight heparin (LMWH) can be achieved by several advanced drug delivery approaches and efficiency has been confirmed in several preclinical trials. One way is its encapsulation into polyaminomethacrylate (Eudragit® RL or RS) based particles using polyethylene glycol derivatives as non-toxic solvents which lead to relative oral bioavailabilities up to 6 to 10% in rabbits [Viehof et al., 2013]. When testing different LMWHs, a decrease in oral availability was found in the order fondaparinux>enoxaparin>nadroparin>certoparin depending mainly on their molecule size.

However, mechanisms of absorption, potentially linked to particle adhesion and enhanced LMWH transport across the intestinal absorption barrier remained to be elucidated. In order to allow a more detailed mechanistic insight into the drug absorption enhancing properties of such LMWH loaded particles, they have been tested in co-cultures of intestinal cells mimicking the intestinal barrier including the highly relevant mucus secretion [Béduneau et al., 2014]. To our current understanding the Eudragit particles provide a high LMWH at the absorption barrier enhancing the drug transport across the mucosa but do not cross the epithelial layer themselves (figure 1).

2. Oral delivery for local drug therapy

The main forms of inflammatory bowel disease (IBD) are Crohn's disease and ulcerative colitis which are both chronic relapsing inflammations of the gut. A major challenge for current drug carrier systems in IBD therapy is the selective delivery of the active ingredient to the site of inflammation. Although many dosage forms are on the market none of them can satisfy in terms of selectivity of the drug delivery. A site-directed targeting should lead to higher local drug concentrations, less systemic absorption, and therewith to less adverse effects.

One important therapeutic drug in IBD therapy is 5-aminosalicylic acid (5-ASA) which is usually topically delivered to the colonic mucosa in order to achieve effective drug concentration in the site of inflammation and to minimize its systemic availability. When combining 5-ASA with the mucoadhesive biopolymer chitosan in a pellet formulation and drug release was controlled by pH-sensitive polymer coating, these pellets were able to decrease the systemic availability of 5-ASA in rats while ensuring an enhanced anti-inflammatory effect. Such bioadhesive chitosan pellets showed additional beneficial properties for colonic 5-ASA delivery in the treatment of IBD by increasing the drug concentration locally [Bautzova et al., 2012].

Due to lack of selective drug delivery by such ‘classical’ systems (including incomplete release by diarrhoea or drop of the luminal pH) other delivery strategies have been sought. Because nanoparticulate drug carrier systems have the ability to accumulate in the inflamed regions, they offer a new targeting approach in IBD [Lamprecht, 2015].

The particle accumulation mechanism is essentially triggered by the epithelial permeability of the inflamed mucosal tissue and the particle uptake by immune related cells in this area [Lamprecht et al., 2001] (Figure 2). This leads in turn to a distinct increase in local drug concentrations inside the inflamed tissues as well as a strong reduction of drug availability to the healthy surrounding tissue. Exemplarily, FK506 (tacrolimus) entrapped into NP was administered to rats suffering from a pre-existing experimental colitis. Such tacrolimus loaded nanoparticles allow an enhanced and selective drug penetration into the inflammation site presumably by protecting the encapsulated drug against influences from efflux systems and mucosal metabolism. The relative drug penetration into the inflamed tissue is about 3-fold higher compared to healthy tissue when using nanoparticles. Thus, due to a higher selectivity in adhesion and enhanced drug penetration into the inflamed tissue, the level of adverse effects is reduced and a prolonged efficiency is observed [Lamprecht et al., 2005].

One exiting feature of this nanoparticle-based drug delivery approach is the possibility of the intracellular delivery since drug carriers are in a size range that allows for their cell uptake. Accordingly, this can broaden the choice of anti-inflammatory actives towards those drug candidates that are currently not applicable due to the drug’s inability to reach the intracellular receptor and to exercise its therapeutic effect. This was confirmed by a study in

murine colitis where clodronate loaded nanoparticles were able to reduce significantly the inflammatory reaction while free clodronate did not show a mitigating effect. Similarly, in cultured mouse macrophages, only clodronate entrapped in nanoparticles but not clodronate alone led to a decrease in tumor necrosis factor-alpha and interleukin-6 secretion of the activated macrophages [Niebel et al., 2012].

Although many studies have underlined the therapeutic benefit of nanoparticle-based targeting in colitis therapy, one technical drawback is the risk of premature release of the drug during the intestinal passage. When 5-ASA was covalently bound to silica nanoparticles significant drug retention was achieved ensuring the drug delivery towards the inflamed colon [Moulari et al., 2008]. By this strategy a 3 to 5-fold 5-ASA dose reduction was possible. These 5-ASA silica nanoparticles allow to combine advantages from drug targeting and prodrugs appearing to be a promising therapeutic approach.

One question arising from these observation is whether the accumulation of drug carriers is exclusively related to targeting in IBD or generally exploitable as a therapeutic strategy in anti-inflammatory treatment. Subsequently, size-dependent gastrointestinal deposition of nanoparticles was examined after oral administration to mice suffering from an experimental gastric ulcer model. Related to therapeutic benefit, local drug delivery could reduce side effects and would be a distinct improvement compared to existing therapeutic approaches, e.g. in the local therapy of Helicobacter pylori. Similar to observations in IBD, highest relative particle accumulation was found with the smallest particles (50nm). Although peptic ulcer disease and IBD distinctly differ in a variety of factors, from a mechanistic point of view, the selective accumulation of small particulate drug-loaded carriers at inflamed tissue is similar in these two disorders [Hassani et al., 2009]. It can be concluded therefrom that there exists generally a targeting potential in these inflammatory disorders that is related to the increased permeability of the epithelium. We named it ‘epithelial’ enhanced permeability and retention (EPR) effect in accordance with postulations made from the endothelial fenestration in cancer therapy [Lamprecht, 2010].

A step towards the next generation of nanocarriers for IBD therapy is the active targeting of the inflammation site by a molecular recognition mechanism, such as antigen–antibody reactions. Usually antibodies are not sufficiently stable to withstand the intestinal passage which turned us towards the use of lectins. Such lectins are less specific, however provide a higher stability and a study reporting the selective adhesion to inflamed colitis tissue suggested them to be a promising tool to actively target the inflammation site in colitis [Ryder et al., 1994]. Lectin-conjugated nanoparticles showed a dramatic increase in adhesion to the inflamed tissue however non-specific adhesion to other sugar moieties during the intestinal passage can reduce the therapeutic efficiency. It was found out that epithelial active nanoparticle targeting by peanut agglutinin was suitable for drug delivery in IBD. A specific

binding was proven by co-administering the specific sugar which lowered the binding efficiency down to non-modified or albumin-conjugated nanoparticles. Also the therapeutic benefit from peanut agglutinin nanoparticles loaded with betamethasone as model glucocorticoid is significantly increased compared plain nanoparticles or compared to peanut agglutinin nanoparticles co-administered with the inhibiting sugar. This selectivity of the bioadhesion by surface modified nanoparticles towards inflamed intestinal tissues holds great promise for future therapies however requires surely a technological progress to enable the production at industrial scale [Moulari et al., 2014].

3. Conclusions

The design of advanced drug delivery systems enables to new therapeutic approaches where classical dosage forms fail. On the one hand they can provide enhanced drug transport across the absorption barriers for drugs that are usually 'non-absorbable' but also on the other hand provide targeting strategies where the dosage form acts as a depot locally releasing the entrapped drug reducing necessary drug dose and adverse effects at the same time. Future investigations will certainly be necessary since not all mechanisms of delivery are fully understood and further increase of targeting efficiency is surely in reach.

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Captions:

Figure 1: local adhesion of the dosage form provides enhanced diffusion-dependent drug transport across the epithelial barrier.

Figure 2: nanoparticle-based targeting in the therapy of IBD: the breakdown of the mucosal barrier in ulcerated tissue together with a high number of immune-related cells in the inflamed tissue are responsible for a distinct accumulation of the nanoscale drug delivery system.

Figure 1

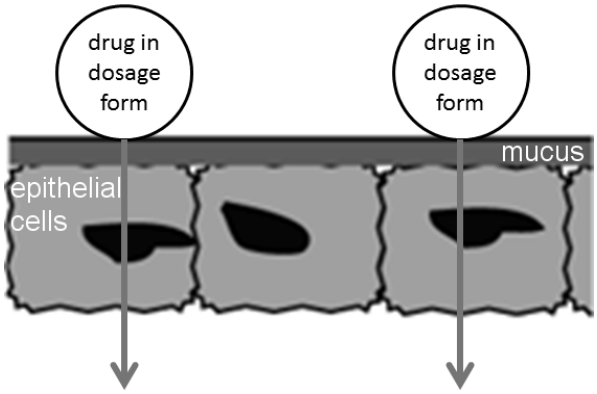
drug in dosage form
drug in dosage form
mucus
epithelial cells

Figure 2