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Drug delivery strategies in the therapy of inflammatory bowel disease ☆

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ABSTRACT

Inflammatory bowel disease (IBD) is a frequently occurring disease in young people, which is characterized by a chronic inflammation of the gastrointestinal tract. The therapy of IBD is dominated by the administration of anti-inflammatory and immunosuppressive drugs, which suppress the intestinal inflammatory burden and improve the disease-related symptoms. Established treatment strategies are characterized by a limited therapeutical efficacy and the occurrence of adverse drug reactions. Thus, the development of novel disease-targeted drug delivery strategies is intended for a more effective therapy and demonstrates the potential to address unmet medical needs.

This review gives an overview about the established as well as future-oriented drug targeting strategies, including intestine targeting by conventional drug delivery systems (DDS), disease targeted drug delivery by synthetic DDS and disease targeted drug delivery by biological DDS. Furthermore, this review analyses the targeting mechanisms of the respective DDS and discusses the possible field of utilization in IBD.

Contents

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1. Introduction

1.1. A brief insight in inflammatory bowel disease

Crohn's disease (CD) and ulcerative colitis (UC) collectively referred to as inflammatory bowel disease (IBD), are characterized as a chronic inflammatory disease of the gastrointestinal tract with unknown aetiology (see Fig. 1). IBD is very common in the Western industrialized countries and it is estimated that 1.4 million people in the United States as well as 2.2 million people in Europe are affected by IBD [1]. The prevalence of 50–250/100.000 per year is similar in CD and UC [2,3]. The onset of IBD is verifiably associated with a complex and elusive interaction between genetic and environmental factors, such as oral contraceptive use, breastfeeding, infections, microbial agents, smoking, appendectomy, sanitation and stress [4]. Genetic alterations in intestinal barrier function, innate and acquired immunity, autophagy, apoptosis and signal transduction modulate the onset, severity and course of IBD [5].

The clinical picture of CD and UC is associated with a variety of intestinal complaints, such as bloody diarrhoea, fever, weight loss, abdominal pain, or vomiting. Extra-intestinal manifestations of CD and UC are relatively common and affect mostly joints, skin, eyes and bile ducts [6–8]. Presently, a permanent cure for IBD is not established, so a lifetime administration of drugs for the maintenance of the health-related quality of life is often necessary.

The treatment of UC and CD is dependent on the severity of IBD, on the disease subtype, on pre-existing illnesses and on the patient's tolerance of drugs. The most common classes of drugs are anti-inflammatory and immunosuppressive agents. The treatment pyramid of UC and CD include 5-aminosalicylates (5-ASA, mainly in UC) and corticosteroids as the mainstays for therapy. 5-ASA drugs, like mesalazine or olsalazine, are mainly used for the treatment of mild attacks and for the maintenance of remission in UC. Corticosteroids, like prednisolone are more effective drugs in the treatment of moderate to severe IBD [9]. Immunosuppressive agents, like azathioprine, 6-mercaptopurine, methotrexate, calcineurin inhibitors and most important anti-TNF-α-antibodies have an important role in the treatment of severe disease stages [10]. Refractory and fulminate disease stages may require surgery as an acceptable option to improve the medical conditions of these IBD patients [11].

A major challenge in the therapy of IBD is the prevention and the reduction of drug-related side effects. Most drugs in the treatment of IBD have a large list from mild to severe adverse drug reactions, including mortality. Corticosteroids show short- and long-term side effects including hypertension, hyperglycaemia, osteoporosis, glaucoma, depression and many others [12]. The treatment with immunosuppressive agents is unmistakably associated with an increased susceptibility to infections and malignoma [13,14]. In consequence, the treatment of IBD requires a balance between high therapeutic efficacy and the risk of adverse drug reactions, because short- and long-term adverse drug reactions may deteriorate the health-related quality of life and thus may counteract a successful therapy of the condition [15,16].

1.2. Paul Ehrlich's concept of drug targeting

Paul Ehrlich (1854–1915) was a German physician, scientist and Nobel laureate in physiology or medicine (1908) and the first one who designed the concept of a drug targeting of active agents to pathogens and cancer cells to maximize the therapeutic efficacy with a simultaneous prevention/reduction of side effects [17].

More than a hundred years later, this concept is as topical as never before. Many efforts in the research of cancerous tumours and autoimmune diseases were performed to design such drug targeting systems. New insights in the pathophysiology of IBD make it possible to develop new and innovative drug carrier systems, including disease targeted drug delivery by synthetic or biological drug delivery systems. Many efforts and attempts have been made to ensure a more effective disease-oriented therapy in IBD compared to the established treatment options. The aspiring and rising natural sciences enable the development of innovative drug carriers, which can accumulate efficiently into inflamed intestinal areas via luminal or endothelial pathways. Sufficient drug carriers demonstrate advanced potential for a targeted drug as well as gene therapy in IBD specific to the site of inflammation.

1.3. The therapeutic benefit of targeted drug delivery strategy in IBD

The therapy of IBD via targeted drug delivery in the first instance is addressed to patients with a mild to moderate disease activity. The strategy of targeted drug delivery is primarily suitable for an effective medical treatment of luminal IBD manifestation, like isolated ileocecal disease in CD or distal colitis in UC. Whereas a discontinuous and extensive localization of inflammation, like from mouth to rectum in CD patients, is treatable via targeted drug delivery systems (see Fig. 2). An effective treatment strategy via targeted drug delivery systems is more promising compared to the present and established drug delivery strategies. Such novel targeted drug delivery systems offer a range of

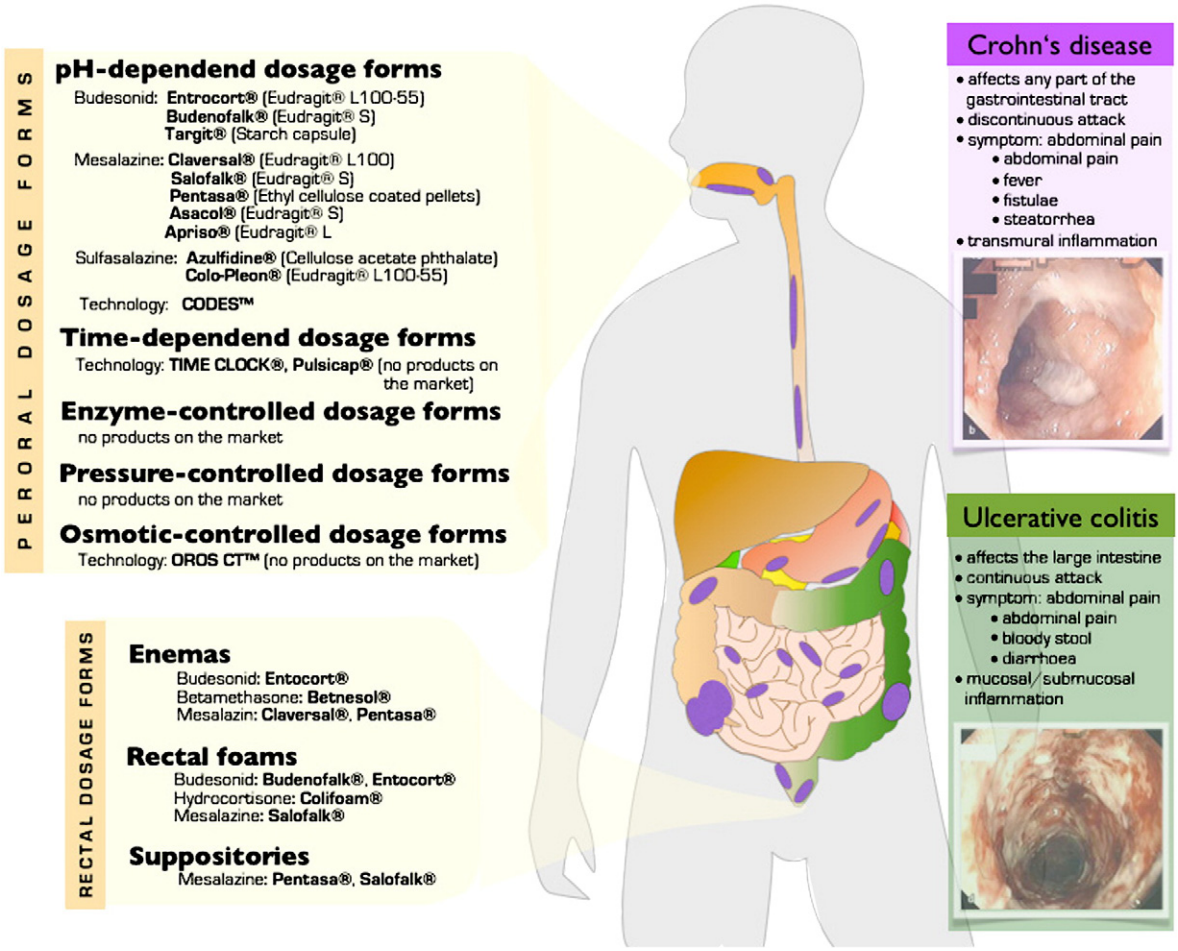


Fig. 1. Conventional dosage forms for the therapy of CD and UC. CD and UC are the two major types of inflammatory bowel disease. CD affects any part of the gastrointestinal tract from mouth to anus and is characterized by transmural inflammations and the involvement of discontinuous segments of the intestine (purple). UC is located in the large intestine and characterized by continuous lesions of the mucosa and submucosa (green) [26]. The current treatment options are based on the administration of anti-inflammatory and immunosuppressive active agents via parenteral, peroral and rectal dosage forms. Rectal dosage forms, like enemas, foams, and suppositories are used for the local and topical treatment of intestinal inflammations in anorectal sections, sigmoid colon and descending colon. The most peroral dosage forms, dependent on drug release mechanism, are applied for the treatment of intestinal inflammations in the small and large intestine. Luminal-released drugs from rectal and peroral dosage forms will absorbed systemically from bowel. Dependent on the active agents, resulting systemic adverse drug effects may have an influence in health-related quality of life, patient compliance.

therapeutic benefits, like a reduction of systemic side effects by a decreased systemic absorption of active agents into the systemic circulation, high local concentrations of active agents at inflamed intestinal tissues, a reduced risk of drug interactions, and finally an improved compliance by a reduced frequency of drug administration.

Summarizing, the current conventional drug delivery strategies are well established in the management of IBD, but disadvantages in terms of an inability to target the drug directly to the site of disease, high risks of adverse drug reaction and limited therapeutic efficacy make the conventional strategies replaceable.

1.4. Targeted drug delivery strategy in IBD — what are the basic requirements for success?

The highest aim for the drug targeting strategy in IBD is a selective delivery and concentration of active agents in the inflamed intestinal tissues to finally improve the therapeutic efficacy while simultaneously reducing side effects. The targeted delivery system has to meet criteria in terms of a complete biodegradation and a high biocompatibility without pro-inflammatory properties. Additionally, the targeted drug delivery systems have to be formulated into the peroral dosage forms to induce and maintain adherence.

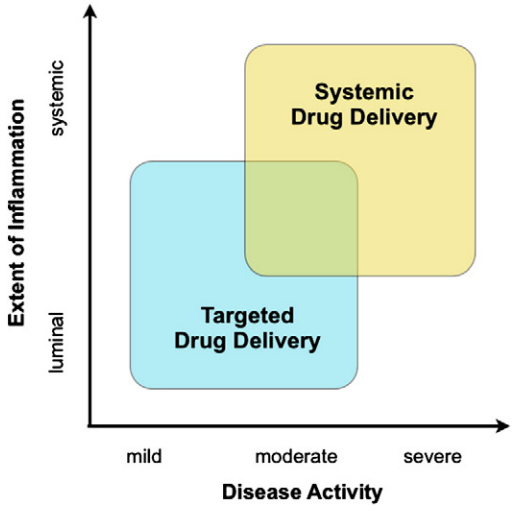


Fig. 2. The therapeutic benefit of a targeted drug delivery strategy. The therapeutical advantage of a targeted drug delivery is mainly the topical treatment of luminal inflammation compared to a systemic drug delivery. A targeted drug delivery benefits IBD patients with a mild to moderate inflammation. Whereas a systemic therapy of severe IBD as well as extra-intestinal manifestations is not directly provided by a targeted drug delivery strategy.

2. Conventional drug delivery strategies

In our view, there is one important fact concerning therapies in IBD: For the majority of IBD patients, standard treatment with 5-ASA or budesonide is sufficient for the induction of remission. With respect to population-based data, fewer than 50% of all patients with IBD need steroids during their lifetime or cannot be sufficiently treated with standard treatments like anti-inflammatory or immunosuppressive agents. Medical guidelines for the therapy of IBD suggest an adequate treatment strategy, including the choice of active agents and route of administration. In general, modes of administration in the therapy of IBD are parenteral, peroral and rectal routes, but the most essential and most common way of administration of active compounds are peroral and rectal routes (see Fig. 1) [10].

2.1. Parenteral route of administration

The parenteral route via intravenous, subcutaneous or intramuscular injection or infusion of solutions, suspensions, emulsions, are used for a systemic immunosuppressive therapy in case of a severe exacerbation as well as severe extra-intestinal disease [18]. Widely used active agents in IBD for the parenteral administration are highly potent anti-inflammatory drugs, like corticosteroids or anti-TNF-α-antibodies [19,20]. The parenteral route shows several advantages over non-parenteral administration, like a fast drug reaction, no difficulties in resorption of drugs and no first-pass metabolism. One major disadvantage of parenteral administration is a nearly 100% bioavailability of parenteral administered active agents, so that an increased risk of systemic adverse drug reactions is provoke.

2.2. Rectal route of administration

The rectal route of administration show several benefits over parenteral or peroral administration. The luminal-released drugs bypass the portal circulation and thus minimize the first-pass effect. For drug delivery to the rectum and lower parts of the distal colon, rectal formulations such as enemas, foams and suppositories are easy-to-use local and topical drug delivery systems to the diseased areas. The rectal administration provides a high concentration of active ingredients to the site of inflammation and results in a decrease of adverse drug reactions due to a diminished systemic absorption [21]. Rectal formulations are indicated for mild to moderate distal UC and ulcerative proctitis [22], but are also administered in addition to systemic drug delivery in extensive disease [23]. Suppositories deliver drugs only to the lower parts of the rectum, whereas enemas and foams based on the dissolved active agents treat diseased rectum, sigmoid and descending colon. The most common drugs in rectal formulations are 5-ASA [24] and corticosteroids [25].

2.3. Peroral route of administration

Peroral dosage forms are characterized by an inexpensive production, easy-to-handle for the patients, accurate dosing and an excellent stability and storability. In contrast, the peroral route is stigmatized by variable intestinal absorption, metabolization in enterocytes and usually ends up in the portal circulation encountering the liver and thus to pass the first-pass effect. In general, the peroral route is the most desired and accepted way to administer drugs in the therapy of IBD. After administration of peroral formulations, the dosage forms release the active ingredients into the intestinal lumen, where they are absorbed by the gastrointestinal mucosa. Finally, the active ingredients reach the systemic circulation and are distributed throughout the body. However, systemic adverse drug reactions can emerge also and may influence the patient's quality of life. The apparent differences in the intestinal environments of the respective sections of the gastrointestinal tract and the differences between healthy and inflamed intestinal areas encourage the pharmaceutical technology to develop innovative drug carrier systems, which deliver the active compounds specifically to the inflamed intestinal areas. Varieties of peroral drug delivery systems for the therapy of IBD have been developed and allow for a more or less effective drug delivery to the site of disease. Based on the continuously inflamed large intestine in UC, most of the peroral dosage forms are indicated for the treatment of the colon. Whereby, treatment of discontinuously inflamed areas in CD is much more difficult by use of peroral drug delivery systems.

2.3.1. Coated drug delivery systems

A simple and inexpensive way to modify drug delivery characteristics of dosage forms is the coating of capsules and tablets with biocompatible polymers (see Fig. 3). The enteric-coating preserves the incorporated active agents against the intestinal surroundings, like gastric juice, bile acids as well as microbial degradation, create an extended and delayed drug release profile to desired intestinal areas and thus enhance therapeutic efficiency. The most common polymers for the coating of tablets and capsules are derivatives of acrylic acids and copolymers of methyl methacrylate (Eudragit®) as well as derivatives of cellulose with threshold pH values between 4.5 to 7.0 (see Table 1) [26]. In general, dosage forms with a solid core, like tablets, pellets, granules, nano- and microparticles are suitable for uniform texture (single-layer) or stratified texture (multi-layer) coating. These coated dosage forms can be filled into capsules or compressed as tablets, which can be additionally coated with the same or other pH-sensitive polymers. These multi-particulate dosage forms have an increased efficiency for a specific drug release to inflamed intestinal areas.

In the 1930s Nana Swartz investigated the therapeutic activity of sulphasalzine (SASP), attributed to the anti-inflammatory action of the 5-ASA moiety. During clinical work at the Karolinska Institute (Sweden), Nana Swartz found a significant improvement of symptoms in IBD patients with 5-ASA therapy. Nowadays, 5-ASA ranges among the most important drugs in the therapy of active disease stages and in maintaining remission in UC and is still available in several dosage forms. Established peroral dosage forms of 5-ASA, coated with pH-sensitive polymers, are Claversal®, Salofalk®, Asacol® and Pentasa® (see Table 2).

Asacol®, a Eudragit S formulation with a pH-release profile of 5-ASA, demonstrated therapeutic success in 80% of patients with active CD, and remission was maintained in 78% when Asacol® was used alone. Adverse reactions of varying severity occurred in 33%, but the drug had to be withdrawn in only 14% [27]. The direct comparison between Asacol® and Pentasa® (microgranules, time dependent drug release formulation of 5-ASA) shows therapeutical benefits of Pentasa® in terms of reduced UC-DAI scores (from 8.18 +/− 0.58 to 6.81 +/− 0.72; $p = 0.013$), improved endoscopic scores and physician global assessment in UC patients. This clinical trial suggested, that Pentasa® provides a better alternative for IBD patients with unsatisfactory response to Asacol® therapy via a time dependent drug release mechanism [28]. But large Cochrane studies identified no difference in efficacy or safety among the various formulations of peroral 5-ASA. In summary, peroral 5-ASA is an effective and safe treatment of mild-to-moderate or quiescent ulcerative colitis regardless of the chosen formulation [29–31]. Furthermore, it is anticipated that more selective drug targeting, including galenic innovations and an optimized dosaging schedule, could result in some improvement of the wide use of 5-ASA [32].

2.3.2. Time dependent drug release systems

Time dependent release systems are designed for the delivery of drugs at predefined time points to a selected site of the gastrointestinal tract. These systems can be used for circadian rhythm dependent treatments or for colonic drug delivery. Unaffected by the individual differences in pH of the gastrointestinal tract or presence of intestinal bacteria, these systems deliver their drugs by different mechanisms,

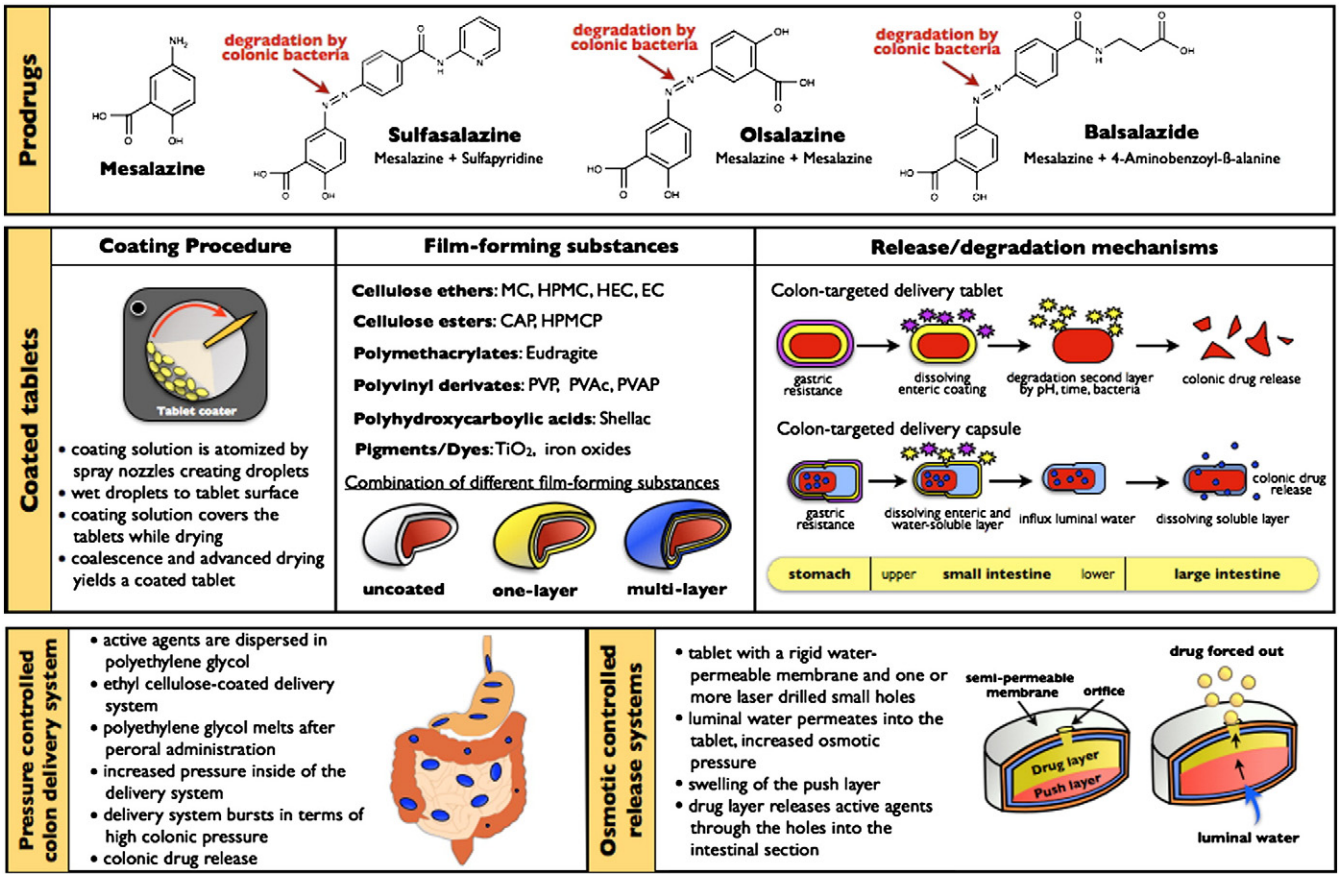


Fig. 3. Overview of pharmaceutical technologies in terms of colon targeted drug delivery.

such as swelling, osmosis or a combination of both [33] (see Table 3). TIME CLOCK® is a drug delivery system of 5-ASA for a time dependent drug release into the distal intestine or inflamed colon. The TIME CLOCK® system consists of a tablet core coated with a dispersion of hydrophobic material and surfactant. The dispersion retains the capacity to rehydrate and redisperse in an aqueous environment in a time proportional to the thickness of the film [34]. Dependent on the coating, the initial tablet disintegration occurred at 5.91 ± 1.47 h post-dose, 8.85 ± 0.90 h post-dose and 12.03 ± 1.25 h post dose for 20%, 35% and 50% w/w formulations [35]. Due to the intersubject variation in GI transit times as well as pathophysiological conditions, the onset of initial drug release occurs in the small intestine in some subjects, while in others the formulations pass the colon intactly [36,37].

2.3.3. Prodrug design

Another strategy for drug delivery is the synthesis of prodrugs as pharmacologically inactive compounds, which require a biotransformation in vivo to release the active agents to the desired intestinal sections (see Table 4). The prodrug approach involves a covalent linkage between active agents and carrier molecules, with the consequence, that the prodrug is "ironclad" in the stomach, jejunum and ileum, but vulnerable in the colon. The colonic conversion of prodrugs into active agents is dependent on the type of linkage. A variety of colonic enzymes, like azoreductase [38], galactosidase [39], xylosidase [40], nitroreductase [41], glycosidase [40] and others, provides a large scope for the development of prodrugs. Based on that, active agents can be conjugated with sugars, amino acids, cyclodextrins, glucuronides, pectins, xylans and others to create compounds with a high stability in the upper gastrointestinal tract, an efficient colonic degradation and a specific absorption in the large intestine. Covalent azo-linkages between 5-ASA and carrier molecules are the most common types of prodrugs in the therapy of IBD. Established azo-linkages of 5-ASA drugs are sulfasalazine, olsalazine and balsalazide [42] (see Fig. 3). Sulfasalazine is formed by combining sulfapyridine and 5-ASA via an azo bond and is indicated for the treatment of IBD and rheumatoid arthritis. In the intestine, sulfasalazine is metabolized by intestinal bacteria in 5-ASA and sulfapyridine. Adverse drug reactions are associated with a high serum sulfapyridine level and are characterized by nausea, headache, anorexia as well as haemolysis [43]. Based on the intolerance of sulfapyridine, other 5-ASA prodrugs were developed to improve the safety and toxicity of 5-ASA medication. Olsalazine is a sulfa prodrug of two 5-ASA molecules [44] whereas balsalazide is a sulfa prodrug in which 5-aminosalicylic acid is linked via a diazo bond to 4-aminobenzoyl-β-alanine (4-ABA), an inert and biologically inactive carrier molecule [45]. Balsalazide as well as olsalazine might be better tolerated than sulfasalazine, as long as the intolerance is based on 5-ASA [46].

In contrast to 5-ASA, in clinical trials of UC patients balsalazide achieved a symptomatic remission after 2 (64% [balsalazide] vs. 43% [5-ASA]), 4 (70% vs. 51%), 8 (78% vs. 45%), and 12 weeks (88% vs. 57%) and complete remission. Patients recognized more asymptomatic days (4 weeks, 24% vs. 14%) and achieved the first asymptomatic day more rapidly (median, 10 vs. 25 days). Additionally, the occurrence adverse drug reactions were reduced by the use of balsalazide (48% vs. 71%) [47]. Olsalazine also improves clinical signs and symptoms of colitis in approximately 60 to 80% of patients with acute ulcerative colitis of mild to moderate severity. This improvement rate is similar to that obtained with sulfasalazine. Furthermore, the occurrence of adverse drug reactions is also similar to sulfasalazine [48–50]. Compared to 5-ASA, olsalazine is superior in therapeutic efficacy, safety and tolerability [51].

Table 1
Selection of pH-dependent coating polymers.

pH-dependent coating		
Polymer	Dissolution	Targeted area
Eudragit L 30 D-55[a]	pH 5.5	Duodenum
Eudragit L 100-55[a]	>pH 5.5	Duodenum
Eudragit L 100[a]	>pH 6.0	Jejunum
Eudragit S 100[a]	pH 7.0	Colon
Eudragit S 12,5[a]	>pH 7.0	Colon
Eudragit E 100[a]	<pH 5.0 swell/permeable > 5.0	Stomach
Methylhydroxypropyl cellulosephthalat	>pH 4.5 soluble <pH 4.5 insoluble	Stomach
Celluloseacetatphthalat	>pH 6.0	Duodenum

[a] http://eudragit.evonik.com.

2.3.4. Embedding in polysaccharide matrices

Biodegradable polysaccharides as a further variant for colon targeted drug delivery were intensively investigated (see Table 5) [52]. Polysaccharides, like amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans and locust bean gum, remain stable within the physiological environment of the stomach and small intestine. The degradation of the polysaccharide matrices is caused by colonic bacterial flora, so the drug release is ensured for delivery exclusively in the colon. Modifications of the polysaccharides, like derivatizations or chemical changes in polymer structure, improve the properties in drug release, biocompatibility, stability and bioadhesion [53]. Nowadays, no polysaccharide-based dosage forms are commercially available for the therapy of IBD or investigated in clinical trials for colon targeted drug delivery. [54]. In IBD, altered microbial intestinal flora [55] may influence the degradation rates of these polysaccharide-embedded systems and a controlled drug release into the diseased colon is not guaranteed. Therapeutical advantages are colonic delivery rates independent of intestinal pH/pressure and the possibilities of higher release rates compared to conventional controlled drug delivery systems. More pharmaceutical investigations for polysaccharide-embedded drug delivery systems are essential to evaluate the therapeutical potential for the therapy of IBD.

2.3.5. Osmotic-controlled drug delivery systems

Osmotic-controlled drug delivery systems are an attractive alternative for delayed or pulsed delivery of active ingredients to the colon. The driving force for the delivery is an osmotic gradient, which arises from the water diffusion into to core of the osmotic system through a semi-permeable membrane. Based on an increased hydrostatic pressure, the active agents are pressed out of the core through laser drilled small holes and are distributed at the target site. The special feature of this formulation is a constant drug release per time unit (zero order kinetic), which is controlled by the diffusion rate of the water into the system [56]. The therapeutic benefits of osmotic-controlled release oral delivery systems (OROS) are characterized by an increased local intestinal resorption, increased bioavailability and a drug release independent of the environment of the gastrointestinal tract. OROS CT has been designed to deliver active agents to the inflamed colon 3–4 h after gastric emptying. A constant drug release follows that may last up to 24 h [57] (see Fig. 3). Today, no OROS CT drug delivery systems are commercial available for the therapy of IBD. The altered gastro-intestinal motility [58] and water absorption [59] in IBD limit the therapeutical benefits of osmotic drug delivery systems by a variable residence time of the system in the body and an uncontrolled drug release. Furthermore, osmotic drug delivery systems may cause irritation or ulcer due to the release of saturated solutions of the drug. Therapeutical advantages of osmotic drug delivery systems are delivery rates of zero-order independent of gastric pH and hydrodynamic conditions and the possibilities of higher release rates compared to conventional diffusion-controlled drug delivery systems [60]. More pharmaceutical investigations for osmotic-controlled drug delivery systems are essential to evaluate the therapeutical potential for the therapy of IBD.

2.3.6. Pressure-controlled drug delivery systems

Given the fact, that luminal pressure as well as the viscosity of the luminal content in the colon are considerably increased compared to the small intestine, it is attractive to develop another colonic drug delivery system. Pressure-controlled drug delivery systems are constructed to bear up against luminal pressure in the small intestine, but to collapse at the higher colonic pressure with a final drug release in the colon 3 h–7 h after peroral administration [61]. Usually, the preparation of pressure-controlled drug delivery systems is based on the coating of gelatine capsules with ethyl cellulose. The active agents, embedded in pharmaceutical excipients, are filled into the gelatine capsule [36,62] (see Table 6, Fig. 3). Nowadays, no pressure-controlled drug delivery systems are commercially available for the therapy of IBD patients. The altered gastro-intestinal motility [58] and water absorption [59] in IBD limit the therapeutical benefits of pressure-controlled drug delivery systems. The residence times of the system in the body may vary and a controlled colonic drug release is not guaranteed. Therapeutical advantages of pressure-controlled drug delivery systems are constant delivery rates independent of gastric pH and hydrodynamic conditions and the possibility of a colon-targeted drug release compared to conventional drug delivery systems. More pharmaceutical investigations for pressure-controlled drug delivery systems are essential to evaluate the therapeutical potential for the therapy of IBD.

Table 2
Coated peroral dosage forms.

Peroral dosage forms in IBD		
Drug	Composition	Release profile
Mesalazine (Asacol®) [172]	Eudragit S	Release at > pH 7.0 terminal ileum, colon
Mesalazine (Salofalk®) [173]	Eudragit L	Release at > pH 6.0 distal ileum, colon
Mesalazine (Salofalk® Granu-Stix) [174]	Eudragit L100, Eudragit NE 40 D	80% colon, sigmoid colon, rectum
Mesalazine (Claversal®) [173]	Eudragit L	Release at > pH 6.0 distal ileum, colon
Mesalazine (Pentasa®) [173]	Ethyl cellulose microgranules in capsules, tablets	Duodenum, ileum colon
Mesalazine [175]	Ethyl cellulose	Terminal ileum proximal colon
Mesalazine [176]	Methylhydroxypropyl-cellulosephthalat; Celluloseacetatphthalat	Stomach duodenum
Beclomethasone (Clipper®) [177]	Eudragit L 100-55	Distal small intestine
Budesonide (Entocort®) [178]	Eudragit L	Colon, rectum
Prednisolone[179]	Eudragit L	Colon, rectum
Prednisolone[180]	Eudragit RS/RL (inner) chitosan (middle) Eudragit L (outer)	Colon
Prednisolone [181]	Eudragit S	Release at > pH 7.0 terminal ileum, colon
Dexamethasone [182]	Eudragit E	Inflamed colon

Table 3
Selection of time-dependent coating polymers.

Time-dependent coating		
Polymer	Dissolution	Characteristics
Eudragit RL 100[a]	Insoluble in water	High permeable, pH dependent swelling
Eudragit RS 100[a]	Insoluble in water	Low permeable, pH dependent swelling
Eudragit NE 30 D[a]	Insoluble in water	Low permeable, pH dependent swelling, highly flexible
Ethyl cellulose, Hydroyethylcellulose	Insoluble in water	Polymer matrix; swells in water

[a] http://eudragit.evonik.com.

2.4. Self micro-emulsifying drug delivery systems (SMEDDS)

SMEDDS are innovative pharmaceutical products to overcome the formulation difficulties of various hydrophilic/hydrophobic drugs in order to improve the peroral bioavailability of poorly absorbed drugs. In general, SMEDDS consist of oil, surfactants and the incorporated drug. After peroral administration, SMEDDS emulsify in the presence of intestinal water and bile fluids into o/w (micro)emulsions. Thus, micro- as well as nanosized drug-loaded droplets will be generated and distributed throughout the gastrointestinal tract. Based on the drug delivery technique of SMEDDS, the peroral bioavailability of drugs is improved by an enhanced drug dissolution and increased absorption due to surfactant-mediated membrane induced permeation changes [63–65]. In terms of IBD, SMEDDS are a promising pharmaceutical approach for a rapid peroral absorption of poorly water soluble anti-inflammatory, immune-modulating and anti-infective drugs, like tacrolimus [66,67] but, until now no clinical or experimental studies of SMEDDS as innovative dosage forms have been published. In IBD, an abnormal bile fluid secretion, metabolism, and secretion and an altered water/electrolyte absorption [59] limit the therapeutical use of SMEDDS. Thus, a controlled formation of micro- as well as nanosized drug-loaded droplets is not guaranteed and aggravates the therapeutical use of SMEDDS in the therapy of IBD. More pharmaceutical investigations for SMEDDS are essential to evaluate the therapeutical potential for the therapy of IBD.

3. Disease targeted drug delivery by synthetic drug delivery systems

The disadvantages of conventional drug delivery systems like increased risk of systemic adverse drug reactions and the challenge to deliver ingredients only to the desired gastrointestinal sections, inspired and encouraged the pharmaceutical technology to design and construct apposite drug delivery systems with a more effective drug targeting strategy. Micro- and nanosized drug carriers, like polymeric micro- and nanoparticles, liposomes and many possible variations have been synthesized and intensively evaluated for an application in IBD patients [68].

3.1. Healthy and diseased intestinal barrier and their role in drug targeting strategies

A healthy intestinal barrier is composed of a secreted mucus layer, a layer of epithelial cells and underlying non-epithelial mucosal cells including the gut-associated lymphatic tissue. The secreted mucus with a thickness of 50 to 800 μm as a physical and chemical barrier provides protection against the adhesion and invasion of microorganisms, toxins, viruses and other foreign antigens [69]. The structure of the mucus layer is highly complex and not fully understood in greater detail. The negative surface charge and the hydrophobic domains of the mucin proteoglycans generate a periodic polyvalent adhesive profile, which limits the passage of pathogens into the deeper tissue layers [70]. A mucosal flow rate of about 5 mm per minute and a regeneration time of approximately 20 min afford a mucosa turn over time of 4 to 6 h [71]. The combination of impenetrable and movable mucus provides an effective protection against mucus-trapped pathogens. The epithelial cells form the structural obstacle of the intestinal barrier and are considered as the control centre between the external environment and the gut-associated lymphoid tissue [72]. The underlying mucosal cells (goblet cells, Paneth cells) produce some components of the secreted barrier and influence epithelial cell function as well as the secreted barrier [73]. The metaphor of an efficient intestinal barrier cannot be reflected in the clinical picture of IBD. The intestinal barrier in IBD is characterized by a disrupted and disturbed structure including a reduction of antimicrobial secretion by a reduced number of secretory cells [74], increased permeability by disabled tight junctions [75] and even the complete loss of the epithelium where ulceration occurs [76]. Furthermore, the mucus layer in IBD is markedly decreased compared to non-inflamed areas and is caused by a reduction in goblet cells, reduced size of goblet cell thecae, decreased mucin production, and decreased mucin sulfation [77]. Based on the dysfunction of the intestinal barrier, bacteria from the luminal side invade the mucosal surface, progressively involving the epithelial layer, submucosa and deep tissue, according to the degree of inflammation. The microbial invasion provokes an exaggerated mucosal immune response and finally constitutes the intestinal inflammation [78]. In IBD, the conditions of an intact intestinal barrier are not fulfilled, alterations

Table 4
Prodrug design strategies for peroral dosage forms.

Prodrugs					
Type of conjugation	Drug	Active agent	Conjugates	Release mechanism	Target area
Azo-linkage	Sulfasalazine (Azulfidine® [183])	5-ASA	Sulfapyridine	Bacterial azo reductase	Colon
Azo-linkage	Balsalazide (Colazal® [184])	5-ASA	4-aminobenzoyl-ß-alanaine	Bacterial azo reductase	Colon
Azo-linkage	Olsalazine (Dipentum® [185])	5-ASA	5-ASA	Bacterial azo reductase	Colon
Amino-acid	5-ASA-Gly [186,187]	5-ASA	Glycine	Hydrolysis by peptidases	Colon
Glycoside	Galac-5-ASA [188]	5-ASA	ß-D-glalactose	Hydrolysis by glycosidases	Colon
	Gluco-Dex [189]	Dexamethasone	ß-D-glucoside		
Glucuronide	Glucu-Dex [190]	Dexamethasone	ß-D-glucuronide	Hydrolysis by glycuronidases	Colon
Cyclodextrins	CyD-5-ASA [191]	5-ASA	Cyclodextrins	Hydrolysis by bacterial enzymatic degradation	Colon
	CyD-Pred [192]	Prednisolone			
Dextrans	Dex-5-ASA [193]	5-ASA	Dextrans	Hydrolysis by esterases and endodextranases	Colon

Table 5
Polysaccharide-based drug delivery for peroral dosage forms.

Polysaccharides				
Type of polysaccharides	Active agents	Degradation	Release mechanism	Target area
Amylose [194]	5-ASA	Bacteria	Swelling	Colon
N-Succinyl-chitosan [195]	5-ASA	Bacteria	pH-dependent swelling	Colon
Guar Guar [196]	5-ASA	Bacteria	Forming viscous colloidal dispersions	Colon
Pectin [197]	5-ASA	Bacteria	Erosion/degradation	Colon
Starch (ENCODE® Phloral) [198]	Not named	Bacteria	Pore formation	Colon

in the composition and thickness of the mucus and a disrupted barrier combined with an increased infiltration of immune related cells in the mucosa characterize the pathophysiological condition [79,80] (see Fig. 5). At this time, a variety of different drug carrier systems, which are qualified for a drug targeting in IBD, are extensively tested and described subsequently (see Table 7). Polymeric micro- and nanoparticles as well as liposomes are very promising in the drug design as well as drug targeting for the therapy of IBD.

3.2. Polymeric drug carriers

3.2.1. Micro- and nanoparticles

An early pioneer in the area of retarded and controlled drug release was Peter Paul Speiser at the ETH in Zurich. His research group investigated and constructed miniaturised drug delivery systems for one-term oral vaccination against tetanus, diphtheria and other infections in the 1950s and 1960s, which usually require multiple injections for an adequate immune stimulation [81]. New drug delivery strategies including improved and modified polymers, innovative drug carriers as well as drug release systems have been extensively evaluated and investigated in models of experimental colitis. Nowadays, nano- and microparticles are an important field in the research of disease targeted drug delivery, like PEGylation, active targeting to specific cells by ligands or passive tissue targeting via pathophysiological changes of barriers to solid tumours or inflamed tissues [82]. A number of polymers are investigated for the preparation of biodegradable particles, like poly(-3-hydroxybutyric acid), polycaprolactone, polyglycolic acid, polylactic acid, poly(lactide-co-glycolide) acid, polyanhydrides, polyester, polyphosphazenes and polyphosphoesters [83]. Poly(lactide-co-glycolide) acid (PLGA) is the most investigated, biocompatible and biodegradable polymer, which has been approved by the United States Food and Drug Administration (FDA) for numerous medical applications, like suture, bone plates, implants, prosthetic devices and pharmaceutical drug delivery systems [84,85].

The particle size as well as particle surface plays a key role in the adhesion and interaction with cells as well as tissues. The uptake of particles from the healthy gastrointestinal tract is clearly depending on the particle size. Extremely small particles of <50 nm pass the intestinal barrier by paracellular pathways. Particles of <500 nm can be taken up via endocytosis by intestinal enterocytes. Large microparticles of <5 μm, can be absorbed by M cells of the Peyer's patches [86]. In contrast to healthy colonic mucosa, the accumulation of micro- and nanoparticles in inflamed tissue is characterized by an increased deposition of particles in inflamed tissue areas. The deposition of particles seems to be size-dependent, while large particles of 10 μm are detected only in traces in inflamed areas, whereby smaller particles of 1000 nm and 100 nm showed a higher accumulation tendency in inflamed sections [87]. The ratio of inflamed/non-inflamed deposition increases with smaller particle sizes. Investigation of the pharmacological/clinical efficiency of drug-loaded nanoparticles compared to drug solution in experimental colitis showed an advantage for drug-loaded nanoparticles in terms of myeloperoxidase activity and colon/body weight ratio ($p < 0.05$). Furthermore the therapeutic efficiency of peroral and rectal administration routes of drug solutions and drug-loaded nanoparticles in experimental colitis proved 3-times enhanced drug penetration of nanoparticles into the inflamed area compared to the healthy tissue [87–89]. In summary, smaller particles more effectively pass the mucus barrier compared to larger particles. This size-dependent effect can be explained firmly by the diffusion of smaller particles through low viscosity pores within the highly elastic mucin fibre matrix. The average pore size of the mucus is below 100 nm, so that drug carriers smaller than 100 nm can diffuse smoothly through the mucus. With increasing size, the diffusion as well as the translocation of drug carriers are considerably hindered, so the probability of microparticles passing an intact mucus layer is rather limited [71]. This size-dependent effect of particles to hurdle the intact mucus layer can be transferred to IBD therapy. Probably, this size-dependent effect remains constant, but the diffusion of particles is facilitated by a different mucus composition or mucus thickness.

In addition to particle size, the particle surface also plays a crucial role in the interaction with the mucus layer and epithelial cells. In the development of drug delivery systems, many strategies to modify the particle surface have been realized and extensively evaluated, like pH-sensitive particulate drug carriers (see Table 8). To be more specific, many pharmaceutical options have been discussed to improve the therapy in IBD, e.g. muco-adhesion [90,91], bio-adhesion [91], muco-penetration [71], active uptake by M cells [92] and endothelial targeting [93].

3.2.2. Muco-adhesion

Muco-adhesion is a condition where an increased attraction between the drug delivery system and the mucus is present. Muco-adhesive particles are bound to the mucus layer through interactions with mucin glycoproteins, including hydrogen bonding, van der Waals interactions, polymer chain interpenetration, hydrophobic forces, and electrostatic/ionic interactions [90]. The most intensively investigated type of muco-adhesion is the electrostatic interaction. The cationic polymer chitosan, obtained by the deacetylation of chitin, reacts with the negative surface charge of the mucus and forms a strong electrostatic bonding [94]. Chitosan-based or chitosan-coated nanoparticles were extensively studied for an improved oral bioavailability of poor water soluble active agents, like proteins, peptides and DNA [95] (see Table 9). The incorporation of unstable active agents, like insulin [96], calcitonin and elcatonin [97], into muco-adhesive drug carriers improves the drug stability against protease degradation and thus increases the bioavailability after oral administration. The oral delivery of active agents by muco-adhesive drug carriers is limited by the

Table 6
Advanced colon drug delivery systems.

Advanced colon drug delivery systems	Drug	Release mechanism
Pressure-controlled colon delivery capsule (PCDC) [199]	5-ASA	Colon pressure initiate a burst
Colonic drug delivery system (CODES™) [200]	5-ASA	Erosion/degradation by bacteria
Time-dependent drug release systems (TIME CLOCK®) [201]	5-ASA	Time-dependent drug delivery, independent of pH, digestive state

Table 7
Unmodified particulate drug carriers.

Unmodified drug carriers				
Size	Polymer	Study	Drug	Reference
NP	PLGA	Experimental colitis in rats	Rolipram	[202]
NP	PLGA	Experimental colitis in rats	Tacrolismus	[88]
NP	PLGA	Experimental colitis in rats	5-ASA	[203]
NP	PLC	Experimental colitis in mice	5-ASA	[204]
MP	PLA	Experimental colitis in mice	Dexamethasone	[205]
NP, MP	PLGA	IBD patients	–	[206]

mucosal turnover time, so the expected retention time in the mucus is limited to 5 h [98]. In summary, mucoadhesive drug delivery systems are only qualified and investigated for an intestine-targeted drug release of 5-ASA [99], mesalazine [100], budesonide [101], prednisolone [102]. In IBD, the composition and thickness of the mucus layer is altered in the inflamed sites compared to non-inflamed areas [77]. The mucus layer is thinner and thus the distance between the luminal site and epithelial cells is markedly reduced. Thus, mucoadhesive drug carriers close to the intestinal inflammation adhere onto the thinner mucus surface and can be absorbed in released or intact particulate forms [97]. This strategy is based on an interesting approach to target inflamed areas, but more pharmaceutical investigations for a targeted drug delivery in IBD are essential to evaluate the therapeutical potential of muco-adhesive drug carriers.

3.2.3. Bio-adhesion

Bio-adhesion is a further strategy for drug delivery to intestinal cells. Bio-adhesive drug carriers adhere exclusively to intestinal cells and release their active agents for an intracellular delivery. Lectins, commonly known as sugar-binding proteins, are used for the epithelial adhesion of drug delivery systems. The most investigated lectins are wheat germ agglutinin (WGA) as an N-acetylglucosamine binding lectin and tomatolectin as a poly-N-acetyllactosamine binding lectin [103,104] (see Table 10). The diffusion of lectin-bound particles through the mucus layer is a delicate situation, because the efficiency of the passage is limited by an adsorption to the mucus and a faecal elimination in the same way as muco-adhesive delivery systems. Experimental studies showed that the overall intestinal transit time was strongly increased when drug delivery systems were conjugated to lectins. A significant fraction of the conjugates adhered to the gastric as well as intestinal mucosae [105]. Additionally, lectins also mediate a cytoinvasion of drugs by receptor-associated endocytosis into enterocyctes and the accumulation of drugs in lysosomes as well as intestinal M cell interaction [106–108]. The pharmaco-dynamic profiles of lectins in terms of an increased toxicity and immunogenicity may limit the pharmaceutical use of these compounds.

3.2.4. Muco-penetration

The effect of muco-penetration has been observed in viruses, like poliovirus, norovirus and human papilloma virus, which are capable of diffusing in mucus as fast as in water. These viruses are coated with positively and negatively charged groups, so that a neutral surface charge is present [70]. This allows an unobstructed and rapid transport of viruses into the intestinal cells, where they can initiate an infection accompanied by intestinal inflammations. The viral surface profile creates hydrophilic conditions that minimize hydrophobic, periodic, polyvalent and adhesive interaction with the mucus. These insights into viral capabilities to diffuse unhindered through the mucus have been transferred to the development of muco-penetrating drug delivery systems. Poly(ethylene glycol) (PEG), as an uncharged hydrophilic polymer, can be used for a PEGylation of polymers as well as drug carrier systems (see Table 11). Based on the PEGylation, the association between mucus and the PEGylated drug delivery system is obviously reduced by the creation of a hydrophilic shield around the particle core and the interpenetration into the mucus matrix is increased. A dense surface layer of PEG and a low molecular weight of PEG are required for a rapid and unhindered penetration of PEGylated particles through the mucus by using low-viscosity channels and pores within the mucus [109]. Additionally, the PEGylation enhances the stability of drug delivery systems in digestive fluids and mucus, so that the degradation is delayed [110]. In summary, PEGylated drug carriers represent an attractive technology for the development of disease targeted drug delivery systems. Muco-penetrating drug carriers penetrate through the mucus layer of healthy as well as inflamed intestine. Based on the thinner mucus layer in inflammation, muco-penetrating drug carriers reach more efficiently the epithelial surface, where they accumulate in the intestinal lesions and are absorbed in released or intact particulate forms by immune related cells. The translocation of muco-penetrating drug carriers into an intact epithelial surface is aggravated and finally these drug carriers are eliminated by the mucus turn over.

3.2.5. Uptake by M cells

M cells (microfold cells) are located in the dome region of the follicle-associated epithelium of the Peyer's patches and differ from enterocytes by a lack of microvilli on the luminal surface and an absent secretion of mucus and digestive enzymes. Based on the thin mucus layer, M cells can transport bacteria, viruses or particles from the gut lumen to the Peyer's patches for stimulating the gut-associated lymphoid tissue (GALT). The drug delivery via M cells is very attractive because a reduced mucus layer simplifies the drug delivery to the M cells and the direct connection to the GALT magnifies the pharmacological effect to the immune system [111]. But, the strategy of a drug delivery to M cells is substantially restricted in its efficiency and capacity of the absorption pathway due to a small quantity of M cells at the intestinal surface and a partial inactivation of active agents by immune-related cells [112]. Oral vaccines in terms of micro- and nanoparticles were developed by the surface finishing with IgA and IgG antibodies, staphylococcal enterotoxin B toxoids, tetanus toxoids [113], lectins [114], claudin 4-targeted proteins [115] and different non-peptidic ligands [116]. Therefore, this drug delivery approach is a fetching strategy for oral immunization but presently impractical for disease targeted drug delivery in IBD.

3.2.6. Endothelial targeting via synthetic drug delivery systems

Endothelial targeting is a novel strategy of disease-specific targeted drug delivery. Particles or liposomes are functionalized with specific antibodies against endothelial targets of intestinal inflammation. After the intravenous administration, these drug delivery systems are distributed

Table 8
pH-sensitive particulate drug carriers.

pH-sensitive drug carriers				
Size	Polymer	Study	Drug	Reference
NP	PLGA, Eudragit S100	Experimental colitis in rats	Budesonide	[207]
MP	Eudragit S100	Experimental colitis in rats	Carboxy-fluorescein	[208]
MP	Eudragit P-4135 F	Experimental colitis in rats	Tacrolismus	[209]
MP	Cellulose acetate butyrate, Eudragit S-100	Cell culture	Ondansetron Budesonide	[210]
MP loaded with NP	PLGA, Eudragit P-4135 F	Experimental colitis in rats	Tacrolismus loaded NP	[211]

Table 9
Muco-adhesive particulate drug carriers.

Muco-adhesive drug carriers				
Size	Polymer	Study	Drug	Reference
MP	Chitosan, Eudragit S100	Healthy volunteer	Barium sulphate	[212]
MP	Chitosan Ca-Alginate	Experimental colitis in rats	5-ASA	[213]
MP	N-Succinyl-Chitosan	Experimental colitis in rats	5-ASA	[214]
MP	Chitosan, Eudragit S100	Experimental colitis in rats	Budesonide	[215]
MP	Chitosan, λ-carrageenan alginate	Cell culture	5-ASA	[216]
NP	Chitosan, PLGA	Experimental colitis in rats	NF-KB	[217]

in the systemic circulation and adhere specifically to the overexpressed endothelial targets at the site of inflammation. Antibody-coated nanoparticles against the vascular cell adhesion molecules-1 were tested in a model of experimental colitis in mice [117]. These nanoparticles showed a 12-fold increased adhesion to the inflamed endothelium compared to non-inflamed areas. Selectivity and efficiency were dependent on the number of administered particles. Other endothelial target molecules like selectins as cell adhesion molecules on the surfaces of activated endothelial cells play an important role in the initial recruitment of leukocytes to the site of inflammation. Drug carriers coated with anti-selectins onto the surface can be captured out of the bloodstream by the adhesion to the selectin receptors and can afterwards infiltrate into the inflamed area. The most intensively investigated selectins in this therapeutic field are E-, P- and L-selectins [118].

3.3. Liposomal drug carriers

Liposomes are artificially prepared vesicles consisting of an aqueous core encased by one or more phospholipid layers. The encapsulation of hydrophilic drugs is based on the embedding of aqueous active agents into the liposome core, whereas hydrophobic compounds can dissolve into the lipid membrane. In this way, liposomes can also deliver hydrophilic and hydrophobic active agents in the same carrier. Liposomes are often used for the delivery of drugs, enzymes, vaccines, nutrients and others to the target site of disease. On the pharmaceutical market, liposomes for an intravenous administration of doxorubicin, amphotericin B, morphine, estradiol and vaccines are offered and were successfully introduced in the therapy of metastatic cancer, fungal infection, post-surgical analgesia, postmenopausal therapy, hepatitis A and influenza, resp. [119]. At this time, various types of liposomes are being prepared by the modification of the liposomal surface or liposomal surface charge, like long-circulating liposomes by PEG-coated liposomes, solid tumour targeting by folate-modified liposomes, liver tumour targeting by galactosylated liposomes and many others [120] (see Table 12).

The liposomal strategy for disease target drug delivery is based on the intraluminal administration of liposomal drug carriers. Their persistent effect in the treatment of IBD is very similar to the translocation mechanism of drug-loaded micro- and nanoparticles, wherein the efficiency is dependent on the physico-chemical properties of drug carriers. The major challenge in the development of oral drug carriers is the design of the liposomal surfaces in correlation with the size, surface charge and injury of the intestinal wall. For this reason a variety of modified liposomal drug systems are being tested in experimental colitis and the efficiency of accumulation and the improvement of clinical symptoms are being intensively evaluated. Phospholipid liposomes, loaded with 5-aminosalicylate or 6-mercaptopurine, showed an increased efficiency for local drug delivery in inflamed tissues [121]. Surface modifications of liposomes play a key role for a selective drug delivery. It has been demonstrated that positively charged liposomes better adhered to healthy mucosa, whereas anionically charged liposomes showed an increased adhesion to inflamed mucosa. Finally, liposomal drug delivery systems for disease targeted drug delivery in IBD are in the early stages of development. Many interesting types of liposomes with different physico-chemical properties were prepared and more or less successfully tested in models of cell cultures and experimental colitis. In the course of time, new and auspicious targets and epitopes will be identified and transferred to the surface design of liposomes [122,123].

In general, the drug loading and drug release of liposomal drug carriers are based on low permeability to hydrophilic drugs and high permeability to lipophilic drugs, which is a pharmaceutical challenge for the liposomal retention and release active agents. The drug loading is often performed after the liposomal vesicles are produced. Many drugs are weak bases possessing a primary, secondary or tertiary amine that can be loaded in response to pH gradients to internal acidic buffers. In general, the pharmaceutical disadvantages of liposomal drug carriers is to control drug loading as well as drug release, so that therapeutical benefits of drug-loaded liposomes is guaranteed. Another important pharmaceutical hurdle is the overcoming the rapid clearance by uptake into the cells of the mononuclear phagocyte system. This reduces the drug carrier distribution in the body, the circulation half-life and thus therapeutical benefit. Furthermore, the intracellular delivery of drugs to diseased tissues is another pharmaceutical problem. The intracellular uptake is dependent on the physico-chemical properties of the incorporated drug, and the occurrence of cell membrane transporters as well as receptor-mediated uptake pathways [124].

3.3.1. Endothelial targeting via liposomal drug delivery systems

The endothelial disease-specific targeting strategy for liposomal drug carrier systems is based on the "backside-targeting" of inflamed intestinal areas. An enhanced permeability due to defective endothelial cells with wide fenestrations characterizes the vascular endothelium of inflamed areas. This "enhanced permeation and retention effect", normally observed in malignant tissues, builds up the basis for a tending accumulation of drug carrier systems in the desired tissues. In the context of intestinal inflammation, endothelial defects in forms of gaps

Table 10
Bio-adhesive particulate drug carriers.

Bioadhesive drug carriers				
Size	Polymer	Study	Drug	Reference
NP	Wheat germ agglutinin, PLGA	Cell culture	BSA	[218]
NP	Wheat germ agglutinin PLGA	Rats	Thymopentin	[219]
NP	*Sambucus nigra* lectin, PVM/MA	Rats	BSA	[220]
NP	*E. coli* enterotoxin Polystyrene	Cell culture	–	[221]
MP	Tomato, asparagus pea lectin, PLA	Mucin	BSA	[222]

Table 11
Muco-penetrating particulate drug carriers.

Muco-penetrating drug carriers				
Size	Polymer	Study	Drug	Reference
NP	PEG–PLA	Rats, cell culture	FITC-BSA	[223]
NP	PEG-polystyrene	Human mucus	–	[224]
NP	PEG-polystyrene	Human mucus	–	[225]
NP	PEG-poly(sebacic acid)	Human mucus	–	[226]
NP	PEG–PLGA	Human mucus	–	[109]
NP	PEG–PLA	Human mucus	Rhodamine 6G	[227]

enable the migration of intravenously administered liposomal drug carriers from the bloodstream through the endothelium into the inflamed tissue and release their active compound to the target structures. The manifestation of liposomal adhesion to the endothelium as well as the accumulation efficiency to desired areas is the basis for testing various liposomal modifications, surface charges and liposomal sizes with regard to the severity of the inflammation and injured endothelium [125]. PEGylated liposomes have been evaluated for an endothelial drug delivery to inflamed tissues. An increased accumulation of PEGylated liposomes in inflamed colonic tissues (13.5% vs. 0.1%) and a reduced blood concentration of circulating liposomes in colitis (9% vs. 25.7%) demonstrated the disease-targeting potential of PEGylated liposomes in IBD [126].

3.4. Small interference RNA therapy by polymeric and liposomal drug carriers

The pathogenesis of IBD is characterized by an activation of immune cells and an increased production of pro-inflammatory cytokines, like TNF, colony-stimulating factors, interleukins, and interferons. The most traditional-investigated cytokines in IBD are TNF-α, TGF-β, INF-γ, IL-1, IL-5, IL-6, IL-8 and IL-10 [127]. Whereas, TNF-α plays a crucial role in this process by contributing to the recruitment of immune-competent cells that stimulate the inflammatory immune response in mucosal cells, T cells, and macrophages. In IBD, the level of TNF-α is increased in serum and plasma. The local blockade of TNF-α as well as TNF-α receptors by antibodies is an established strategy to facilitate clinical remission, improve clinical symptoms, and support mucosal healing [128]. A novel strategy to inhibit TNF-α is the use of antisense oligonucleotides and small interfering RNA (siRNA). This gene therapy by antisense technology is based on synthetic strands, which bind selectively the complementary mRNA so that the expression of the target proteins is decreased [129]. Whereas, siRNA are short double-stranded RNA molecules with a complementary nucleotide sequence to the target RNA. This molecular interference of the RNA pathways by siRNA influences the expression of specific disease-related genes. The most investigated cytokine for a siRNA treatment in IBD is TNF-α. Therefore, various polymeric and liposomal drug delivery systems for peroral and rectal administration were developed to decrease TNF-α levels as well as to suppress the expression of other pro-inflammatory cytokines. RNA interference is one of the most promising strategies for a targeted blocking of the activity of one or several genes. This therapy is based on the fact that siRNA-loaded drug carriers reach the target cells and mediates a siRNA release into the cytoplasma. The pharmaceutical advantage of siRNA-drug carriers is the development of peroral or rectal dosage forms, which accumulate/deposit selectively in inflamed intestinal areas and support a siRNA release to target cells (see Table 13). The technology of RNA interference is still in their infancy, but is characterized by a great therapeutic potential for the treatment of autoimmune disease, like IBD.

4. Disease targeted drug delivery by biological drug delivery systems

This strategy is characterized by the utilization of bio-inspired and bio-mimic drug delivery systems. Non-pathogenic bacteria, eukaryotic cells and recreated biological cells are used as drug carriers for delivery of active agents, like peptides, proteins, antibodies or genes to the target structures (see Fig. 4). These bioengineered strategy is based on the specific exploitation of natural mechanisms in protection, recognition, attacking and masking, so that an improved and more efficient drug delivery compared to the conventional drug delivery systems is guaranteed [130]. The research and development of biological drug delivery systems is relatively young, but nowadays it shows enormous therapeutic potential in vaccine, gene and protein delivery in the therapy of cancer, infection and inflammation. Even in IBD, the use of bio-inspired drug carriers could open another window to a drug targeting strategy to the site of inflammation. Some bio-inspired drug carriers have been successfully tested in clinical trials and models of experimental colitis and showed a huge potential for an administration in the therapy of IBD (see Table 14). Auspicious bioengineered drug delivery systems with an alluring prospect for the utilization in IBD are bacteria-based and eukaryotic-based drug delivery system as well as synthetic eukaryotic cells.

4.1. Bacteria-based drug delivery systems

This strategy is based on the utilization of bacteria-based carriers, like recombinant bacteria, bacteria-attached-nanoparticles and bacterial ghosts as drug delivery systems for the therapy of cancer, infection and inflammation. The therapeutic utilization of bacteria-based carriers is characterized by a luminal site of action via peroral and/or rectal route of administration.

4.1.1. Recombinant bacteria

Living, non-invasive and non-pathogenic bacteria, like *Lactococcus lactis* [131–133], *Streptococcus gordonii* [134], *Lactobacillus casei* BL23 [135] and *Lactococcus plantarum* [136] are bioengineered for the production and delivery of proteinogenic active agents, like IL-10 [137], IL-1 receptor antagonist [134], superoxide dismutase [135], Yersinia LcrV Protein [132], trefoil factors [133], and TNF-neutralizing heavy chain-camelid antibodies [138].

The treatment of murine colitis by *L. lactis* secreting IL-10 showed that the therapeutic dose of IL-10 can be reduced by localized drug delivery, and can cause a 50% reduction in dextran sodium sulphate (DSS)-colitis activity and prevent the onset of colitis in IL-10 deficient mice [137]. Clinical trials of *L. lactis* with a synthetic sequence encoding mature human interleukin-10 for the treatment of IBD patients was safe with minor adverse drug reactions and resulted in a decreased Crohn's disease activity index (300 CDAI vs. 200 CDAI) as well as reduced C-reactive protein levels (30 mg/ml vs. 20 mg/ml) [139]. These studies are a solid evidence for the effectiveness of recombinant bacteria in

Table 12
Liposomal drug carriers.

Liposomes				
Size	Polymer	Study	Drug	Reference
Liposomes	B-subunit cholera toxin	Pigs	Antisecretory agents	[228]
Liposomes	Luminal drug targeting	Experimental colitis in rats	Carnitine	[229]
Transferrin- Liposomes	Luminal drug targeting	Experimental colitis in rats	–	[122]
Charged Liposomes	Luminal drug targeting	Experimental colitis in rats	Catalase, TMN, SOD	[123]
Liposomes	Luminal drug targeting	Experimental colitis in rats	Antioxidant enzymes	[230]
Liposomes	Endothelial drug targeting	Experimental colitis in rabbits	tc-99 m	[231]
PEG-Liposomes	Endothelial drug targeting	Experimental colitis in rats	tc-99 m	[126]

Table 13
siRNA drug carriers.

siRNA drug carriers			
Drug carrier system	Study	siRNA for	Reference
Gelatine nanoparticles, further entrapped in poly(epsilon-caprolactone) microspheres for peroral administration	Experimental colitis in mice	TNFα	[232]
Gelatine nanoparticles, further entrapped in poly(epsilon-caprolactone) microspheres for peroral administration	Experimental colitis in mice	TNFα and Cyclin D1	[233]
Poly-(1,4-phenyleneacetone dimethylene thioketal) nanoparticles for peroral administration	Experimental colitis in mice	TNFα	[234]
siRNA with 2′-O-methyl and propanediol modifications in lipofectamine 2000 for rectal administration	experimental colitis in mice	TNFα	[235]
Polyethyleneimine nanoparticles, encapsulated in alginate and chitosan for peroral administration	Experimental colitis in mice	siRNA for TNFα	[236]
Mannosylated cystamine bisacrylamide-branched polyethylenimine-polyethylen glycol nanoparticles	Ex vivo: experimental colitis in mice	siRNA for TNFα	[237]

the therapy of IBD and build an important basis for further developments of this strategy.

4.1.2. Bacteria-attached-nanoparticles

The combination of nanoparticles as efficient drug carriers and bacteria as targeted delivery systems may generate a promising drug targeting strategy for vaccination, and cancer therapy. Moreover, this drug delivery strategy theoretically seems to be an excellent approach for a successful treatment of immune-related pathogenesis in terms of IBD. Nanoparticle-carrying bacteria can be used as drug carriers of therapeutic molecules or for an advanced bactofection strategy [140]: Luminal nanoparticle-carrying bacteria can be phagocytised by immune-related cells. Anti-inflammatory agents released inside of the immune cells reduce their immunological activity in terms of phagocytosis, cytokine production and recognition. Finally, drug targeting by bacteria-attached-nanoparticles increases the therapeutic benefit of anti-inflammatory and immunosuppressive agents. A promising gene therapy in IBD is also conceivable [141]. However, no clinical trials or animal studies in terms of bacteria-attached-nanoparticle therapy in IBD are published.

4.1.3. Bacterial ghosts

Bacterial ghosts are empty, non-living bacterial envelopes of pathogenic and non-pathogenic Gram-negative bacteria, which are characterized by a natural and intact outer surface including all immunogenic and bioadhesive surface structures, like fimbriae, flagella, polysaccharides and others [142]. These provide the original targeting functions of the bacterial ghost to bind and/or to be taken up by dendritic cells[143], macrophages[144], tumour cells [145], antigen presenting cells [146] or other target cells. The bacterial ghost system represents a platform technology for creating new qualities in non-living carriers, which can be used for the specific targeting of proteins, peptides, DNA or other active agents [142]. Enteropathogens, such as *Vibrio cholera* [147] or enterohemorrhagic *Escherichia coli* (EHEC) [148] could be useful as drug vehicles for the luminal targeting of inflamed areas in IBD. The presence of toxin-co-regulated pili and fimbriae induce the binding and uptake of ghosts by immune-related cells in targeted tissues [149]. Hitherto, no clinical trials or experimental studies in terms of bacteria-ghosts therapy of IBD are published.

4.2. Eukaryotic-based drug delivery system

This strategy is based on the utilization of eukaryotic cells, like red blood cells, macrophages and lymphocytes as drug delivery systems for the therapy of cancer, infection and inflammation. The therapeutic utilization of eukaryotic-based carriers is characterized by a parenteral route of administration, like intravenous via infusion or injection.

4.2.1. Red blood cells

Based on the prolonged circulation time of 120 days and the large size of 90 μm^3, RBCs can be used for a continuous and slow drug release into the systemic circulation [150]. A variety of active agents, like antiretroviral drugs [151], antiparasitic drugs [152], antineoplasmic drugs [153], cardiovascular drugs [154], anti-inflammatory drugs and agents for imaging [155], are prepared in RBCs to generate a consistent and retarded drug release during the residence time. This endothelial drug targeting to inflamed tissues by bioengineered RBCs could be a new and innovative strategy to modify the inflammatory processes in IBD. Clinical trials with autologous RBC, loaded with dexamethasone-21-phosphate in paediatric patients affected by steroid-dependent CD demonstrated a significant reduction of pCDAI ($p < 0.05$), while 78% of the patients discontinued conventional steroids. Furthermore, endoscopic findings showed remission in 44% of the patients. Adverse drug reactions were not observed [156]. In another clinical trial, plasma dexamethasone concentrations were detected after as long as 28 days and were completely withdrawn by the second month. Erythrocyte sedimentation rate levels dropped from 47 ± 27 mm/h at baseline to 27 ± 16 mm/h ($p < 0.02$), and C-reactive protein levels from 1.6 ± 1.3 to 0.6 ± 0.5 mg/dl ($p < 0.02$) after 3 months. After a mean follow-up of 12 ± 3 months, six patients relapsed, and the remaining four patients stayed in remission [157]. A randomized and controlled trial of RBC-mediated delivery of dexamethasone in patients with mild-to-moderate UC showed a clinical and endoscopic remission compared to the sham group (75% vs. 10%; $p = 0.001$) and the levels of C-reactive protein were significantly decreased (1.6 mg/dL vs. 0.4 mg/dL, $p = 0.006$). No steroid-related adverse events were observed in the patients treated with autologous RBC-mediated delivery of dexamethasone. Additionally, the therapy was similar effective as peroral prednisolone administration [158].

4.2.2. Macrophages

Macrophages play a key role in the regulation of immune responses by the production and secretion of interleukins, complement factors, enzymes and many others [159]. Additionally, the antigen presentation of macrophages stimulates B-cells to produce antibodies as well as helper T-cells to proliferate and orchestrate the inflammatory process. Macrophages can be used as drug carriers for the delivery of active agents into the heart of the immune response at the site of inflammation. For this purpose, macrophages were loaded ex vivo with drug carriers by phagocytosis and afterwards re-injected into to the body. These bioengineered macrophages circulate through the bloodstream and accumulate in the tissues of high inflammatory states as well as tumour-infiltrated tissues [160]. Hitherto, this macrophage-based drug targeting strategy has been evaluated in antiretroviral, neuroprotective and gene therapy of HIV-associated neurological disease [161], Parkinson disease [162] and cancer [163]. Macrophage delivery could also be used as a worth mentioning alternative to an endothelial treatment strategy in IBD. Macrophages can be used as a 'Trojan horse' to deliver anti-inflammatory compounds, embedded in nanoparticles, to the immune cells at the site of inflammation. However, no clinical trials or experimental studies in terms of a macrophage-mediated drug therapy in IBD have been published so far.

4.2.3. Lymphocytes

Lymphocytes can be differentiated into T-cells, B-cells and natural killer cells, which play a key role in the innate and especially adaptive immune system. T-cells and B-cells can be bioengineered by the surface conjugation of drug-loaded liposomes and nanoparticles, without any interference with cell proliferation and killing efficiency of modified cells. In order to lead the bioengineered lymphocytes to the target

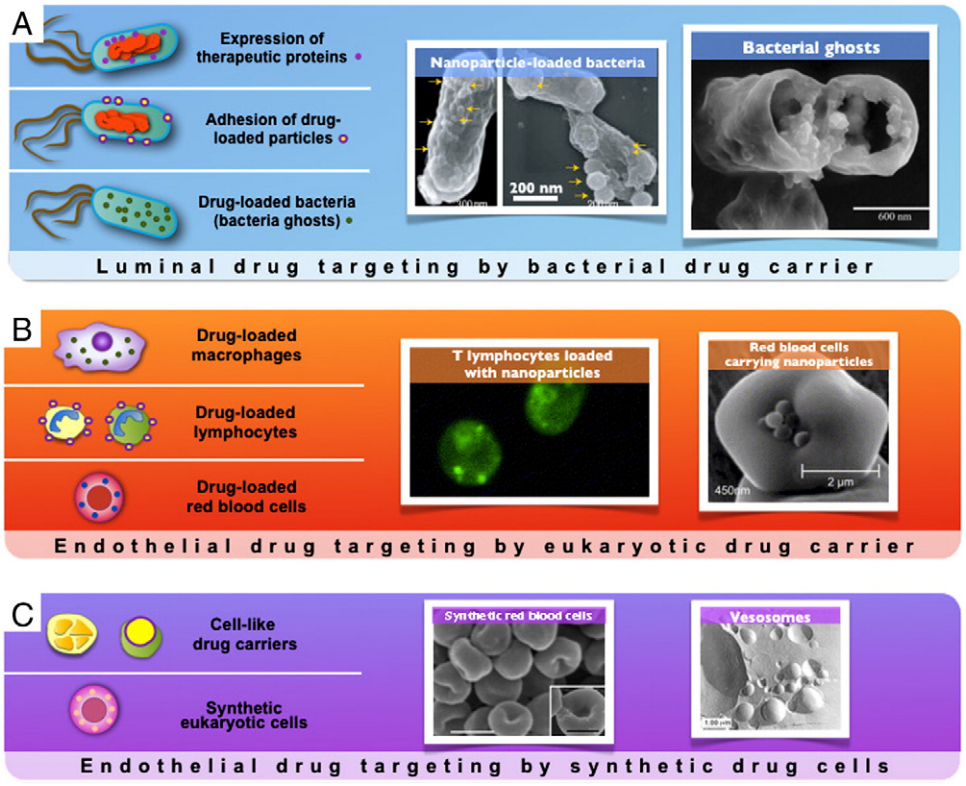


Fig. 4. Disease targeted drug delivery by bioengineered drug delivery systems. The strategy of disease targeted drug delivery by bioengineered drug delivery systems is characterized by the utilization and mimicry of natural cells, like bacteria and eukaryotic cells for a luminal and/or endothelial drug delivery to inflamed areas in IBD. A: Bacteria can be used as producer of therapeutic peptides and proteins for a luminal drug delivery system. Based on the natural recognition of bacteria by the human immune system, bacterial drug carriers can be phagocytosed by immune-related cells and thus influence the inflammatory processes in IBD. B: The body's own cells, like macrophages, lymphocytes or red blood cells can be modified by the load with active agents into the cells or onto the cell surfaces. From the endothelial side, drug loaded immune-related cells agitate against the immune system and thus improve the inflamed areas. C: Cell-like drug carriers with multiple compartments and synthesized eukaryotic cells provide a precedent-setting alternative for an endothelial drug delivery into inflamed areas of IBD. But principally, cell like drug carriers have the capabilities of a multiple load of two or more active agents into the drug carriers. Surface finishing by an attachment of recognition structures facilitates the targeting of the diseased areas in IBD.
References for images: Nanoparticle-loaded bacteria [125]; *Bacterial ghosts* [126]; *T lymphocyte loaded with nanoparticles* [127]; *Red blood cell carrying nanoparticles* [128]; *synthetic red blood cells* [129]; *vesosomes* [130].

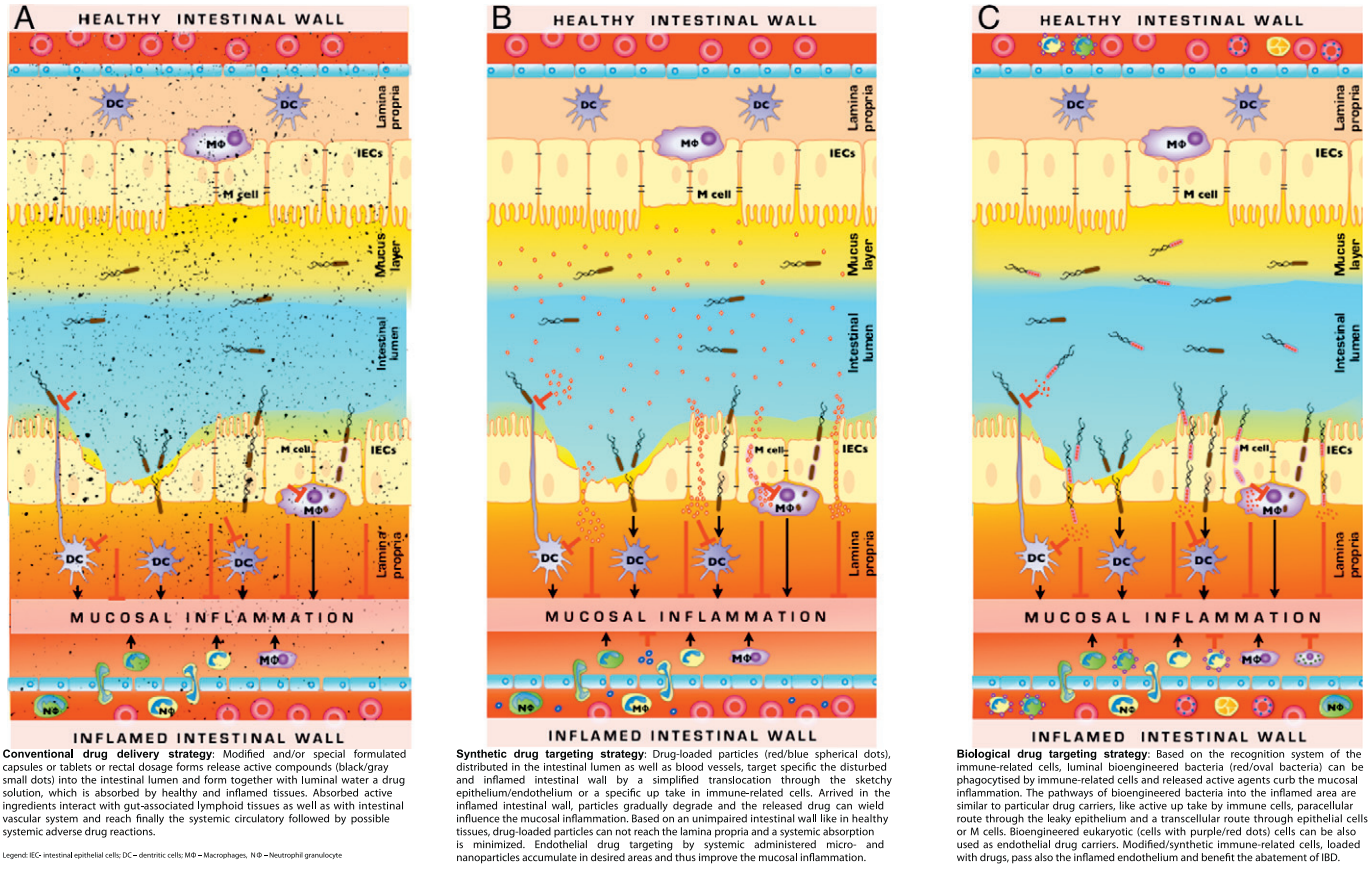
structure, cell-targeting structures or antibodies can be attached to the cell surface. Interestingly, bioengineered lymphocytes have been evaluated in clinical trials as an efficient therapy against cancer and viral infection [164]. This drug targeting strategy by use of bioengineered lymphocytes combined with drug-loaded particles onto the cell surfaces has a great potential for a successful therapy from the "backside" of the inflammatory processes in IBD. But, neither clinical trials nor experimental studies in terms of a lymphocyte-mediated drug therapy in IBD have been published yet.

4.3. Synthetic eukaryotic cells

Another cunning but sophisticated strategy is the creation of polymeric cells as drug carriers, which are mimicking natural eukaryotic cells, like red blood cells [165] or platelets [166]. Multicompartment or cell-like drug delivery systems based on the complex structure of living cells, can be synthesized for a co-delivery of two or more active agents to target the site of disease [167]. These synthetic drug carriers, like vesosomes [168] and nanocells [169], build the foundation for a

Table 14
A selection of examples of different biological drug carriers.

Eukaryotes				
Delivery system	Developmental stage	Examination subjects	Drug	Reference
Human RBC	Clinical trial (phase 3)	Paediatric CD patients	Dexamethasone	[238]
Human RBC	Clinical trial (phase 2)	Patients with mild-to-moderate UC	Dexamethasone	[158]
Human RBC	Preclinical trial	Steroid-dependent IBD patients	Dexamethasone	[157]
Human RBC	Preclinical trial	IBD patients with MDR1 polymorphism	Dexamethasone	[239]
Lactococcus lactis	Clinical trial (phase 1)	Crohn's diseased patients	Human IL-10	[240]
Lactococcus lactis	Experimental study	Two murine models of colitis	LcrV protein	[132]
Streptococcus gordonii	Experimental study	Murine model of colitis	Human IL-1 receptor antagonist	[241]
Lactobacillus plantarum	Experimental study	Murine model of colitis	Modified teichoic acids	[242]
Salmonella typhimurium	Experimental study	Murine model of colitis	SOD, monocyte chemoattractant protein	[243]
Salmonella typhimurium	Experimental study	Rat model of colitis	SOD, monocyte chemoattractant protein	[244]
Lactobacillus casei	Experimental study	Murine model of colitis	Manganese-dependant catalase	[245]
Escherichia coli	Experimental study	Murine model of colitis	pDNA (TGF-ß1 gene)	[246]



Conventional drug delivery strategy: Modified and/or special formulated capsules or tablets or rectal dosage forms release active compounds (black/gray small dots) into the intestinal lumen and form together with luminal water a drug solution, which is absorbed by healthy and inflamed tissues. Absorbed active ingredients interact with gut-associated lymphoid tissues as well as with intestinal vascular system and reach finally the systemic circulatory followed by possible systemic adverse drug reactions.

Legend: IEC- intestinal epithelial cells; DC – dentritic cells; MΦ – Macrophages, NΦ – Neutrophil granulocyte

Synthetic drug targeting strategy: Drug-loaded particles (red/blue spherical dots), distributed in the intestinal lumen as well as blood vessels, target specific the disturbed and inflamed intestinal wall by a simplified translocation through the sketchy epithelium/endothelium or a specific up take in immune-related cells. Arrived in the inflamed intestinal wall, particles gradually degrade and the released drug can wield influence the mucosal inflammation. Based on an unimpaired intestinal wall like in healthy tissues, drug-loaded particles can not reach the lamina propria and a systemic absorption is minimized. Endothelial drug targeting by systemic administered micro- and nanoparticles accumulate in desired areas and thus improve the mucosal inflammation.

Biological drug targeting strategy: Based on the recognition system of the immune-related cells, luminal bioengineered bacteria (red/oval bacteria) can be phagocytised by immune-related cells and released active agents curb the mucosal inflammation. The pathways of bioengineered bacteria into the inflamed area are similar to particular drug carriers, like active up take by immune cells, paracellular route through the leaky epithelium and a transcellular route through epithelial cells or M cells. Bioengineered eukaryotic (cells with purple/red dots) cells can be also used as endothelial drug carriers. Modified/synthetic immune-related cells, loaded with drugs, pass also the inflamed endothelium and benefit the abatement of IBD.

Fig. 5. Comparison of different drug targeting strategies in the therapy of IBD.

promising therapy of cancer [169], infection and inflammation. Surface finishing with markers of the human antigen recognition enhanced therapeutic efficiency by an increased drug targeting specificity to diseased areas. This promising strategy is also suitable for an endothelial drug targeting to inflamed areas of IBD, but hitherto no clinical trials or experimental studies in IBD have been published.

5. Comparison of different drug delivery strategies

Bowel targeted drug delivery strategies by conventional drug delivery systems are being used successfully in the treatment of IBD (see Fig. 5). The accurate drug release to the inflamed intestinal section by different release mechanisms and modifications of the active agents is an indispensable method in the therapy of IBD. Oral and rectal dosage forms can adequately reach the diseased small and large bowel and thus ensure a drug delivery to inflamed intestinal sections. These systems are clearly depending on a variety of influential factors for an optimal drug release to desired intestinal areas, like intestinal pH, bacterial colonization, bowel motility, grade of the intestinal inflammation and many others. Based on the disease-mediated intestinal alterations, conventional drug delivery systems are prone to errors or dysfunctions. A major disadvantage is the systemic absorption of luminal-released active agents through the healthy and inflamed intestinal wall to the systemic circulation. In addition to an insufficient reduction of intestinal inflammation, systemic adverse drug reactions may impair the health-related quality of patient's life and jeopardize the successful therapy.

The next steps for an optimized drug delivery to inflamed intestinal areas may come from micro- and nanoparticulate technology. Micro- and nanoparticles in different compositions, particle sizes, surface charges, surface modifications and release profiles were intensely investigated. Modified micro- and nanoparticles are attractive and helpful tools in diagnostics and drug targeting in IBD. During the last fifty years, micro- and nanoparticles showed an excellent potential for an efficient drug targeting to the inflamed areas of the intestine. Altered mucus layers, disrupted and leaky mucosal barriers and the occurrence of dysfunctional tight junctions enhance the particular deposition as well as the particular translocation into the intestinal inflammation and increase drug release at the site of inflammation. Based on an intact intestinal barrier, non-inflamed areas refrain from the particular translocation into the tissue and prevent an absorption of released drugs into the systemic circulation. The major benefits of micro- and nanoparticles are a specific accumulation of particles in inflamed tissues followed by high concentrations of active agents at the target structures as well as reduced systemic adverse drug reactions. In addition, surface-modified micro- and nanoparticles could also show an outstanding profile of endothelial drug targeting into inflamed tissues.

Another innovative drug targeting strategy has a different approach to gain a successful drug delivery into intestinal inflammation. Bio-inspired as well as bioengineered drug delivery systems can be used to circumvent on the one hand and simultaneously to exploit the immune-related defence mechanisms on the other for an effective drug delivery by use of luminal and endothelial pathways. Based on the recognition and clearance of bacteria-based drug carriers by the activated immune system in inflamed intestinal areas, drug-producing-bacteria, particle-loaded-bacteria and bacterial ghosts suggest their therapeutic pertinence in the therapy of IBD. These luminal drug carrier systems enter the inflamed tissues by different uptake mechanisms, like a disrupted and leaky intestinal barrier, increased uptake by M cells and paracellular pathways between epithelial cells due to dysfunctional tight junctions. Immune-related cells phagocytise the bioengineered bacterial drug carriers that subsequently perform a drug release to the

site of inflammation. An accumulation of adequate drug carriers into inflamed areas benefits a reduction of inflammatory processes.

Endothelial drug targeting by bio-engineered eukaryotic cells, like drug-loaded macrophages, lymphocytes and red blood cells, are already being used successfully in clinical trials. Based on their natural pathways and recognition structures, drug-loaded cells circulate within the blood stream and reach the target areas by cell-specific uptake mechanisms. An accumulation of these bio-engineered eukaryotic cells with anti-inflammatory properties into inflamed tissues also support an abatement of IBD. Moreover, synthetic eukaryotic cells or cell-like drug carriers, loaded with active agents, can also be used for a drug targeting from the endothelial site to the inflamed intestine. Surface modifications with human recognition structures provide an enhanced efficiency for a targeted, specific accumulation in inflamed tissues.

In general, therapeutic drug carriers in terms of synthetic and biological drug delivery systems are always limited by the mononuclear phagocyte system, which is an important part of the immune system to remove erythrocytes, leukocytes and particles by phagocytosis or to eliminate exogenous microorganisms and biological debris, including bacteria, fungi, parasites and viruses. The mononuclear phagocyte system consists of phagocytic cells (monocytes, macrophages) in blood, bone marrow and reticular connective tissues, like liver, kidney, lymph nodes, lung, skin, bone, brain, spleen, reproductive tract and serosal compartments [170,171]. The clearance of synthetic and biological drug delivery systems from circulatory systems is determined on the uptake by the mononuclear phagocyte system, which depends on their physico-chemical surface properties and their nature of origin.

6. New challenges in regulatory and scientific aspects

The development of such innovative targeted drug delivery systems is also associated with new challenges in regulatory and scientific fields. Novel, tailored polymers as well as polymer-based carriers with complex structures and various physiological functions require updated or even new guidelines and policies for their evaluation and assessment. New methods of investigation, standards as well as criteria must be developed to evaluate biocompatibility and toxicity of such novel targeted drug delivery systems in physiological as well as pathophysiological processes. Furthermore, new standards and evaluation criteria are necessary to investigate clinical efficacy as well as the cost–benefit ratio.

The so called “Nanomedicine” is a new field of investigation with an unknown potential in the therapy of various diseases. The behaviour of nanosized drug carriers in humans is very complex and only partially understood. Thus, the development of innovative nanosized medicine is still limited by the comprehension of the physiological and pathophysiological processes of the human organism and its handling with “Nanomedicine”. Additionally, new disease models, improved verification procedures and criteria of risks/performance must be developed for the evaluation of innovative drug delivery forms.

7. Conclusion

Many ideas and concepts are being investigated and realized in cell cultures, ex vivo and in vivo experiments and even some in clinical trials. The major function of all drug carrier strategies is the targeted delivery of active agents into the site of intestinal inflammation. The drug carriers protect the incorporated active agents against environmental factors of the human body and increase the therapeutic efficiency, so that systemic adverse drug reactions may be prevented.

Research in the therapy of IBD is marked by a steady progression in terms of improved dosage forms, intelligent drug carriers and superior active agents. The idea of an effective drug targeting in the therapy of IBD is getting closer. Many concepts are under investigation and are consecutively optimized in a cycle of development. The construction of more effective drug carriers within the scope of a drug targeting to inflamed tissue nowadays is on an excellent way to a breakthrough in this important field.

Conflict of interest

Consultancy work and scientific support were provided for Abbvie, Falk, MSD, Recordati-Pharma, Schering Plough, Shield Holding, Shire, UCB, and 4SC.

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