

# Interactions between Nanoparticles and Intestine

Subjects: [Gastroenterology & Hepatology](#)

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The use of nanoparticles (NPs) has surely grown in recent years due to their versatility, with a spectrum of applications that range from nanomedicine to the food industry. Recent research focuses on the development of NPs for the oral administration route rather than the intravenous one, placing the interactions between NPs and the intestine at the centre of the attention. This allows the NPs functionalization to exploit the different characteristics of the digestive tract, such as the different pH, the intestinal mucus layer, or the intestinal absorption capacity. On the other hand, these same characteristics can represent a problem for their complexity, also considering the potential interactions with the food matrix or the microbiota.

nanoparticles

nanocarriers

insulin delivery

inflammatory bowel diseases

colon cancer

food additives

## 1. Introduction

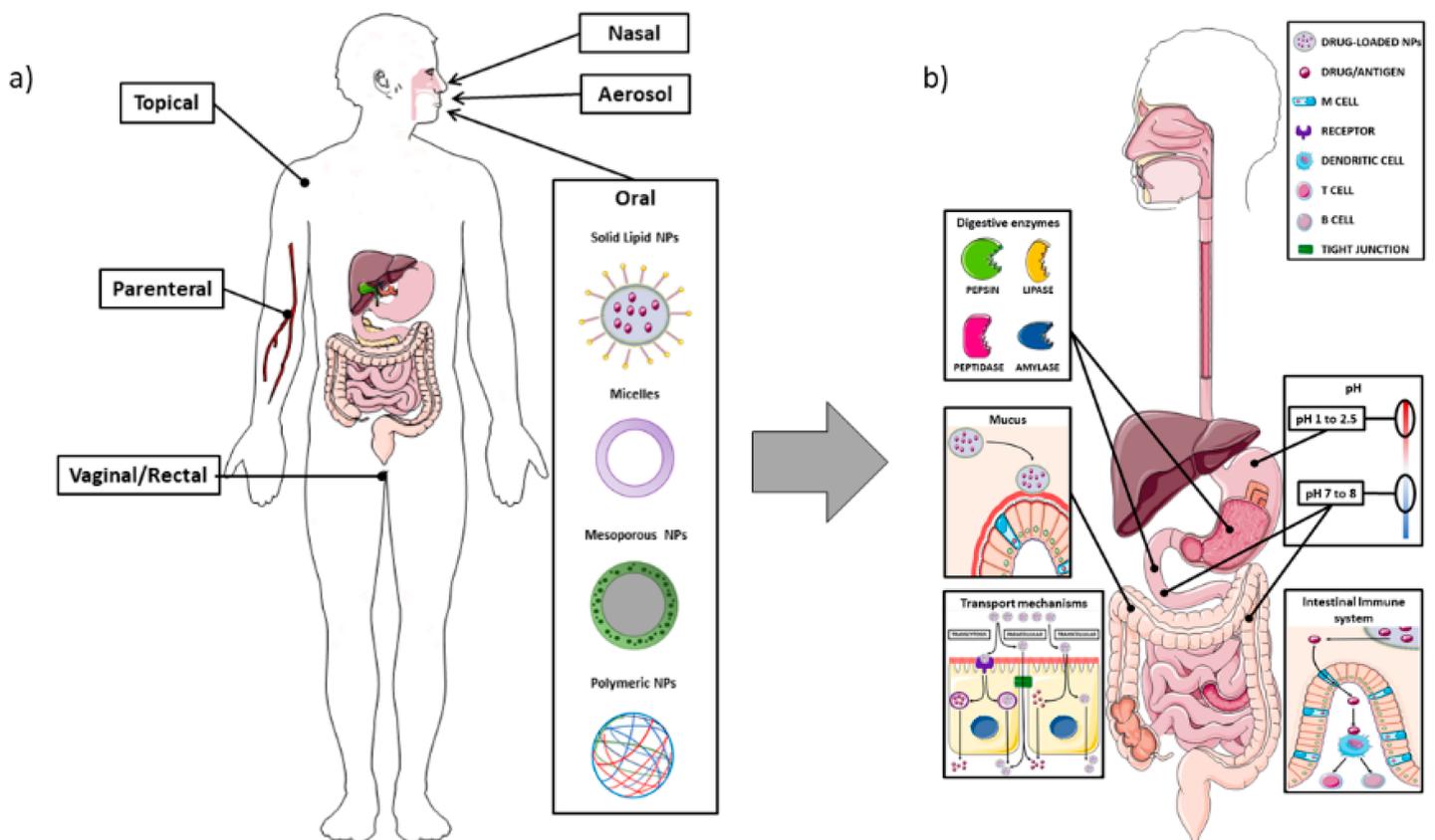
The development of nanotechnology in recent years has dramatically changed the approaches for drug delivery, initially improving the efficacy of the intravenous route for various drugs, such as anti-cancer ones. These results have also prompted researchers and pharma companies to look into the possibility of using nanocarriers for drug delivery through the oral route. On the other hand, in addition to pharmacological use, nanoparticles (NPs) have also been used quite extensively in the food industry, due to their ability to improve food characteristics, as well as product shelf-life. This implies that the interactions between NPs and the intestine can become quite frequent; for this reason, it is necessary to understand the pros and cons of the NPs presence in the intestine, also considering the possible interactions with the lumen components (food, acid environment, enzymes) and the different cell types.

### 1.1. The Intestinal Barrier

The gastrointestinal tract is a difficult environment for nanocarriers, both due to the aggressive conditions present in the lumen, as well as for the presence of the barrier separating the lumen from the rest of the body. The first challenge is a large pH gradient, ranging from pH 1–2.5 in the stomach to pH 7–8 in the colon, fact which can affect the structure of the nanocarriers or of the vehiculated drug. Moreover, the lumen enzymes, both in the stomach (ex. Pepsin) and in the duodenum (biliary and pancreatic secretions that include lipases, peptidases, and

amylases) can affect the nanocarrier stability and/or their capacity to bind different substances (including food components) [1][2].

The intestine is composed of different cell types that have specific functions, and the composition changes according to the anatomical site, i.e., the small or large intestine. In the small intestine the main absorption function is performed by the enterocytes, which are also responsible for the tight junctions, the most important structure creating the intestinal barrier. The mechanisms of uptake of lumen substances could be either paracellular or transcellular, i.e., through the enterocytes. The paracellular pathway usually plays a minor role in the passage of NPs, which are usually transported through the transcellular route. This occurs through vesicle-mediated mechanisms, either endocytosis or pinocytosis; it is easy to understand that the intrinsic characteristics of the NPs can affect the ability to bind to the enterocytes and to be transported through the transcellular route. In **Figure 1**, the main NPs administration routes are represented, along with the main aspects related to the oral administration (**Figure 1**).



**Figure 1.** Schematic representation of the different routes for nanoparticle drug delivery, with attention to the oral administration and the interactions with the intestinal barrier. Panel (a): Overview of the main administration routes for nano-drug delivery; Panel (b): Different enzymes (pepsin, lipase, peptidase, and amylase) located in the gastrointestinal tract can impair nanocarriers stability and their ability to reach the target tissue. The mucus layer also plays an important role in the entrapment of NPs, which may lead to reduced uptake at cellular level. The enterocytes transport mechanisms of NPs can occur through the intestinal cells, either by transcytosis (mediated by endocytic vesicles), or through a direct apical-basolateral passage, or by the paracellular route (passing through

the intercellular space). The difference in pH among the stomach, duodenum, and colon represent one of the main challenges in delivering NPs, particularly in order to avoid their premature degradation through the acidic environment. M cells, as part of the GALT (gut-associated lymphoid tissue), can detect antigens from the intestinal lumen and bring them to antigen presenting cells (APC), which, in turn, are able to present them to B or T lymphocytes located at the mucosal level. The image was created with the use of Servier Medical Art modified templates, licensed under a Creative Common Attribution 3.0 Unported License (<https://smart.servier.com>, accessed on 19 February 2022).

There is also another point that needs to be considered, i.e., the presence of multidrug resistance transporters (MDR) in the epithelium, fact which could dampen the total amount of the drug bound to NPs which had been taken up by the enterocytes. In addition to enterocytes, there are other cells in the small intestine, such as goblet cells (localized in the villi), as well as Paneth and stem cells (in the crypts); the former are producing the mucus which covers the intestinal epithelium, whereas Paneth cells are responsible for the production of antimicrobial peptides and immunomodulating proteins. Mucus is a complex hydrogel composed of water and different types of proteins, among which mucins are the most abundant ones. Most mucins are glycosylated, so they have a negative charge, characteristic which could lead to the adhesion of positively charged nanocarriers through electrostatic interactions. This ability of nanocarriers to bind to the mucus layer could be regarded only partially as positive, since the intestinal mucus is structured in two different layers: the first one, nearer to the intestinal lumen, is more loose whereas the layer in contact with the epithelium is firmly adhered. The firm binding of the NPs to the upper layer can, thus, lead to a prompt clearance and to a reduction in the opportunity to reach the epithelium [3].

## 1.2. Nanoparticles

The NPs that can interact with the intestine can be divided into different categories, mainly according to the material used to generate them.

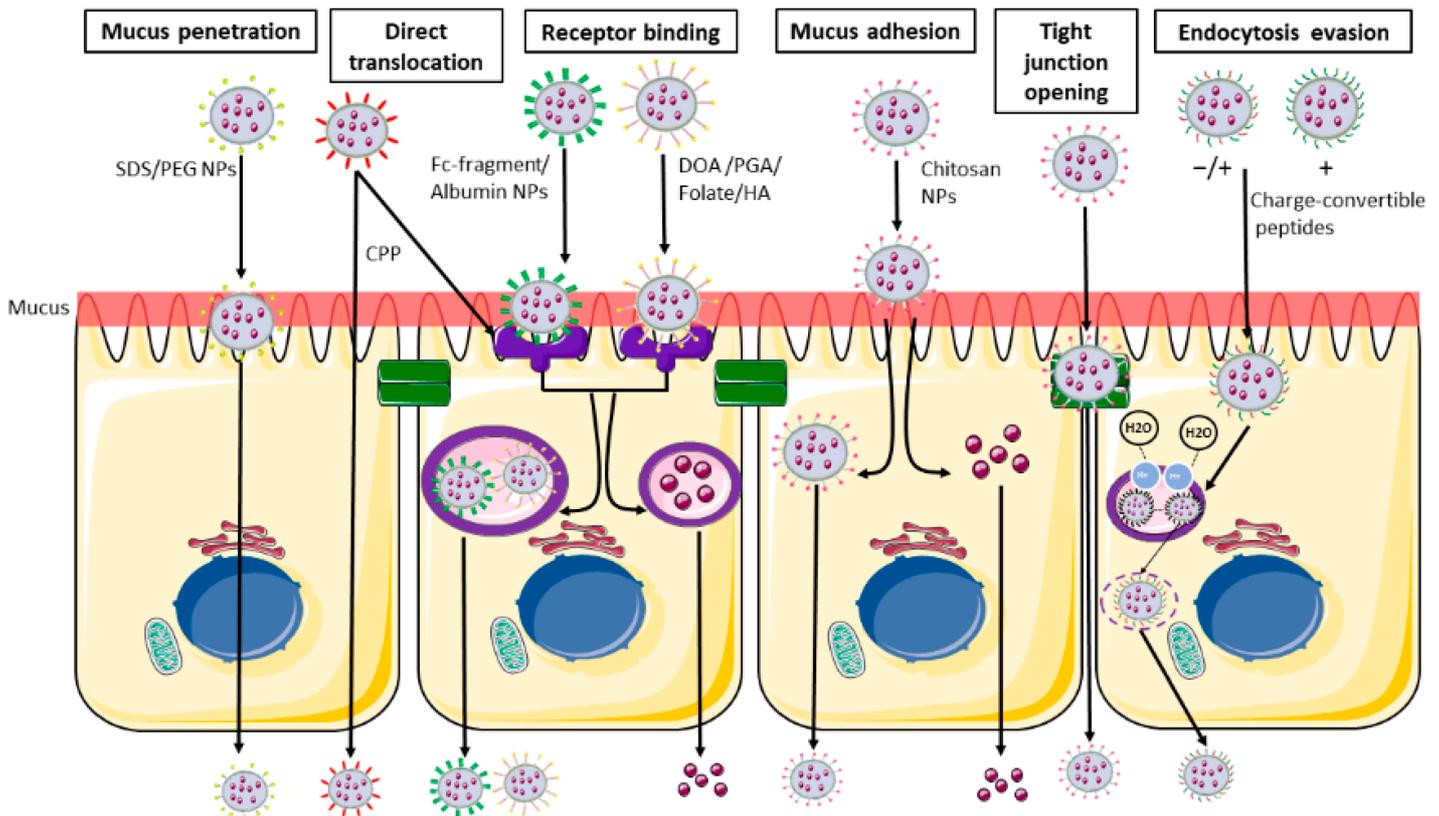
Lipid-based nanocarriers have been quite extensively used in drug delivery because of their versatility, biocompatibility and low toxicity profile, and their use by i.v. administration has already been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) [4] (recently reviewed by Halwani). However, the oral route presents a series of advantages, e.g., ease of administration and high patient compliance, and, thus, a large amount of research is now being undergone, aiming at developing the best lipid-based nanocarriers for oral delivery. This task also takes advantage of the fact that most oils and fats used for the development of these nanocarriers derive from dietary lipids, thus facilitating oral permeability and biodegradability. The term lipid-based nanocarrier includes liposomes, self-nano and microemulsifying drug delivery systems, nanoemulsions and nanocapsules.

Liposomes are spherical vesicles constituted by lipid bilayers and an aqueous inner core. Their basic composition is phospholipids and sterols (such as cholesterol), with the latter ones being used in order to stabilize the liposomal membrane. However, different components can be added to this simple structure, such as surfactants, bile acids, or specific ligands that could help the targeting of the liposomes to intestinal cells (see below). Moreover, due to

their composition, liposomes can carry hydrophilic molecules into their inner cavity, whereas hydrophobic drugs can be inserted into the lipid bilayer [5]. Solid lipid NPs are composed by a lipid core (triglycerides, fatty acids or phospholipids) with a monolayer surfactant shell, such as lecithin or bile salt derivatives [6]. Nanoemulsions are dispersions of an oily and an aqueous phase with the addition of an appropriate surfactant, but due to the percentage of surfactant (3–10%) they are thermodynamically unstable. On the contrary, microemulsions are stabilized by surfactants added in higher concentrations ( $\geq 20\%$ ), thus making them thermodynamically stable [7]. Lipid nanocapsules are constituted by an oily phase and an aqueous one, stabilized by surfactants and a polymeric shell. Due to their nature, lipid nanocapsules can present with different biological properties, which depend on their surface characteristics. In fact, the characteristics of the polymeric shell can determine the ability of the NPs to interact with the intestinal environment, in particular with the mucus and/or the enzymes present in the lumen [8].

MNPs can interact with the intestine either because they are used as therapeutic agents or because they are ingested with food, since they can be used as food preservatives or colouring agents (such as  $\text{TiO}_2$ ) [9][10]. From the medical point of view, the most extensively utilized are Ag or gold (Au) NPs, but data have also been obtained on palladium, titanium, zinc, and copper ones. Due to their chemical properties, their surface can be easily functionalized to conjugate targeting agents and active biomolecules, and multiple drugs can also be loaded on the same MNP. MNPs have been mainly employed as anticancer agents [11] or to counteract infections, either bacterial or viral [12]. Due to their small size MNPs (in particular Ag and Au) can also perform a passive targeting of cancer cells, i.e., reaching them more easily due to the leakiness of the vasculature growing within the tumour mass. Moreover, MNPs, in particular Ag NPs, are extremely reactive and can interact with many cellular components through the induction of ROS, leading to mitochondrial damage and eventually apoptosis. Although this effect could be quite desirable in cancer therapy, it should be definitely avoided in the interaction with normal cells, in this case the enterocytes [13][14].

Polymeric NPs can be of synthetic origin but also made of natural substances, such as polysaccharides; in a biological setting these latter ones are obviously preferred, since they do not provoke or produce toxic effects. Among the natural polymers, the most commonly used are polysaccharides including chitosan, hyaluronic acid (HA), alginates, etc.; due to their chemical structure, they present both hydrophilic groups (necessary for the solubility in water) but also residues able to interact with biological membranes, as further discussed below [15] (Figure 2).



**Figure 2.** Main nanoparticles functionalization and their intestinal transport. From the left: Schematic representation of mucus penetrating NPs (SDS/PEG), able to penetrate the mucus layer and directly pass through the blood flow. Receptor binding NPs (DOA/PGA/folate/HA/albumin/Fc-fragment) able to bind the cell surface using the ligand-receptor binding and are then internalized in endocytic vesicles and released in the systemic circulation. CPP (cell penetrating peptides) are able to undergo both receptor binding internalization and direct translocation. Muco-adhesive NPs and tight junction opening NPs (chitosan) are able to be retained in the mucus layer, and then undergo transcellular passage or pass through the opened tight junction. Charge-convertible peptides are able to evade the lysosomal degradation using the proton sponge mechanism. SDS: sodium dodecyl sulphate; PEG: polyethylene glycol; CS: chondroitin sulphate; DOA: deoxycholic acid; PGA: poly-glutamic acid; HA: hyaluronic acid. The image was created with the use of Servier Medical Art modified templates, licensed under a Creative Common Attribution 3.0 Unported License (<https://smart.servier.com>, accessed on 19 February 2022).

### 1.3. Nanoparticles—Intestine Interaction

The gastrointestinal tract, as mentioned, represents a harsh environment for drug delivery, since the active component has to survive the low pH but also cross the intestinal barrier, i.e., the mucus layers and the enterocytes. For this reason, NPs can be functionalized, in order to prevent the attack of pH and enzymes or to favour their passage through the intestine in order to have a systemic effect.

The protection from low pH can use polymers that have been already employed in the drug industry, such as all the different formulations of the Eudragit<sup>®</sup>, which can be dissolved above specific pHs, thus allowing the drug delivery in the various regions of the gastrointestinal tract, i.e., small intestine or colon [16]. Other molecules can be used to

create a shell, and among them there is alginate, which can provide resistance to low pH and, if associated with other molecules, also to enzyme digestion. Alginate is a linear anionic polymer derived from brown seaweed consisting of  $\beta$ -D-mannuronic acid (M) and  $\alpha$ -L-guluronic acid (G) linked by glycosidic bonds [17]. The monomer composition can affect the general structure of alginate, making it more rigid and with larger pores (thus with a higher release of the drug) or more soft with smaller pores according to a high or low presence of G blocks, respectively [18][19]. Alginate also responds to pH, and researchers have developed specific emulsions able to swell or shrink according to the environmental pH [20]; in particular, the presence of low pH will maintain alginate in a stable hydrogel form, thus protecting the associated drug, whereas neutral pH will cause the hydrogel dissolution and the release of the active compound.

Since mucus covers the apical part of the enterocytes, the NPs need to attach to it, but also be able to cross the two different layers in order to reach the enterocytes. In order to design NPs able to deliver their load, several mucus characteristics should be kept in mind; mucins, the main mucus component, contain glycosylated section with negative charges that could bind positively charged NPs, trapping them. Moreover, some part of these proteins are hydrophobic, and this strongly reduces the transport of hydrophobic particles, such as PLGA and polystyrene (PS), which are quite used as NPs. Last but not least, mucins create a sieve-like structure, thus the size of the NPs should also be kept to a minimum.

Substances employed in NPs can interact with the mucus either increasing NPs ability to adhere to it or augmenting their penetration.

One of the most used molecules belonging to the first group is chitosan, a nontoxic, cationic polysaccharide derived from chitin (naturally obtained from marine organisms) which has been approved by FDA for biomedical applications. It is biocompatible, biodegradable, and non-toxic; in addition the presence in its sequence of positively-charged N-acetyl glucosamine units favours the binding to the mucus [15]. Chitosan is also rich in hydroxyl, amino, and carboxyl groups, which allow a series of chemical modifications that can increase, for example, its water solubility or its stability [21]. In addition to mucus adhesion, chitosan can induce the opening of the tight junctions, as demonstrated by alteration in the trans-epithelial resistance and by electron microscopy [22][23][24][25]; these opening has been demonstrated to be reversible, at least in in vitro experiments on Caco2 cells, and associated with a redistribution of claudin-4, an essential component of tight junctions [26]. This effect is mediated by a direct interaction between positively charged chitosan and negatively charged integrin  $\alpha\beta3$ , fact which causes a conformational change of this latter proteins that aggregate along cell boundaries, reorganization of F-actin and a downregulation of claudin-4 [27].

Another molecule widely used in NPs that is able to increase mucus binding is HA, a natural linear glycosaminoglycan, biocompatible, and biodegradable through the action of the host enzymes. Its ability to bind to biological substrates is mediated by the presence of abundant COOH groups [28] and also by the molecular weight ( $M_w$ ), with a higher efficiency of the adhesion being observed in presence of a lower  $M_w$  [29].

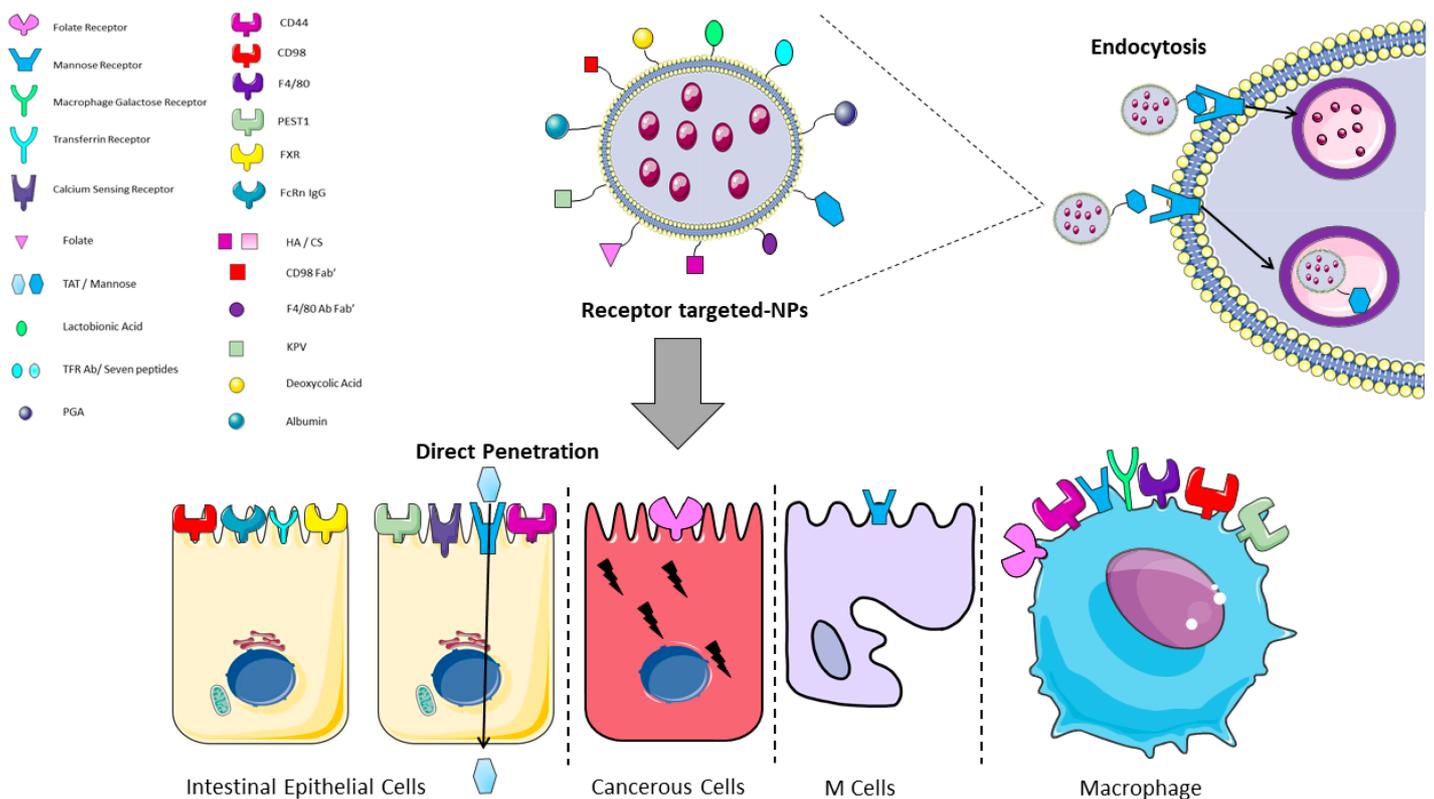
The most used substance which helps the passage of NPs through the mucus is polyethylene glycol (PEG) [30]; the addition of this component can change, even in an important manner, the ability of the NPs to cross the mucus layer; Xu et al. observed that, in the case of PLGA NPs, a percentage of at least 5% is necessary to reduce the interaction with mucus, and higher PEG concentrations improved the passage [30]. This could be explained by a “shielding effect” by the PEG molecules, which prevented the interactions between mucin proteins and the NPs core. These data were obtained using a 5 kDa PEG molecule and the authors used as in vivo model mouse vaginal mucosa; the situation could be totally different in the intestine, and also the PEG size could influence the mucus penetration, as demonstrated by Inchaurreaga et al., who analysed the effect of different  $M_w$  PEGs on the ability of NPs to reach the enterocytes [31]. Interestingly, better results were obtained using PEG 2000 or 6000, whereas the 10,000 molecule showed a worse performance. Other polymers have been developed, such as poly-N-2-hydroxypropyl methacrylamide (HPMA), a water-soluble polymer with excellent mucus-permeating properties similar to PEG. This compound can dissociate from chitosan NPs during the passage in the mucus, as demonstrated by Liu M et al., but it can also cause an opening of the tight junctions [32].

To increase the passage through the intestinal barrier there are, in theory, two possibilities, i.e., cause a loosening of the tight junction or increase the uptake of the NPs by the M cells or the enterocytes. Several compounds can actually interfere with the proteins that are forming the junctions sealing off the intestinal content, such as occludins, claudins, and integrins. Natural food compounds can have an effect on the permeability of in vitro systems, as reviewed by Kosińska et al., and, more recently, demonstrated by Haasbroek et al. that focused their attention on aloe extracts that were able to decrease trans-epithelial resistance in a trans-well Caco<sub>2</sub> cell model and increase the passage of 4 kDa dextran [33][34]. Chen et al. developed an hydrogel able to adhere to the mucosa and, at the same time, to chelate calcium ions, which are essential for the maintenance of the junctions [35]. They tested these particles, carrying HbS antigen, in mice and were able to demonstrate a higher intestinal immune response compared to the usual vaccination route. Last, but not least, it should be remembered that bacteria causing gastrointestinal disorders are able to secrete toxins acting on the integrity of the tight junctions, causing a damage or a rearrangement of their protein components. Although this kind of intervention could cause the passage of a large quantity of the cargo drug through the barrier, it could be hazardous; for this reason synthetic peptides mimicking the effect of these toxins have been produced. In particular, AT-1002 is a hexamer peptide (FCIGRL) derived from zonula occludens toxin (ZOT) produced by *Vibrio cholera* [36]. This toxin is able to bind to a receptor present on the apical portion of the enterocytes, activate protein kinase C and cause a transitory disassemble of the tight junctions. It can be added to other NPs components, such as chitosan, as reported in a delivery system for insulin [37] that was able to obtain a good glycaemic control in diabetic rats. It must be kept in mind, however, that increasing the permeability of the junctions could also allow the passage of intestinal antigens; further studies on this aspect must be performed in vivo, although a paper by Sonaje et al. failed to detect an increased passage of LPS following chitosan NPs administration [38].

The passage through cells, either M or enterocytes, could be increased by adding to the NPs peptides that are able to interact with specific receptors present of the apical part of the cells. As regards M cells, studies in mice demonstrated that various types of lectins added to NPs can increase the uptake due to their ability to interact with cellular  $\alpha$ -L-fucose moieties [39][40]; unfortunately, these specific moieties are not present on human cells, thus NPs

should be functionalized with other peptides. Among them, the Gly-Arg-Gly-Asp-Ser (GRGDS) pentapeptide could be a good candidate, since it binds B1 integrins, present also on human cells. Up to now, it has only been evaluated in a human cell model (Caco2 + Raji), and demonstrated able to increase the passage through Raji cells [41]. Last but not least the route through which NPs can reach other organs can be important in order to avoid the hepatic first pass; for this reason, NPs can be designed to use the lymphatic system, and this means that intestinal absorption should occur through M cells.

As regards enterocytes, several receptors have been described on the apical surface, and known enterocyte-targeting ligands include lectins, transferrin, vitamins, oligopeptides, and monoclonal antibody fragments as summarized in **Table 1**. The cell entry could also occur through the action of some specific peptides, identified as cell-penetrating peptides (CPPs), that are able to allow the attachment and penetration of the NPs (such as Trans-Activator of Transcription (TAT)), or through a classical receptor-mediated endocytotic process (**Table 1** and **Figure 2** and **Figure 3**) [42].



**Figure 3.** Graphical representation of receptor/ligand NPs interactions in the intestine. Functionalized receptor-binding NPs are able to bind the cell membrane through the binding of the NP (ligand) to the receptor on the cell surface and then to undergo the endocytotic process. Trans-Activator of Transcription (TAT) is the only mentioned ligand that undergoes direct penetration. CS: chondroitin sulphate; FXR: farnesoid X receptor; HA: hyaluronic acid; KPV: lysine-proline-valine; PEST1: peptide transporter1; PGA: polyglutamic acid; TFR: transferrin receptor. The image was created with the use of Servier Medical Art modified templates, licensed under a Creative Common Attribution 3.0 Unported License (<https://smart.servier.com>, accessed on 19 February 2022).

**Table 1.** Main receptor-ligand interactions used for NPs functionalization in the intestine.

Reference	Receptor	Ligand	Cell Type Expression	Direct Penetration	Endocytosis
Hua S 2020 <a href="#">[43]</a>	Mannose Receptor	Mannose	Macrophages, Enterocytes, M cells	No	Yes
Tian 2018 <a href="#">[44]</a>	CD44	HA/CS	Macrophages, Intestinal Epithelial Cells	No	Yes
Xiao, 2018 <a href="#">[45]</a>	CD98	CD98 Fab'/single chain CD98 Ab	Intestinal Epithelial Cells, Macrophages	No	Yes
Peng L, 2021 <a href="#">[46]</a>	F4/80	F4/80 Ab Fab'	Macrophages	No	Yes
Liu W, 2018 <a href="#">[47]</a>	Macrophage Galactose Receptor	Lactobionic Acid	Macrophages	No	Yes
Xi Z 2022, Álvarez-González, 2020 <a href="#">[48][49]</a>	Folate Receptor	Folate	Macrophages, Epithelial Cancer Cells	No	Yes
Yong, 2019 <a href="#">[50]</a>	Transferrin Receptor	TFR Ab/Seven peptides	Intestinal Epithelial Cells	No	Yes
Zhang W, 2021 <a href="#">[51]</a>	PEST1	KPV	Macrophages, Intestinal Epithelial Cells	No	Yes
Liu L, 2018 <a href="#">[52]</a>	Mannose Receptor	TAT	Intestinal Epithelial Cells, Macrophages	Yes	No
Azevedo, 2020 <a href="#">[53]</a>	FcRn IgG	Albumin	Intestinal Epithelial Cells	No	Yes
Huang X, 2021 <a href="#">[54]</a>	FXR	Deoxycolic Acid	Intestinal Epithelial Cells	No	Yes
Urmi, 2019 <a href="#">[55]</a>	Calcium Sensing Receptor	PGA	Intestinal Epithelial Cells	No	Yes

Various bacteria-derived peptides can also be used, since they are recognized by TLR4, but these peptides carry the risk of activating the intestinal immune system. Li et al. recently evaluated the possibility of employing a non-toxic form of *Pseudomonas aeruginosa* exotoxin A associated with alginate/chitosan particles; the presence of the exotoxin favoured the trans-EPICs and the *Nive* receptor. In addition, all these NPs, to KPVs showed that the *Nive*-based peptide transporter, *Nive* have a very important role in intestinal activation of response, *Nive* at least for the *Nive* and their

cargos should be vehiculated to the basolateral side of the cells, thus requiring transcytosis (**Figure 1b** and **Figure 2**). This step should not be regarded as trivial, since there is the risk that the fusion of endocytotic vesicles with lysosomes damages the NPs, both in its structure or inactivating the carried drug. For this reason, some researchers developed NPs associated with charge-convertible peptides [48][57]. The presence of these components allows the NPs to survive the acidic pH of late endosomes, since they can act as “sponge” for H<sup>+</sup> ions. Last, but not least, the NPs have to cross the basolateral membranes of enterocytes and be released into the circulation; interestingly, Xi et al. observed that the addition of the charge-convertible peptides increased the interaction of the NPs with the proton-coupled oligopeptide transporter present in the basolateral membrane, thus boosting the exocytosis [48]. The interactions between NPs and the intestine could be subdivided in three main categories, i.e., the use of NPs to deliver systemic drugs, which implies the passage through the intestinal barrier and reaching the blood or lymphatic flow, NPs as carriers for drugs that should act on the intestinal mucosa or the “involuntary” interaction due to NPs used as food additives. In this entry, researchers are going to discuss some examples in each category, pointing out advantages and pitfalls.

## 2. Nanoparticles for Systemic Drug Delivery

The possibility to deliver drugs through the intestinal route rather than using other more invasive ways has been quite captivating for various pharma products, in particular anti-cancer drugs or vaccines. However, due to the large number of the employed molecules and the great differences among the NPs, researchers decided to focus on a single molecule tackling another disorder, i.e., insulin. Due to the high social impact of diabetes and the need to administer the drug few times during the day, several groups throughout the world have been involved in the development of NPs able to provide the oral delivery of recombinant insulin.

The most used cores for NPs are polymers, either natural or synthetic ones; among the natural polymers there is chitosan, either alone or in combination with alginate; these NPs have some characteristics that make them suitable for insulin delivery, such as biodegradability, nontoxicity, muco-adhesiveness, and low immunogenicity, as previously described (see **Table 2**). Other employed natural polymers are HA, albumin, starch (amylose), zein, and lignin, as reported in **Table 2**.

**Table 2.** Summary of the different NPs and functionalization for the delivery of insulin.

Reference	Core of the NPs	Further Functionalization for Adhesion/Passage	Release Control	Reduces Glycaemia in Animal Model
Li L 2017 [58]	Chitosan	CPP	n/a	Yes
Wu J-Z 2017 [59]	diethylene glycol dimethacrylate	n/a	phenylboronic acid	Yes
Alfatama 2018 [60]	Alginate/Chitosan	n/a	n/a	Yes

Reference	Core of the NPs	Further Functionalization for Adhesion/Passage	Release Control	Reduces Glycaemia in Animal Model
Czuba 2018 <a href="#">[61]</a>	PLGA	SDS	n/a	Yes
Fan 2018 <a href="#">[62]</a>	Chitosan	Deoxycholic acid	n/a	Yes
Hou 2018 <a href="#">[63]</a>	Mesoporous silica nanoparticle	n/a	phenylboronic acid	Yes
Jamshidi 2018 <a href="#">[64]</a>	Chitosan	n/a	n/a	Yes
Ji N 2018 <a href="#">[65]</a>	Zein + CSA	n/a	n/a	n/a
Liu L 2018 <a href="#">[52]</a>	Chitosan + hydrogel	n/a	n/a	Yes
Song M 2018 <a href="#">[66]</a>	Cyclodextrin/chitosan	n/a	n/a	Yes
Tian 2018 <a href="#">[44]</a>	Chitosan/hyaluronic acid	n/a	n/a	Yes
Wang W 2018 <a href="#">[67]</a>	Polyamidoamine/polyaspartic acid/phenylboronic acid/PEG	PEG	phenylboronic acid	Yes
Xu Y 2018 <a href="#">[68]</a>	solid lipid nanoparticle + endosomal escape agent	n/a	n/a	Yes
Zhang Y 2018 <a href="#">[69]</a>	hydroxyapatite	PEG	n/a	Yes
Zhang L. 2018 <a href="#">[70]</a>	PLGA + chitosan + alginate	n/a	pH dependent	Yes
Alsulays 2019 <a href="#">[71]</a>	Solid lipid nanoparticles	CPP	n/a	Yes
Guo 2019 <a href="#">[72]</a>	Chitosan	CPP	n/a	yes
Hu 2019 <a href="#">[73]</a>	phospholipids	n/a	n/a	Yes
Jamwal 2019 <a href="#">[74]</a>	dextran	n/a	Glucose oxidase	n/a
Ji 2019 <a href="#">[75]</a>	Chitosan/zein-carboxymethylated short-chain amylose	n/a	n/a	Yes
Mohammadpour 2019 <a href="#">[76]</a>	PLGA + chitosan	n/a	Glucose oxidase	Yes

Reference	Core of the NPs	Further Functionalization for Adhesion/Passage	Release Control	Reduces Glycaemia in Animal Model
Muntoni 2019 [77]	Lipid nanoparticles	n/a	n/a	Yes
Mudassir 2019 [78]	Methyl methacrylate/itaconic acid nanogels	n/a	pH dependent	Yes
Tsai 2019 [79]	Chitosan + fucoidan	n/a	pH dependent	n/a
Urimi 2019 [55]	Chitosan	<b>Polyglutamic acid</b>	n/a	Yes
Azevedo 2020 [53]	Albumin	n/a	n/a	Yes
Bai 2020 [80]	PLGA + glutamic acid conjugated amphiphilic dendrimer	n/a	n/a	Yes
Chai 2020 [81]	Poly (acrylamido phenylboronic acid)/sodium alginate	n/a	Cicloborate (Glucose sensing) and glucose oxidase	Yes
Chen Z 2020 [82]	Chitosan/Hyaluronic acid	<b>CPP</b>	n/a	Yes
Cheng 2020 [83]	Poly (n-butylcyanoacrylate)	<b>Ratio insulin/Poly (n-butylcyanoacrylate)</b>	Ratio insulin/Poly (n-butylcyanoacrylate)	Yes
Ding 2020 [84]	amphiphilic cholesterol-phosphate conjugate	n/a	pH dependent	Yes
Han X 2020 [85]	Zwitterionic micelles	<b>Betaine</b>	n/a	Yes
Jana 2020 [86]	hyaluronic acid	n/a	Glucose oxidase	n/a
Mumuni 2020 [87]	Chitosan/mucin	n/a	n/a	yes
Sladek 2020 [88]	Hyaluronic acid/chitosan	<b>Sucrose laurate</b>	n/a	Yes
Sudhakar 2020 [89]	Chitosan	n/a	pH dependent	Yes
Tan X 2020 [90]	Mesoporous silica	<b>PEG + CPP</b>	n/a	Yes
Wang T 2020 [91]	Lipid nanoparticles	n/a	n/a	Yes

Reference	Core of the NPs	Further Functionalization for Adhesion/Passage	Release Control	Reduces Glycaemia in Animal Model
Zhou S 2020 <a href="#">[92]</a>	Chitosan	PC6	pH dependent	Yes
Zhou X 2020 <a href="#">[93]</a>	Alginate	n/a	Glucose oxidase	Yes
Zhou Y 2020 <a href="#">[94]</a>	FeCl <sub>3</sub> ·6H <sub>2</sub> O + BTC	SDS	pH dependent	Yes
Bao X 2021 <a href="#">[95]</a>	Zein/casein-dextran	Cholic acid	n/a	Yes
Benyettou 2021 <a href="#">[96]</a>	Nanoscale imine-linked covalent organic frameworks	n/a	pH dependent	Yes
Cui 2021 <a href="#">[97]</a>	Chitosan + Hyaluronic acid	Biotin	n/a	Yes
Huang X 2021 <a href="#">[54]</a>	layered double hydroxide nanoparticle + hyaluronic acid	Deoxycholic acid	n/a	Yes
Kim WJ 2021 <a href="#">[98]</a>	POSS-APBA	n/a	phenylboronic acid	n/a
Li H 2021 <a href="#">[99]</a>	polyphosphoesters-based copolymer	n/a	phenylboronic acid	Yes
Li J 2021 <a href="#">[100]</a>	Alginate/chitosan	n/a	pH dependent	Yes
Liu X 2021 <a href="#">[101]</a>	PLGA/PEG	Angiopep-2	n/a	Yes
Qin 2021 <a href="#">[102]</a>	Mesoporous silica + Alginate + Boronic acid Mesoporous silica + Chitosan + boronic acid	n/a	phenylboronic acid	Yes
Rao 2021 <a href="#">[103]</a>	Porous silicon nanoparticles	Zwitterionic dodecyl sulfobetaine	n/a	Yes
Volpatti 2021 <a href="#">[104]</a>	Polycation	n/a	Glucose oxidase	Yes
Wang W 2021 <a href="#">[105]</a>	PLGA	Chitosan + Cholic acid	n/a	Yes
Zhang Y 2021 <a href="#">[106]</a>	mesoporous silica nanoparticles	CPP	n/a <a href="#">[113]</a>	Yes
Fu 2022 <a href="#">[107]</a>	Glycopolymer	n/a	phenylboronic acid	Yes
Li J 2022 <a href="#">[108]</a>	PLGA-Hyd-PEG	PEG	n/a	Yes

tics of the s regards npatibility, ported by olized by (PMAA), ave been employed for insulin delivery, using liposomes containing bile salts, such as sodium glycocholate (SGC), sodium taurocholate (STC), or sodium deoxycholate (SDC). All the described polymers and liposomes were able to generate NPs with a high rate of incorporation of insulin and to protect the drug from the degradation that could

Reference	Core of the NPs	Further Functionalization for Adhesion/Passage	Release Control	Reduces Glycaemia in Animal Model	added to
Martins 2022 [109]	Lignin-encapsulated silicon	Fc fragment of IgG	pH dependent	n/a	episodes.
Reboredo 2022 [110]	Zein	PEG	n/a	Yes	le insulin
Rohra 2022 [111] [114]	Gold nanoparticle-encapsulated zeolitic imidazolate framework-8	n/a	Glucose oxidase	n/a	chemical stems are
Xi Z 2022 [48]	PLGA/PEG	PEG, folate and charge-convertible tripeptide	n/a	Yes	is of $\beta$ -D- rs the pH apsulated the same et al. [81].
Xu 2022 [112]	konjac glucomannan/concanavalin A	n/a	Glucose sensing	Yes	irst one, it etween its increases

causing the release of insulin. In the second mechanism, called competitive, glucose displaces the drug that was bound to PBA, thus causing its release [115].

Most recent articles were considered (starting from 2017). APBA: 3-Aminophenylboronic acid monohydrate; BTC;

1,3,5-Benzenetricarboxylic acid; CPP: cell-penetrating peptides; CSA: Carboxymethylated Short-Chain Amylose; Last, but not least, these NPs must be able to provide an in vivo response; although this demonstration has been provided in animal models, as reported in Table 2, trials in humans are still under way (as discussed below), thus, (3,4-epoxycyclohexyl)ethyl]-heptaisobutyl substituted. an accurate evaluation of these data will be necessary before these NPs can be moved to clinic.

## 3. Nanoparticles with Intestinal Targets

### 3.1. Inflammatory Bowel Diseases

IBD, which include both Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders characterized by mucosal immune system dysregulation, which has an impact in the small intestine and colon. In recent decades, the necessity to conceive a novel therapeutic approach to IBD treatment has led to the increased interest in nanobased drug delivery systems [116][117][118]. This is due to the many side effects caused by the commonly used drugs to treat chronic inflammatory disorders, such as IBD. In particular, 5-aminosalicylates (5-ASA), antibiotics, and corticosteroids can cause, in the long-term, several side effects, including bone damage, such as the steroid-induced necrosis of the femoral head. Genome-wide association studies have demonstrated that genetic background is only one of the factors involved in the pathogenesis of the disease together with the environmental ones. The recent advances in understanding the pathways involved in the development of IBD have allowed to provide some more therapies, but since the exact cause is not completely understood, there is currently no cure tackling the primum movens of the disease. However, even classical drugs used to treat IBD could take advantage of new-targeted delivery systems that give the possibility to load drugs, natural compounds, antibodies, and other biological compounds inside functionalized NPs able to reach the colon. On the other hand, as described by Hartwig et al. [119], researchers must consider that the research on NPs was usually performed considering

colonic drug delivery in healthy individuals and not in a pathological condition, so the data should be regarded with caution in IBD patients. In fact, these individuals have important changes in colon microbiota composition and pH mean values, in addition to the diarrhoea that may affect the gastrointestinal transit time.

### 3.2. Nanoparticles Loading Drugs

Drugs available to treat IBD, such as Budesonide or Prednisolone, could have better efficacy and less side effects if properly conveyed, since a targeted delivery could, in theory, allow to reduce the total amount of drug administered to the patient. Naeem et al. designed a system in which budesonide loading-PLGA NPs were covered by Eudragit®s100, thus generating microparticles (NPinMP). Their findings showed that the orally delivered NPinMP in a mouse model of DSS-induced colitis was able to reduce the number of macrophages and neutrophils assessed by immunofluorescence imaging, reduce TNF $\alpha$  serum levels, and cause a restoration of normal colon length. This treatment was superior to the use of NPs alone, which failed to significantly mitigate inflammation; these data can be explained by the better protection through the gastrointestinal tract provided by the double coating of the drug, which allowed a higher quantity of budesonide to be released in the colon [120]. Zhou et al. created a negatively charged Prednisolone-loading nanogel with a high affinity for the damaged colon tissue due to the positive charges located at the inflamed intestinal site. The persistence of this NPs administered by enema in the large intestine was able to provide, through the gradual release, a reduction in inflammatory parameters in a TNBS-induced colitis rat model [121]. Patients with IBD (in particular UC) can also combine the oral treatment with the enema one to achieve better effectiveness. Date et al., tested both nano-suspensions (NS) and micro-suspensions (MS) of budesonide, embedded in an inert mucus substance (Pluronic f127) for the in vivo enema treatment. The particles were tested in TNBS-induced UC mouse model, demonstrating that both formulations were able to restore the colon length and the weight loss. However, the NS showed a better efficacy in decreasing the inflammatory state of the colon, significantly lowering the number of colon-infiltrating monocytes and the levels of pro-inflammatory cytokines within the tissue [122]. In another study, the authors used different drugs (budesonide, vancomycin, and GM-CSF) loaded in NPs composed of human serum albumin covered with heparin; this second coating was chosen since, in theory, it should be able to selectively bind to the inflamed colon area thanks to the negative charges of its glycosaminoglycan molecule. The formulation was delivered by enema in DSS- induced colitis and showed that the NPs can be efficiently loaded with different drugs at the same time. The authors also observed that smaller particles were better retained in a healthy colon, whereas larger particles preferred the binding in the inflamed area, obtaining a reduction in the inflammatory parameters [123]. Lee et al. used Dexamethasone (Dexa) to create spherical polymeric nano-constructs, composed by PLGA and Dexa core and then covered with PEG, for the treatment of IBD. These NPs were injected performing an intravenous infusion to a mouse model of UC. The near infrared imaging results demonstrated the powerful anti-inflammatory action together with the rapid intracellular release of the NPs [124]. Although i.v. administration could be extremely effective, its use in everyday treatment of IBD patients results very difficult, and this kind of approach should be reserved for biologicals.

Ceria NPs (Ce NPs) are defined as nanozymes since they behave as enzymes with the ability of scavenging multiple ROS types, thus providing anti-redox and anti-inflammatory activity [125]. These nanozymes can exist in

both reduced ( $Ce^{3+}$ ) and oxidized ( $Ce^{4+}$ ) state, mimicking, respectively, catalase and superoxide dismutase enzyme activity. In the work of Zhao et al., PEG-loaded Ce NPs were administered in a mouse model of UC, and showed an important reduction in colonic inflammation, as demonstrated by histology and cytokine analysis [125]. In this regard, in a report by Asgharzade et al., Ce NPs were used to deliver Sulfasalazine [126]; Sulfasalazine is the drug resulting from the combination of a sulphonamide and salicylic acid, that are released after the ingestion. Its main mechanism of action includes intrinsic anti-inflammatory and anti-redox activities, and the important reduction in iNOS levels.

In a preclinical mouse model of DSS-induced colitis, these particles improved the disease activity index, as well as the histopathological score, and upregulated antioxidant molecules, such as glutathione [126]. In another work performed by Ahmada et al., Sulfasalazine was encapsulated in gelatin NPs and was then coated with Eudragit®s100. The nanodrug was then orally delivered to mice affected by UC and tested in a cellular model of Caco2 treated with DSS. The major protective effect was observed in 5-ASA NPs compared to the free drug, with an improvement at the histological level, increase in colon length, and decrease in serum inflammatory markers [127]. A model of intestinal organoid has been proposed for the study of IBD, conveying PLGA NPs covered with alginate or chitosan and loaded with 5-ASA. In particular, the alginate and chitosan coating negatively or positively charged the NPs. As expected, chitosan-covered NPs were preferentially transported through the epithelium to the intestinal organoid lumen [128].

Interestingly, the possible application of drugs not currently used to treat IBD, delivered in form of NPs, could open other possibilities in the treatment of the disease. Some of these drugs have a role in the modulation of the inflammatory state, such as Isoniazid (INH), an anti-tuberculosis drug known to have important anti-inflammatory actions and a structure similar to COX II inhibitors. The agent was entrapped into an enteric polymer Eudragit®s100, that was degraded at colon pH 7. In the DSS-induced colitis in mice, the comparison of the effect of the free drug and the drug-loaded NPs, assessed by H&E staining, revealed the restorative effect of the NPs-loaded with INH as compared to the free drug. In addition, the authors also demonstrated a possible synergistic effect of the nanodrug in combination with 5-ASA [129]. Another example is Raloxifene, an anti-cancer drug that modulates the estrogen receptor; Greish et al. proved its inhibitory effect on the pathway of NF- $\kappa$ B, a central player able to regulate the production of inflammatory cytokines in IBD. Their report compared the use of the free drug with the drug loaded on PS co-maleic acid micelles, testing them on in vitro and in vivo IBD models. Both formulations were able to induce a protective effect downregulating the NF- $\kappa$ B-dependent signalling pathway, even though the NPs-associated drugs had a major inhibiting power, particularly in lowering the production of IL-6 and TNF $\alpha$  [130]. Cai et al. studied a pH responsive system based on the administration of Tacrolimus, a calcineurin inhibitor that regulates the expression IL-2 and T cells signalling. The drug was loaded onto chitosan NPs functionalized with tripolyphosphate (TPP), a polyanion linked together by crosslinking, HA (with high affinity for the CD44 receptors), and Eudragit®s100 as enteric coating material. In vivo, their experiments suggested that the orally delivered NPs were able to restore colon length, reduce histological damage and prevent the development of the inflammatory cascade typical of IBD [131]. Antibiotics can also have a role in IBD by changing the microbiota composition, which could be altered in this disease; moreover, a subsequent targeted supplementation could help to restore a normal microbiota diversity. One example is Rifaximin a non-systemic antibiotic with antimicrobial

capacity, which was loaded on tamarind gum NPs. These NPs were able to resist the degradation of the upper intestinal tract and showed a mucus adhesive capacity in the colon, allowing a prolonged release of the loaded drug. This experiment was carried out on Wistar rats with TNBS-induced colitis showing that these NPs were able to improve the colon length and decrease the serum levels of inflammatory cytokines as compared to the not-treated rats [132].

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