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Review

Impact of Surface Design and Coating on The Efficacy of Nano-Carriers as Drug Delivery Systems: A Review

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ABSTRACT

The bioavailability of poorly soluble medications can be greatly improved by the use of nanocarriers (NCs) where; loading of drugs within NCs could improve the solubility, prevent degradation through enzymes of GIT and enhance the passage crosswise the gel mucus layer and absorption membrane. The surface chemistry of most of nanocarriers greatly affects all properties of NCs, specifically, food interaction, diffusion behavior through the gel mucus layer, and providence on the absorption membrane. Bioinert surfaces greatly decrease the interaction with GI fluids. Adhesive surfaces offer near connection with the mucosa of GIT and absorption. Moreover, charge-converting surfaces facilitate targeted drug release by shifting their zeta potential from negative to positive at absorption membranes. In addition, Active surfaces may cleave mucus glycoproteins. In this review, we deliberate the different types of surface modification of NCs and their impact on the efficacy of NCs as successful drug delivery systems. Moreover, the different techniques applied for NCs surface modifications through the use of diverse biomaterials to change their physicochemical characteristics, pharmacokinetic qualities, and pharmacological activity. Surface engineering may be utilized by undercoating the NCs either through the use of non-covalent bonds, covalent bonds, or special techniques.

Keywords: Nanocarriers, Surface-modification, Bioinert surfaces, Active surfaces.

Introduction

Novel nano-carriers (NCs), as drug delivery systems, show a promising solution to traditional dosage forms' problems (1). NCs are able to overcome many obstacles of the traditional dosage forms by targeting desired sites, increasing blood circulation time, and improving drug pharmacokinetic properties, water solubility, and bioavailability which leads to the development of NCs loaded drugs showing high efficacy with minimal adverse effects (1–3). Besides, NCs can transport drugs well crosswise many body barriers and can prolong their residence times (4). Moreover, they are capable of sustaining drug delivery and encouraging drug passage transversely the absorption membrane (2,5). Among the numerous numbers of the developed vectors are lipid-based nanocarriers like solid lipid nanocarriers (SLN), nanostructured lipid carriers (NLC), liposomes and self-emulsifying nanocarriers, nano-emulsion, organic/inorganic nanocarriers and polymeric nanocarriers (2,6). Due to this wide versatility, NCs are favored for their nanosized range and their high drug loading capacities for hydrophilic and lipophilic drugs, high shelf-life stability (5).

Despite these advantages, NCs suffer from some limitations as they can be quickly eliminated by the reticuloendothelial system and their wide biodistribution (1,7–9). Therefore, addressing NCs issues become of interest in current research to reach an efficient drug delivery. Hence, the approach of surface design of nano-carriers established a basic role in improving intact NCs surfaces for enhancing drug efficacy and reducing their un-desired effects(1,10). Surface functionalization of nanocarriers was performed according to several criteria including the properties of nanocarrier surfaces and the types of coating materials. Countless number of ligands as polysaccharides, oligonucleotides, proteins, polymers, and antibodies have been utilized for disease investigation and treatment via an active targeting strategy that ensures high drug internalization to specific diseased sites with controlled release of drugs (1,11,12). Additionally, surface modification of nanocarriers was able to extend the blood circulation time of nanocarriers by escaping from macrophages to attain target recognition and localization(13). Surface engineering of nanocarriers can be performed by different techniques either via covalent/non-covalent bonding or deposition of additional layers on the surface of nanocarriers (1). Thus, such applications are being widely established in the treatment of many diseases such as cancer (14), viral infections (15), cerebrovascular (16), and immunological diseases (1).

Eventually, within this review we will focus on advances in surface engineering nanocarriers, here we will focus on different techniques that had been utilized for nanocarriers' coating, the most suitable types of nanocarrier coats, and will describe the effect of surface modifications on nanocarriers ability for increasing drug targeting and efficacy.

Types of nanocarrier surfaces coats

1-Bioinert surfaces

The stability of uncoated nanocarriers is being affected unintendedly by body fluids as GI content. Particularly, for lipidic based nanocarriers and emulsified systems that are composed of different types of phospholipids and triglycerides may suffer from a decrease in absorption and an increase in drug leakage due to the interaction of the intact nanocarriers with the lipases leading to enzymatic degradation of nanocarriers (17,18). In order to tackle this problem bioinert surface is being established using several strategies as will be discussed (2).

1.1 Zwitter-ion surfaces

Electric neutral zwitterion is made up of cation and anion groups, as carboxybetaine (CB), sulfobetaine (SB) and phosphorylcholine (PC). Zwitter ions are often regarded very hydrophilic, biosafe, and inert to life (19). Cell membrane and mucus layers are able to be invaded by viruses due to their zwitterion surfaces (20). Mimic zwitterionic surface of viruses by decorating nanocarriers with anionic and cationic charges provides them with bioinert property which helps them to shield from body interactions by forming a stable solvation shell, interactions with ionic structures in the human body controlled by forming a high-density of super-hydrophilic shell formed due to the opposite charges on the surface (21). According to many reports, NCs made with zwitterions are compact and resistant to protein-binding, this might be a viable mucus penetration delivery method (19).

The nanoparticles (NPs) made of zwitterionic lipids, in contrast to the non-ionic PEGylated surface, have a surface characteristic akin to the phospholipid membrane of cells (19). Lipid-coated polymeric nanocarriers are beneficial for drug administration because they have a variety of flexible techniques, are simple to surface design, have a longer circulation half-life, are less cytotoxic, and have greater target selectivity. Natural phospholipids such as phosphatidylglycerol and phosphatidylcholine are frequently applied to make an effective coat on the surface of NCs. A membrane-like structure on NCs can be formed by phospholipids because of their amphiphilic

nature. Electrostatic attraction and hydrophobic interactions may lead to lipidic self-assembly on NCs surfaces (22). Lipid bilayers normally form thin, homogenous films around the nanoparticles. While, polymers and synthetic molecules, frequently result in coatings with heterogeneous shapes. As a result, following coating, the NPs' hydrodynamic diameter does not significantly alter. Additionally, as mentioned, the excellent uniformity of the coatings is a crucial element in preventing protein adsorption. The intended stabilizing effect of many polymers may not be realized due to the occurrence of areas of the surfaces of NP uncoated. On the other hand, it has been claimed that covering gold nanoparticles with a lipid bilayer (1,2-dimyristoyl-n-glycero-3-phosphocholine (1,2 DMPC) offers high stability of gold nanoparticles in different solutions (23). Further evidence suggested that negatively and positively charged nanoparticles were quickly removed, but zwitterionic gold-loaded nanoparticles showed longer blood circulation life-span and greater accumulation in tumor cells. Moreover, zwitterionic NPs' surface charge distribution may have an impact on absorption and biodistribution (23).

Amphoteric surfactants such as Dilauroyl phosphatidylcholine and polymers as polycarboxybetaine showed a higher diffusivity in mucus and satisfactory cellular uptake efficiency than PEG-coated NCs (19,24). Using inactive cationic or anionic polymers as chitosan/alginate, chitosan/chondroitin sulfate, and chitosan/carboxymethyldextran exhibit high mucus permeating properties, higher folds of diffusion ability (25–27). They have been extensively employed for a variety of purposes comprising implant coatings drug delivery systems and medical diagnosis (21).

1.2 Polyethylene glycol (PEG) surfaces

PEG is an adaptable and biocompatible polymer extensively used in the application of drug delivery and gene delivery. The usage of PEG on NCs surfaces is termed as “PEGylation”(1). The surface of a nanoparticle PEGylation reduces immunogenicity and prolongs systemic circulation by protecting nanoparticle surfaces against opsonization, aggregation, and phagocytosis (1). PEG coating is very beneficial in protecting NCs from body fluids and mucus by forming dense hydrated brush shielding. Poor protein binding and high penetration ability is being achieved in decorating NCs with PEG (28,29). Numerous studies using PEG with a chain length range from 0.3 to 0.5 kDa look to be enough to provide a muco- inert property. Nonetheless, PEG with a chain length of 2 kDa and 6 kDa coated NCs shows a high mucus penetrating properties

than 10 kDa. Studies revealed that excessive PEG densities have lower mucus penetration properties as they are entangled in the mucus network. Thus, utilizing a combination of short and long PEG chains along with 'hetero-brushes' PEG surfaces is being noted to improve bio-inertness properties (30,31). In recent studies, for improving the distribution and bioavailability of antibiotics, PEG was widely employed for modification of the surface of the antibiotic loaded NCs. PEGylation of ciprofloxacin loaded NLCs has been investigated and the stability of the formulation, penetration ability of the drug and drug distribution within ocular tissues has demonstrated the results that Ciprofloxacin was released significantly and continuously from PEGylated NLCs (30%) as opposed to un-coated NLCs (40%) and free drug (80%) at similar time intervals. Furthermore, NLCs PEGylation demonstrated two and three-fold greater corneal penetration than free and uncoated NCs. However, in vivo bioavailability tests revealed that PEGylated NLCs had a 2-fold better ocular bioavailability than un-coated NLCs. Also, it was declared that ciprofloxacin's trans-corneal penetration increased when the PEG coating's molecular weight rose from 2 to 10 kDa. According to this study, NLC PEGylation has the ability to regulate delivery and release of drugs from NCs, leading to improved corneal penetration and absorption. Researchers reported the needed usage of PEG with other polymers, in addition to investigating the potential of this mixture as a surface modification of antibacterial nanoparticles (1).

1.3 Poloxamer/Poloxamine surfaces

Block copolymers polyoxyethylene(PEO)–polyoxypropylene(PPO) (Pluronic F127) is considered an example of poloxamers used in coating nanoparticles to improve their mucus penetrating properties. The hydrophobic domain constitutes of poloxamers enables them to incorporate in hydrophobic NCs as lipid-based NCs and self-emulsifying NCs (32,33). Unfortunately, it is difficult to integrate and handle many biocompatible block polymers, so studies are performed hardly through which one parameter is varied. This variation influences on the characterization of the formed micelle like size, stability, entrapment ability, and release. For this reason, it may be hard to manipulate all the factors in a systemic way. Even though PPO-PEO proved to be assessable accordingly it has been utilized in many studies (34). Hu et al. achieved a high mucus penetrating property by coating poly-lactic-co-glycolic acid (PLGA)with different bio-inert coats, comparing the uncoated PLGA formula to the coated formula with zwitterion surface, PEG and Pluronic F127 showed that the high penetrating mucus property attained by zwitterion formula followed by PEG coat and Pluronic F127 (35). On the other hand, Poloxamine

forms a self-aggregated polymeric micelle due to its cationic charge, this micellar system exhibits a hydrophobic core that facilitates the entrapment of lipophilic drugs in addition to the outer shell formed of hydrophilic blocks (34,36). Recently, the transfection of plasmid DNA in cardiac and skeletal muscle has been established in vivo via Poloxamines (36).

1.4 Polyglycerol (PG) surfaces

Polyglycerol (PG), which has a lot of OH groups on the PEG main structure, is anticipated to have a better ability to avoid the adsorption of protein. Actually, it has been shown that PG has comparable or even greater protein resistance than PEG to proteins such as fibrinogen, lysozyme, albumin, and pepsin (37). Superior hydration and higher hydrophilic property are being expressed via utilizing polyglycerol (PG) surfaces. Its hydroxyl structure is allowed to be formed in linear and branched shapes (38). Bio-inert property has been studied by comparing different chain lengths of PEG and PG coated formulae declaring that bio-inert character increases in the following order: unmodified < low PEG < medium PEG < low PG < medium PG < high PG. consequently, 1.5 kDa chain length appeared to be adequate in the prevention of surface-proteins interactions (37,39,40). Furthermore, Oxygen radicles that are responsible for the decomposition of many drugs and hypersensitivity reactions showed to be less eminent by PGs (41). Zouy et al. quantitatively compared the PG- and PEG-functionalized NPs in protein corona formation and macrophage uptake in order to fully explore the potential of PG as a substitute for PEG. The results made it clear that PG resists protein adsorption and macrophage uptake much more effectively than PEG. (37).

2- Adhesive surfaces

The conception of muco-inert surfaces NCs was to bring NCs close to the absorption membrane, wherever it may bind to epithelial cells and supply an enhanced internalization drug character. Alternately, muco-adhesive NCs surfaces are assumed to stay attached to the layer of mucus for extended release of drugs in constant concentration near to the membrane. Therefore, the pattern of modeling adhesive surfaces instead of bioinert surfaces is supposed to be favorable, especially in the oral delivery route (42). A great number of in vivo studies are been carried out to investigate these two strategies. Different binding modes of NCs mucoadhesive substances were furnished in such ways, adhesiveness could be achieved by chain entanglements or by bonding using either covalent (disulfide bonds) or non-covalent (hydrogen bond) formed between

NCs surfaces and mucus gel layer. From the components commonly used to form an adhesive NCs surface are polymers. Polymers are well known for their wide usage in either forming NCs or coating them using anionic, cationic (chitosan) or multivalent cations such as (Ca 2+, Mg2+, or Fe3+) units to form mucoadhesive surfaces. Despite their bifunctional property as muco-inert and mucoadhesive, muco-inert character obtained from the polymer is able to exceed their mucoadhesive character (43).

Formation of a polymer with more pronounced mucoadhesive properties using a whole anionic or whole cationic polymer is required. Rather, polymers possess multivalent cations uncommonly used for their unstable characteristics compared to thiolated polymers. For instance, thiolated chitosan and thiolated surfactants used for NCs coating are able to increase entrapped drug concentration in affected sites by enhancing the mucoadhesive property than un-coated areas (44–46).

Unfortunately, increasing the mucoadhesive character of NCs disliked as remaining for a long time on the mucus gel layer will certain its elimination in mucus turnover process. So, the ideal formed mucoadhesive NCs is that having ability to be closer to the epithelium layer. This technique was achieved by thiolated NCs that owned the potentiality of forming disulfide bonds with mucus glycoprotein enhancing the nanocarriers to get deeper into the cellular epithelium (47).

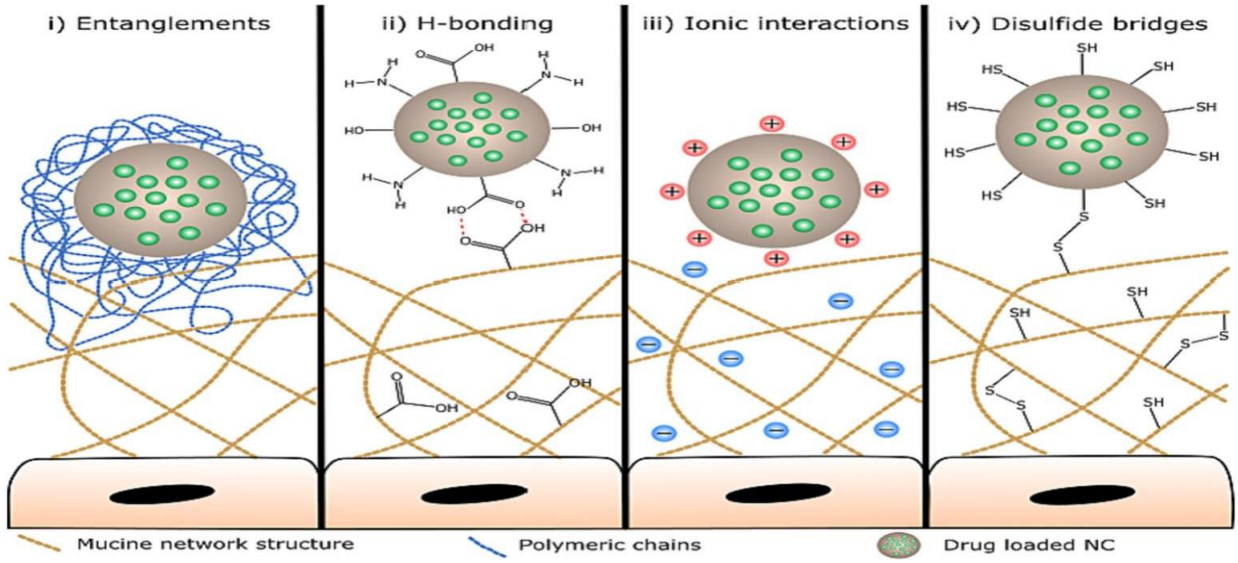

Fig. 1. Graphical representation of different mechanisms for the delivery of mucoadhesive properties (2).

As illustrated in Fig. 1 mucoadhesive properties can be achieved by different mechanistic pathways such as Entanglements, H-bonding, ionic interactions, and disulfide bridges.

4- Aptamers:

Aptamers are defined as three-dimensional secondary and tertiary structures that are single-stranded (ss) short oligonucleotides (6-30 kDa) that may interact with biological targets such as nucleic acids, transmembrane proteins, or sugars with great affinity and selectivity. Systematic evolution of ligands by exponential enrichment (SELEX), an in vitro selection method, is used to synthesize aptamers from an initial library of 1013–1016 randomly distributed single-strand ssDNA or ssRNA sequences. In this cell-based approach, a library of oligonucleotides is first incubated with the desired target, and the oligonucleotides with the highest affinity are then selected and purified. The simplicity of isolation, smaller size, greater ratio of target accumulation, absence of immunogenicity, and increased in vivo stability of aptamers make them preferable to conventional antibodies. An aptamer's molecular weight is typically between 6 and 30 kDa, significantly lower than an antibody's molecular weight (150 kDa), which frequently results in superior tumor absorption kinetics. An aptamer also costs less to produce and is more stable in biological fluids than a protein. Although their circulation half-life is limited in comparison to that of an antibody due to the absence of a fragment crystallizable region (Fc domain), but this is not a significant barrier when employing the aptamer as a targeted ligand (22). Thiol bonding enables the direct assembly of aptamers with thiol modifications onto the surface of plasmonic NPs. For example, by adding a 50-alkyl-thiol-modified S. aureus aptamer directly to the colloidal solution in the presence of sodium dodecyl sulfate, tris/borate/EDTA buffer (TBE), and sodium chloride, 18 of 28 Ag NPs self-assembled onto the surface. In this instance, the aptamer surface modification preserved the colloidal integrity of the NCs, therefore further stabilizing agents were not required. The modified particles have been demonstrated to maintain their biorecognition abilities while remaining stable in serum and varieties of actual human fluids, including urine, blood, pleural effusion, and ascites (23).

5- Antibodies

A good target specificity and affinity make antibodies appealing as targeting ligands. High target recognition capabilities may be added to nanoparticles by coupling of polymer nanoparticles with antibodies. But for effective functionalization, a stable conjugation of the antibody to a

nanoparticle surface in the right orientation without aggregation is essential. An appropriate functional group is required to covalently attach the antibody to nanoparticles. The three functional groups that are most frequently employed in antibodies are amino (lysine), carboxy (glutamic acid and aspartic acid), and sulfhydryl (cysteine) (22).

It has also been explored how antibodies physically adhere to nanoparticle surfaces. In a recent work, researchers showed that, in contrast to nanoparticles that were chemically bonded to the antibody, pre-adsorption of antibodies on the surface of polymer nanoparticles resulted in effective targeting of nanocarrier. In that study, the protein corona created when nanoparticles were injected into a biological fluid had a considerable impact on the binding affinity of the antibody chemically attached to nanoparticles. On the other hand, proteins in the corona did not affect functionally adsorbed antibodies. For the purpose of nanoparticle functionalization, monoclonal antibodies (mAb) have been utilized to target a variety of markers and receptors found on cancer cells, including, the human epidermal growth factor receptor-2 (HER2), the v3 integrin, the prostate-specific membrane antigen (PSMA), and the CD20 antigen on B-cell lymphomas. However, the inclusion of full-length mAbs (150 kDa) might impact the nanoparticle's ability to penetrate tumors and can also cause an increase in macrophage absorption by allowing the Fc receptor (FcR) to be recognized. Antibody fragments like the single-chain variable fragment (scFv) and antigen-binding fragment (Fab) have been studied as targeted ligands to reduce these problems (22).

6. Absorption-enhancing surfaces

Enhancement of drug absorption from gastrointestinal mucosa can be done by using NCs through their interaction with epithelial cells in various mechanisms. Opening of tight junctions is one of these mechanisms or fusion with cellular membranes facilitating their entrance through endocytosis (48). Internalization of endocytosed NCs occurs by intracellular vesicles such as phagosomes, endosomes, or macropinosomes preventing them to access cytoplasm in a direct way (48).

6.1. Anionic surfaces

Tight junctions (TJs) are opened more easily through the use of anionic surfaces of NCs. For example, Carboxymethyl chitosan/chitosan nanocarriers having anionic surfaces extensively disintegrate TJs leading to more strong permeability if compared to similar nanovesicles carrying

positive charge on their surfaces. Another clear example, insulin bioavailability is significantly higher when administered in anionic surface nanocarriers (49).

6.2. Cationic surfaces

Regarding cationic polymers such as polyethyleneimine, chitosan, and trimethylated chitosan have proven efficacy in opening the TJs (50). Through opening TJs, enhanced permeation through the Caco-2 monolayer could be achieved and extensively enhanced by using chitosan-coated silica nanocarriers (2). The presence of cell-surface endocytosis receptor, heparin sulfate proteoglycan imparts a negative charge to cellular membranes (51). So, positively charged NCs can ionically attach to cellular membranes encouraging endocytosis through different stages as shown in Fig.2. Studies on non-phagocytic cell lines had proved that the uptake for positively charged NCs was greatly enhanced compared to anionic surfaces NCs. On another hand, no difference in cellular uptake on phagocytic cell lines was observed proving a cell-dependent cellular uptake mechanism (52). Crucial cytotoxic effects of the cationic charge of NCs such as degradation enzyme release, change in the action of enzymes in the cytoplasm, and release of reactive oxygen species may occur so, it's very important to precisely adjust the cationic charge on the NCs.

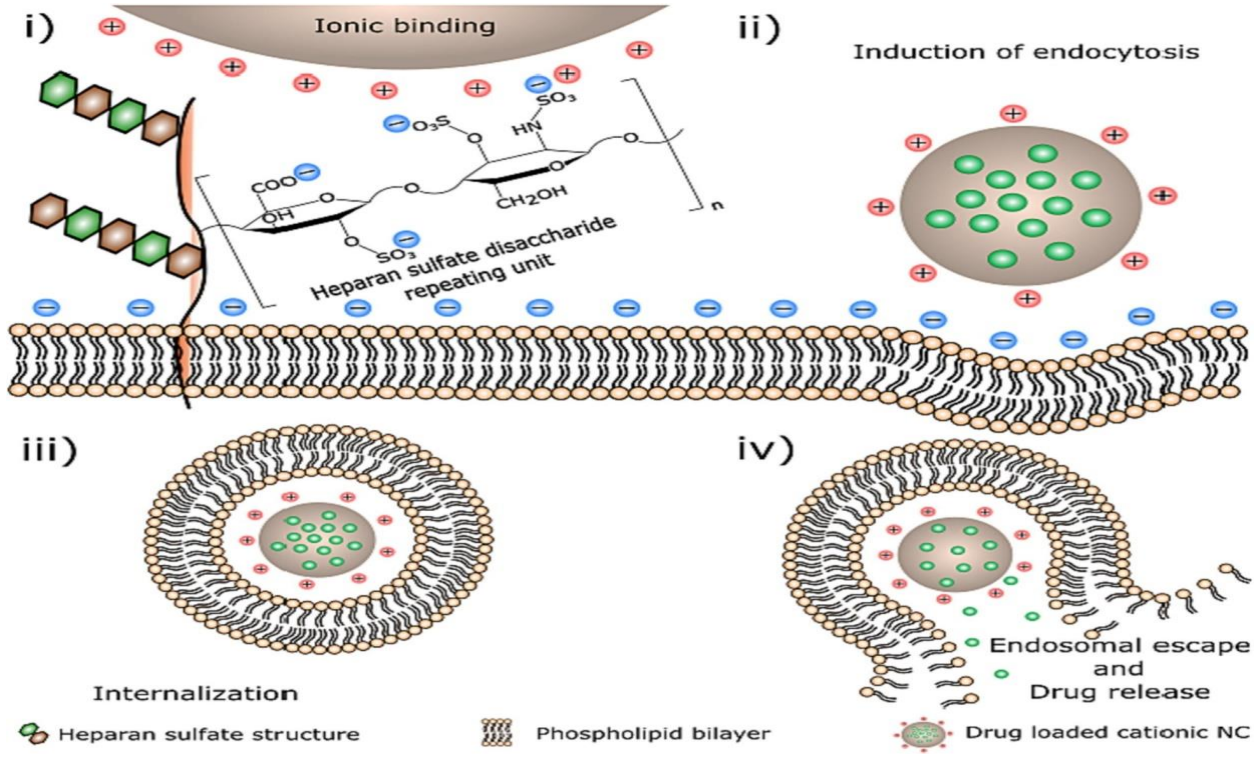

Fig. 2. Stages of cationic NCs with cellular membrane (2).

Notwithstanding their adverse effects, the efficacy of positively charged NCs to overcome all absorption barriers and gel-like mucus was applied to successfully orally deliver insulin using a protein corona around the cationic liposomes to enhance permeation through the layer of mucus (53). Cationic PLGA nanoparticles which were linked electrostatically with the cell membrane showed high cellular uptake (54). Moreover, the interaction of cationic NCs with a negatively charged mucus layer helps to prolong the carrier residence time on the absorption site for example chitosan and polymyxin B surface modified rifampicin loaded nanoemulsions with greater mucoadhesive action (55). Another great application for cationic nanocarriers was the delivery of nucleic acids. The interaction between nucleic acids and NCs could be achieved through the electrostatic interaction between the negative charge on nucleic acids and the positive charge on the surface of cationic NCs(56).

6.3. Cell-penetrating Peptides

The use of cell-penetrating peptides (CPPs) is another way applied to enhance oral drug uptake where; they are composed of five to thirty amino acids which may assist the intracellular uptake of different biomolecules on their target site (57). Various uptake mechanisms were shown by CPPs dependent on physicochemical properties. Approaches could be divided into energy-independent mechanisms for example the membrane lysis and energy-dependent mechanisms such as caveolin-mediated endocytosis as well as micropinocytosis (58). CPPs offer several advantages including low toxicity and various uptake mechanisms so, they have a great focus to be used in combination with nanocarriers to improve cellular uptake (59).

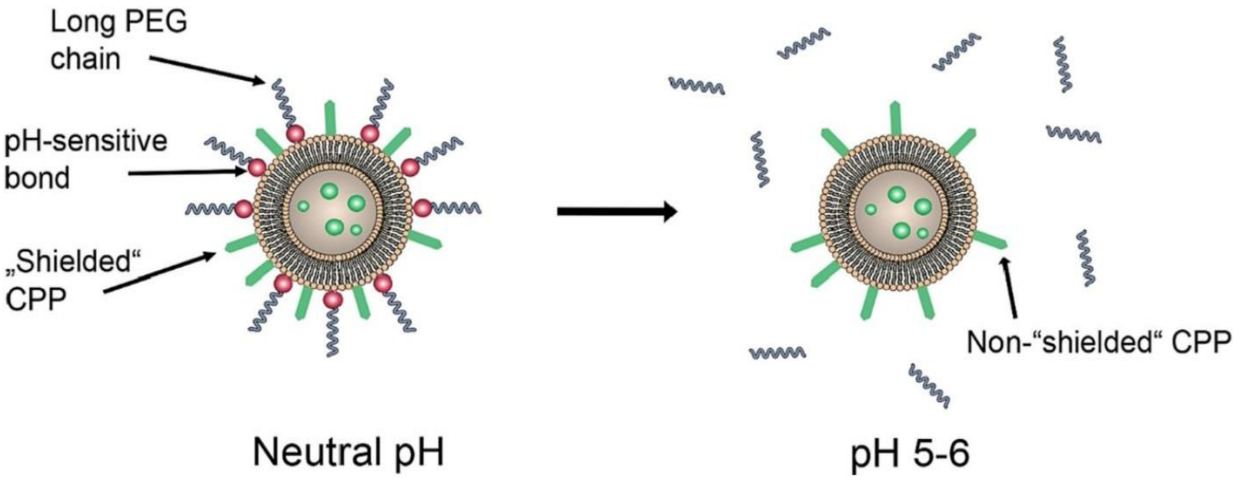

Fig. 3. Concept of CPPs protection “smart nanocarriers” (59).

In spite of having major clinical potential CPPs display limitations concerned with oral drug delivery. Degradation by enzymes is a well-known problem accompanying to the usage of CPPs. It may be prohibited by protease-resistant D-form CPPs as an alternative to natural L-forms (60). The arginine addition is another modification that may be applied to CPPs in order to enhance cell penetrating abilities. Also, histidine addition may result in pH-responsive CPPs. The use of 'smart' nanocarriers delivers a promising method. In these systems, CPPs are sterically protected till entrance at the target site, where a local stimulus leads to CPPs deprotection and consequently targeted uptake. The concept of such systems is illustrated in Fig. 3 (57,61,62).

6.4. Thiolated surfaces

Thiol groups on the surface of NCs can open TJs with subsequent enhancement of endocytosis (63). The opening of TJs which is considered the main mechanism could be facilitated through the interaction between the thiol group found on the proteins on the membranes and the thiol group attached to NCs. Moreover, inhibition of protein tyrosine phosphatase intermediated by glutathione is another suggested mechanism of thiolated NCs. This inhibition leads to blockage of the dephosphorylation of the extracellular loops of occluding leading to TJs Opening (64,65). Zhang et al. confirmed also thiol-dependent interactions with epidermal growth factor and insulin-like growth factor leading to the disruption of claudin-4 causing TJ opening. A fluorescence-labeled dextran achieved three to five folds improvements in permeation on a Caco-2 monolayer by using NCs that were formulated through in situ gelation of thiolated poly-acrylic acid and thiolated chitosan if compared to unthiolated NCs (66). Insulin-loaded chitosan NCs coated with polyacrylic acid-cysteine-6-mercaptonicotinic acid (S-protected thiolated NCs) showed increased paracellular transport of insulin through the intestinal mucosa and subsequent increase by 16% in oral bioavailability (67).

7. Charge converting surfaces

Charge converting NCs count on the brush border membrane-bound enzyme intestinal alkaline phosphatase (ALP) that splits and releases phosphates from NLCs surface (68). The conversion of the charge from negative to neutral or positive and/or loss of the characteristics of zwitter ion is attributed to the loss of the anionic phosphate substructures from the NCs surface as mentioned. Fig 4 illustrates the principle of this conversion. The first charge-converting NCs for drugs

delivered orally were obtained by coacervation of polyethylenimine-6-phosphogluconic acid conjugate and a chitosan phosphotyrosine conjugate with carboxymethylcellulose (69).

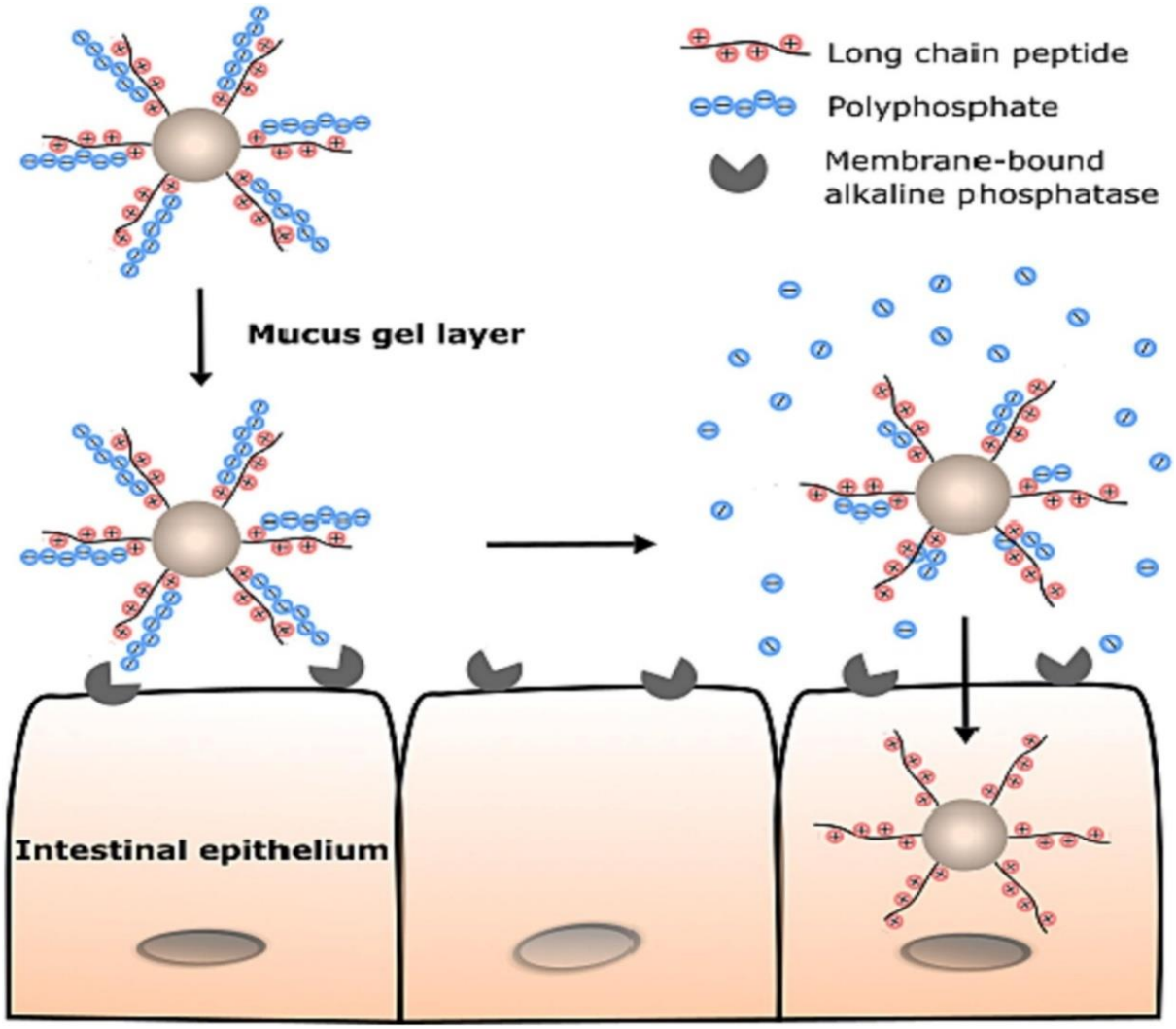

Fig.4. Concept of charge conversion of zwitter ion (2).

The limited access for phosphatase enzyme to NCs prevents the cleavage of all phosphate groups from thiolated NCs, However, zeta potential values of NCs could be converted from negative values to positive values for example the shift of zeta potential of Polyethylenimine-6-phosphogluconic acid NCs from -6 mV to +3 mV (69). In an alternative way, immobilization of the phosphate group from the surface of NCs can be achieved enzymatically which facilitates the access of phosphatase enzyme. In case of lipid-based formulations like NLCs, SLNs or SEDDS attached in the lipophilic core of these NCs. The very first charge-changing lipid-based NCs shifted

their zeta potential from just -1 mV to +1 mV (70,71). High mucus penetrating ability is the main advantage of converting NCs intended for oral drug delivery facilitating the reach of these NCs to the absorption membrane with great improved cellular uptake (72).

Surface modification techniques

Surface modification of nano drug delivery systems involves the use of diverse biomaterials to change their physicochemical characteristics, pharmacokinetic qualities, and pharmacological activity. Surface engineering can be utilized by coating the nanocarrier either through covalent bonds, non-covalent bonds, or special techniques (1).

Non-covalent bonding techniques

It has been demonstrated that surface non-covalent bonding can increase the efficacy of nanocarriers and improve the pharmacokinetics of incorporated drugs. Various techniques can be applied for non-covalent bonding between nanovesicles and coating materials, including hydrophobic interactions, hydrogen bonding, van der Waal bonds, electrostatic interactions, and deposition, or a combination of them.

Electrostatic interactions can be done by the adsorption of different materials, polyelectrolytes or saccharides based on their charge, on the nano-system surface without covalent conjugation. On the other hand, electrostatic deposition is carried out by the coating of a colloidal core, with a certain charge, with a polyelectrolyte with an opposite charge. This leads to the development of nanoparticles surrounded by an electrostatic film. This method can be used to add targeting moieties to the nanovesicles and boost the stability and plasma half-life of bioactive cell-penetrating peptides.

In addition to electrostatic interactions, coating colloidal nano-systems that are prone to Ostwald ripening, and condensation into larger particles could be done using hydrogen bonds and hydrophobic interactions. These systems are coated using amphiphilic materials which form a protective layer against condensation (73).

Covalent bonding techniques

Another method for altering the surface of nano-systems is the covalent conjugation of compounds on nanocarriers. Using this method, biomolecules are attached to the surface of nanovesicles using covalent bonds that are physiologically labile. This method is now in use and

serves as a potent and potentially flexible tool for creating nano-delivery systems containing a range of covalently functionalized proteins (74). Using the covalent modification method, several nano-drug delivery systems containing organic as well as inorganic functional groups have been created (75).

A variety of chemical bonds can be applied to this technique, which includes amide, polycyclic, ester, and thiol biodegradable bonds. Each type of the mentioned covalent bond has its unique cleavage mechanism. Before coating is done, the nanomaterials' surface, including nanoparticles, micelles, or carbon nanotubes, is initially modified by introducing alkoxy, amine, amino, and alkyl functional groups. Subsequently, in order to create biodegradable covalent connections that make it easier to coat nanoparticles, these surface functional groups interact chemically with the functional groups of the materials utilized in coating (76).

Special coating techniques

Lipid nanoparticles coated with chitosan polymer are commonly created using a co-incubation technique, whereby uncoated lipid nanoparticles are first created and then incubated in an acidic aqueous solution of chitosan. The polymer is self-assembled through electrostatic interactions at the oil/water interface. Additional step of cross-linking can be used to stabilize the chitosan coating, however, this step is industrially undesirable because it involves an additional chemical reaction step (77).

For the production of PEGylated lipid-based nanoparticles, PEG esters are commonly added to the lipid phase through a simple one-step process. For example, PEGylated liposomes were developed utilizing a thin film hydration method from a mixture of phospholipids, cholesterol, and PEG-2000. On the other hand, PEGylated SLN was prepared was prepared using a mixture of tripalmitin, and PEG-stearic acid polymer, as a lipid phase, that was emulsified in a surfactant's aqueous solution through sonication. For the production of PEGylated NLCs, the same method can be used with the substitution of a part of tripalmitin with Miglyol which acts as a liquid lipid (78).

Applications of surface-modified nanoparticles as targeted oral drug delivery systems

Enhanced efficacy and reduction in adverse drug reactions of oral formulations can be achieved by targeting specific segments of the gastrointestinal tract (GIT) and subsequently releasing the

loaded drug. Different systems can be applied to successfully target these segments including pH, enzyme, and redox triggered systems.

pH triggered systems

The pH values of different parts of the GIT range from about 1.2 for the stomach to 6.5 and 7.5 for the small intestine and ileum, respectively (79). Due to this diversity, the pH is considered a perfect targeted drug delivery trigger, especially in the local GIT disorders including ulcerative colitis, Crohn's disease, colon cancer, and inflammatory bowel disease. To design a pH-sensitive nanocarrier simply and effectively, suitable polymers are utilized to achieve an enteric-coated drug delivery system. Eudragits® are a family of methacrylic acid copolymers that are the most widely applied coating polymers for targeted oral drug delivery (79,80). In the acidic pH of the upper part of the GIT, the polymer's carboxylic acid groups are protonated which prevents the unwanted drug release in this segment. Increasing the pH in the lower parts of the tract will cause the ionization and deprotonation of these groups. This will lead to electrostatic repulsion and subsequently coating material disintegrates and releases the entrapped drug in the colon (81).

PLGA nanocarriers containing 5-flourouracil and coated with Eudragit S100 were developed by Wang et al. for oral drug delivery of the anticancer drug. At pH less than 7, the drug release was prevented through the coating which was confirmed by the in vitro studies. Increasing the pH to 7.4 resulted initially in burst drug release then sustained and slow release over 5 days depending on erosion and swelling of the PLGA polymer (82).

Another study conducted by Tummala et al. demonstrated that targeting colorectal cancer with 5-flourouracil was successfully achieved. It was found that drug nanocarriers coated with Eudragit L100 released about 82% of the drug in a sustained release manner, while the non-coated formulations released more than 50% of the entrapped drug before the colon was reached (83).

These results are in agreement with previous findings by Ali et al. who developed an Eudragit S100 coated nanocarriers carrying glucocorticoid budesonide in a core of PLGA. The results showed that more than 75% of the incorporated drug was released after 2 hours at acidic pH of the stomach from the uncoated nanocarriers, while less than 20% of the coated formulations was released in the same period. Increasing the pH to 7.4 resulted in significantly enhanced drug release to about 80% within 8 hours (84).

Jain et al. also demonstrated the potential of Eudragit-coated nanocarriers as a potential targeted drug delivery system (85). The colon cancer oral medication, oxaliplatin, was incorporated in chitosan-hyaluronic acid nanocarriers coated with Eudragit S100. The in vivo studies utilizing tumor-carrying mice demonstrated that coated nanocarriers accumulated in the cancer tissue significantly higher than uncoated formulations. This could be attributed to the overexpression of hyaluronic acid receptors in most cancerous tissues (86).

The modification of the surface of mesoporous silica nanoparticles is another highly effective and promising strategy for targeted drug delivery. The silanol groups present on the nanoparticles' surface enhance the conjugation with different polymers to create a pH-sensitive coating (79,87). Polyacrylic acid was linked to these nanoparticles' surface by Tian et al. (88). Doxorubicin was studied as a model drug and the results showed that during 12 hours 20% only of the drug was released in the stomach (pH 2), while 64% was released in regions with higher pH values. The H-bonds present between polyacrylic acid carboxylic groups could explain the decreased drug release at low pH value. On the other hand, increasing the pH to a weak basic environment will cause the ionization of the functional groups, and subsequently repulsive forces will open the pore channels and eventually rapid release of the carried drug will occur (88). Compared to these results, the uncoated silica nanoparticles showed an initial rapid release of most of the incorporated drug at acidic pH with only 10% of the drug is released in the lower GIT.

These findings are in accordance with Nguyen et al. results which showed that surface-modified silica nanoparticles, by succinylated polylysine polymer, successfully led to the colon-targeted release of prednisolone (89). Compared to uncoated particles, the surface-modified mesoporous silica nanoparticles released less than 14% of the incorporated drug in an acidic pH environment. Polymer swelling, due to repulsion between polymeric chains, and subsequently drug release was demonstrated by studies conducted in conditions simulating the pH environment of the colon.

Lee et al. developed another surface-manipulated system based on silica nanoparticles. Sulfasalazine, an anionic drug used for the treatment of ulcerative colitis and Crohn's disease, was successfully incorporated in surface-modified silica nanoparticles. At acidic pH, there is an electrostatic attraction between sulfasalazine and uncharged silanol groups of silica nanoparticles, so less drug is released. Strong repulsive forces are observed at higher pH regions due to the

ionization of OH groups of the mesoporous silica and the anionic drug, resulting in targeted drug release in lower parts of the GIT (90).

Enzyme triggered systems

Endogenous enzymes have the ability to cleave enzymatically labile bonds contained in the nanocarriers resulting in the targeted and controlled release of the incorporated drugs (91). Targeted drug delivery to the intestinal segments containing alkaline phosphatase (ALP) enzyme was investigated. Tripolyphosphate/chitosan nanoparticles were developed by Leichner et al. and proved to achieve targeted β-galactosidase delivery to the mucus gel layer of the intestine at the absorption membrane (92). Upon reaching the target site, ALP hydrolyzes the tripolyphosphate cross-links which led to the degradation of particles and release of the drug. Results showed that the presence of ALP led to a 2.5-fold increase in the amount of β-galactosidase in comparison to the ALP absence (92).

Another study by Saleh et al. showed that shielding the surface of polymyxin B, a cationic drug, with anionic polyphosphate led protected the drug from lipase enzyme degradation. Targeted polymyxin release at absorption sites can be achieved by the action of ALP on the phosphate residues (93).

Camptothecin, a drug used for colorectal cancer, was incorporated in cyclodextrin by Ünal et al. to protect the drug against stomach and intestinal degradation and absorption. Upon reaching the colon, the colonic microflora degrades the cyclodextrin complexes, and the drug is released. To prolong the residence time at the targeted site, chitosan is utilized in the coating as a cationic polymer to interact with the negatively charged mucus layer. Release studies using simulated GI conditions showed that initially half of the incorporated drug reached the colon followed by 90% released after 24 hours (94).

The work of Ünal et al. led to the identification of microflora-dependent delivery systems as highly promising for oral treatment of local GIT inflammations including ulcerative colitis, Crohn's disease, and inflammatory bowel disease because of their ability to achieve targeted drug release. The colonic microflora enzymes that could cleave the azo-bond and release drugs in the colon were studied by Cai et al. (95). The surface of mesoporous silica nanospheres was modified using chitosan through the formation of azo-bonds. These bonds are enzymatically degraded leading to chitosan detachment and subsequently release of the drug. These findings were

confirmed by measuring the percentage of drug released in the presence and absence of the colonic enzymes which was found to be 40% and 10%, respectively. Additionally, increasing the concentration of the enzyme resulted in significantly enhanced drug release (95).

It was found that certain enzymes, such as esterases, are overexpressed in pathological inflammatory conditions. This fact can be applied to enzyme-triggered drug release (96). Dexamethasone-loaded Lipid nanocarriers were developed by Chen et al. through modification of their surfaces by chitosan via an ester linkage to treat ulcerative colitis. Using the simulated intestinal fluid model, the in vitro dexamethasone release after 48 hours was found to be 24% and 49% in the absence and presence of esterase, respectively. Additionally, drug release was found to be released faster in the presence of chitosan than in the absence of the polymer indicating the role of surface modification on the rate of drug release. These results were confirmed by the in vivo studies conducted in mice models infected with ulcerative colitis (97).

Redox triggered systems

Abnormal levels of reactive oxygen species (ROS) and glutathione were observed in patients suffering from intestinal cancer or inflammation. Thus, the redox gradient was employed as a trigger for drug release from surface-manipulated nanocarriers at the desired sites.

Redox-sensitive solid lipid nanoparticles incorporating camptothecin linked by a disulfide bond to palmitic acid conjugates have been designed by Du et al. (98). The hypothesis was that glutathione is overexpressed in the tumor cells; thus, it can cleave the disulfide linkage and subsequently camptothecin is released. This assumption was confirmed by in vitro studies of redox sensitivity which utilized dithiotreitol as a reducing agent. The solution containing dithiotreitol showed an 80% degradation of the drug-polymer conjugate within the first 20 minutes while less than 10% was degraded in the absence of the reducing agent over 24 hours (98).

Dinarvand et al. studied the effect of the presence of disulfide bonds on glutathione responsiveness as a targeted drug delivery module (99). The active metabolite of irinotecan, SN-38, was investigated as an antineoplastic drug for the treatment of colon cancer. Two types of nanocarriers were developed; the first consisted of cysteine trimethyl chitosan conjugated to carboxymethyl dextran and the second was developed without the disulfide bond of cysteine. The in vitro release study using low concentration of glutathione, to simulate the extracellular environment, revealed that only 9% of SN-38 was released from the second system after 8 hours

compared to 20-25% from the first nanocarriers. On the other hand, at high concentrations of glutathione, simulating intracellular environment, the drug release after 6 hours was 13% and 61% from the first and second nanocarriers, respectively. These findings showed the significance of the presence of disulfide bonds in enhancing the response of glutathione as a colon-targeting trigger (99).

Another research by Qiao et al. was carried out to develop a redox-dependent system for the intracellular targeted drug release relied upon disulfide bond cleavage. The results showed that PEG-modified curcumin via disulfide linkage released a significantly higher percentage of the drug in a glutathione-rich environment compared to low glutathione media.

An amphiphilic self-assembling polymer of inulin was also developed for the oral administration of budesonide for the treatment of inflammatory bowel disease. The in vitro studies confirmed the redox-triggered budesonide release after the cleavage of the disulfide bond and the disassembly of the polymer chains. In the glutathione-free environment, the drug release studies revealed that only 45% of the drug was released compared to 80% in release media with 20 mM glutathione. Furthermore, the in vivo studies showed an enhanced therapeutic efficacy of the modified nanocarriers compared to drug suspension (100).

Thioketal bonds are another category of bonds that proved to achieve targeted budesonide release triggered by ROS. For the oral administration of budesonide, Li et al. created a self-assembling, redox-sensitive prodrug, which contains the antioxidant tempol and the ROS-responsive aromatized thioketal (101,102). In the presence of H_2O_2, rapid hydrolysis of the thioketal bonds and subsequently drug release occurred. In vivo, studies in colitis-induced mice were carried out and revealed that developed nanocarriers were highly accumulated in the diseased part of the colon (101).

Another system based on thioketal bonds cleavage was developed by Wilson et al. (103). Nanocarriers composed of phenylene acetone thioketal polymer were prepared and found to be stable against degradation by acids, bases, and protease enzyme. However, these carriers could release the incorporated drug at the site of action through a ROS-dependent drug release mechanism (103).

Using a biocompatible oxidative-labile ß-cyclodextrin derivative, Zhang et al. employed a similar method for Tempol oral delivery (104). Studies conducted in 1 mM H_2O_2, to simulate high ROS conditions, revealed that within 6 hours the nanocarriers were hydrolyzed completely and as

a result, a redox-triggered Tempol release was observed. The in vivo studies, using ulcerative colitis mice models, showed effective colon targeting and reduced non-specific drug distribution (104).

Although redox-triggered release nanocarriers have high potential as oral drug delivery systems, they suffer from some drawbacks such as the instability and enzymatic decomposition in the upper region of the GIT, the unintended drug release before reaching the desired site of action, and the limited number of ROS that can be targeted by these systems (80).

Mixed mechanisms systems

Targeting certain parts of the GIT can be achieved through the use of different triggering systems together. In this approach, nanocarriers were modified using pH-sensitive moieties, which protect the drug from hydrolysis in the upper part of the GIT, and an enzyme-sensitive part which aids in the release of the drug in the desired regions through the enzyme-triggered mechanism. One of these systems is the one developed by Huang et al. who developed nanocarriers modified with both chitosan and hyaluronic acid (105). In regions with pH up to 6.8, these nanocarriers resisted acidic degradation due to chitosan coat, however, chitosan deprotonation occurred at pH 7.4 leading to the reduction in the electrostatic interactions with molecules of opposite charge. This led to chitosan detachment and hyaluronic acid exposure and binding to the cancer cells through CD-44 receptors. Finally, the drug is released after the destruction of the integrity of the hyaluronic acid-coated nanocarriers through the action of the hyaluronidase enzyme (105).

Another system that employed both pH- and enzyme-triggered mechanisms for curcumin oral delivery was developed by Li et al. (106). He prepared curcumin-cyclodextrin complexes that were modified by both chitosan and sodium alginate. At low pH, this system formed a gel due to interaction between oppositely charged carboxylic and amino groups of alginate and chitosan, respectively. The formed gel protected the entrapped drug from degradation in the stomach and the upper part of the intestine. Upon reaching the ileum, about 90% of the drug was released due to the action of α-amylase which cleaved the cyclodextrin complex structure (106).

Conclusion

Different categories of nanocarriers have emerged in recent years offering benefits such as increased solubility, permeation, and stability of entrapped drug moiety. Surface-manipulated nanocarriers can further enhance their properties in terms of improved efficacy and reduced

unintended drug release far from the site of action. Different surface modifications can be utilized such as zwitterions, PEG, PG, mucoadhesives, and charge converting surfaces. These modifications have the ability to prevent drug interaction with GIT components, protect the entrapped drug from mucus, and increase the residence of the drug in the GIT through adhesion to GI epithelium. Different techniques can be utilized to develop surface-modified nanocarriers including non-covalent bonding through hydrophobic interactions, hydrogen bonding, van der Waal bonds, and electrostatic interactions. Covalent bonding is another technique used for the production of surface-modified nanocarriers and includes chemical bonding via amide, polycyclic, ester, and thiol bonds. Modified nanocarriers can be applied for targeted oral drug delivery to certain parts of the GIT. Different mechanisms can be utilized to trigger the drug release at the desired site of action including pH, enzyme, and redox triggered systems. Generally, nanocarrier surface design has a lot of flexibility due to the variety of materials available for modification and the large number of potential triggers applied for targeted drug release.

Conflict of Interest

The authors have declared no conflicts of interest for this article.

References

1. Osman N, Devnarain N, Omolo CA, Fasiku V, Jaglal Y, Govender T. Surface modification of nano-drug delivery systems for enhancing antibiotic delivery and activity. Wiley Interdiscip Rev Nanomedicine Nanobiotechnology. 2022;14(1):1–24.
2. Spleis H, Sandmeier M, Claus V, Bernkop-Schnürch A. Surface design of nanocarriers: Key to more efficient oral drug delivery systems. Adv Colloid Interface Sci [Internet]. 2023;313(February):102848. Available from: https://doi.org/10.1016/j.cis.2023.102848
3. Vithani K, Jannin V, Pouton CW, Boyd BJ. Colloidal aspects of dispersion and digestion of self-dispersing lipid-based formulations for poorly water-soluble drugs. Adv Drug Deliv Rev [Internet]. 2019;142:16–34. Available from: https://doi.org/10.1016/j.addr.2019.01.008
4. Kali G, Knoll P, Bernkop-Schnürch A. Emerging technologies to increase gastrointestinal transit times of drug delivery systems. J Control Release [Internet]. 2022;346(February):289–99. Available from:

https://doi.org/10.1016/j.jconrel.2022.04.016

5. Dumont C, Bourgeois S, Fessi H, Jannin V. Lipid-based nanosuspensions for oral delivery of peptides, a critical review. Int J Pharm [Internet]. 2018;541(1–2):117–35. Available from: https://doi.org/10.1016/j.ijpharm.2018.02.038
6. Dhaval M, Vaghela P, Patel K, Sojitra K, Patel M, Patel S, et al. Lipid-based emulsion drug delivery systems — a comprehensive review. Drug Deliv Transl Res [Internet]. 2022;12(7):1616–39. Available from: https://doi.org/10.1007/s13346-021-01071-9
7. Sharma A, Kumar Arya D, Dua M, Chhatwal GS, Johri AK. Nano-technology for targeted drug delivery to combat antibiotic resistance. Expert Opin Drug Deliv. 2012;9(11):1325–32.
8. Weiwei Gao, Yijie Chen, Yue Zhang, Qiangzhe Zhang and LZ. Nanoparticle-Based Local Antimicrobial Drug Delivery. Adv Drug Deliv Rev. 2018;127(3):46–57.
9. Huh AJ, Kwon YJ. "Nanoantibiotics": A new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J Control Release [Internet]. 2011;156(2):128–45. Available from: http://dx.doi.org/10.1016/j.jconrel.2011.07.002
10. Bahrami A, Delshadi R, Jafari SM. Active delivery of antimicrobial nanoparticles into microbial cells through surface functionalization strategies. Trends Food Sci Technol [Internet]. 2020;99(March):217–28. Available from: https://doi.org/10.1016/j.tifs.2020.03.008
11. Tomitaka A, Kaushik A, Kevadiya B, Mukadam I, Howard E, Khalili K, et al. Surface-engineered multimodal magnetic nanoparticles to manage CNS diseases. Drug Discov Today. 2020;24(3):873–82.
12. Wei Y, Gao L, Wang L, Shi L, Wei E, Zhou B, et al. Polydopamine and peptide decorated doxorubicin-loaded mesoporous silica nanoparticles as a targeted drug delivery system for bladder cancer therapy. Drug Deliv. 2017;24(1):681–91.
13. Khodabandehloo H, Zahednasab H, Hafez AA. Nanocarriers usage for drug delivery in cancer therapy. Int J Cancer Manag. 2016;9(2).
14. Shenoy DB, Amiji MM. Poly(ethylene oxide)-modified poly(ε-caprolactone) nanoparticles for targeted delivery of tamoxifen in breast cancer. Int J Pharm. 2005;293(1–2):261–70.
15. Giri N, Tomar P, Karwasara VS, Pandey RS, Dixit VK. Targeted novel surface-modified

nanoparticles for interferon delivery for the treatment of hepatitis B. Acta Biochim Biophys Sin (Shanghai). 2011;43(11):877–83.

16. Ahmad N, Ahmad R, Alam MA, Ahmad FJ. Quantification and Brain Targeting of Eugenol-Loaded Surface Modified Nanoparticles Through Intranasal Route in the Treatment of Cerebral Ischemia. Drug Res (Stuttg). 2018;68(10):584–95.
17. Leonaviciute G, Prüfert F, Rohrer J, Bernkop-schnürch A. Impact of lipases on the protective effect of SEDDS for incorporated peptide drugs towards intestinal peptidases. Int joumal Pharm. 2016;508:102–8.
18. Hu S, Niu M, Hu F, Lu Y, Qi J, Yin Z, et al. Integrity and stability of oral liposomes containing bile salts studied in simulated and ex vivo gastrointestinal media. Int joumal Pharm. 2013;441:693–700.
19. Shan W, Zhu X, Tao W, Cui Y, Liu M, Wu L, et al. Enhanced Oral Delivery of Protein Drugs Using Zwitterion-Functionalized Nanoparticles to Overcome both the Diffusion and Absorption Barriers. ACS Appl Mater Interfaces. 2016;8(38):25444–53.
20. Olmsted SS, Padgett JL, Yudin AI, Whaley KJ, Moench TR, Cone RA. Diffusion of macromolecules and virus-like particles in human cervical mucus. Biophys J [Internet]. 2001;81(4):1930–7. Available from: http://dx.doi.org/10.1016/S0006-3495(01)75844-4
21. Wu J, Lin W, Wang Z, Chen S, Chang Y. Investigation of the hydration of nonfouling material poly(sulfobetaine methacrylate) by low-field nuclear magnetic resonance. Langmuir. 2012;28(19):7436–41.
22. Moku G, Gopalsamuthiram VR, Hoye TR, Panyam J. Surface modification of nanoparticles: Methods and applications. Surf Modif Polym Methods Appl. 2019;317–46.
23. Guerrini L, Alvarez-Puebla RA, Pazos-Perez N. Surface modifications of nanoparticles for stability in biological fluids. Materials (Basel). 2018;11(7):1–28.
24. Han X, Lu Y, Xie J, Zhang E, Zhu H, Du H, et al. Zwitterionic micelles efficiently deliver oral insulin without opening tight junctions. Nat Nanotechnol [Internet]. 2020;15(7):605–14. Available from: http://dx.doi.org/10.1038/s41565-020-0693-6
25. Pereira De Sousa I, Steiner C, Schmutzler M, Wilcox MD, Veldhuis GJ, Pearson JP, et al. Mucus permeating carriers: formulation and characterization of highly densely charged nanoparticles. Eur J Pharm Biopharm [Internet]. 2015;97(January):273–9. Available from: http://dx.doi.org/10.1016/j.ejpb.2014.12.024

26. Zhang X, Cheng H, Dong W, Zhang M, Liu Q, Wang X, et al. Design and intestinal mucus penetration mechanism of core-shell nanocomplex. J Control Release [Internet]. 2018;272:29–38. Available from: http://dx.doi.org/10.1016/j.jconrel.2017.12.034
27. Tekie FSM, Hajiramezanali M, Geramifar P, Raoufi M, Dinarvand R, Soleimani M, et al. Controlling evolution of protein corona: a prosperous approach to improve chitosan-based nanoparticle biodistribution and half-life. Sci Rep. 2020;10(1):9664.
28. Yu T, Chan KWY, Anonuevo A, Song X, Schuster BS, Chattopadhyay S, et al. Liposome-based mucus-penetrating particles (MPP) for mucosal theranostics: Demonstration of diamagnetic chemical exchange saturation transfer (diaCEST) magnetic resonance imaging (MRI). Nanomedicine Nanotechnology, Biol Med [Internet]. 2015;11(2):401–5. Available from: http://dx.doi.org/10.1016/j.nano.2014.09.019
29. Xu Q, Ensign LM, Boylan NJ, Schön A, Gong X, Yang JC, et al. Impact of Surface Polyethylene Glycol (PEG) Density on Biodegradable Nanoparticle Transport in Mucus ex Vivo and Distribution in Vivo. ACS Nano. 2015;9(9):9217–27.
30. Dai Q, Walkey C, Chan WCW. Polyethylene glycol backfilling mitigates the negative impact of the protein corona on nanoparticle cell targeting. Angew Chemie - Int Ed. 2014;53(20):5093–6.
31. Rabanel JM, Hildgen P, Banquy X. Assessment of PEG on polymeric particles surface, a key step in drug carrier translation. J Control Release [Internet]. 2014;185(1):71–87. Available from: http://dx.doi.org/10.1016/j.jconrel.2014.04.017
32. Huang Y, Canup BSB, Gou S, Chen N, Dai F, Xiao B, et al. Oral nanotherapeutics with enhanced mucus penetration and ROS-responsive drug release capacities for delivery of curcumin to colitis tissues. J Mater Chem B. 2021;9(6):1604–15.
33. Chen D, Xia D, Li X, Zhu Q, Yu H, Zhu C, et al. Comparative study of Pluronic® F127-modified liposomes and chitosan-modified liposomes for mucus penetration and oral absorption of cyclosporine A in rats. Int J Pharm [Internet]. 2013;449(1–2):1–9. Available from: http://dx.doi.org/10.1016/j.ijpharm.2013.04.002
34. Allen C, Maysinger D, Eisenberg A. Nano-engineering block copolymer aggregates for drug delivery Christine. Colloids surfaces B Biointerfaces. 1999;16:3–27.
35. Hu S, Yang Z, Wang S, Wang L, He Q, Tang H, et al. Zwitterionic polydopamine modified nanoparticles as an efficient nanoplatform to overcome both the mucus and

epithelial barriers. Chem Eng J [Internet]. 2022;428(June 2021):132107. Available from: https://doi.org/10.1016/j.cej.2021.132107

36. Chiappetta DA, Alvarez-Lorenzo C, Rey-Rico A, Taboada P, Concheiro A, Sosnik A. N-alkylation of poloxamines modulates micellar assembly and encapsulation and release of the antiretroviral efavirenz. Eur J Pharm Biopharm [Internet]. 2010;76(1):24–37. Available from: http://dx.doi.org/10.1016/j.ejpb.2010.05.007
37. Zou Y, Ito S, Yoshino F, Suzuki Y, Zhao L, Komatsu N. Polyglycerol Grafting Shields Nanoparticles from Protein Corona Formation to Avoid Macrophage Uptake. ACS Nano. 2020;14(6):7216–26.
38. Thomas A, Müller SS, Frey H. Beyond poly(ethylene glycol): Linear polyglycerol as a multifunctional polyether for biomedical and pharmaceutical applications. Biomacromolecules. 2014;15(6):1935–54.
39. Friedl JD, Steinbring C, Zaichik S, Le NMN, Bernkop-Schnürch A. Cellular uptake of self-emulsifying drug-delivery systems: Polyethylene glycol versus polyglycerol surface. Nanomedicine. 2020;15(19):1829–41.
40. Du H, De Oliveira FA, Albuquerque LJC, Tresset G, Pavlova E, Huin C, et al. Polyglycidol-Stabilized Nanoparticles as a Promising Alternative to Nanoparticle PEGylation: Polymer Synthesis and Protein Fouling Considerations. Langmuir. 2020;36(5):1266–78.
41. Brockow K, Mathes S, Fischer J, Volc S, Darsow U, Eberlein B, et al. Experience with polyethylene glycol allergy-guided risk management for COVID-19 vaccine anaphylaxis. Allergy Eur J Allergy Clin Immunol. 2022;77(7):2200–10.
42. Netsomboon K, Bernkop-Schnürch A. Mucoadhesive vs. mucopenetrating particulate drug delivery. Eur J Pharm Biopharm [Internet]. 2016;98:76–89. Available from: http://dx.doi.org/10.1016/j.ejpb.2015.11.003
43. Ways TMM, Lau WM, Khutoryanskiy V V. Chitosan and its derivatives for application in mucoadhesive drug delivery systems. Polymers (Basel). 2018;10(3).
44. Gradauer K, Barthelmes J, Vonach C, Almer G, Mangge H, Teubl B, et al. Liposomes coated with thiolated chitosan enhance oral peptide delivery to rats. J Control Release [Internet]. 2013;172(3):872–8. Available from: http://dx.doi.org/10.1016/j.jconrel.2013.10.011

45. Arshad S, Masood-ur-Rehman, Hussain Asim M, Nazir I, Shahzadi I, Mousli M, et al. S-Protected thiolated nanostructured lipid carriers exhibiting improved mucoadhesive properties. Int J Pharm [Internet]. 2020;587(June):119690. Available from: https://doi.org/10.1016/j.ijpharm.2020.119690
46. Racaniello GF, Knoll P, Jörgensen AM, Arduino I, Laquintana V, Lopedota AA, et al. Thiolation of non-ionic surfactants for the development of lipid-based mucoadhesive drug delivery systems. Eur J Pharm Biopharm. 2022;179(September):95–104.
47. Leichner C, Jelkmann M, Bernkop-Schnürch A. Thiolated polymers: Bioinspired polymers utilizing one of the most important bridging structures in nature. Adv Drug Deliv Rev [Internet]. 2019;151–152:191–221. Available from: https://doi.org/10.1016/j.addr.2019.04.007
48. Donahue ND, Acar H, Wilhelm S. Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine. Adv Drug Deliv Rev. 2019;143:68–96.
49. Wang J, Wang A, Tian X, Wang H, Xu M, Yang L. Development of palygorskite-SO42−/ZnAl2O4 composites as a novel solid acid catalyst for the esterification of acetic acid with n-butanol. Appl Clay Sci. 2017;135:596–602.
50. Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. Eur J Pharm Biopharm. 2012;81(3):463–9.
51. Christianson HC, Belting M. Heparan sulfate proteoglycan as a cell-surface endocytosis receptor. Matrix Biol. 2014;35:51–5.
52. He C, Hu Y, Yin L, Tang C, Yin C. Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. Biomaterials. 2010;31(13):3657–66.
53. Wang A, Yang T, Fan W, Yang Y, Zhu Q, Guo S, et al. Protein Corona Liposomes Achieve Efficient Oral Insulin Delivery by Overcoming Mucus and Epithelial Barriers. Adv Healthc Mater. 2019;8(12):1–11.
54. Xu A, Yao M, Xu G, Ying J, Ma W, Li B, et al. A physical model for the size-dependent cellular uptake of nanoparticles modified with cationic surfactants. Int J Nanomedicine. 2012;7:3547–54.
55. Bazán Henostroza MA, Curo Melo KJ, Nishitani Yukuyama M, Löbenberg R, Araci Bou-Chacra N. Cationic rifampicin nanoemulsion for the treatment of ocular tuberculosis.

Colloids Surfaces A Physicochem Eng Asp. 2020;597(January):124755.

56. Roberts TC, Langer R, Wood MJA. Advances in oligonucleotide drug delivery. Nat Rev Drug Discov. 2020;19(10):673–94.
57. Borrelli A, Tornesello AL, Tornesello ML, Buonaguro FM. Cell penetrating peptides as molecular carriers for anti-cancer agents. Molecules. 2018;23(2).
58. Kauffman WB, Fuselier T, He J, Wimley WC. Mechanism Matters: A Taxonomy of Cell Penetrating Peptides. Trends Biochem Sci. 2015;40(12):749–64.
59. Koren E, Torchilin VP. Cell-penetrating peptides: Breaking through to the other side. Trends Mol Med. 2012;18(7):385–93.
60. Verdurmen WPR, Bovee-Geurts PH, Wadhwani P, Ulrich AS, Hällbrink M, Van Kuppevelt TH, et al. Preferential uptake of L-versus D-amino acid cell-penetrating peptides in a cell type-dependent manner. Chem Biol. 2011;18(8):1000–10.
61. Torchilin V. Multifunctional and stimuli-sensitive pharmaceutical nanocarriers. Eur J Pharm Biopharm. 2009;71(3):431–44.
62. Koren E, Apte A, Jani A, Torchilin VP. Multifunctional PEGylated 2C5-immunoliposomes containing pH-sensitive bonds and TAT peptide for enhanced tumor cell internalization and cytotoxicity. J Control Release. 2012;160(2):264–73.
63. Hock N, Racaniello GF, Aspinall S, Denora N, Khutoryanskiy V V., Bernkop-Schnürch A. Thiolated Nanoparticles for Biomedical Applications: Mimicking the Workhorses of Our Body. Adv Sci. 2022;9(1):1–24.
64. Clausen AE, Kast CE, Bernkop-Schnürch A. The role of glutathione in the permeation enhancing effect of thiolated polymers. Pharm Res. 2002;19(5):602–8.
65. Zhang Y, Zhou S, Deng F, Chen X, Wang X, Wang Y, et al. The function and mechanism of preactivated thiomers in triggering epithelial tight junctions opening. Eur J Pharm Biopharm. 2018;133:188–99.
66. Dünnhaupt S, Barthelmes J, Köllner S, Sakloetsakun D, Shahnaz G, Düregger A, et al. Thiolated nanocarriers for oral delivery of hydrophilic macromolecular drugs. Carbohydr Polym. 2015;117:577–84.
67. Zhou S, Deng H, Zhang Y, Wu P, He B, Dai W, et al. Thiolated Nanoparticles Overcome the Mucus Barrier and Epithelial Barrier for Oral Delivery of Insulin. Mol Pharm. 2020;17(1):239–50.

68. Le-Vinh B, Akkuş-Dağdeviren ZB, Le NMN, Nazir I, Bernkop-Schnürch A. Alkaline Phosphatase: A Reliable Endogenous Partner for Drug Delivery and Diagnostics. Adv Ther. 2022;5(2).
69. Bonengel S, Prüfert F, Perera G, Schauer J, Bernkop-Schnürch A. Polyethylene imine-6-phosphogluconic acid nanoparticles - A novel zeta potential changing system. Int J Pharm. 2015;483(1–2):19–25.
70. Nazir I, Leichner C, Le-Vinh B, Bernkop-Schnürch A. Surface phosphorylation of nanoparticles by hexokinase: A powerful tool for cellular uptake improvement. J Colloid Interface Sci. 2018;516:384–91.
71. Suchaoin W, Pereira de Sousa I, Netsomboon K, Lam HT, Laffleur F, Bernkop-Schnürch A. Development and in vitro evaluation of zeta potential changing self-emulsifying drug delivery systems for enhanced mucus permeation. Int J Pharm. 2016;510(1):255–62.
72. Fabiano A, Zambito Y, Bernkop-Schnürch A. About the impact of water movement on the permeation behaviour of nanoparticles in mucus. Int J Pharm. 2017;517(1–2):279–85.
73. Sanità G, Carrese B, Lamberti A. Nanoparticle Surface Functionalization: How to Improve Biocompatibility and Cellular Internalization. Front Mol Biosci. 2020 Nov;7:587012.
74. Oriana S, Fracassi A, Archer C, Yamakoshi Y. Covalent Surface Modification of Lipid Nanoparticles by Rapid Potassium Acyltrifluoroborate Amide Ligation. Langmuir. 2018 Nov;34(44):13244–51.
75. Kuila T, Bose S, Mishra AK, Khanra P, Kim NH, Lee JH. Chemical functionalization of graphene and its applications. Prog Mater Sci. 2012 Sep;57(7):1061–105.
76. Ribeiro H, Da Silva WM, Neves JC, Calado HDR, Paniago R, Seara LM, et al. Multifunctional nanocomposites based on tetraethylenepentamine-modified graphene oxide/epoxy. Polym Test. 2015 May;43:182–92.
77. Zaky MF, Hammady TM, Gad S, Alattar A, Alshaman R, Hegazy A, et al. Influence of Surface-Modification via PEGylation or Chitosanization of Lipidic Nanocarriers on In Vivo Pharmacokinetic/Pharmacodynamic Profiles of Apixaban. Pharm 2023, Vol 15, Page 1668. 2023 Jun;15(6):1668.
78. Garcia-Fuentes M, Torres D, Alonso MJ. New surface-modified lipid nanoparticles as delivery vehicles for salmon calcitonin. Int J Pharm. 2005 May;296(1–2):122–32.

79. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharm Sci. 2003;6(1):33–66.
80. Zhang M, Merlin D. Nanoparticle-Based Oral Drug Delivery Systems Targeting the Colon for Treatment of Ulcerative Colitis. Inflamm Bowel Dis. 2018 Jun;24(7):1401–15.
81. You YC, Dong LY, Dong K, Xu W, Yan Y, Zhang L, et al. In vitro and in vivo application of pH-sensitive colon-targeting polysaccharide hydrogel used for ulcerative colitis therapy. Carbohydr Polym. 2015 Oct;130:243–53.
82. Wang Y, Li P, Peng Z, She FH, Kong LX. Microencapsulation of nanoparticles with enhanced drug loading for pH-sensitive oral drug delivery for the treatment of colon cancer. J Appl Polym Sci. 2013 Jul;129(2):714–20.
83. Tummala S, Satish Kumar MN, Prakash A. Formulation and characterization of 5-Fluorouracil enteric coated nanoparticles for sustained and localized release in treating colorectal cancer. Saudi Pharm J. 2015 Jul;23(3):308–14.
84. Ali H, Weigmann B, Neurath MF, Collnot EM, Windbergs M, Lehr CM. Budesonide loaded nanoparticles with pH-sensitive coating for improved mucosal targeting in mouse models of inflammatory bowel diseases. J Control Release. 2014 Jun;183(1):167–77.
85. Jain A, Jain SK, Ganesh N, Barve J, Beg AM. Design and development of ligand-appended polysaccharidic nanoparticles for the delivery of oxaliplatin in colorectal cancer. Nanomedicine Nanotechnology, Biol Med. 2010 Feb;6(1):179–90.
86. Day AJ, Prestwich GD. Hyaluronan-binding Proteins: Tying Up the Giant. J Biol Chem. 2002 Feb;277(7):4585–8.
87. Vinu A, Hossain KZ, Ariga K. Recent advances in functionalization of mesoporous silica. J Nanosci Nanotechnol. 2005;5(3):347–71.
88. Tian B, Liu S, Wu S, Lu W, Wang D, Jin L, et al. pH-responsive poly (acrylic acid)-gated mesoporous silica and its application in oral colon targeted drug delivery for doxorubicin. Colloids Surfaces B Biointerfaces. 2017 Jun;154:287–96.
89. Nguyen CTH, Webb RI, Lambert LK, Strounina E, Lee EC, Parat MO, et al. Bifunctional Succinylated ε-Polylysine-Coated Mesoporous Silica Nanoparticles for pH-Responsive and Intracellular Drug Delivery Targeting the Colon. ACS Appl Mater Interfaces. 2017 Mar;9(11):9470–83.
90. Lee CH, Lo LW, Mou CY, Yang CS. Synthesis and Characterization of Positive-Charge

Functionalized Mesoporous Silica Nanoparticles for Oral Drug Delivery of an Anti-Inflammatory Drug. Adv Funct Mater. 2008 Oct;18(20):3283–92.

91. Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials for controlled drug delivery. Nanoscale. 2014 Oct;6(21):12273–86.
92. Leichner C, Jelkmann M, Prüfert F, Laffleur F, Bernkop-Schnürch A. Intestinal enzyme delivery: Chitosan/tripolyphosphate nanoparticles providing a targeted release behind the mucus gel barrier. Eur J Pharm Biopharm. 2019 Nov;144:125–31.
93. Saleh A, Burcu Z, Deviren A-D, Haddadzadegan S, Wibel R, Bernkop-Schnü Rch A. Peptide Antibiotic–Polyphosphate Nanoparticles: A Promising Strategy to Overcome the Enzymatic and Mucus Barrier of the Intestine. Biomacromolecules. 2023 Jun;24(6):2587–95.
94. Ünal S, Aktaş Y, Benito JM, Bilensoy E. Cyclodextrin nanoparticle bound oral camptothecin for colorectal cancer: Formulation development and optimization. Int J Pharm. 2020 Jun;584:119468.
95. Cai D, Han C, Liu C, Ma X, Qian J, Zhou J, et al. Chitosan-capped enzyme-responsive hollow mesoporous silica nanoplatforms for colon-specific drug delivery. Nanoscale Res Lett. 2020 Jun;15(1):1–13.
96. Mendoza JL, Abreu MT. Biological markers in inflammatory bowel disease: Practical consideration for clinicians. Gastroentérologie Clin Biol. 2009 Jun;33:S158–73.
97. Chen S qing, Song Y qing, Wang C, Tao S, Yu F ying, Lou H ya, et al. Chitosan-modified lipid nanodrug delivery system for the targeted and responsive treatment of ulcerative colitis. Carbohydr Polym. 2020 Feb;230:115613.
98. Du Y, Ling L, Ismail M, He W, Xia Q, Zhou W, et al. Redox sensitive lipid-camptothecin conjugate encapsulated solid lipid nanoparticles for oral delivery. Int J Pharm. 2018 Oct;549(1–2):352–62.
99. Dinarvand M, Kiani M, Mirzazadeh F, Esmaeili A, Mirzaie Z, Soleimani M, et al. Oral delivery of nanoparticles containing anticancer SN38 and hSET1 antisense for dual therapy of colon cancer. Int J Biol Macromol. 2015 Jul;78:112–21.
100. Sun Q, Luan L, Arif M, Li J, Dong QJ, Gao Y, et al. Redox-sensitive nanoparticles based on 4-aminothiophenol-carboxymethyl inulin conjugate for budesonide delivery in inflammatory bowel diseases. Carbohydr Polym. 2018 Jun;189:352–9.

101. Li S, Xie A, Li H, Zou X, Zhang Q. A self-assembled, ROS-responsive Janus-prodrug for targeted therapy of inflammatory bowel disease. J Control Release. 2019 Dec;316:66–78.
102. Yang M, Zhang Y, Ma Y, Yan X, Gong L, Zhang M, et al. Nanoparticle-based therapeutics of inflammatory bowel diseases: A narrative review of the current state and prospects. J Bio-X Res. 2020 Dec;3(4):157–73.
103. Wilson DS, Dalmasso G, Wang L, Sitaraman S V., Merlin D, Murthy N. Orally delivered thioketal nanoparticles loaded with TNF-α–siRNA target inflammation and inhibit gene expression in the intestines. Nat Mater 2010 911. 2010 Oct;9(11):923–8.
104. Zhang Q, Tao H, Lin Y, Hu Y, An H, Zhang D, et al. A superoxide dismutase/catalase mimetic nanomedicine for targeted therapy of inflammatory bowel disease. Biomaterials. 2016 Oct;105:206–21.
105. Huang P, Yang C, Liiu J, Wang W, Guo S, Li J, et al. Improving the oral delivery efficiency of anticancer drugs by chitosan coated polycaprolactone-grafted hyaluronic acid nanoparticles. J Mater Chem B. 2014 Jun;2(25):4021–33.
106. Li S, Jin M, Wu Y, Jung S, Li D, He N, et al. An efficient enzyme-triggered controlled release system for colon-targeted oral delivery to combat dextran sodium sulfate (DSS)-induced colitis in mice. Drug Deliv. 2021;28(1):1120–31.