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Carbohydrate-based nanocarriers and their application to target macrophages and deliver antimicrobial agents

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ABSTRACT

Many deadly infections are produced by microorganisms capable of sustained survival in macrophages. This reduces exposure to chemadrotherapy, prevents immune detection, and is akin to criminals hiding in police stations. Therefore, the use of glyco-nanoparticles (GNPs) as carriers of therapeutic agents is a burgeoning field. Such an approach can enhance the penetration of drugs into macrophages with specific carbohydrate targeting molecules on the nanocarrier to interact with macrophage lectins. Carbohydrates are natural biological molecules and the key constituents in a large variety of biological events such as cellular communication, infection, inflammation, enzyme trafficking, cellular migration, cancer metastasis and immune functions. The prominent characteristics of carbohydrates including biodegradability, biocompatibility, hydrophilicity and the highly specific interaction of targeting cell-surface receptors support their potential application to drug delivery systems (DDS). This review presents the 21st century development of carbohydrate-based nanocarriers for drug targeting of therapeutic agents for diseases localized in macrophages. The significance of natural carbohydrate-derived nanoparticles (GNPs) as anti-microbial drug carriers is highlighted in several areas of treatment including tuberculosis, salmonellosis, leishmaniasis, candidiasis, and HIV/AIDS.

Contents

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1. Introduction

Recent developments in medicine and biotechnology have fortified the requirement to improve nanoengineered non-viral delivery systems able to encapsulate a range of novel biological and chemo-therapeutics [1–5]. In addition, these delivery systems should be designed and prepared in an intelligent way such that they can deliver their encapsulated therapeutics at a well-defined time, place, or in response to a specific stimulus with minimum cytotoxicity in comparison with viral systems. Delivery of therapeutic agents to the major sites of infection is still a major concern in the treatment of infectious diseases. Traditional development of many potential therapeutics is often limited by lack of selectivity and poor biodistribution that can be circumvented by targeted drug delivery [6]. In drug delivery systems (DDS), the therapeutic agent is escorted to the specific target site such that it influences the maximum absorption of the drug as well as minimizes the undesirable side effects. Moreover, DDS protect the therapeutic from quick degradation or clearance, thereby increasing the amount of drug in target tissues/cells, and hence lowering the effective dose [7,8].

The development of glycotechnology, glycobiology and glycomics and their continual adaptation by pharmaceutical scientists have highlighted the enormous potential of carbohydrates for medicinal applications [9]. Carbohydrates represent the third class of informational biomolecules after proteins and nucleic acids which play vital roles in both physiological and pathological events including cell signalling, differentiation, proliferation, tumor metastasis, inflammatory response and viral infection [9]. Carbohydrate-based non-viral nanoparticulate systems are commonly known as glyconanoparticles (GNPs) [10]. GNPs have gained considerable attention in studies of carbohydrate-carbohydrate and carbohydrate-protein interactions in the fields of targeted drug (chemical and biological) delivery systems. With recent advances in polymerization techniques and glycoscience, the design and preparation of carbohydrate-based biomaterials has been a field of rapidly expanding research in the 21st century. For example, biocompatible polysaccharides have been exploited for designing and preparing GNPs and the targeting efficacies of these GNPs toward certain organs can be modulated either by incorporating specific ligands on the nanoparticle surface or by increasing the densities of carbohydrates.

In general, drugs can be delivered to macrophages by incorporating specific targeting ligands (active targeting) or can be targeted to particular organs or cells based on their own or their drug carrier's size and physicochemical properties (passive targeting) [9]. When most drugs are applied in free form to treat macrophage-mediated disease this often prompts undesirable side effects because of lower bioavailability at the desired site. Therefore, it necessitates high drug doses to induce a therapeutic effect to overcome systemic dilution. For this, the application of drug-loaded GNPs offer a useful circumvention of many side effects and increased potency at the site of infection [11]. This review summarizes (1) the synthetic methods for the preparation of various GNPs and (2) their application in the delivery of antimicrobial agents to macrophages. The first of these areas is covered as a broad overview to highlight the various methods of GNP assembly. Comprehensive coverage is beyond the scope of this review and many examples relate to cancer drug delivery; however, these also have potential application as macrophage DDS.

2. Nanocarriers used in drug delivery systems

Nanoparticle DDS are nanometric carriers used as a delivery vector of different drugs and biomolecules. According to the National Nanotechnology Initiative of the United States, nanotechnology is the research and development of technology at the atomic, molecular, or macromolecular levels to provide a fundamental understanding of materials and phenomena on the nanometer scale and creation of structure, devices or systems that have novel properties and functions [12,13]. Recent nanotechnology research and development shows that nanoparticles measuring under 100 nm in at least one dimension are potential drug transporters. Due to their small sizes and large surface areas, the nanostructures provide unique biological and physicochemical properties that make them a favourable material in healthcare management including nanotherapeutics.

2.1. Advantages of nanoparticle-based DDS

Nanotechnology has opened a new field in DDS by the widespread utilization of nanocarriers including nanospheres, nanocapsules, nanovesicles, nanoemulsions, nanoliposomes, nanosuspensions, nanocrystals, micelles, virosomes, solid-lipid nanoparticles (SLN), and protein-based nanoparticles. The application of nanoparticles as a drug delivery tool has outstanding benefits [13–15]: (a) they possess the ability of drug targeting to the site of action and enhancing drug uptake that enables it to reduce toxic side effects; (b) they can exhibit controlled drug release properties against different physicochemical and metabolic responses (pH, ionic strength, biodegradability); (c) they may cross the blood-brain barrier and also accumulate in organs (brain, lung, liver, spleen, lymph nodes); (d) they are able to encapsulate drugs into their interior structures or adsorb them onto their exterior to improve the stability of the pharmaceutical agents.

2.2. Preparation and application of nanoparticles in DDS

At present, nanoparticles are being comprehensively developed to deliver drugs, vaccines, polypeptides, genes, photo/fluorophores, photo-responsive molecules, and photo-thermal agents. However, the potential application of nanoparticles is continually expanding, and some of these new areas are summarized in Fig. 1 [16,17]. The preparation of nanoparticles for DDS depends on the selection of carrier materials to attain desired release properties and their surface modification to enhance their targeting capability [18,19]. Researchers

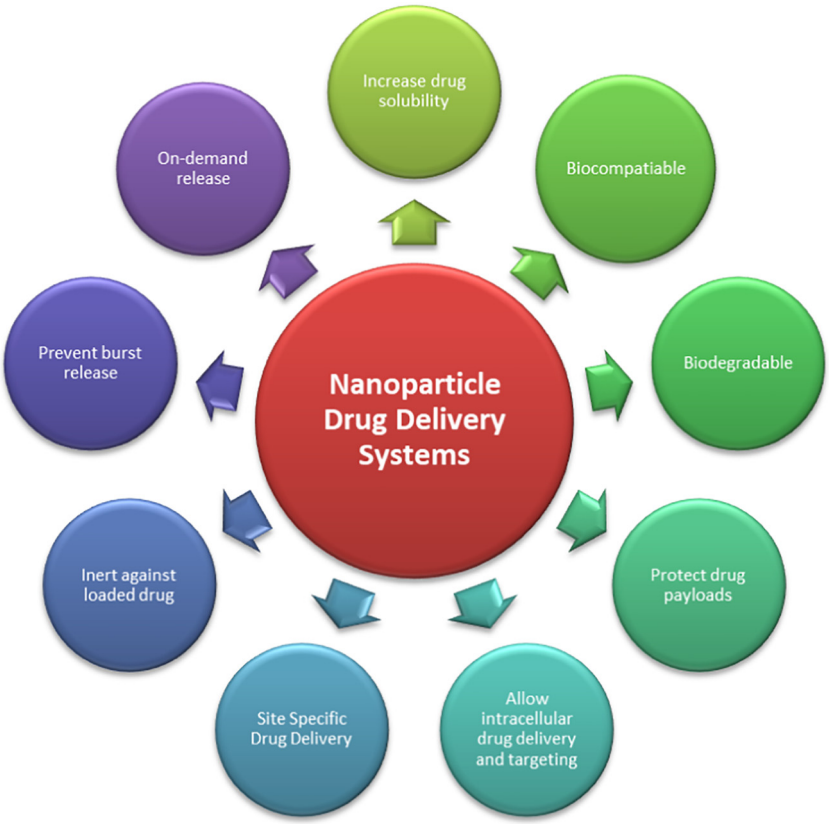


Fig. 1. Important features of nanoparticle DDS for intracellular applications.

have also investigated *in vivo* processes to reveal the interaction of nanoparticles with blood and target tissues and organs [20–22]. Furthermore, development of nanocarriers for application in a clinical setting must address their large scale production [13,23–25].

Polymeric GNPs prepared from either natural polysaccharides or synthetic polymers have been studied extensively by researchers due to their stability and simplicity of modification. It is important that polymeric nanocarriers for DDS be biocompatible and ultimately biodegradable. For this reason, many synthetic and natural polymers have been used such as poly(ethylene glycol), poly(glycolic acid), Pluronic, poly (vinyl pyrrolidone), poly(lactic acid), poly(lactic-co-glycolic acid), poly (acrylic acid) family, polytrimethylenecarbonate, polysaccharides (i.e., alginate, amylose, chitosan, heparin, hyaluronic acid, cyclodextrin), proteins or polypeptides (i.e., gelatin) [26–28]. Natural polymers such as polysaccharides and proteins can be readily internalized and degraded promoting intracellular drug/biomolecule release. Thus, polysaccharides have been frequently applied in the preparation of DDS in preference to other polymeric materials due to their biodegradability, general stability, biocompatibility, and often low immunogenic activity [29].

3. Polysaccharide-based nanoparticles and their advantages

Polysaccharides are a unique class of natural (plant, animal, algal, microbial) origin polymeric materials formed *via* glycosidic linkages between monosaccharides. Polysaccharides can form linear or branched chemical structures depending on the nature of the monosaccharides. Polysaccharides exhibit diverse structural variations consisting of modifiable groups including hydroxyl, amino, and carboxylic acid functionality. Additionally, the molecular weight of polysaccharides is widely distributed in ranges from hundreds to thousands of Daltons providing further structural diversity. Moreover, polysaccharides can exist in anionic, cationic and neutral charge states [30]. In addition, certain polysaccharides such as chitosan [31] display antimicrobial properties and may display synergism with antibiotic cargo. Also, the abundance of hydroxyl groups imparts non-covalent bioadhesion with biological tissue like epithelia and mucous membranes, and this can improve drug targeting. Unlike some synthetic polymers, polysaccharides generally display very low toxicity with a high biocompatibility and are subject to enzymatic degradation [32]. and their breakdown products are building blocks that can be reused by the cell [33]. Finally, polysaccharides are an inexpensive renewable natural resource. All of these advantages support their use as an effective carrier platform for DDS. A list of polysaccharides used for macrophage targeted drug delivery is shown in Table 1.

3.1. Preparation methods of glyconanoparticles (GNPs)

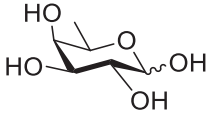
3.1.1. Covalently crosslinked glyconanoparticles

Initially, preparation of GNPs was carried out by means of covalent crosslinking. Covalently crosslinked GNPs form permanent network structures that still permit absorption of drug molecules even if pH is significantly changed [91,92]. Depending on the crosslinker, these networks can be biodegradable or stimuli-responsive to factors such as pH, temperature and light. These attributes are particularly useful in macrophage-promoted drug release where intracellular pH is lower than the bloodstream. The most commonly used polysaccharide for GNP development is chitosan. Chitosan is a linear polysaccharide, composed of glucosamine and *N*-acetyl glucosamine units *via* β-(1→4) linkages. Chitosan, the *N*-deacetylation product of chitin, is much more water soluble than chitin and highly soluble at acidic pH. Importantly, it undergoes enzymatic degradation from lysozymes, some proteases and lipases [93]. Crosslinking of chitosan can be carried out with many agents: glutaraldehyde, dopamine, genipin, and non-toxic acids such as citric acid, malic acid, succinic acid, tartaric acid [94–98]. Recently, Meng and co-workers have synthesized dual pH-/light-responsive crosslinked nanocarriers by using glycol chitosan-*o*-nitrobenzyl

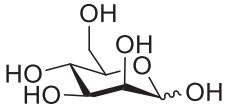
Table 1
Chemical structures of mono-, oligo-, and polysaccharides that are used in the development glyconanoparticle drug delivery systems are shown below.

Monosaccharides

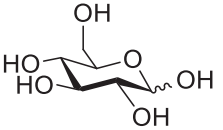
Fucose [34,35]



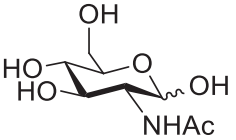
Mannose [19,40,41]



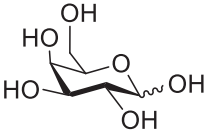
Glucose [36,37]



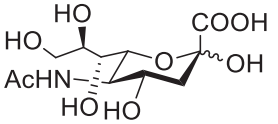
N-acetyl glucosamine [42,43]



Galactose [38,39]

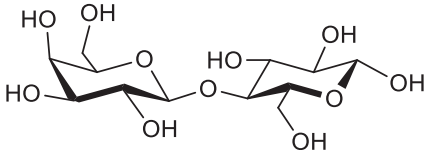


Sialic acid [44,45]

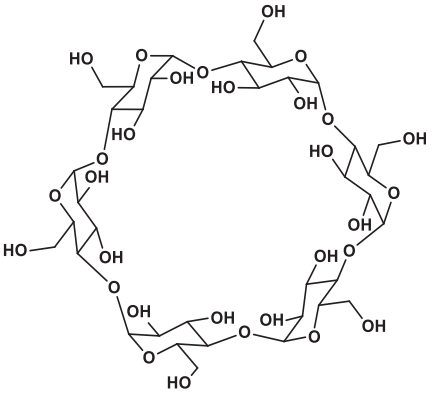


Di- or Oligosaccharides

Lactose [38,46]

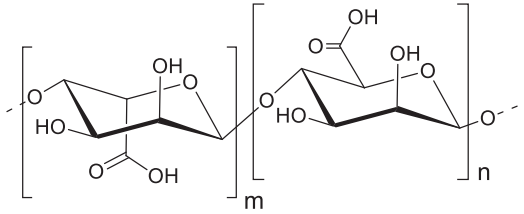


α-Cyclodextrin [47–49]

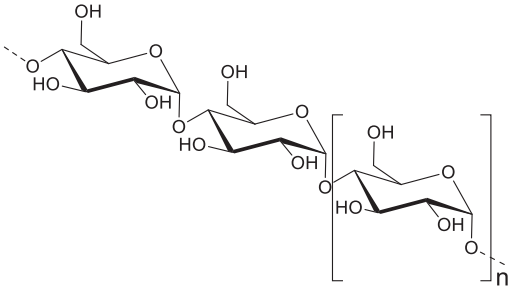


Polysaccharides

Alginate [23,50,51]



Amylose [26,52]



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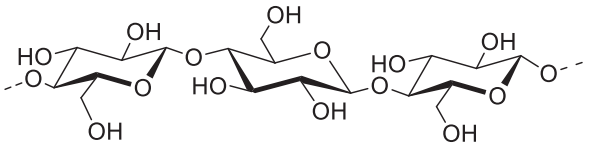
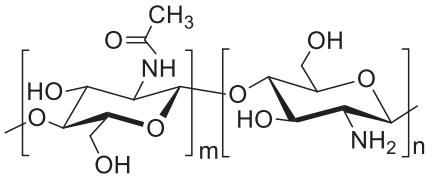
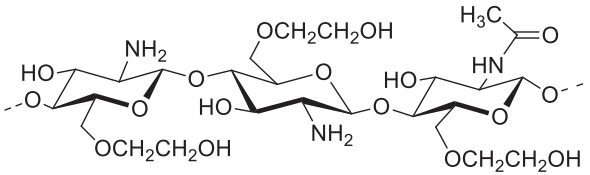
Cellulose [53,54]



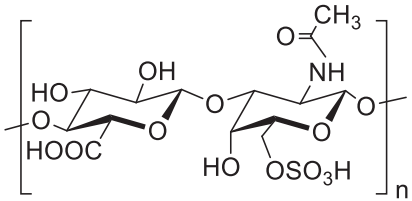
Chitosan [57,58]



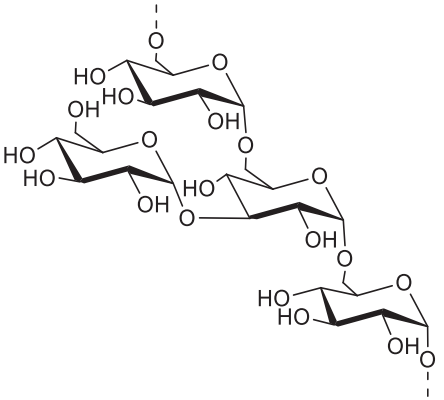
Glycol chitosan [61,62]



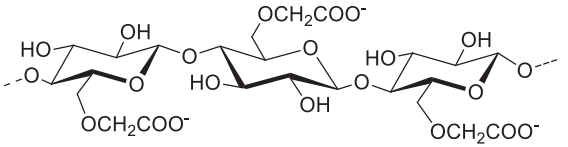
Chondroitin sulphate [19,65]



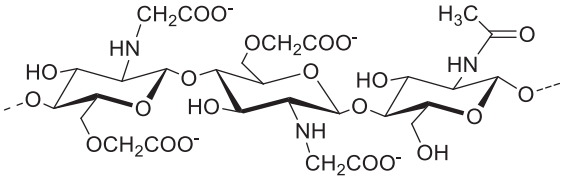
Dextran [68,69]



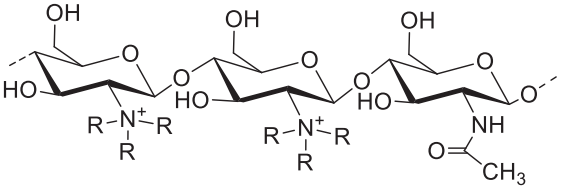
Carboxymethyl cellulose [55,56]



Carboxymethyl chitosan [59,60]

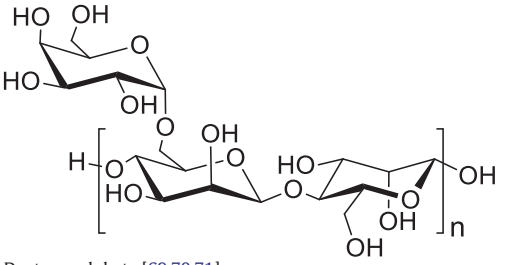


N-trimethyl or triethyl chitosan [63,64]

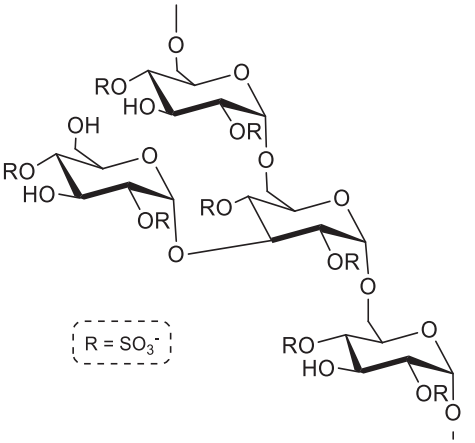


R = CH_3 or -CH_2CH_3

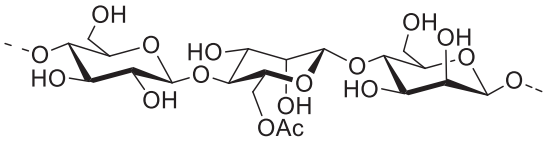
Guar gum (guaran) [66,67]



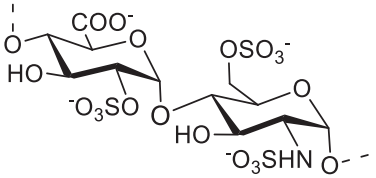
Dextran sulphate [69,70,71]



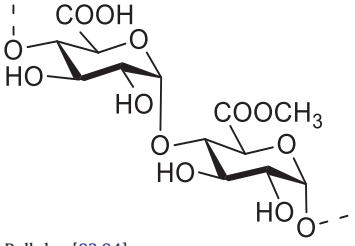
Glucomannan [72,73]



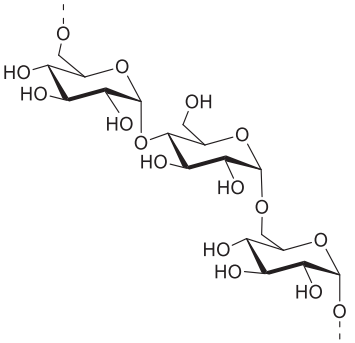
Heparin [34,75]



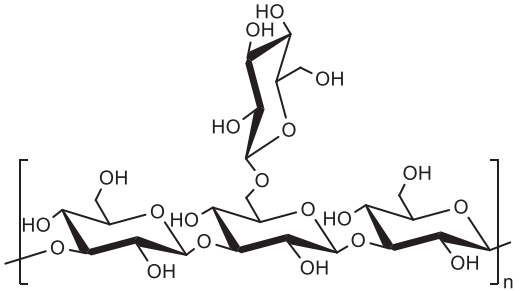
Pectin [79,80]



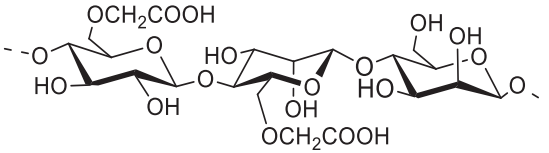
Pullulan [83,84]



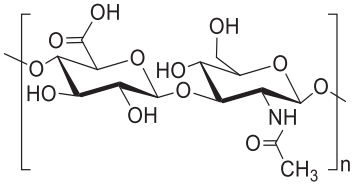
Schizophyllan [87,88]



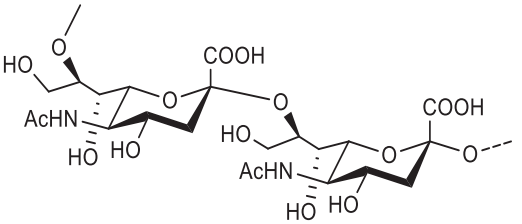
Carboxymethyl konjac glucomannan [72,74]



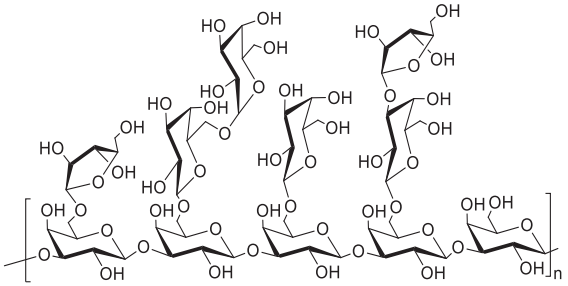
Hyaluronic acid [76–78]



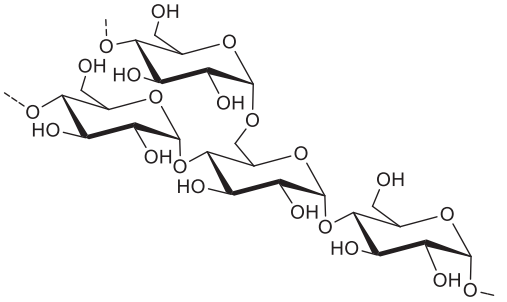
Poly(sialic acid) [81,82]



Arabinogalactan [85,86]



Starch [89,90]



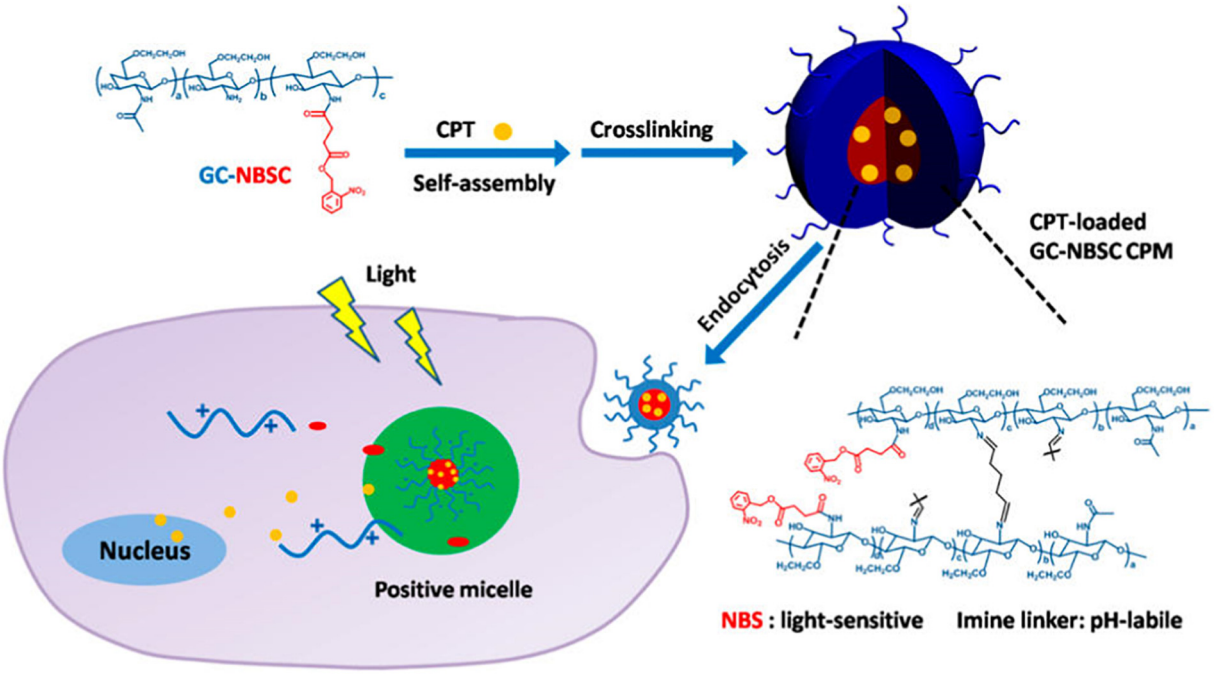


Fig. 2. Schematic representation of preparation method of chitosan based camptothecin (CPT) encapsulated nanocarrier and intracellular drug release triggered by pH and UV light. Taken with permission from Meng et al. Copyright © American Chemical Society [99].

succinate (GC-NBSCs) conjugates to crosslink with glutaraldehyde [99]. Following succinate conjugation, nanosized micelles were prepared by the self-assembly of GC-NBSCs under aqueous conditions and further stabilized by cross-linking their GC shells with glutaraldehyde to form dual responsive nanocarriers (Fig. 2).

Genipin, a naturally occurring crosslinking agent, has been used as cross-linkers of amino groups on chitosan backbones using water-in-oil (w/o) microemulsion method and also provided significantly less cell cytotoxicity compared to glutaraldehyde in crosslinking amine group containing biomaterials. For instance, multifunctional genipin-crosslinked fucose-chitosan/heparin GNPs have been created by Yu-Hsin and co-workers [34]. In this study, they combined genipin with fucose-conjugated chitosan to prepare pH-responsive chitosan/heparin nanoparticles (180–230 nm) (Fig. 3).

Chih and Kuang have developed pH-responsive chitosan nanocapsules with tuneable sizes through interfacial crosslinking of *N*-maleoyl-functionalized chitosan (MCS) using a thiol-ene reaction in a w/o mini-emulsion. This chemistry is shown below in Fig. 4 [91].

Hyaluronic acid (HA) is another common polysaccharide employed in the preparation of GNPs due to its presence in mammalian cells making it biocompatible. The chemical composition of HA consists of nonsulfated glycosaminoglycan containing repeat units of disaccharide, β-1,4-D-glucuronic acid and β-1,3-*N*-acetyl-D-glucosamine, with a molecular weight ranging from 100 kDa to 8000 kDa. Bondar and co-workers have prepared spherical GNPs by covalently cross-linking HA chains using carbodiimide techniques. An injectable hydrogel showing excellent tissue adhesion was developed using catechol-thiol reactions between the two biocompatible copolymers of HA and pluronic copolymer. HA-dopamine conjugates and thiol terminated Pluronic F127 copolymers were mixed to produce HA/Pluronic hybrid hydrogels using catechol-thiol reactions [100]. Rolf and co-workers have obtained covalently stabilized trimethyl chitosan-hyaluronic acid nanoparticles with sizes of about 200–300 nm for nasal and intradermal vaccination [101]. Recently, robust GNPs were prepared by conjugating HA and branched polyethyleneimine (bPEI) through carbodiimide chemistry and these were consequently capped at the copolymer termini with mannose [102]. Martinez et al. synthesized GNPs with a size range of ca. 40–400 nm based on thiolated alginate and modified albumin, which were created by the formation of disulphide bonds crosslinks [103]. Jayanta and co-workers used an w/o emulsion polymer using glutaraldehyde as a crosslinker to prepare tamoxifen-loaded guar gum GNPs [104].

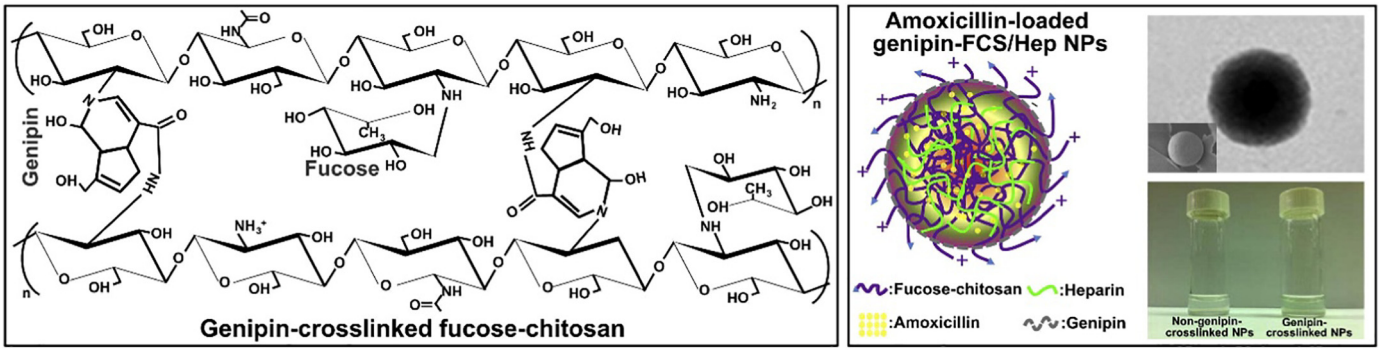


Fig. 3. A schematic representation of prepared amoxicillin-loaded genipin-crosslinked fucose-chitosan/heparin nanoparticles. Adapted with permission from Yu-Hsin et al. Copyright © 2013 Elsevier Ltd [34].

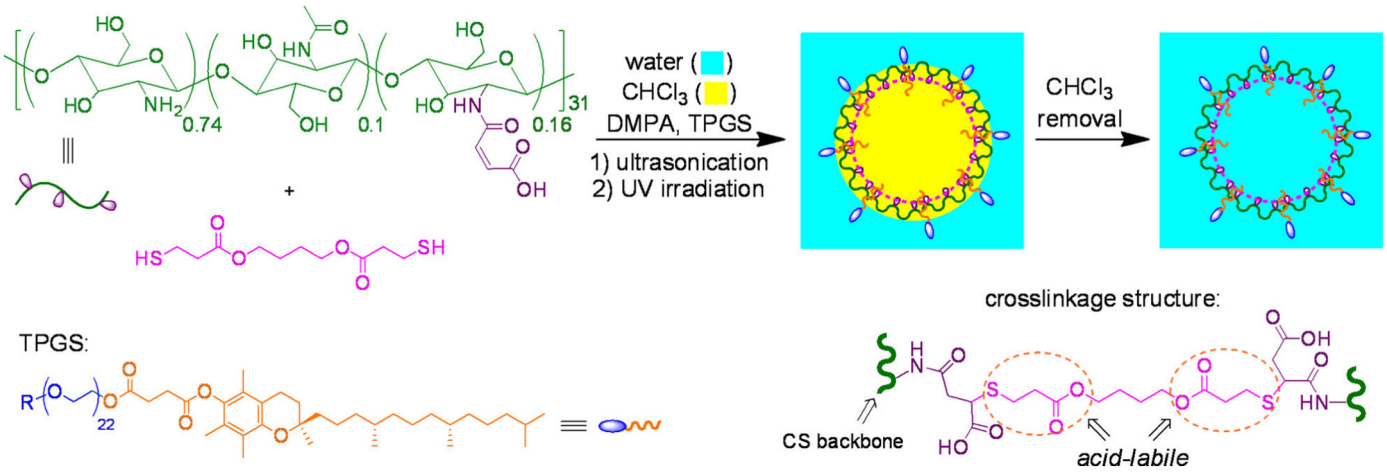


Fig. 4. Preparation of chitosan nanocapsules *via* miniemulsion interfacial cross-linking. Taken with permission from Chih-Kuang et al. Copyright © American Chemical Society [91].

3.1.2. Ionically crosslinked glyconanoparticles

GNPs can be formed by ionic cross-linkers and charged polysaccharides through electrostatic interactions. This reversible process provides GNPs that are biocompatible due to the lack of complex synthetic conditions or toxic cross-linkers. These GNPs are pH sensitive, and thus can potentially be used for stimuli-responsive drug release. GNPs can be obtained using polycations and polyanions acting as crosslinkers with polyanionic and polycationic polysaccharides, respectively. In this process, very dilute solutions of the polysaccharide are used to form GNPs with oppositely charged electrolytes [105].

To date, tripolyphosphate (TPP), a non-toxic and multivalent polyanion, is the most used crosslinker for the generation of GNPs with cationic chitosan [106–110]. The positive charge of chitosan in an acidic solution (pH ca. 4–6) will create GNPs resulting from inter- and intrastrand linkages between chitosan's amino groups and negatively charged TPP phosphates in basic solutions (pH 7–9) [111,112]. An ionotropic gelation method employed by Domaratzki & Ghanemin created smooth, spherical chitosan GNPs using the TPP crosslinker [110]. Their results show that nanoparticle size depends on degree of hydration, and crosslinking conditions, with the smallest GNPs in the size range of 160–270 nm. TPP-chitosan GNPs have been developed to deliver DNA, siRNA, proteins, doxorubicin, cladribine, and some antibiotics (such as aminoglycosides, rifampicin, ceftriaxone, ciprofloxacin) with high encapsulation efficiency [69,113–116].

Water soluble chitosan derivatives (*N*-trimethyl chitosan, mannose-conjugated chitosan, galactosylated *N*-trimethyl chitosan, PEGylated chitosan, glycyrrhetinic acid-modified chitosan) have been also ionically crosslinked using TPP as ionic crosslinkers to prepare GNPs [41,63,117–122]. These GNPs are capable of swelling and shrinking based on physical and chemical stimuli including temperature, pH and ionic strength, consequently promoting release of the encapsulated drug. Recently, Xu et al. developed chitosan-TPP/IL-12 nanoparticles to deliver therapeutic macromolecules [123]. The modified chitosan-TPP shows a mean diameter that ranges from 178 to 372 nm along with an increasing in the chitosan/TPP weight ratio. They also measured the zeta potential of these GNPs in ranges between 24 and 53 mV depending on the feeding ratio of chitosan and TPP [123].

Other researchers have obtained chitosan GNPs *via* more subtle physical crosslinking using functionality on the drug to cross-link forming H-bonding with compounds such as retinol, cladribine, or glabridine [110,124,125]. Recently, chitosan and adenosine-5'-triphosphate (ATP) were combined to form spherical aggregates based on electrostatic interactions (Fig. 5) [126]. Since the ratio between ATP and chitosan varies during dropwise addition of the former to the latter, part of the chitosan is associated with ATP and rest of the chitosan remains cationic and hydrophilic (Fig. 5). In this way, a polymeric supra-amphiphile is fabricated and is responsible for chitosan-ATP aggregated by self-assembly with sizes between 50 and 68 nm.

Amongst the more abundant anionic polysaccharides, alginate is widely used to obtain GNPs. Alginate is a polysaccharide from brown algae made of alternating blocks of 1–4 linked α-L-guluronic (G-block) and β-D-mannuronic acid (M-block) residues. These are arranged in a pattern of different proportions of M-M, M-G and G-G blocks [57]. Carboxylate groups on the main chain of alginate structure can be crosslinked through small cations like bivalent calcium, strontium, zinc, or barium ions to form GNPs [57]. Alginate can be crosslinked to create gels either directly in a solution of calcium salts or by mixing with an insoluble calcium salt [127,128]. Polylysine can form a polyelectrolyte

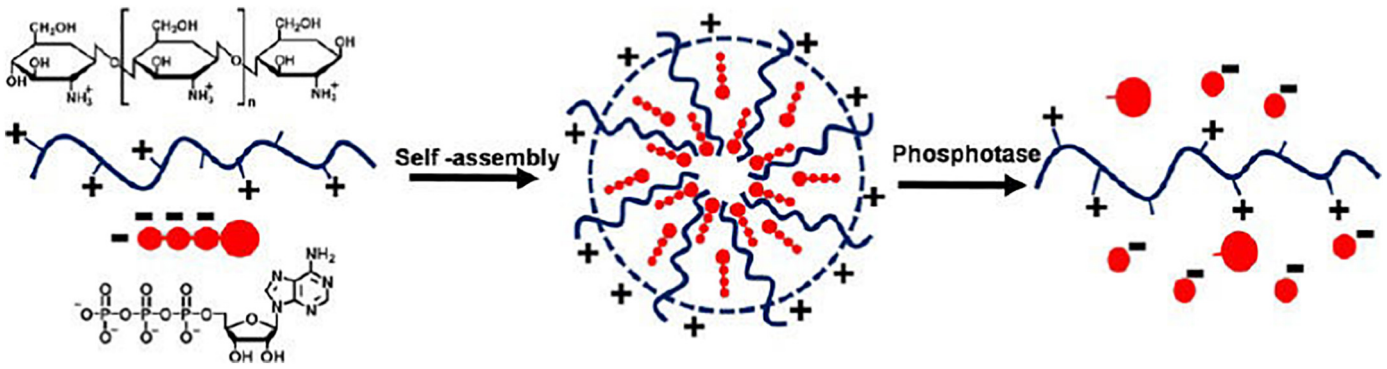


Fig. 5. Schematic illustration of the formation and the phosphatase-induced degradation of the polymeric supra-amphiphiles and the spherical aggregates. Adapted with permission from the Yuetong et al. Copyright © American Chemical Society [126].

complex (PEC) with alginate without pre-gel formation with Ca^{2+} [129]; however, more compact GNPs are formed otherwise [130]. The synthesized GNPs can be developed in various particle sizes and such PEC are an important class of GNP's.

3.1.3. GNPs by polyelectrolyte complexation (PEC)

GNPs can be prepared using oppositely charged polysaccharides without the addition of covalent cross-linkers. The major interaction between two polyelectrolytes is achieved by the strong but reversible electrostatic interaction, along with hydrogen bond and hydrophobic interactions. The stability of polyelectrolyte complexes (PEC) is dependent on a number of factors including pH, temperature, mixing ratio, and the molecular weight of the polyelectrolytes. Compared to chemically crosslinked complexes, PEC derived GNPs are generally less toxic, more biocompatible and well-tolerated due to ease of preparation and modification. Based on the type and concentration of the polysaccharides used, positively or negatively charged GNPs can be prepared. The hydrophobic interior of the GNPs comprises complexed neutral segments ("salt bridges") whereas the exterior extrudes the positive or negative charge of the GNPs from the excess components of polyelectrolytes not incorporated during the PEC process [105].

In general, aqueous soluble and biocompatible polysaccharides are utilized to form GNPs, however a variety of polyelectrolytes can be used to prepare PEC nanoparticles. Chitosan is extensively utilized among the known polyanionic and polycationic polysaccharides because of its improved solubility and safety characteristics. The cationic nature of chitosan is derived from its free amino groups subsequently yielding a cationic polyelectrolyte which can develop PEC with negatively charged polyelectrolytes [57]. Extensive research has been conducted on PEC with chitosan and many polyanions from different categories such as alginate, pectin, carboxymethyl cellulose (CMC), heparin, dextran sulphate, hyaluronic acid, carrageenan, collagen, xanthum gum, carboxymethyl pachyman, poly(acrylic acid) (PAA), or nucleic acids [23,46,57,79,111,131–136].

Motwani et al. have synthesized chitosan-sodium alginate nanoparticles based on the formation of PEC between the free amines on chitosan and alginate carboxylates [131]. In this case, particle sizes of the prepared GNPs were between 62 and 193 nm under optimal conditions with a maximum zeta potential value of 47.8 mV. Guo and co-workers developed alginate-coated chitosan PEC using hydrophobic modification for delivery of bovine serum albumin (BSA) [137]. In this study, the amphiphilic molecule deoxycholic acid was grafted into chitosan to form nano-sized self-aggregated GNPs in water. Then the positively charged chitosan-deoxycholic acid nanoparticles were coated with a linear alginate to obtain stable self-assembled alginate-coated hydrophobically-modified chitosan nanoparticles. Chitosan/carrageenan nanoparticles were prepared by PEC as means of interaction of ammonium groups with sulfate anions [136]. The reported nanoparticles can be readily prepared *via* a ionic gelation method. The surface charge of the prepared GNPs depends on both the mixing order and ratio of these polymers resulting in nanoparticles with sizes between 350 and 650 nm and positive zeta potentials were obtained within a range of 50–60 mV. Rodrigues and co-workers reported that the particle size of carrageenan and chitosan formed GNPs could be reduced from 500 nm to 200 nm with the incorporation of TPP into the polymer solution. The addition of tripolyphosphate (TPP) into the nanoparticle solution also improved yields from 20% to 35% [138].

Chitosan PECs have been prepared by Lee et al. for siRNA delivery using the alginate-related polyguluronate to produce GNPs ranging in size from 110 to 430 nm [139]. Dextran sulphate and pectin have also been used as negative polyelectrolytes to form PEC with chitosan or its derivatives for antibiotic and protein drug delivery [32,70,79,140]. GNPs *via* PEC of chitosan and carboxymethyl cellulose (CMC) have also been developed and applied to antibiotic delivery [56,135]. Cafaggi et al. obtained GNPs by PEC of a cisplatin-hyaluronate complex with a modified chitosan and found a mean particle size of approximately 195 nm [141]. More recently, Ramasamy and co-workers developed layer-by-layer (LBL) method to produce GNPs through a sequential deposition of chitosan and HA on negatively charged hybrid solid lipid nanoparticles (SLNs) for drug delivery to tumour cells (Fig. 6) [142]. The reported GNPs (ca. 265 nm diameter, zetapotential ca. –12 mV) showed both controlled and time dependent doxorubicin release characteristics.

The formation of GNPs from poly(acrylic acid) (PAA) and chitosan using PEC have been investigated by several groups. For instance, Chen and co-workers developed GNPs under different experimental conditions *via* complexation between polyanionic PAA and polycationic chitosan solutions forming nanoparticles with diverse microstructure [143]. Rolland et al. developed PEC based GNPs from chitosan and PAA homopolymers and polystyrene-block-PAA diblock copolymers [144]. They also investigated nanoparticle size and found the particles sizes were less than 100 and 200 nm for PEC of chitosan with homopolymer and copolymer, respectively. Tang et al. obtained a thermoresponsive chitosan/PVA hydrogel consisting of GNPs with charge differences through the electrostatic effect of the quaternary amines from trimethyl ammonium chitosan and carboxylates from carboxymethyl chitosan [145]. They also found the release of the positive or negative charged drugs were the slowest from hydrogels containing negative or positive charged nanoparticles, respectively. Davidenko and co-workers reported chitosan/PAA PEC nanoparticles and found it was possible to obtain suspensions of GNPs for solution concentration of 0.1 wt% [146]. They also demonstrated the pH values affected both the yield and the particle size of the complex that was formed. A pH value of 4.5–5.5 for chitosan and 3.2 for PAA resulted in optimal nanoparticle yields of around 90%.

Apart from chitosan, PEC GNPs can also be formed using negatively charged polysaccharides combined with a positively charged peptides like poly-L-lysine (PLL) [80,147,148]. For example, Boissiere et al. have studied silica/poly-L-lysine/alginate nanocomposites for targeted drug delivery applications [149]. PLL/alginate and silica/PLL/alginate nanoparticles were obtained by a spray-drying technique that exhibits a homogenous structure. PLL-alginate nanospheres were prepared by De & Robinson *via* formation of the calcium alginate aggregates, and subsequent transfer to an aqueous solution of PLL to obtain more compact nanospheres (ca. 300–400 nm) [130]. Recently, polyanionic PEGylated hyaluronic acid (HA-g-PEG) was created to interact with cationic polycaprolactone-graft-poly(*N*,*N*-dimethylaminoethyl-methacrylates) and DNA forming GNPs *via* PEC (Fig. 7) [150]. The obtained nanoparticles size was ca. 54 nm with a negative Z of approximately –10 mV.

3.1.4. Self-assembled GNP's

Amphiphilic polymers are generated when hydrophobic fragments are grafted onto hydrophilic polymers allowing them to form micelles/vesicles. Therefore, introduction of hydrophilic polysaccharide backbones into hydrophobic segments generates self-assembled micelles/vesicles *via* undergoing intra- or intermolecular associations. Nanoparticles can be formed by maintaining the relative lengths and molar ratios of both polysaccharides and hydrophobic segments. Hydrophobic segments on polysaccharides are obtained by adding hydrophobic molecules onto hydroxyl, amino, or carboxylic groups on the polysaccharide's chain. In general, self-assembled GNPs can become reservoirs for hydrophobic drugs. The hydrophobic compounds useful for self-assembled nanostructures include pluronic copolymers, poly(ε-caprolactone), cholesterol, deoxycholic acid, long-chain fatty acids, and other hydrophobic carboxylic acids.

Amphiphilic poly(ethylene glycol) (PEG) is extensively used in drug delivery because of its excellent physico-chemical and biocompatible properties such as high hydrophilicity, low toxicity and biodegradability. In recent years, chitosan has been decorated with various PEG derivatives producing GNPs with a size range of 60–280 nm [151–155]. A pH-sensitive, self-assembled GNP of PEGylated carboxymethyl chitosan

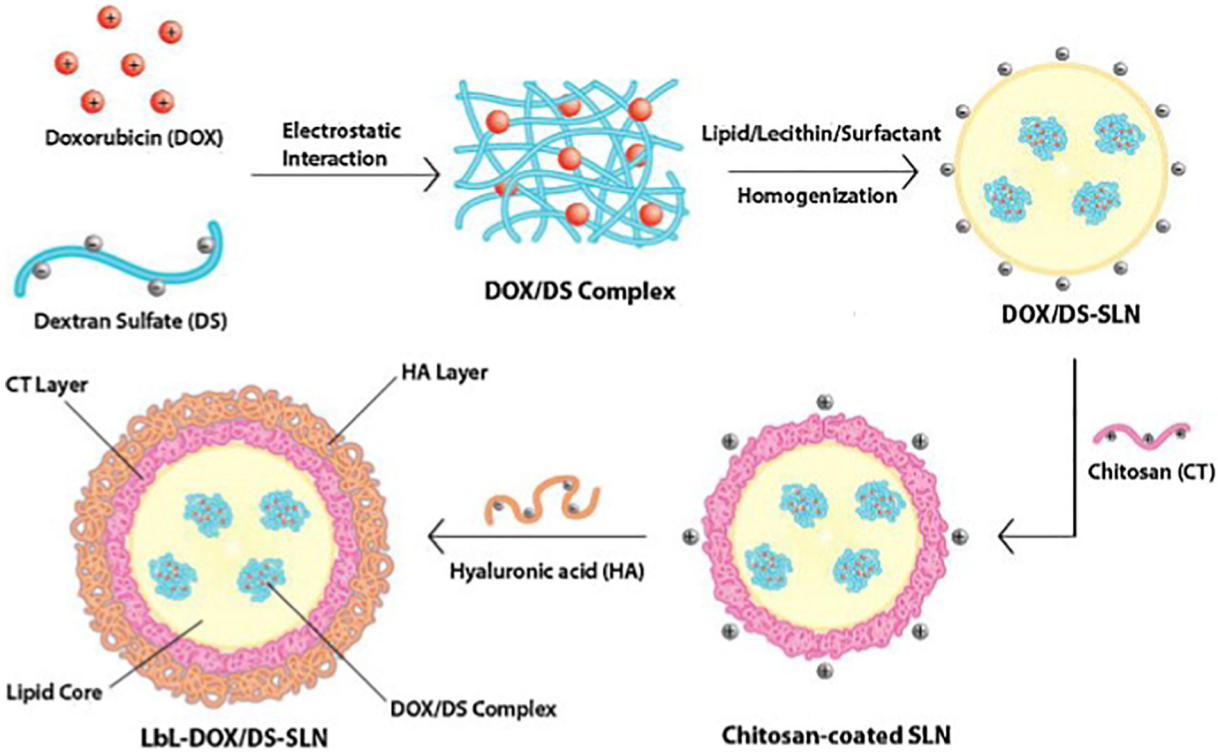


Fig. 6. Diagram illustrating the preparation process for layer-by-layer (LBL)-coated solid lipid nanoparticles (SLN) containing DOX/DS complexes. Taken with permission from Ramasamy et al. Copyright © 2013 Elsevier Ltd [142].

(PEG-CMCS) was reported by Xie et al. to deliver siRNA for anticancer therapy (Fig. 8) [134]. The amphiphilic PEG groups actually assemble on the GNP surface while the polysaccharide creates an internal shell around the RNA cargo. Vasquez and co-workers reported GNPs using PEGylated chitosan *Bombyxmori* copolymers by self-assembly in dilute aqueous solution [151]. Gao et al. developed siRNA/trimethylated chitosan/PEG complexes through bifunctional PEG for improved oligonucleotide delivery to the brain and obtained particles sizes between 115 and 325 nm with positive surface charges ranging from 3.3 to 11.5 mV [155]. Guo et al. synthesized PEGylated sodium alginate nanoparticles *via* a self-assembly method to improve the drug loading and efficacy of antitumor drugs [156].

Cholesterol is one of the most utilized cyclic hydrophobic molecules to create self-assembled GNPs. Yuan et al. developed cholesterol-modified chitosan GNPs (<230 nm) for ocular drug delivery using 1.7–4.7% cholesterol substitution per glucosamine unit [157]. Self-assembled cholesterol-chitosan GNPs were prepared with varying degrees of substitution by a probe sonication method to provide spherical nanoparticles in the 100–235 nm size range [158–160]. Wang et al. also applied a probe sonication method to obtain self-aggregated cholesterol-modified chitosan nanoparticles [161]. Other steroids have been used to modify polysaccharides to create self-assembled GNPs. Recently, glycyrrhetinic acid-sulphated chitosan conjugates were synthesized to create liver targeted drug delivery systems [162,163].

3.1.5. GNPs obtained by copolymerization

Glycopolymers are a class of synthetic polymers derived from traditional monomers decorated with carbohydrates. Glyconanoparticles are formed using various glycopolymer chains in aqueous conditions by introducing a hydrophilic block into the glycopolymer. Glycopolymers can mimic cell surface distribution of glycoconjugates and act as multivalent binding ligands for lectins. Self-assembly of amphiphilic diblock copolymers permits formation of wide ranging nanoparticles that have application in nanomedicine including drug delivery [164–166]. For instance, glycopolymers are very attractive for use in the self-assembly of GNPs and the delivery of therapeutics [167]. This is due to the synthetic glycopolymer exhibiting carbohydrate functionalities that are similar to those of natural glycoconjugates and promote their performance in specific biomedical applications. Moreover, glycopolymers permit greater structural diversity in the construction

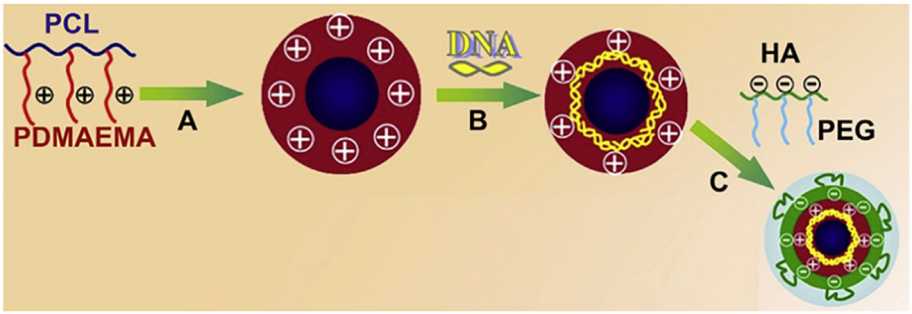


Fig. 7. Schematic illustration of (A) self-assembly of PCL-g-PDMAEMA NPs (B) formation of binary polycation/DNA complexes (C) formation of polycation/DNA/HA-g-PEG complexes. Taken with permission from Zhang et al. Copyright © 2013 Elsevier Ltd [150].

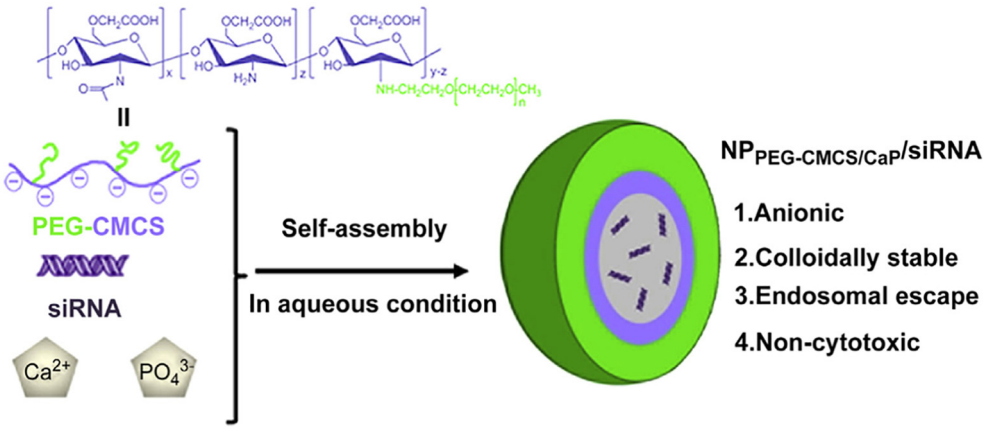


Fig. 8. Schematic representation of the formation of siRNA loaded PEG-CMCS/CaP hybrid anionic nanoparticles (NPPEG-CMCS/CaP/siRNA). Taken with permission from Xie et al. Copyright © 2014 Elsevier Ltd [134].

of GNPs to allow for a wider range of engineered properties to be explored.

Copolymers are synthesized through the sequential addition of two polymerizable monomers. Copolymers can be developed mechanistically through sequential, anionic, cationic, non-radical metal-catalysed and controlled radical polymerization [164,168]. All of these synthetic procedures allow exquisite control over copolymer composition, structure, molecular weight, dispersity, solubility, and stability [165]. Synthesis of such glycopolymers was first developed by Kiessling using ring-opening polymerization [169–171]. and expanded with advances in controlled radical polymerization. Glycopolymers can be prepared either by the polymerization of "glycol-monomers" or by polymer modification with glycosyl donors [172]. To prepare GNPs, radical polymerization, emulsion polymerization, and preformed copolymer are each utilized.

3.1.5.1. GNPs by radical polymerization. Radical polymerization has attracted much attention due to its use in the synthesis of glycopolymers in aqueous solution. Controlled radical polymerization is an excellent method for the preparation of glycopolymers and this area has been reviewed recently [173]. In one example, radical polymerization of monomers (e.g.- alkyl cyanoacrylate, methyl methacrylate) in the presence of dextran or heparin was initiated by cerium IV ions [30]. The acidic conditions lead to the diblock copolymer formation between polysaccharides and monomers by the cleavage of polysaccharides *via* cerium ions. The formation of nanoparticles with surface carbohydrate residues occurs in aqueous media due of the amphiphilic nature of the copolymer. In general, amphiphilic diblock copolymers bearing both a hydrophobic block and a hydrophilic block can assemble into larger aggregates. The GNPs prepared by this method show less cytotoxicity due to the lack of organic solvents and surfactants as well as creating nanostructures exhibiting a high degree of stability [30].

Alternatively, living radical polymerization has been reported to synthesize GNPs allowing a facile tuning of the molecular weight and the structure of these polymers [174]. Recent progress in these techniques allows synthesis of polymers with well-defined α- and ω-terminal functionality, which is ideal for terminal functionalization and bioconjugation. Methods including reversible addition-fragmentation chain transfer (RAFT) [175–178]. atom transfer polymerization (ATRP) [179–181]. nitoxide-mediated polymerization (NMP) [182]. cyanoxyl-mediated radical polymerization (CMRP) [183]. and iodine transfer polymerization [184]. have been reported to prepare well-defined GNPs.

Reversible addition fragmentation chain transfer (RAFT) allows the synthesis of a variety of desired molecular weight ranges and narrow polydispersity (PDI) under relatively mild reaction conditions [175]. RAFT is highly tolerant and can be utilized on functional groups common to carbohydrates [185]. The GNPs of varying molecular weights and architecture have been prepared *via* RAFT polymerization. The first glycopolymers synthesized by RAFT polymerization were reported in 2003 using a glucose-functionalized methacrylate monomer and showed "living" properties [186]. Briefly, 2-methacryloxyethyl glucoside was polymerized directly in water at 70 °C in the presence of (4-cyanopentanoic acid)-4-dithibenzoate and the resultant materials exhibited a low polydispersity and displayed "living" properties characteristic of the RAFT technique [186]. A related method was extrapolated to monodisperse and stable GNPs based on cationic glycopolymers which was composed of D-gluconolactone and aminoalkyl methacryamides [178]. Bertozzi's group has developed glycopolymers using facile modification of ketone-derivatized RAFT polymers with amino-oxy sugars to create mucin analogues [187–189]. In a recent example, these have been used to engineer the glycocalyx in vivo and increase cell survival [190]. Additionally, glycopolymers were constructed by combining anionic and RAFT polymerization to prepare highly stable polymeric nanostructures [191–195]. An example of this technique using a 2-(methacrylamido) glucopyranose monomer is shown in Fig. 9 [191].

Copolymers of 2-(methacrylamido) glucopyranose (MAG) and methacrylic acid have been polymerized by RAFT creating polymers with low dispersity (1.20) and a particle size of about 5 nm by this process [196]. Wu et al. also created a series of glycopolycations by copolymerizing MAG with an aminopropyl-methacrylate utilizing aqueous RAFT [197]. The prepared copolymers were able to bind plasmid DNA to create polyplex structures with diameters of about 45 nm and able to inhibit colloidal aggregation under physiological salt conditions [197]. Bernard et al. have synthesized linear poly-glucosamine in aqueous solution with unprotected hydroxyl groups using trithiocarbonate mediated RAFT and further chain extension with *N*-isopropylacrylamide to obtain narrowly dispersed (1.20) thermoresponsive diblocks [198]. Moreover, Stenzel and co-workers have reported the synthesis of novel glycopolymers by employing RAFT, such as the synthesis of unprotected poly(methyl 6-*O*-methacryloyl-α-D-glucoside) and its block copolymer as well as glycopolymer stars (dispersity ≤ 1.20) [185,198–200].

A number of galactosylated diblock copolymers were prepared by RAFT polymerization using polymerization-induced self-assembly (PISA) which were demonstrated to interact *in vitro* with galectins [39]. In this study, 1-thio-β-D-galactose was easily synthesized and subsequently reacted by thia-Michael addition prior to RAFT polymerization. After PISA, the polymer formed nanospheres, "worm-like micelles", or vesicles based on the PHPMA block length (Fig. 10) [39]. These were identified by transmission electron microscopic (TEM) imaging.

Recently, Chen and co-workers have developed glyconanoparticles of about 200 nm through a one-pot synthesis method using poly(2-(methacrylamido) glucopyranose) (PMAG) and porphyrin for the

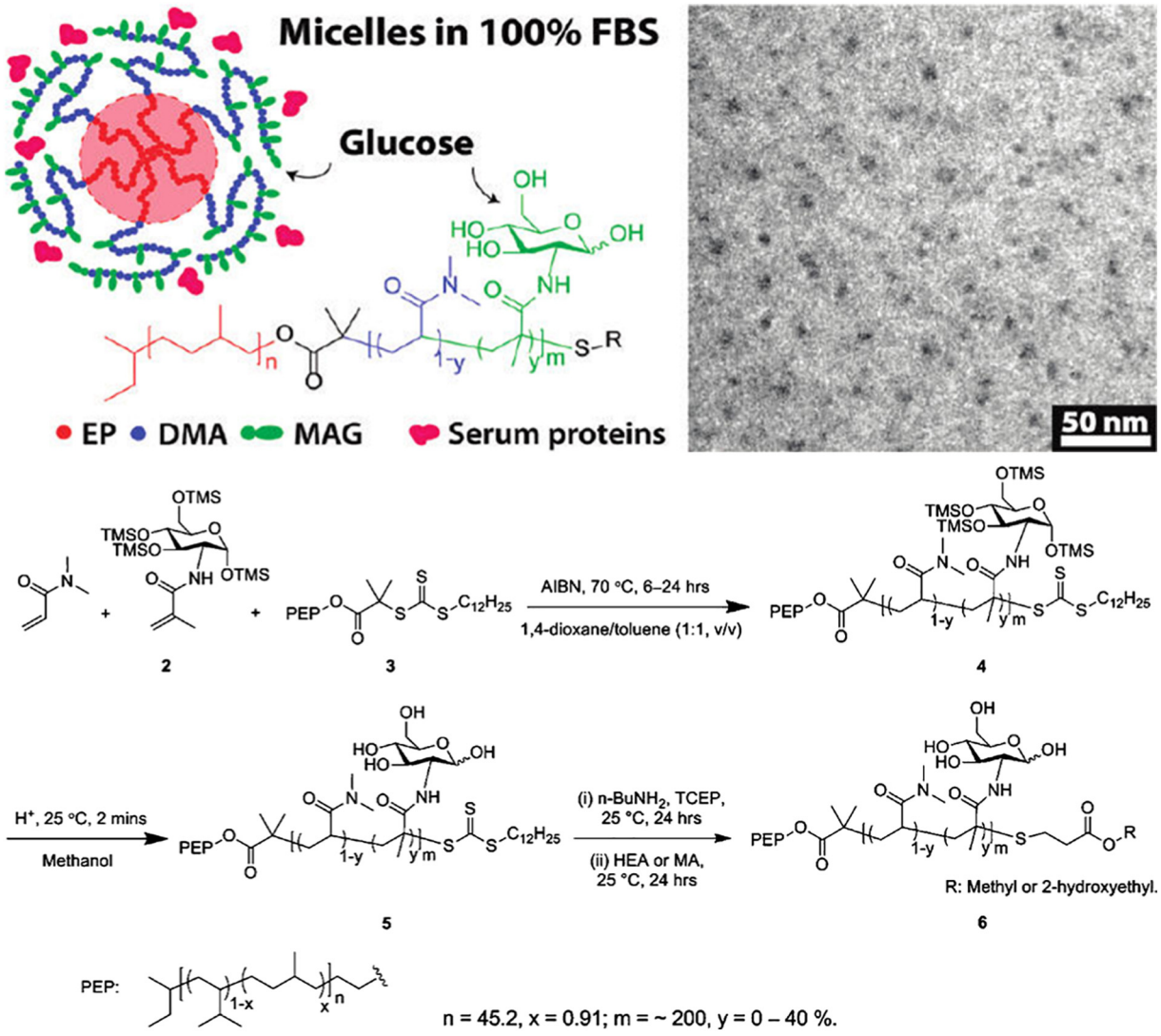


Fig. 9. Preparation of PEP-Poly(DMA-grad-MAG) Diblock Terpolymers. Taken with permission from Ligeng et al. Copyright © American Chemical Society [191].

purpose of cancer imaging and therapy [203]. More recently, the same group developed a highly efficient method to synthesize gradient glycopolymers by combining enzyme catalysis and RAFT (Fig. 11) [201]. Furthermore, glycopolymer-coated Fe_2O_3 nanoparticles of different shapes were synthesized using PMAG, dopamine methacrylamide (DMA), iron oxide nanoparticles as a core *via* catecholic chemistry and thiol-ene chemistry by the same group (Fig. 11 d,e) [202].

Well-defined glycopolymers were prepared using mannose, galactose, and *N*-acetylglucosamine conjugated ethyl methacrylate (EMA) as glycomonomers *via* RAFT polymerization for targeting macrophages (Fig. 12) [204]. Then a pyridyl disulphide monomer was incorporated into the polymerization to conjugate a maleimide-containing fluorophore for tracking the glycoconjugates inside the macrophages [205]. Ahmed and Narain have synthesized a family of cationic glycopolymers of narrow dispersity (3–30 kDa) using RAFT techniques, and this was one of the first uses of synthetic glycopolymers designed to carry DNA [206]. The same research group have also created pH-sensitive linear or hyperbranched glycopolymers *via* RAFT polymerization to explore the cellular uptake and transfection efficiencies [207]. The anionic glycopolymers were then complexed with the branched poly(ethyleneimine) and this reduced its toxicity. Glycopolymer based dithiocarbamates-conjugates were synthesized by Ahmed et al. using RAFT polymerization and these were then treated with gold (I) phosphine to test as an anticancer agent [208]. Furthermore, Narain and co-workers have provided excellent reviews in the preparation of glycopolymers using RAFT polymerization [209–211].

Atom transfer radical polymerization (ATRP) has also proven to be a useful procedure in developing glycopolymers with poly(acrylate) backbones that create self-assembled GNPs. ATRP is also a controlled radical polymerization method like RAFT which can produce polymers with predictable molecular weight profiles. Various structures of glycopolymers have been successfully synthesized by ATRP such as multi-block, hyperbranched and graft glycopolymers, stars, and cylindrical brushes. The major advantage of ATRP is the creation of functionalized end groups. For instance, Li and co-workers described one of the first examples of glycopolymeric self-assembled nanostructures using an glucose modified ethyl acrylate for synthesis using ATRP [213]. Shortly thereafter, Fukuda et al. developed glucose substituted polymers *via* ATRP using a surface-immobilized initiator [214]. Maynard and Vazquez-Dorbatt synthesized biotinylated glycopolymers by ATRP using poly(methacrylate) modified with *N*-acetyl-D-glucosamine [215]. Müller and his group prepared hyperbranched glycopolymers and brushes to graft polystyrene nanospheres [216–218]. This group also designed temperature and pH-responsive spherical brushes using ATRP of galactose- and dimethylamino-modified methacrylates [218].

Temperature sensitive glucose-decorated nanoparticles reported by Alexander and Pasparakis have been shown to interact with bacteria that express glucose-binding lectins [219]. These GNPs were prepared

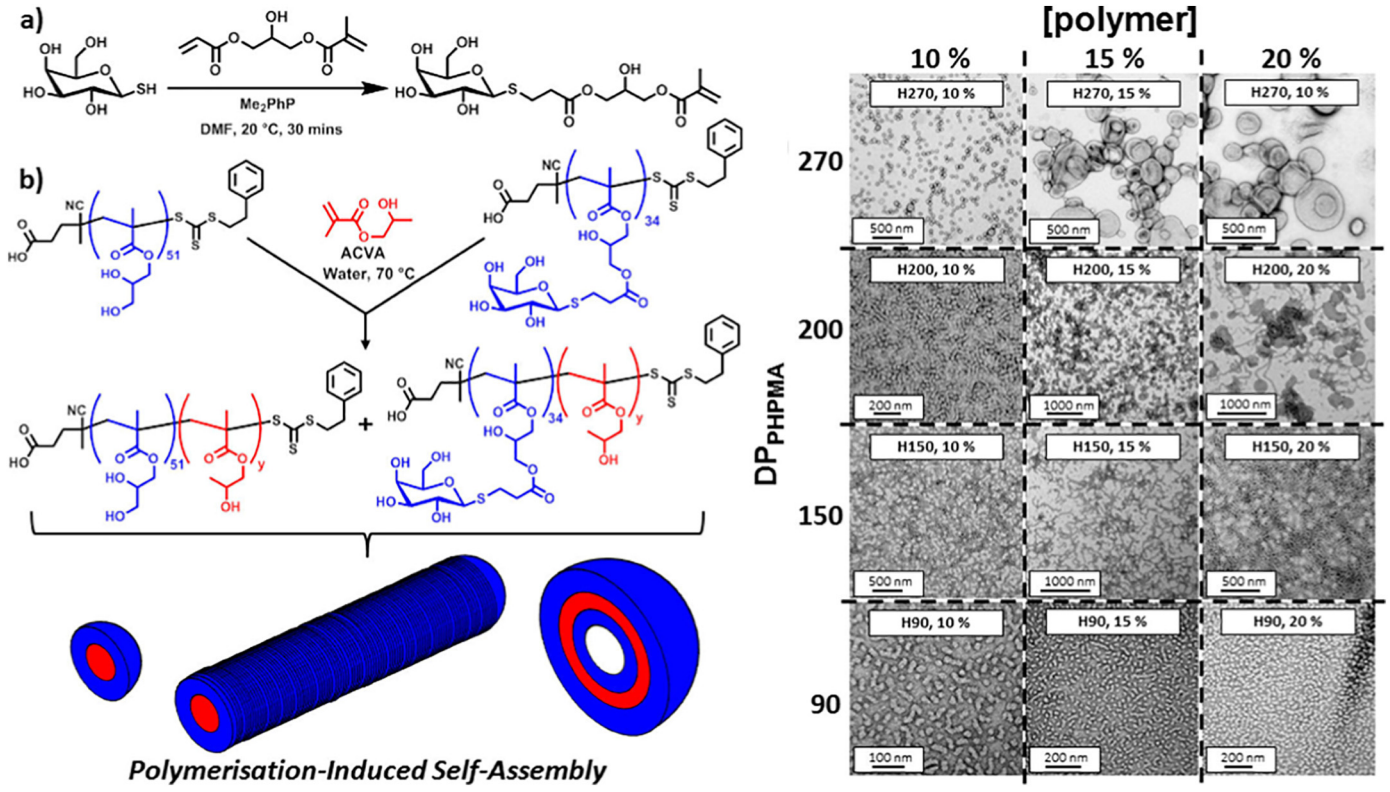


Fig. 10. (left) (a) Preparation of a GalSMA monomer using thia-Michael addition. (b) Development of self-assembled block copolymer nanoobjects (spheres, worms or vesicles) through PISA of HPMA using RAFT aqueous dispersion polymerization at 70 °C. (Right) Representative transmission electron microscopic (TEM) images attained for (1:9 $PGalSMA_{34}$ + $PGMA_{51}$)-PHPMA copolymer nano-objects. Taken with permission from Ladmiral et al. Copyright © American Chemical Society [39].

as copolymers obtained by ATRP and RAFT polymerization. Armes and co-workers described the preparation of a number of glycopolymers using ATRP polymerization in solution without the use of protecting groups [220–222]. Sun et al. incorporated sugar regioisomers (C1- and C6-linked galactose) as pendant groups in glycopolymers to create fluorescent nanoparticles (Fig. 13) [212]. The anomeric-linked (C1) isomers reached the late endosome and lysosome of the macrophage while the C6-linked isomers reached only the early endosomes. This group also developed glycopolymers with the same molecular weight and polydispersity containing respective monosaccharide stereoisomers, i.e. α-mannopyranoside, α-galactopyranoside and α-glucopyranoside utilizing ATRP to explore the stereoisomeric impact of the monosaccharide units of glycopolymers on hydrogelation [223].

Currently, single-electron transfer living radical polymerization (SET-LRP) has also been used to create functional glycopolymers and is a useful method of controlling vinyl polymerization [225,226]. In the case of SET-LRP, Cu(0) activates the polymerization and is oxidized to Cu(I) in the process and a disproportionation of the intermediate generates a Cu(II) deactivator [180]. As an example, Xue et al. synthesized thermoresponsive glucosamine-armed brushes by SET-LRP in water that produced micelles for binding and targeting applications [227]. An unprotected mannosylacrylate (ManA) has been polymerized by copper activation to obtain self-assembled, well-defined GNPs with narrow PDi's (Fig. 14) [224]. Haddleton and co-workers reported a novel SET-LRP approach in order to obtain a water-soluble glycopolymer with a narrow PDI dispersity by premixing Cu(0) with Cu(I) and Cu(II) salts prior to adding glycomonomer [225].

Diblock copolymers are generally synthesised through RAFT polymerisation containing a macro-RAFT agent to be further used for polymerization of the second monomer. The advent of "click chemistry" provides methods to expand this methodology, allowing for site-specific modifications [229]. Step growth polymerization using Cu(I)-catalyzed alkyne-azide cycloaddition (CuAAC) was explored [230]. and applied to the synthesis of mannose glycopolymers [185]. The resulting slightly amphiphilic glycopolymer-block-poly(vinyl acetate) was formed self-assembled GNPs with a hydrodynamic diameter around 200 nm [185]. Biocompatible glyconanocapsules have been successfully synthesised *via* interfacial step growth polymerization using CuAAC between a diazidosucrose derivative and bis(propargyloxy)butane [228]. Glyconanocapsules of 200 nm diameter were formed through optimization of the interfacial polymerization process in dispersed medium (Fig. 15). Moreover, Haddleton and co-workers studied different azido-sugar derived polymers prepared using ATRP containing alkyne side chain through CuAAC [231]. Recently, they synthesized a series of cyclodextrin (CD)-based glycoclusters by combination of two Cu-promoted steps: CuAAC and living radical polymerization (Fig. 16) which allowed high loading of anticancer and antiviral cargo [232]. The glycoconjugates also displayed significant interaction with immune lectin DC-SIGN that is normally hijacked by HIV envelop glycoprotein gp120 [232].

Nitroxide-mediated polymerization (NMP) is the oldest technique for controlled/living radical polymerization compared to ATRP and RAFT; however, it is infrequently employed for the synthesis of glycopolymers. A major limitation of NMP is that it requires extensive heating to permit the homolytic cleavage of an alkoxyamine initiator. Polymerization temperature is important as glycoconjugates and their monosaccharides are typically unstable at greater than 120 °C [233]. However, toxicity is usually reduced in NMP compared to polymers synthesized *via* ATRP and RAFT due to the fact that nitroxide compounds have been extensively developed as biocompatible probes for multiple applications in biological systems [234,235]. A major advantage of NMP compared to other polymerization methods is that it does not require use of toxic catalysts. For instance, polymers prepared using phosphonate-based NMP provide safer materials for biological applications [236].

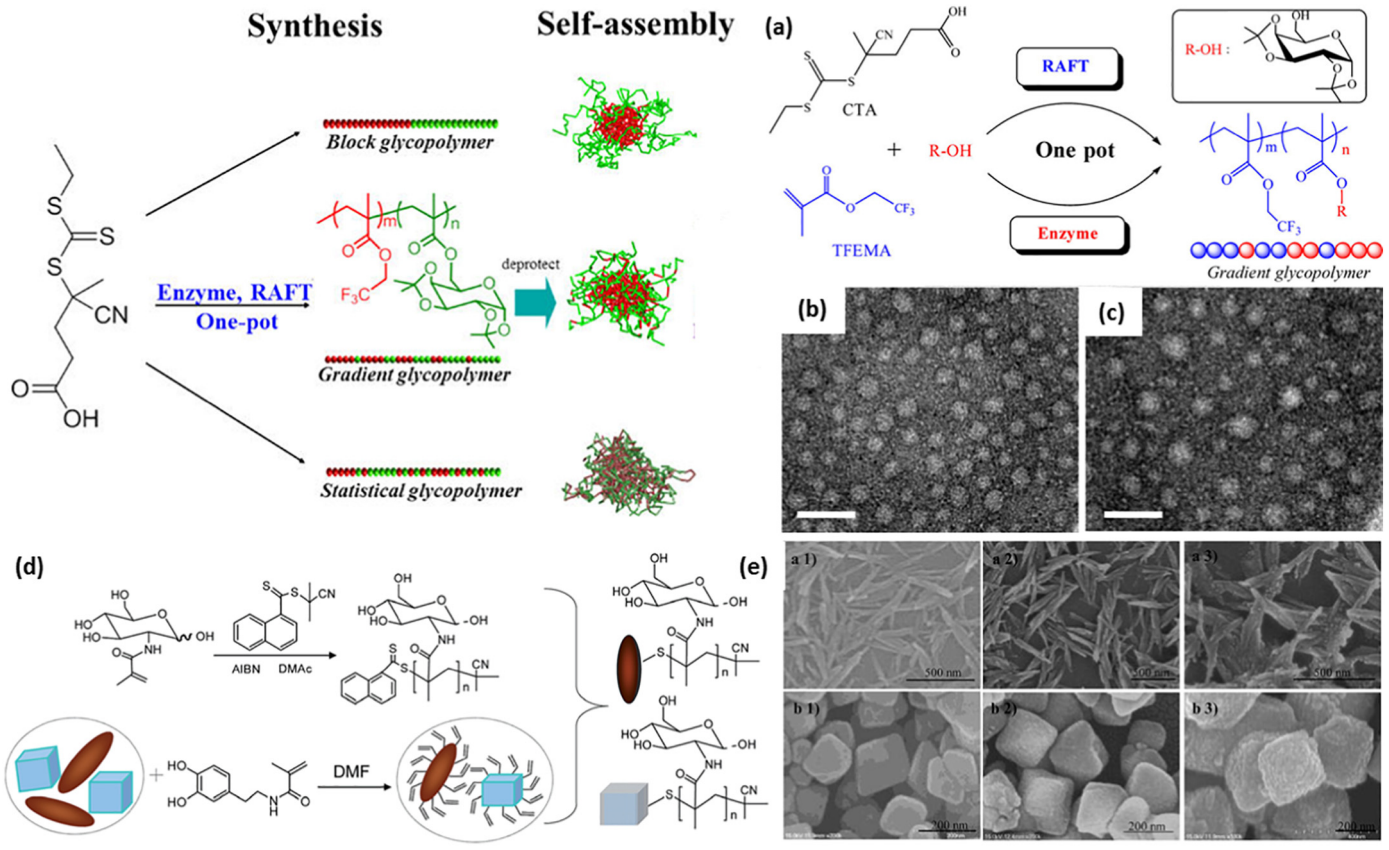


Fig. 11. (a) One-pot synthesis of the gradient glycopolymer through simultaneous enzymatic monomer transformation and RAFT polymerization. TEM images of the micelles with different architectures: (b) PMAG-g- PTFEMA; (c) PMAG-s-PTFEMA. Scale bars are 100 nm. Taken with permission from Jiawei et al. Copyright © American Chemical Society [201]. (d) Synthesis of glycopolymer-coated iron oxide nanoparticles and (e) SEM micrograph of (a1) Fe_2O_3 NPs; (a2) Fe_2O_3@DMA; (a3) Fe_2O_3@PMAG; (b1) Fe_3O_4 NPs; (b2) Fe_3O_4@DMA; (b3) Fe_3O_4@PMAG. Taken with permission from Li et al. Copyright © Royal Society of Chemistry [202].

Ohno et al. reported one of the first glycopolymers obtained by NMP, which was synthesized from acrylate and styrene glycosyl-monomers using a di-*tert*-butyl nitroxide initiator [233,237,238]. Kakuchi's group prepared star-shaped glycopolymers with amphiphilic properties using two styrene-glucoside derivatives [239]. To overcome the thermal demands of NMP reactions, Stenzel and co-workers prepared glycopolymers using methylacryloyl glycomonomer and styrene with *N*-*tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl) (SG1) and BlocBuilder® alkoxyamine mediator at 85°C [236]. The obtained amphiphilic glycopolymers showed self-assembled properties when polymerized in low concentrations of styrene and were used to prepare honeycomb shaped bioactive porous films for liver-targeted drug delivery (Fig. 17). Schubert and co-workers demonstrated the utility of a thiol-fluorine "click" reaction to generate a glucosyl tetrafluorostyryl monomer and carried out subsequent NMP polymerization at 110 °C for coating the magnetic iron oxide nanoparticles [240]. This group also synthesized similar glycopolymers using the same "click" reaction onto a preformed copolymer of styrene and tetrafluorostyrene [233]. Subsequently, a solvent displacement method was used to prepare GNPs with diameters of 15–40 nm (Fig. 18) [241].

Cyanoxyl-mediated radical polymerization (CMRP) was explored by Chaikof et al. for the synthesis of well-defined glycopolymers directly from unprotected glycomonomers [242–244]. In CMRP, selective and controlled polymerization has been described using metha-acrylate monomers in the presence of "persistent" cyanoxyl radical (•OC≡N) species. In a glycopolymer example, CMRP has been utilized to polymerize acrylate-derived glycomonomers (and co-polymerize with acrylamide) directly in aqueous conditions or with the use of THF as a co-solvent [245]. Moreover, multiple biotin-terminated glycopolymers have been developed by CMRP using lactose haptasulfate-based glycomonomers [244,246]. The resulting polymers were used to modify both quantum dots and magnetic beads [238]. Narla et al. synthesized sialyllactose-containing glycopolymers using sialyltransferases to modify a lactose-containing polymer prepared by CMRP [247]. More recently, Konradsson and co-workers reported the facile construction of long fucoidan-like glycopolymers chains using CMRP polymerization of monofucoside-pendant monomers [248]. The resulting sulfated methacrylamido α-L-fucoside glycopolymers exhibited comparable characteristics to natural fucoidan displaying simular levels of inhibition of HSV-1 binding and cellular uptake. Wibowo et al. designed fucosylated glycopolymers comprising of a proximal photoactivated group to trap glycan-binding lectins [35]. To synthesize glycopolymers with narrow dispersity, they explored *in situ* CMRP polymerization using fucose-α(1-2)-galactose and acrylamide in 1:1 ratio using H_2O/THF at 60 °C (Fig. 19) [35].

3.1.6. GNPs from preformed copolymer

Preformed polymers have been modified using aminosugars offering a simple alternative pathway to obtain GNPs as these glycopolymers have the tendency to self-assemble to form GNPs. Modification has focused on aminosugars as amines exhibit excellent nucleophilicity in comparison to alcohols and selective modification can be achieved without the use of protecting group chemistry [249]. In general, polymers with pendant carbonyl compounds including carboxylic acids, *N*-hydroxysuccinimide anhydrides and esters are reported to react with aminosugars such as lactosamine [250].

Alkylation reactions have also been used to append sugars to preformed polymers. Recently, Stenzel and co-workers developed glycopolymer-based nanoparticles using *N*-isopropyl acrylamide and *N*-homocysteine thiolactone acrylamide *via* RAFT polymerization [251]. The ring opening polymerization of amines and thiolactone

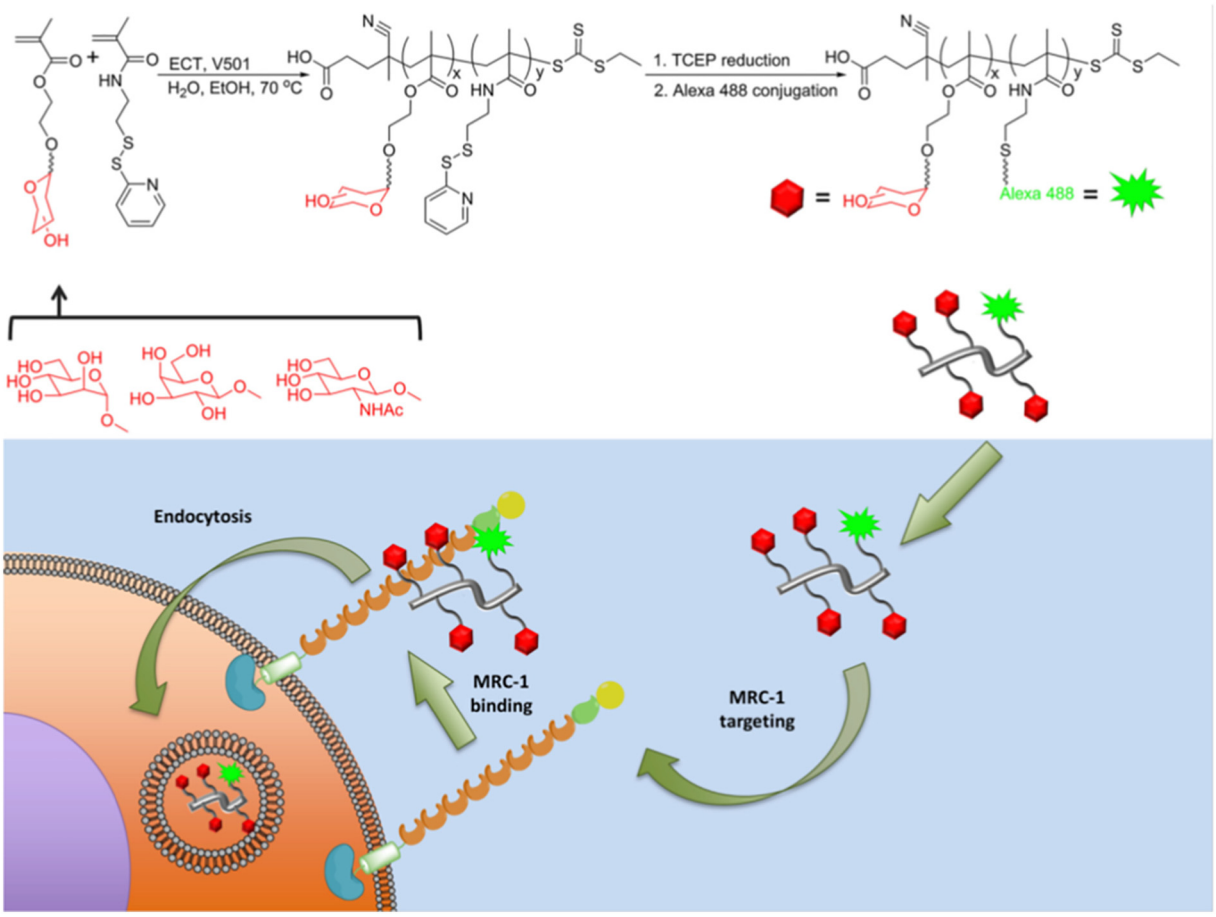


Fig. 12. The synthesis of fluorophore conjugated RAFT-mediated glycopolymers and their suggested mechanism of murine mannose receptor-mediated macrophage internalization. Taken with permission from Song et al. Copyright © 2012 Elsevier Ltd [204].

groups enabled subsequent thiol alkylation with a halogenated mannose derivative that further formed GNPs in aqueous solution with particle sizes between 200 and 600 nm [251].

3.1.7. GNPs developed via nanoprecipitation

Nanoprecipitation is a widely utilized method to prepare GNPs due to its simplicity and economy. This requires two solvents: one in which the polymer dissolves and a "non-solvent" in which it does not (usually water). The polymer solution is mixed with the non-solvent to produce nanoparticles. Briefly, the polymer is dissolved in a completely or partly water-miscible solvent (THF, ethyl acetate, acetone etc.) then is added to an aqueous solution which may contain a surfactant. Rapid de-solvation of the core polymer results in precipitation of nano-scale vesicles. Polysaccharide derivatives such as chitosan and amphiphilic cyclodextrins have been used to obtain nanoparticles through nanoprecipitation. One main drawback of nanoprecipitation is the large dilution of prepared dispersions, since dilute organic polymer solutions have to be used to avoid aggregate formation during polymer precipitation. However, several interesting GNPs have been prepared by this method.

Sodium sulphate is a widely utilized precipitating agent for generation of chitosan-based nanoparticles. Addition of this salt to a stirred solution of chitosan and polysorbate 80 yields particulate chitosan in the micro/nano range of 900–1100 nm following ultrasonication [253]. Amphiphilic cyclodextrin nanospheres have been synthesized by nanoprecipitation and were obtained in the range of 90 and 150 nm [254]. Gavory et al. reported the dextran-covered poly(lactic acid) nanoparticles *via* nanoprecipitation and produced small particles, with convenient yield and good colloidal stability [255]. Recently, surfactant-free glyconanocapsules have been synthesized through nanoprecipitation by Yan et al. using water soluble glycopolymers (Fig. 20) [252]. They showed initial addition of diisocyanate in the organic solvent allows the nanocapsules to be stitched *via* polymer shell cross-links enabling it to encapsulate hydrophobic molecules as well as to attach bioactive molecules of interest after introduction in the water phase [252].

4. Macrophage targeting

Macrophages are crucial components of the immune system and play a vital role to engulf and destroy microbes. However, pathogenic microorganisms sometimes have the ability to survive and replicate following ingestion by these sentinel immune cells, and this results in less effective treatments against infections occurring from facultative or obligate intracellular microorganisms. Furthermore, these reservoirs may cause chronic disease or delayed onset through latency. Since microorganisms can circumvent the effectiveness of antibiotics by surviving inside host cells, this can amplify the potential for drug resistance. Antibiotics in current use to treat intracellular infections belong to various classes including aminoglycosides, macrolides, fluoroquinolones, beta-lactams and glycopeptides. These therapeutics have varying ability to enter macrophages, limiting their efficiency as antimicrobial agents. Therefore, use of GNP delivery systems capable of directly targeting and modulating macrophages as well as possessing the ability for selective distribution in macrophages is critical to improve chemotherapeutic activity against intracellular infections.

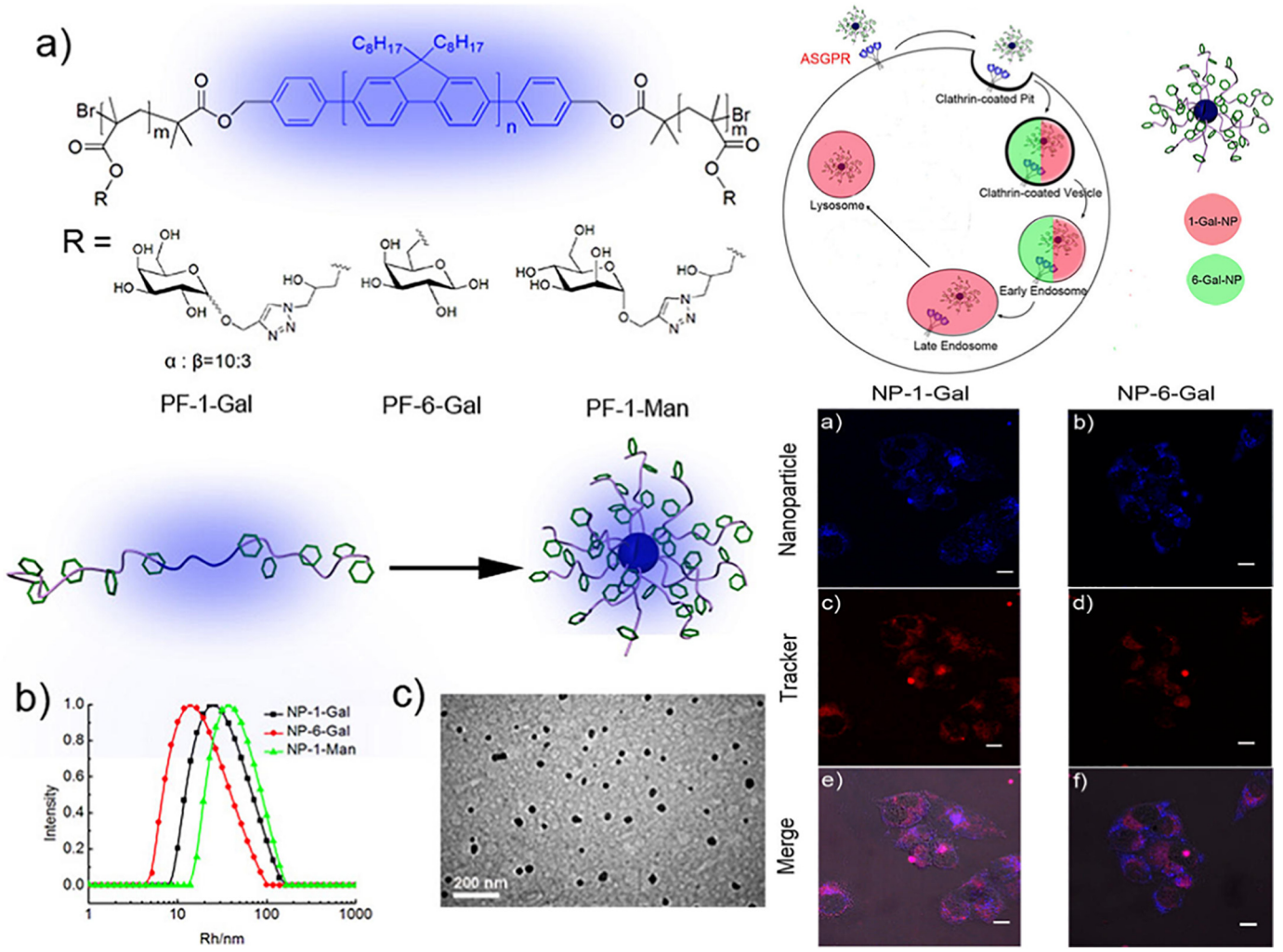


Fig. 13. (Left) (a) Chemical compositions of PF-1-Gal, PF-6-Gal, and PF-1- Man and the schematic illustration of the self-assembled nanoparticles. (b) Rh distributions of NP-1-Gal, NP-6-Gal, and NP-1-Man (c) TEM image of NP-1-Gal. (Right) schematic representation of cellular uptake and confocal fluorescence microscopy images show the subcellular of NP-1-Gal and NP-6-Gal within early endosomes of Hep G2 cells with scale bar 10 μm. Adapted with permission from Sun et al. Copyright © American Chemical Society [212].

Phenotypically distinct macrophage subsets are most often defined by two types of activation, termed M1 and M2. Classically-activated macrophages (M1 macrophages) are essential for host antimicrobial defence and play a role in antitumor immune response, whereas alternatively-activated macrophages (M2 macrophages) are critical for injury resolution and wound healing [256]. Additionally, disturbances in regulation of these functions are linked to autoimmune diseases, allergic asthma, atherosclerosis, and other conditions [256]. However, the simple M1 and M2 dichotomy of macrophage activation conceptualized in the pre-genomic era has become too broad to encompass the complexity of macrophage activation. Instead macrophage activation occurs by a response to several stimuli and macrophages acquire specialized functional phenotypes that exist on a spectrum that cannot be easily defined by two subsets [257–259]. To unify macrophage terminology many in the field proposed that the nomenclature should encompasses the macrophage source, definition of activators and markers to describe macrophage activation [260].

4.1. Phagocytosis and nanoparticle uptake by macrophages

Macrophages play vital roles in immunity against microorganisms through the phagocytotic process. Phagocytosis is the ingestion of foreign microorganisms by macrophages resulting in their subsequent destruction and elimination from the host. The cellular uptake of the microorganism occurs *via* surface receptors to form a phagosome, and this then fuses with lysosomes to form a phagolysosome [22]. Macrophages also generate antibactericidal agents including nitric oxide and cationic proteins contributing to the destruction of foreign microorganisms (Fig. 21a). In some diseases, macrophages are rendered incapable of destroying infectious microbes due to the latter's ability to prevent fusion of the lysosome and phagosome or by inhibiting the antimicrobial response within the phagolysosome. Consequently, microorganisms can lie dormant or even replicate within various organelles and/or cytosol of macrophages and this allows immune evasion (Fig. 21b).

Intracellular bacterial pathogens use several sophisticated mechanisms that facilitate replication within macrophages by invading host defence and influencing host processes such as membrane trafficking, signalling pathways, metabolism and modulation of host cell lifecycle pathways [261]. Intracellular bacteria can be broadly defined according to their colonization niche being either intravacuolar or cytosolic. Most intracellular bacterial species however have unique intracellular life cycles and adaptive mechanisms to survive intracellularly.

Intravacuolar bacteria generate specialized vacuoles that are biochemically and morphologically different to unaffected cells allowing them to avoid being trafficked by the phagolysosome and prevent cytosolic innate immune sensor detection [262]. The common function of these across species is to support intracellular replication however several strategies are used to remodel membrane bounded compartments

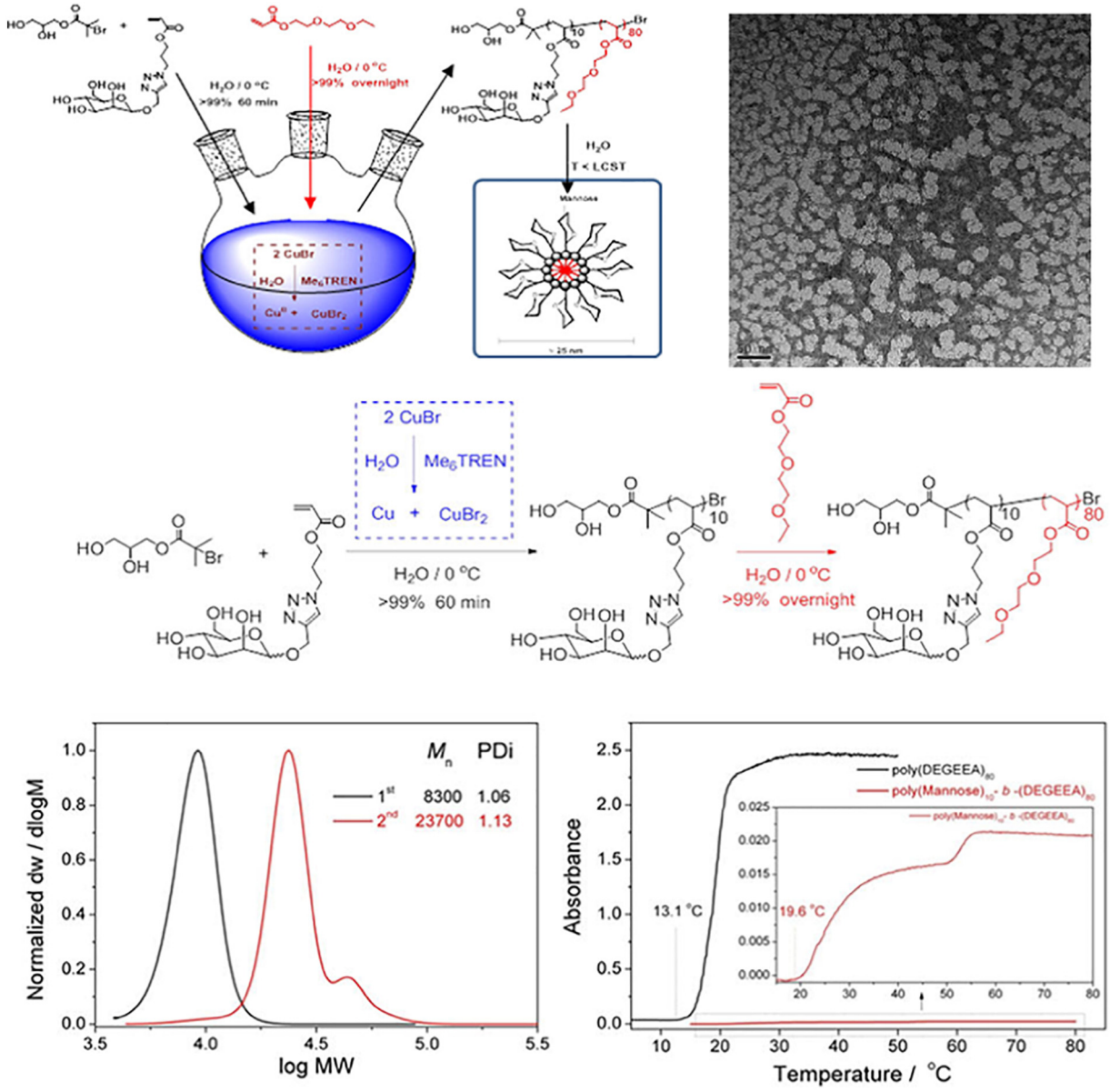


Fig. 14. Synthesis and characterization of poly(ManA)$_{10}$-*b*-(DEGEEA)$_{80}$ by SEC (DMF), UV—vis, and TEM image confirms the sugar-decorated nanoparticle micelles ≈25 nm. Taken with permission from Zhang et al. Copyright © American Chemical Society [224].

among different intravacuolar pathogens. Shortly after entry intravacuolar bacteria hijack host cell endomembrane systems to prevent or delay fusion with lysosomes [262]. Intravacuolar bacteria utilize specialized secretion systems to deliver effector proteins into the host cell to modify host physiology creating environments accommodating bacterial proliferation. Four major accessory secretion systems are known to establish intravacuolar bacterial replication niches through alteration of vesicular trafficking and host immune response [261]. Maintenance of these vacuoles is essential towards survival and intravacuolar bacteria target multiple host components and signalling pathways to maintain these replication niches [262,263,264].

Escape from the phagosome is crucial to cytosolic bacterial pathogen survival. Once inside the vacuole cytosolic bacteria secrete virulence factors that facilitate vacuole escape by disruption of the vascular membrane, where they go on to establish infection through manipulation of host innate immune responses [265,266]. Cytosolic bacteria are protected from extracellular immune responses and escape the microbicidal lysosomal environment; however, their detection by cytosolic pattern recognition receptors (PRRs) activates defence mechanisms including autophagy, host cell death and secretion of cytokines. As cytosolic bacteria are directly exposed to cytosolic sensing machinery, they down regulate pathogen-associated molecular patterns (PAMPs) expression to delay recognition [261]. Common to both intravacuolar and cytosolic bacteria is inhibition of the host autophagy pathway and manipulation of host apoptotic pathways to maintain their replication niche through inhibition of pro-apoptotic pathways and activation of pro-survival pathways [261,265,267,268].

Recently, it has been shown that macrophage-mediated therapies are a promising and effective approach towards the treatment of many diseases. Macrophages facilitate uptake, degradation and clearance of nanoparticles from the circulatory system [269]. However, cellular uptake of hydrophilic drugs and macromolecules remains a challenge for effective treatments of intracellular infections. The internalization of nanoparticles by macrophages involves interaction between the macrophage cell membrane and the nanoparticle outer surface, resulting in internalization of this nanoparticle *via* the formation of plasma membrane surrounded vesicles (Fig. 22) [25]. Based on the internalization pathway, the resulting membrane-bound vesicles can vary

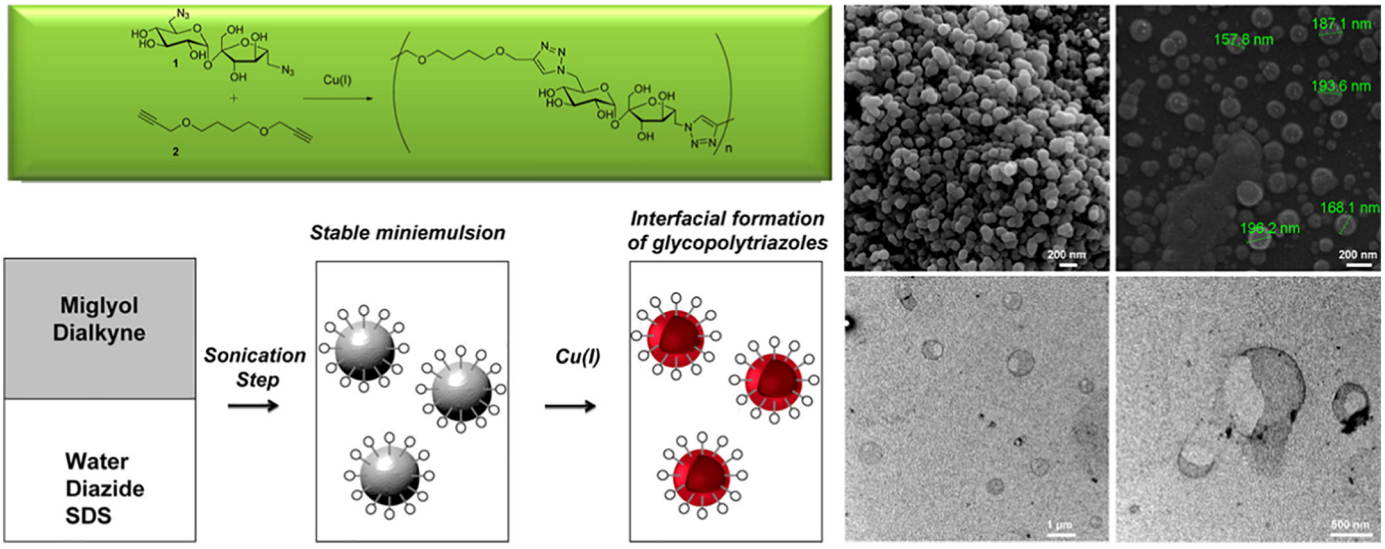


Fig. 15. (Left) CuAAC polyaddition of 1 (6,6′-diazido-6,6′-dideoxysucrose) and 2 (bis(propargyloxy)butane) (top) and the preparation method of glyconanocapsules from interfacial CuAAC polyaddition (bottom). (Right) SEM (top) and TEM (bottom) images of glyconanocapsules obtained by interfacial CuAAC polyaddition. Taken with permission from Roux et al. Copyright © American Chemical Society [228].

in size, composition and internal environments and subsequently form endosomes, phagosomes, or macropinosomes. There are five known mechanisms for the uptake of nanoparticles that vary based on the proteins assisting in the endocytosis process including phagocytosis, macropinocytosis, and endocytosic uptake mediated by either clathrin or caveolin, or endocytosis that is independent of both [270].

Cellular uptake of nanoparticles by macrophages involves a two-step process and the initial binding of nanoparticles to the macrophage exterior is greatly influenced by the nanoparticle's surface charge. Subsequent uptake following binding can occur through several processes such as pinocytosis, non-specific or receptor-mediated endocytosis which are energy dependent processes. The uptake mechanism is based on different cell types, the cellular location and the nanoparticle's surface properties [271–273]. Furthermore, both the energy-independent and receptor-independent routes involve direct translocation of nanoparticles across the membrane and do not rely on the cell's metabolic activity [274]. Such an uptake process results in the direct transport of nanoparticles through the cell membrane into the cytoplasm. Moreover, the receptor-independent uptake pathway can be utilized to design simplified nanoparticles

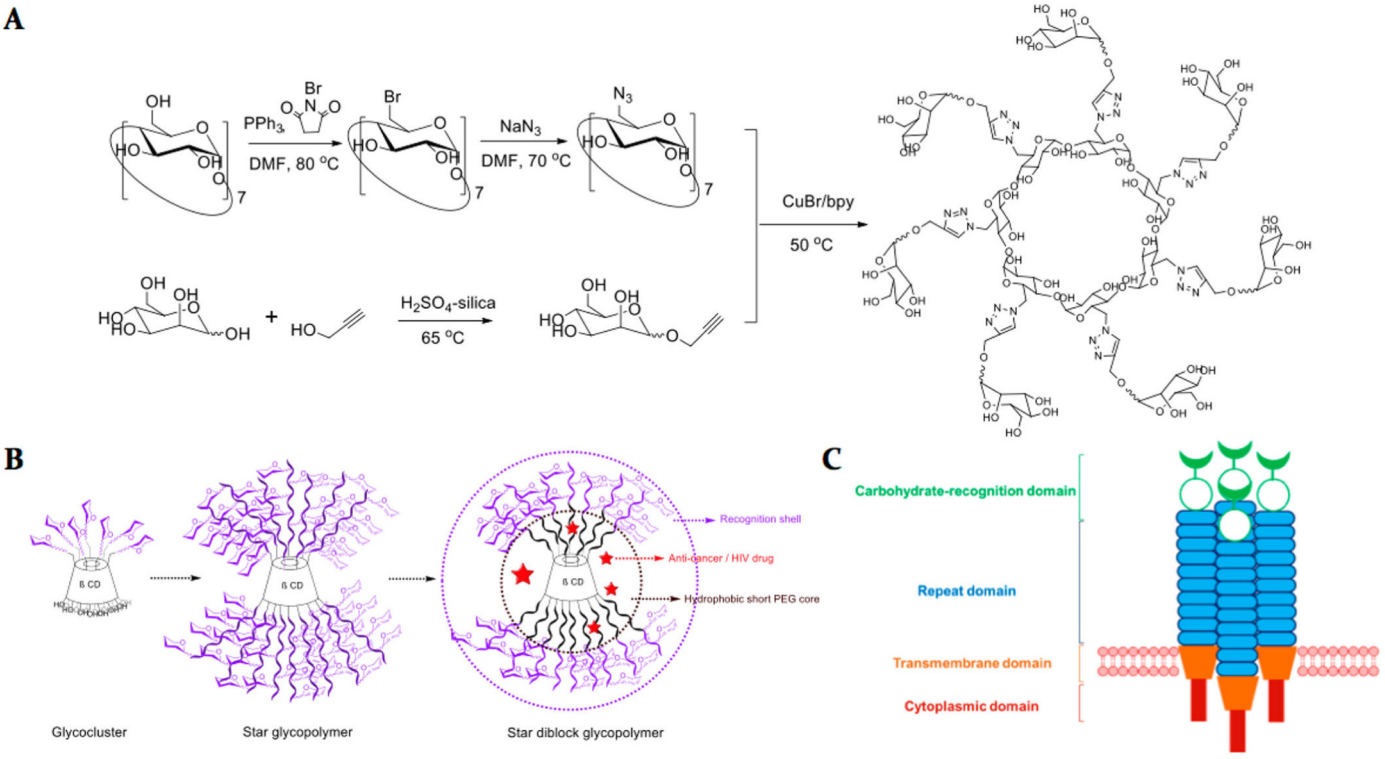


Fig. 16. The preparation of CD-Based glycoclusters using CuAAC (A) and the evolution route from glycocluster to star diblock glycopolymer (B) and schematic representation of human dendritic cell specific ICAM-3 grabbing nonintegrin lectin (C). Adapted with permission from Zhang et al. Copyright © American Chemical Society [232].

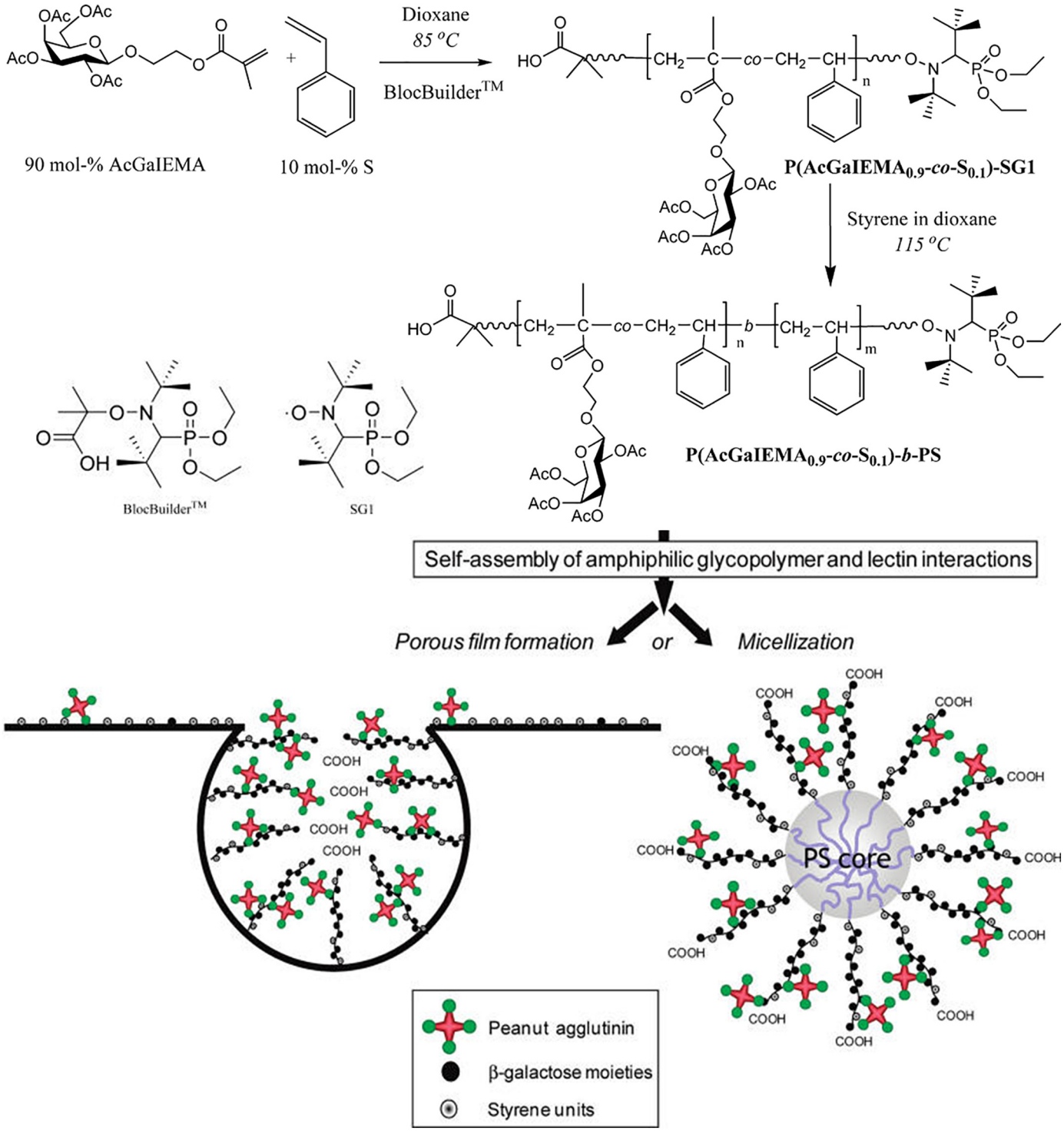


Fig. 17. (Top) The preparation pathway of diblock copolymers by NMP to produce poly(2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-galactosyloxy)ethyl methacrylate-*co*-styrene)-*b*-Polystyrene, namely P(AcGaIEMA-co-S)-b-PS) and (bottom) the formation of micelles with glycopolymer shell depend on *β*-galactose residues and honeycomb structured porous films with glycopolymer enriched inside the pore. Taken with permission from Ting et al. Copyright © American Chemical Society [236].

without additional structural modifications required to disrupt the endocytic vesicles.

Nanocarrier systems permit site specific drug delivery to macrophages providing an enhanced bioavailability of antibiotics towards intracellular infection, particularly for antibiotics with poor pharmacokinetic properties [14,16,275]. They also provide protection from metabolic clearance, enhance membrane transport as well as prevent enzymatic and environmental degradation of antibiotics allowing for a therapeutically effective drug concentration at the site of infection [276]. In addition, antibiotic-loaded nanoparticles can maintain the suitable drug concentration for a prolonged period by means of slow drug release, thus reducing the number of doses required, while administration of free antibiotics often demonstrates a more fleeting effect and requires multiple doses per day [16].

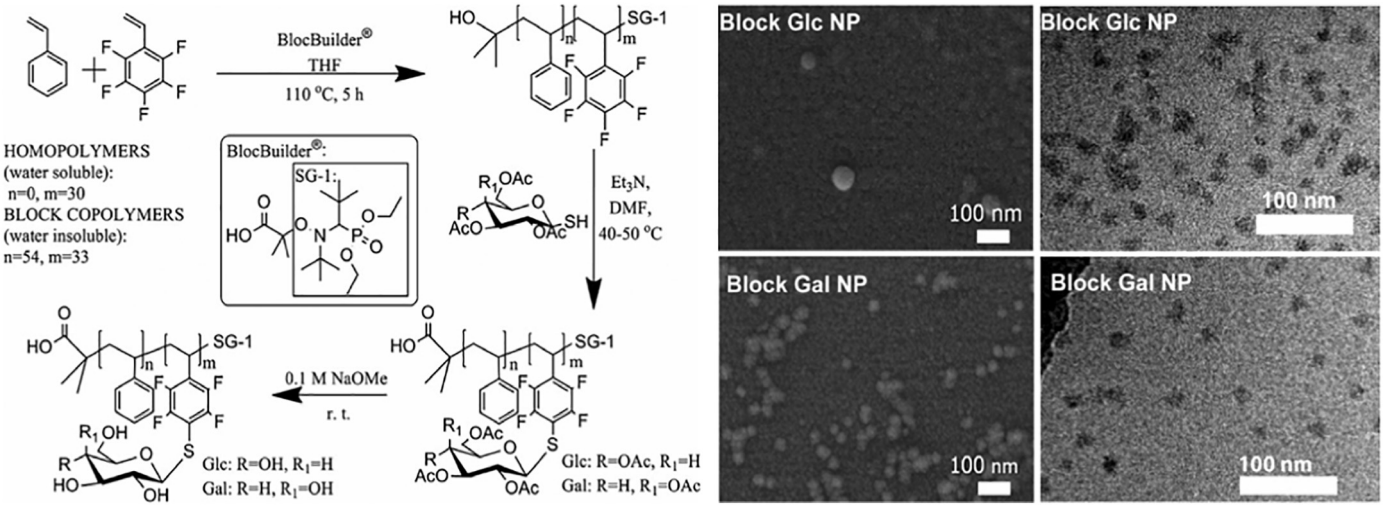


Fig. 18. (Left) Schematic representation of the synthesis of the glucosylated and galactosylated homo and block copolymers. (Right) SEM and cryo-TEM images of the glycosylated nanoparticles sizes between 15 and 40 nm. Taken with permission from Babiuch et al. Copyright © John Wiley and Sons [241].

4.2. Physicochemical properties of nanoparticles to penetrate macrophages

The phagocytic uptake of the nanoparticles is related to physical characteristics and morphology (particle size and shape), physicochemical attributes (surface charge, hydrophobicity/hydrophilicity), interaction with plasma protein (opsonins), biodistribution and targeted drug delivery to cells [11]. For example, improved hydrophobicity of the nanocarrier can allow better interaction with the macrophage to enhance ingestion. In addition to GNP size and surface composition, the overall shape is a crucial component that impacts cellular uptake and efficient delivery of therapeutics [277]. These areas, along with use of targeting ligands and the role of GNP elasticity and mechanical properties in cellular uptake are covered in detail below.

4.2.1. Nanoparticle size

The size of a nanoparticle represents an impactful variable to GNPs influencing several factors including endocytosis, cellular uptake, and efficacy of endocytic processing [278,279]. For effective delivery of therapeutics to diseased cells, nanoparticles must avoid clearance by reticuloendothelial system (RES) or filtration by liver or kidneys. Nanoparticles within the 40–50 nm size range exhibited the strongest impact on basic cell signalling pathways [280,281]. Furthermore, polymeric nanoparticles with an intermediate size between 20 and 100 nm have been shown to be internalized readily by cells, compared to smaller or larger nanoparticles [282].

The cellular uptake of GNPs by macrophages is also related to particle size [280,283]. Larger particles are more readily up compared to smaller particles that have a more curved surface and this may be related to complement activation [284]. For example, the uptake kinetics of rhodamin B labelled carboxymethyl chitosan-based GNPs in murine macrophages vary with size, and GNPs with 300 and 500 nm showed greater uptakes by cells when compared to 150 nm GNPs [278]. The size of particles themselves can determine the pathway of endocytosis [285]. Uptake of nanoparticles less than 200 nm involves

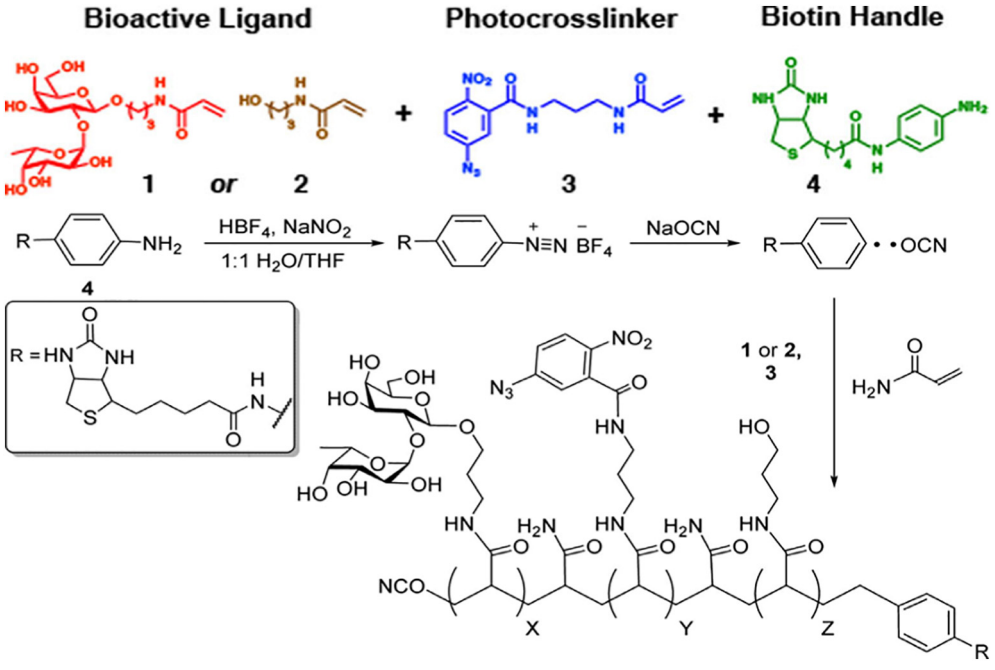


Fig. 19. Synthesis of biotin-functionalized, photoactivatable glycopolymers. Taken with permission from Wibowo et al. Copyright © American Chemical Society [35].

clathrin-coated pits whereas particles with a diameter up to 500 nm are internalized through an energy-dependent process. Nanoparticles with a size greater than 500 nm are internalized predominantly by a coaveolae-mediated mechanism [285]. In general, particles that have a diameter greater than 1 μm are internalized through phagocytosis and smaller particles (0.2–1 μm) uptaken by endocytosis. Nonetheless, particles with a diameter of 5 μm have been shown to undergo receptor-mediated endocytosis, and this could be utilized to target drug delivery to the vascular system [279,286]. Caldorera-Moore, Roy, and co-workers have reviewed "top-down" nanofabrication techniques to control both particle size and shape for drug delivery purposes [287].

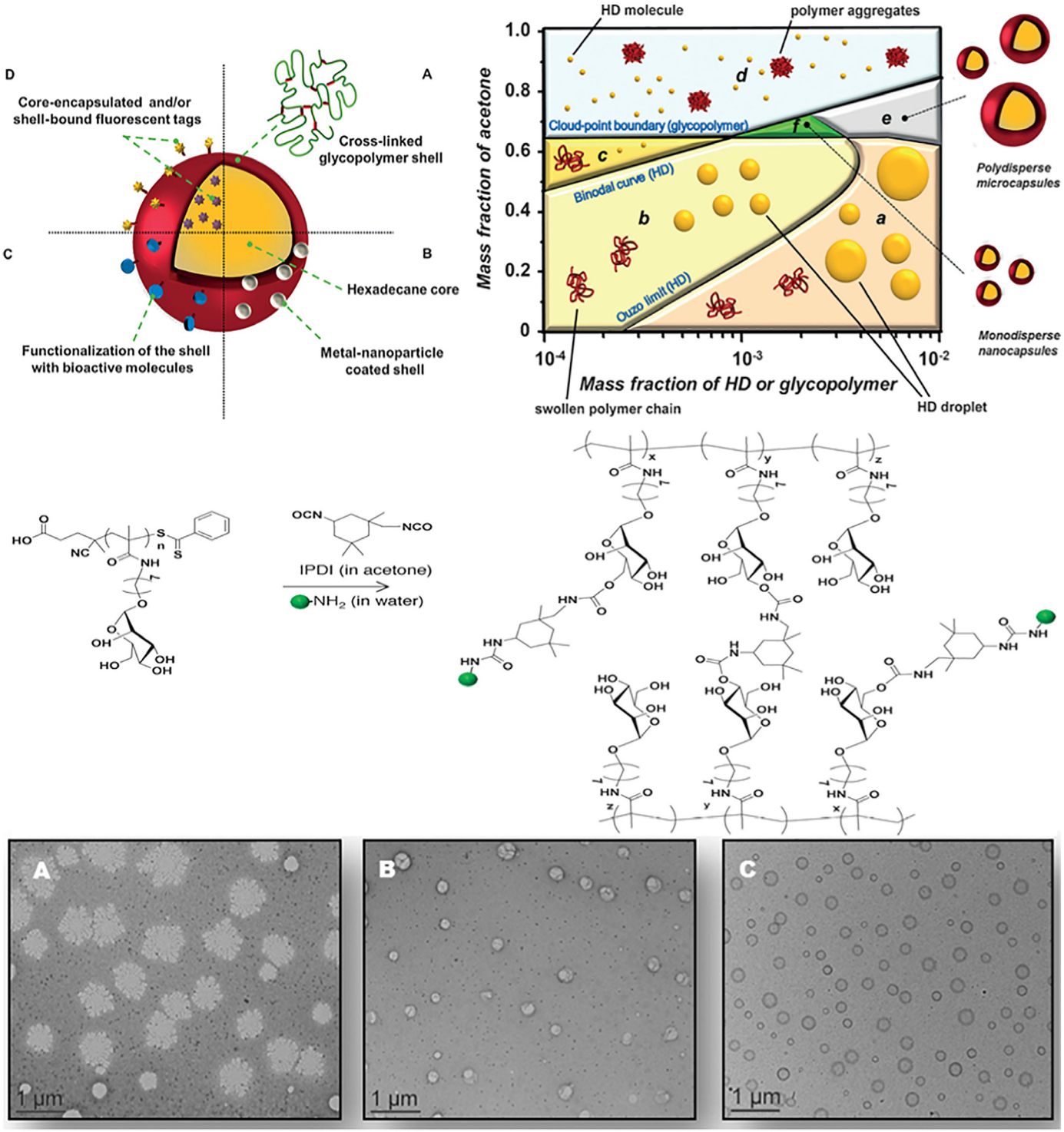


Fig. 20. (Top) General representation of nanoprecipitation manufactured functional nanocapsules A) cross-linked oil-filled nanocapsules; B) metal-nanoparticle-coated nanocapsules; C) nanocapsules with bioactive molecules within the shell; D) core- or shell-tagged fluorescent nanocapsules and overlapped phase diagrams of PHMM and HD in acetone/water mixtures. (Middle) one-pot cross-linking and functionalization of the polymer shell. (Bottom) A, B, C) TEM images of nanocapsules obtained by adding a solution of HD (2 mg) in acetone (0.65 g) to an aqueous polymer solution (0.35 g of water and 1 mg of PHMM2) and cross-linking with 0.5 (A), 1 (B), and 24 equivalents (C) of a crosslinker isophorone diisocyanate (IPDI) with respect to the glycopolymers chains. Taken with permission from Yan et al. Copyright © John Wiley and Sons [252].

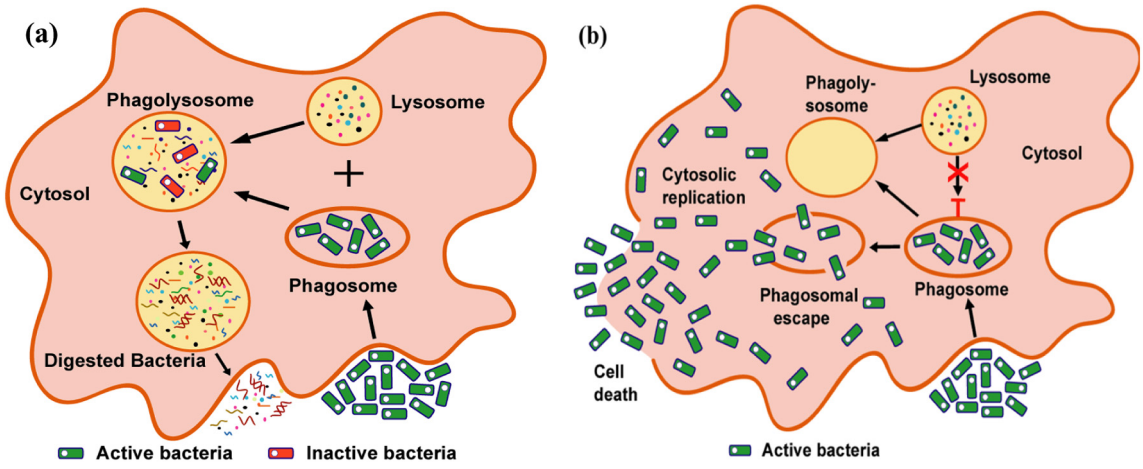


Fig. 21. (a) Schematic representation of phagocytosis of microorganisms within the macrophages (b) upon phagocytosis, bacteria reside in phagosome and do not interact with lysosomes. Bacteria then rapidly disrupt the phagosome membrane and reach the cytosol where they undergo extensive replication, followed by cell death and bacterial release.

4.2.2. Nanoparticle shape

Additionally, shape is one of the essential characteristics of nanoparticles that play a role in internalization *via* macrophages. A wide range of nanoparticles with non-spherical shapes have been reported such as cones, cubes, cylinders, discs, ellipsoids, hemispheres, stars, urchins, and other complex shapes including red blood cell-like biconcave discoids, and filovirus-mimicking filamentous particles [288–291]. Experimental studies on several different shaped nanoparticles revealed that their phagocytic uptake by immune cells is shape-dependent [292,293]. Recent studies proved that endocytosis by macrophages including phagocytosis follow similar shape dependence and not only ingest larger particles but also engulf highly curved targets [294]. The surface geometry of the particle that interacts with the cell membrane determines whether the particle will internalize or maintain only surface interaction without uptake [292]. For instance, when a macrophage interacts at the terminal end of a particle with an ellipse it can be fully internalized within minutes, while interaction at the flat surface can take up to 12 h for internalization to occur (Fig. 23) [292]. As shown in Fig. 23, the internalization velocity of the nanoparticles is dependent on the angle between tangential angle average (T) and the membrane normal (N) which is denoted as omega (Ω). Nanoparticles can be uptaken quickly when $\Omega \leq 45°$, but the internalization is inhibited in case of $\Omega > 45°$ [292]. Therefore, nanoparticles with greater aspect ratios may interact with $\Omega > 45°$ and are less susceptible to be phagocytosed and this may be useful in other DDS [295]. Increasing the aspect ratios of particles results in a reduced rate of phagocytosis by macrophages; elongated particles show significantly reduced rates of phagocytosis. For example, worm-like particles that have high aspect ratios show a reduced rate of phagocytosis relative to spheres of similar volume [289]. However, other research has found higher aspect ratios allow nanoparticle uptake into the macrophage more readily and at a greater extent [279,296]. Nanoparticle rods that have an aspect ratio between 2.1 and 2.5 are internalized more readily in greater amounts relative to longer or shorter particles [297]. Nanoparticle rods that have an aspect ratio between 2.1 and 2.5 are internalized more readily in greater amounts relative to longer or shorter particles [298]. These conflicting reports indicate internalization is determined by more than a nanoparticles' geometry such as those factors discussed below.

4.2.3. Surface charge

Overall surface charge influences the recognition, adsorption, phagocytosis and elimination of nanoparticles with macrophages which subsequently affects their biodistribution [299]. Nanoparticles with a negative surface charge exhibit a low phagocytic internalization, resulting in a prolonged circulation in the blood stream. However, positively charged nanoparticles are more susceptible to phagocytosis resulting from their enhanced interaction with the anionic plasma membrane of macrophages. For instance, nanoparticles possessing a positive zeta potential (Z) have been found more phagocytable through the proton sponge effect in comparison with non-charged nanoparticles [300]. Vadakkan et al. reported the first step of the cellular uptake for cationic nanocarriers was likely fusion into the cell membrane [301]. The linear correlation between Z value of the nanoparticles and their cellular uptake has also been reported [302].

Due to their free amines, chitosan-based GNPs have a positive zeta potential and show higher cellular uptake in comparison to negatively-charged or neutral nanoparticles (Fig. 24) [303,304]. The rhodamin B labelled chitosan-based GNPs with positive zeta potential (25 mV) have been found to increase the phagocytic uptake by nearly 1.3-fold when compared to negatively charged GNPs with the similar absolute value of zeta potential (-25 mV) [278]. It is believed this involves a concomitant influx with chloride anions in order to achieve charge balance, in turn resulting in osmotic internalization (also known as 'Proton-Sponge' effect) [284]. It has however also been reported that cationic and neutral nanoparticles can diminish macrophage uptake, while nanoparticles that are anionic can bind to the positively charged sites on the macrophages thus facilitating uptake by RES as they can be recognized by scavenger receptors [305]. In addition to this, nanoparticles with negative zeta potential can cluster at the cationic site due to repulsion by more surface-abundant anions; consequently these nanoparticles are internalized more efficiently [306–308]. These conflicting results are due to variation in nanoparticle scaffolds, surface hydrophobicity or composition and other factors including nonhomogeneous particle sizes, and the variation of cell type under investigation. The most significant factor affecting nanoparticle phagocytosis is the absolute value of the zeta potential, nanoparticles with a low absolute zeta potential can effectively avoid internalization by macrophages [278,309]. In addition to this, cationic nanoparticles are more effectively ingested by proliferation cells, while anionic systems may provide improved therapeutic effectiveness for the delivery of drugs into deep tissues due to faster diffusion and less cellular internalization [310]. Additionally, nanoparticles bearing a high positive charge may induce toxicity and provoke immunological responses. In the context of GNP's, both cationic and anionic polysaccharides have been used successfully and this allows tuning of additional electrostatic interactions between the drug and its carrier.

4.2.4. Surface composition and hydrophobicity

Surface composition of nanoparticles impacts the rate and even route of internalization into macrophages [311]. Generally, the surface's

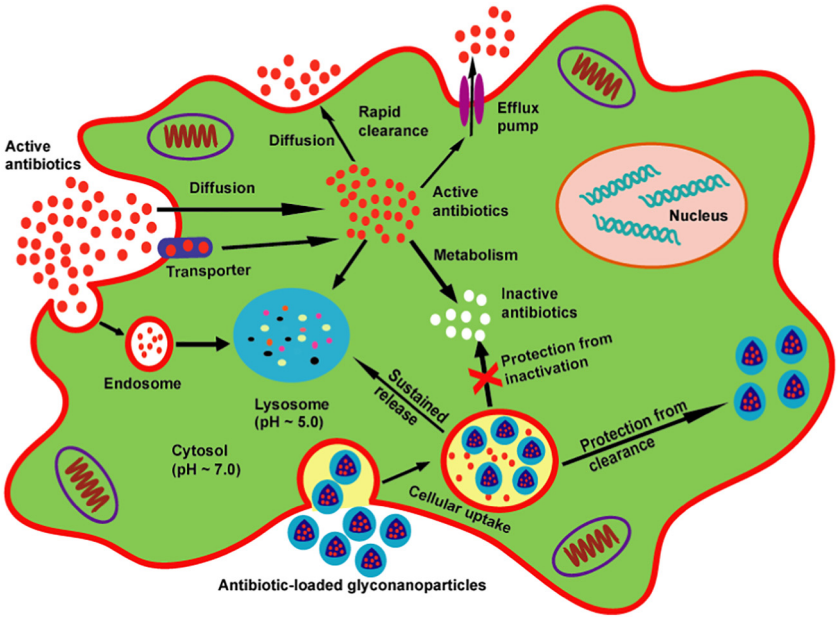


Fig. 22. Factors affecting the intracellular activity of antibiotics and mechanism of glyconanoparticles as a carrier of antibiotics in macrophages.

composition and physicochemical properties control the type of biomolecules (e.g., proteins, aptamers, and antibodies) that interact with it to achieve targeted delivery of therapeutic agents [312–315]. The interaction of the nanoparticle with the plasma membrane also depends on the thickness of the adsorbed bio-layer [316,317]. Nanoparticles that contain a hydrophobic surface have higher affinities for the lipid bilayer present on macrophages resulting in an enhanced cellular internalization.

Hydrophilic modification also has potentially useful impact on GNP performance. The chemical modification of nanoparticles surface composition with polyethylene glycol (PEG) or an analogue is common as it prolongs the circulatory half-life and effective tissue accumulation. The PEGylation of the nanoparticle's surface results in prolonged circulation time as a hydrophilic steric barrier is formed that prevents interaction with circulating macrophages or plasma protein [284,318]. PEGylated nanoparticles can effectively suppress the macrophage internalization and extend circulatory half-life, thus decreasing their accumulation in the liver [319–321]. For example, it was found that macrophage uptake of PEGylated polyelectrolyte nanoshells at 24 h was reduced three fold compared with either positively- or negatively-charged nanoshells [318].

4.2.5. Targeting ligand

Macrophage targeting can be enhanced by using ligands on the nanoparticle's surface that are recognized by specific receptors of macrophages and this can facilitate their internalization through pattern recognition receptor (PPR) mediated endocytosis [322]. As macrophages' PPRs have evolved to identify pathogen-associated molecular patterns (PAMPs), a restricted number of phagocytic receptors are involved including the mannosyl, fucosyl, scavenger, and Fc (fragment, crystallizable) receptors [34,43,117,323]. A general method for macrophage targeting is to apply polysaccharides or glycoproteins ending in mannose or fucose residues for the binding of macrophage receptors [19]. In addition, the affinity of carbohydrate ligands for these receptors can be enhanced by multivalent display creating a "cluster glycoside effect" [232]. Uniquely, the macrophage mannose receptor has the capability to mediate the phagocytosis of sugar-coated nanoparticles and the pinocytosis of soluble glycoconjugates [324]. It can be exploited in the development of nanocarrier based macrophage-mediated therapies through the incorporation of specific ligands that may promote their cellular uptake [19].

The number and nature of macrophage receptors is dependent on their activation and differentiation state and this is essential to consider when attempting to target macrophages. For example, Xiong and co-workers reported a macrophage targeted antibacterial drug delivery system using an enzymatically degradable mannosylated nanogel as the drug carrier (Fig. 24) [325]. The mannose are conjugated to the shell of PEG arms, thus offering targeted antibiotic delivery to macrophages expressing multiple mannose receptors. The crosslinked polyphosphoester core carries drug cargo and can undergo degradation by enzymes produced by the intracellular bacteria. In related work, Jiang et al. developed mannosylated chitosan-graft-polyethyleneimine copolymer for uptake by mannose receptors on antigen presenting cells [326].

Recently, Ratner and co-workers reported that mannose-based glycopolymers showed increased uptake by macrophages relative to galactose-containing glycopolymers [204]. To determine the macrophage-specific targeting, various glycopolymers displaying pendent carbohydrate moieties were fluorescently labelled. In an *in vivo* mouse experiment using alveolar macrophages, they demonstrated higher internalization (6-fold) of mannose glycopolymer relative to galactose and a *N*-acetylglucosamine polymer also showed significant uptake (Fig. 25) [204,205].

Considerations around the macrophage's binding affinity of nanoparticles must also involve their charge. For instance, macrophages that contain anionic sialic acid on their surface can bind to the positively charged nanoparticle consequently resulting in an enhanced phagocytosis [327]. Paulson and co-workers developed an in silico-aided ligand of sialoadhesin for macrophage targeting [327] and prepared liposomal nanoparticles for targeting sialoadhesin to deliver antigen to macrophages [328,329]. In these cases, the synthesized liposomal GNPs targeting sialoadhesin were selectively bound as well as internalized by macrophages, but not by sialoadhesin-negative mice [329]. Cho et al. developed fluorescent, lectin-modified polymeric nanoparticles 35 nm in diameter for targeting of sialic acid on macrophages [330]. Gupta et al. reported macrophage targeting by lectinized lipopolymersome GNPs that enhanced macrophages uptake >2-fold and had significantly higher internalization in J774A and RAW 246.7 macrophages cell lines as compared to non-functionalized polymersome [331].

Overall, nanoparticles with various surface properties may be internalized through several endocytic mechanisms. For example, albumin, cholesterol or folic acid decorated nanoparticles favour caveolin-

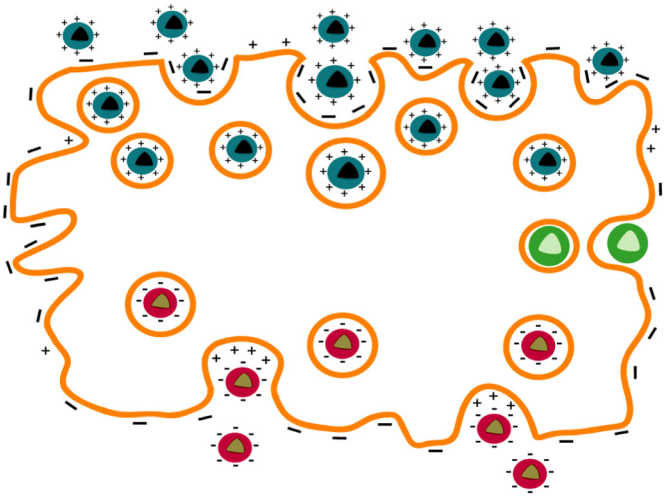


Fig. 23. Effect of surface properties on nanoparticle internalization. Charged nanoparticles can lead to high internalization, presumably because of better interactions with the cationic and/or anionic domains of the cell surfaces. In contrast, coating with hydrophilic polymers (e.g., PEG) will form a 'cloud' of hydrophilic steric barrier for non-charged nanoparticles, which prevents interactions with cells, resulting in less internalization. Redrawn with permission from Duan et al. Copyright © John Wiley and Sons [284].

mediated endocytosis, which circumvents the lysosomal degradation pathways. Alternatively, transferring and cell penetrating peptides enhance the internalization by clathrin-mediated endocytosis and macropinocytosis, respectively. It is still challenging to manufacture nanoparticles for specific endocytic pathways [332]. The endocytic pathways are interchangeable and blocking the uptake of one pathway may result in an enhanced internalization of nanoparticle *via* another endocytic process [25]. Recent reviews on the effect of nanoparticle shape and surface properties on biodistribution and nanocarrier function have been published elsewhere [25,284,333].

4.2.6. Mechanical properties and elasticity

Finally, there have been recent studies identifying mechanical properties as important to macrophage uptake as they internalize rigid particulates to a greater extent than "soft" elastic particles [334,335]. The energy involved in "winding up" a particle within the plasma membrane declines as a function of increasing stiffness, resulting in favourable uptake of rigid nanoparticles [336]. Stenzel and co-workers have explored the relationship between nanoparticle length and stiffness in breast cancer cell uptake fructose-modified rod-shaped micelles. They developed a model to explain preferential uptake of larger, more rigid particles [337]. However, more rigid nanoparticles are easily excreted during *in vivo* administration compared to elastic nanoparticles which may simply deform to squeeze through narrow blood vessels [338]. Therefore, improving the elasticity of the nanoparticles might be an option for enhancing the circulation of the nanoparticles. Among the common natural polysaccharides used in drug delivery, many are linear 1,4-linked polymers (alginate, amylose, cellulose, chitosan) and would be expected to provide more rigidity to a GNP. Hyaluronic acid and polysialic (colominic) acid have a natural curvature to their backbone structure and this may prove to provide more flexibility to GNPs. Further research to confirm this generalization is required.

5. Glyconanoparticles for macrophage-mediated therapies

As stated previously, macrophage-specific drug delivery systems are considered of clinical importance because macrophages are host cells for many pathogenic bacteria and parasites that can produce outbreaks of deadly diseases. In designing nanoparticulate drug carriers for macrophage-mediated infections, issues of host toxicity and bioavailability must be considered. Therefore, GNPs are emerging as new promising technologies to overcome these issues upon macrophage targeting. Some recent examples of GNP-based macrophage delivery system are described below in terms of bacterial, protozoan, and viral infectious diseases.

5.1. Bacterial infectious diseases

The intracellular localization of bacteria protects them from the host immune response as well as the bactericidal actions of antibiotics. Thus, novel therapeutic approaches are required in order to overcome these limitations, and GNPs loaded with antimicrobial drugs represent a promising approach. As shown in previous sections, it is possible to load therapeutic compounds into a variety GNPs to deliver their payloads intracellularly. For instance, GNPs prepared from alginate, chitosan, dextran sulphate, mannose, cyclodextrin, carboxymethyl cellulose, hyaluronic acid have been used to deliver various antibiotics such as amoxicillin [339–341], ampicillin [342]. clarithromycin [343]. ciprofloxacin [344–347]. daptomycin [348], doxycycline [349]. erythromycin [49]. gentamicin [77,350], tetracycline [351]. trimethoprim [135]. vancomycin [325,352]. to treat brucellosis, tubercular, salmonellosis, skin, ocular, osteomyelitis, typhoid, and cholera infections.

5.1.1. Tuberculosis

Tuberculosis is a widespread lung infection caused by *Mycobacterium tuberculosis,* the deadliest bacterial disease in the world, which is widely endemic in certain regions [353]. Furthermore, the incidence of tuberculosis has increased recently due to its association with AIDS. Pulmonary TB is treated through a combination therapy of orally administered rifampicin, isoniazid, pyrazinamide, and ethambutol, until the infection is proven susceptible (i.e.- not drug resistant) at which point the latter drug can be removed. In total, a multidrug treatment is given for 6–9 months for drug susceptible strains and 18–24 months for multidrug resistant strains. In the latter case, this can involve roughly 10,000 doses (12–13/day), thus it can lead to non-compliance and development of undesired side-effects. Moreover, most of the known anti-tubercular agents are less effective *in vivo* due to the low macrophage permeability and rapid degradation of these drugs. Therefore, the use of antibiotic-loaded, macrophage-targeted GNPs can enable a prolonged and systemic dose of antibiotics allowing for a reduced treatment time.

Antibiotic encapsulated GNPs have shown promising anti-tubercular activity both *in vitro* and *in vivo* [354–359]. The aminoglycoside (AG) antibiotics including amikacin, apramycin, gentamycin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, and tobramycin, are very efficacious against mycobacterial infections, but

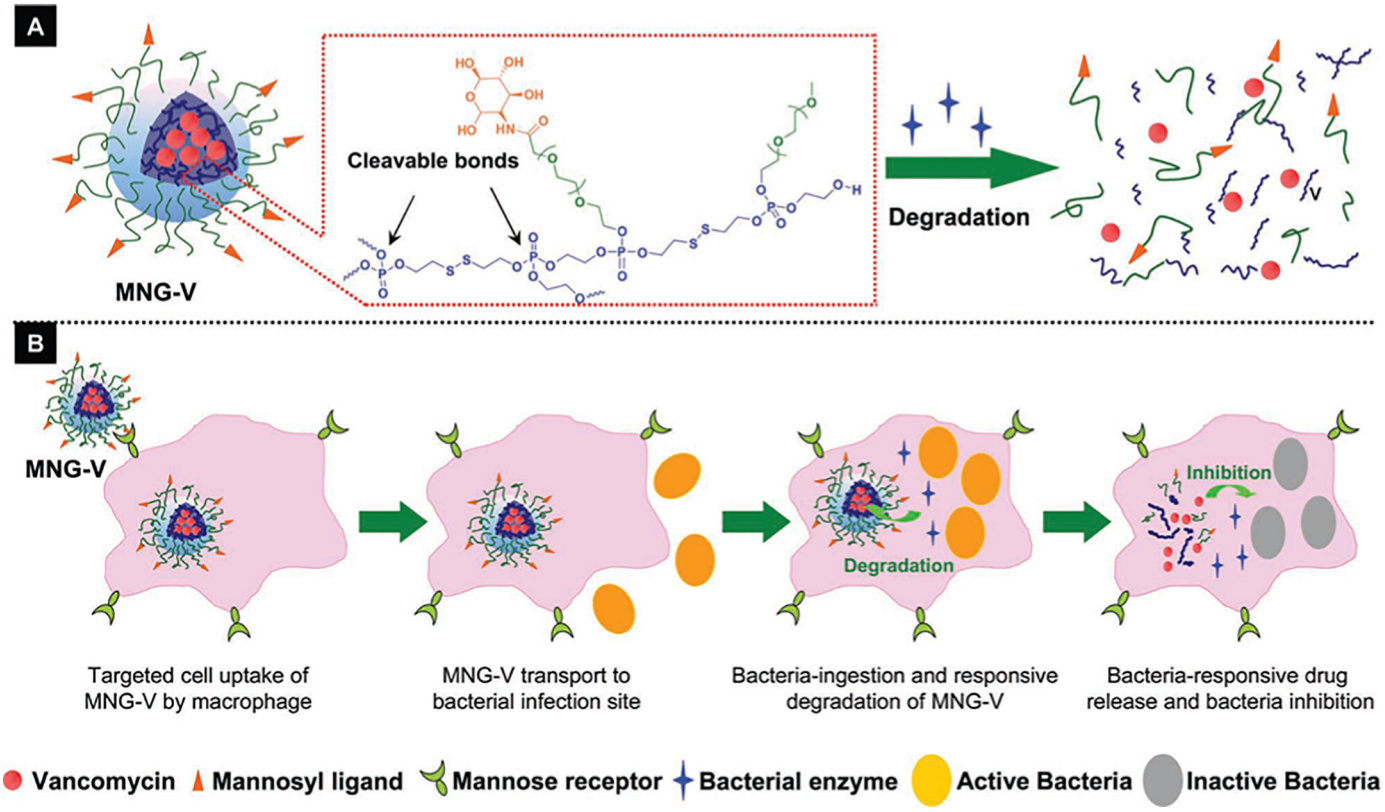


Fig. 24. (A) Graphical representation of vancomycin-loaded mannosylated nanogels (MNG-V) and the bacteria-responsive drug release; (B) Schematic illustration of targeted uptake of MNG-V, transport, degradation, drug release and bacteria inhibition. Mannose is incorrectly presented in this published Fig. 26. Taken with permission from Xiong et al. Copyright © John Wiley and Sons [325].

they are not highly membrane permeable, thus causing side effects, particularly nephro- and oto-toxicity. Aminoglycoside-loaded chitosan nanoparticles have been prepared by Lu et al. and in order to increase antibiotic loading efficiency of the chitosan based GNPs dextran sulphate was used as a counter ion to shield the positive charge of the AG [69]. They incorporated three AGs—streptomycin, gentamycin, and tobramycin—into the GNPs and obtained drug incorporation efficiencies of 60, 63, and 38%, respectively. The *in vivo* results indicated that oral drug loaded GNPs were effective in killing intracellular *M. tuberculosis* with one log 10 reduction in growth of the bacilli growth for both treated groups, AG loaded GNPs against free AG, at the same concentration of 100 mg/Kg [69]. Recently, Grumezescu and co-workers reported cross-linked magnetic chitosan nanoparticles for AG antibiotics (kanamycin and neomycin) and reported the AG loaded GNPs reduced the needed dose [360]. Hombach et al. studied *in vitro* evaluation of an oral tobramycin GNP using thiolated chitosan and observed almost 90% of the tobramycin was released within 4 h [361]. A number of examples using antibacterial GNPs are shown in Table 2.

Saraogi et al. described mannosylated gelatin nanoparticles for targeted transport of the potent anti-TB agent isoniazid into macrophages [354]. The prepared nanoparticle size was between 260 and 380 nm with a maximum drug payload of 40–55%. The macrophage targeting efficacy of the prepared nanoparticles was evaluated against J774 cell lines using fluorescence activated cell sorters (FACS) [354]. The same group previously studied mannosylated solid lipid GNPs loaded with rifabutin and reported promising alveolar macrophage uptake, drug release, and haematological studies [357]. Kumar et al. reported uptake of rifampicin-loaded GNP dendrimers and found the dendrimer displayed a reduced rate of drug release at pH 7.4, and lowered haemolytic toxicity; but the mannosylated dendritic system stimulated significant alveolar macrophage uptake and elevated drug release at pH 5.0 [362,372].

5.1.2. Salmonellosis

Salmonella infections occur after ingestion of contaminated food or after contact with another person with this infection and are caused by the salmonella bacteria. Salmonella bacteria also cause typhoid fever when they enter the lymphatic system, which makes treatment more difficult as Salmonella can produce biofilms and create associated gallstones [371]. Dipshikha et al. prepared chitosan-dextran sulphate nanocapsule (CD) for efficient targeting and killing intracellular *Salmonella* infection after successfully loading ciprofloxacin into the nanocapsule [133]. These displayed significant inhibition of *Salmonella* infections *in vivo* in time-dependent manner upon treatment with antibiotic loaded CD compared to free drug. Noha and Mohamed developed ceftriaxone sodium (CTX)-loaded chitosan GNPs and these nanoparticles exhibited considerable reduction of *Salmonella typhimurium* in J774.2 macrophage cells compared to placebo nanoparticles [114].

5.1.3. Staphylococcus aureus

Staphylococcus aureus is a leading cause of death in hospital settings and causes illnesses such as skin infections, pneumonia, meningitis, osteomyelitis, endocarditis and sepsis. *S. aureus* occasionally causes intracellular infections by invading macrophages, and can survive intracellularly for up to a week [351]. Maya et al. reported a tetracycline-loaded chitosan-based GNP that displayed sixfold more effective killing of *S. aureus* within macrophages compared to free tetracycline treatment [351]. Wu and co-workers developed another chitosan GNP (CM-chitosan) formulation with gentamycin sulfate (GS) to achieve potent bacterial growth inhibition of *S. aureus* [373]. They also reported the loaded GS was beneficial for the osteoblastic MC3T3-E1 cell responses as well as enhancing the antibacterial efficiency [373].

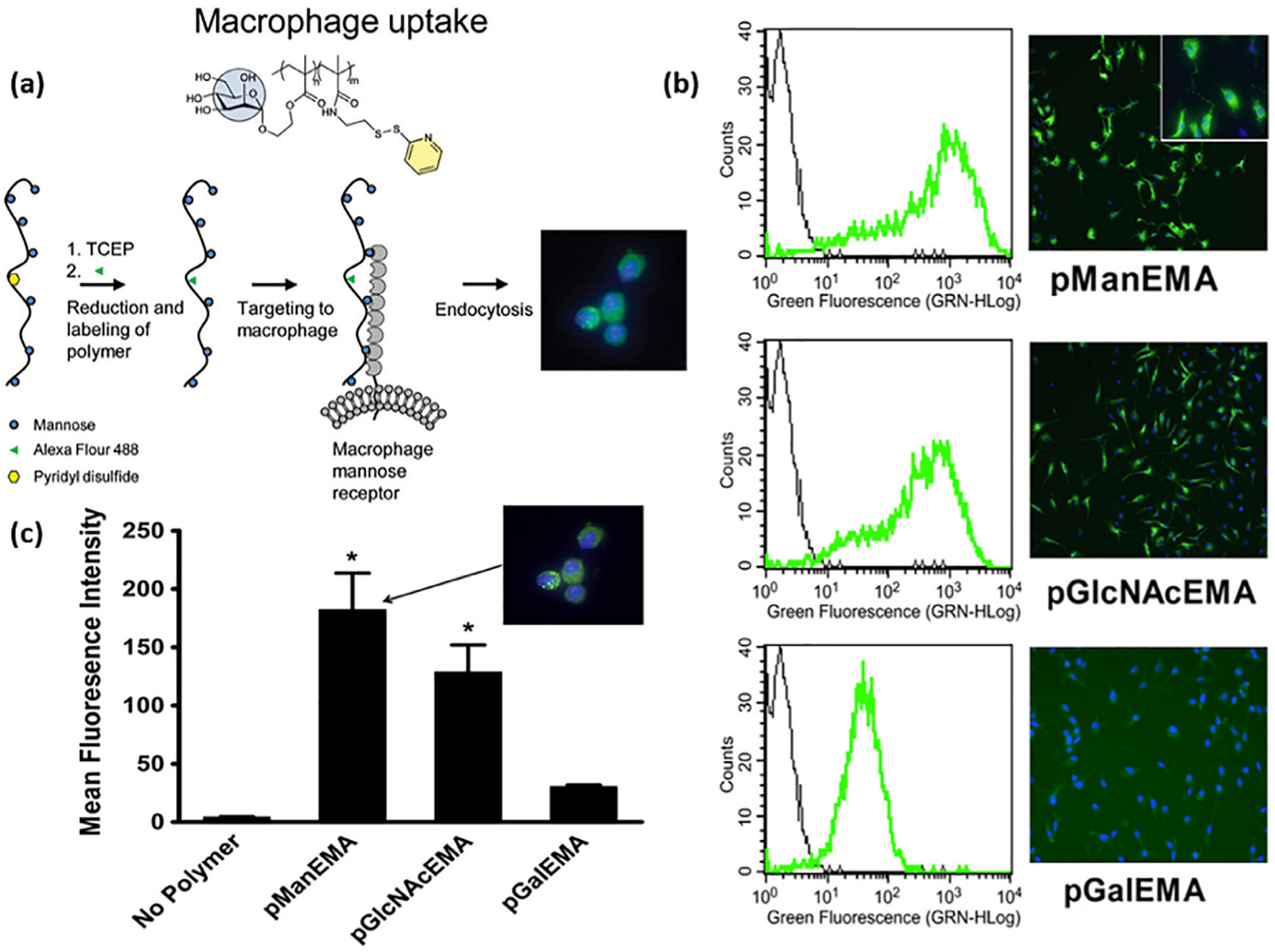


Fig. 25. (a) The binding and subsequent endocytosis of fluorescent mannose glycopolymers by the macrophage mannose receptor [205]. (b) *In vitro* BMDM glycopolymer uptake. Inset shows a higher magnification image of the AF488-pManEMA treated cells. (c) Internalization of glycopolymers by alveolar macrophages *in vivo*. Mice were given 10 mM AF488-glycopolymers intratracheally. Bronchoalveolar lavage (BAL) was performed after 30 min and BAL cells were analyzed by flow cytometry. Taken with permission from Song et al. Copyright © 2012 Elsevier Ltd [204].

5.2. Protozoan infectious diseases

Leishmania is a protozoa that causes a number of infectious diseases and is transmitted through vector insects (sandflies). The infection can spread to vital organs including liver and spleen, subsequently causing visceral leishmaniasis. Leishmaniasis is endemic in many developing countries and often results in death if not treated correctly. The infection has a co-synergism with the HIV infection resulting in an increasing incidence of leishmaniasis [22]. The intracellular localization of *Leishmania* inside the phagolysosome of host macrophages limits chemotherapy treatment [11]. There are many compounds with antileishmanial activity, but their use is compromised because of their toxicity or limited bioavailability. The oldest frontline antileishmanial agents used are pentavalent antimonials including meglumine antimonials, or sodium stibogluconate, but these are toxic for both the liver and the skin. Liposomal formulation of amphotericin B is also used as an antileishmanial treatment, but this is toxic to the liver and heart. Other antileishmanial drugs include the recently FDA-approved miltofesine, as well as aphidicolin, atovaquone, pentamidine, primaquine, and natural products such as amarogentin, andrographolide and the aminoglycoside paromomycin [22].

Recently, lectin-functionalized lipo-polymersome encapsulated amphotericin B (AmB) has been designed to target macrophage receptors for treatment of visceral leishmaniasis [331]. Chaubey et al. studied curcumin-loaded GNPs for the treatment of visceral *Leishmania donovani* infection [112]. Their pharmacokinetic study of the drug-loaded mannosylated chitosan GNPs exhibited significant improvement of mean resident time and an uptake study showed the effective endocytosis of GNPs within the macrophages of reticuloendothelial system [112]. This group also studied use of the antitubercular rifampicin loaded into the same mannose-chitosan GNPs for the treatment of leishmaniasis [117]. Astana and co-workers reported an amphotericin B-loaded GNP for visceral leishmaniasis treatment where the *in vitro* result showed 50% inhibitory concentration (IC_{50}) of 0.2 μg AmB/ml compare to free drug and these GNPs were also successful *in vivo* [374].

5.3. Viral infectious diseases

Human immunodeficiency virus (HIV) is a Lentivirus that leads to acquired immunodeficiency syndrome (AIDS), an immunocompromised condition that increases susceptibility to macrophage resident diseases, particularly TB [375]. The joint United Nations Programme on HIV Rand AIDS (UNAIDS) reported around 2.1 million new cases with 1.1 million AIDS-related death just in 2015 [376]. Although two viral types of HIV are responsible for AIDS, type 1 (HIV-1) exhibits higher transmission rates and more rapid progression [377]. White

Table 2
Polysaccharide-based nanoparticles tested for drug delivery to bacteria infected macrophages.

Nanocarrier composition	Targeted microbes	Encapsulated drug (s)	Targeted cells	Advantages	Ref.
Alginate	*Mycobacterium tuberculosis*	Isoniazid, rifampicin, pyrazinamide	Murine macrophage	Inhalable drug loaded GNPs with efficient activity against MTB	[359]
Chitosan	*Salmonella typhimurium*	Ceftriaxone sodium	J744.2 cells	Inhibits the growth of intracellular *S. typhimurium*	[114]
Mannosylated dendrimers	*Mycobacterium tuberculosis*	Rifampicin	Alveolar macrophages	Enhanced macrophage uptake of rifampicin	[362]
Chitosan and Galactomannan	*Mycobacterium tuberculosis*	Rifampicin	RAW 264.7 cells	Increased intracellular concentration of rifampicin	[363]
Chitosan	*Mycobacterium tuberculosis*	siRNA (targeting luciferase)	Murine alveolar macrophages	Inhalable dry siRNA powders have the possibility of effective pulmonary gene silencing	[364]
Dextran	*Mycobacterium tuberculosis*	siRNA (targeting CD45)	Murine alveolar macrophages	Effective siRNA delivery to resident alveolar macrophages	[365,366]
Chitosan	*Mycobacterium tuberculosis*	Isoniazid, rifampicin	Murine alveolar macrophages	Drug loaded nanoparticles more effective against the mycobacterium than free drugs.	[367]
Chitin	*Escherichia coli*, *Staphylococcus aureus*	Rifampicin	Human monocytes	Exhibits sustained release of antibiotics until 72 h	[368]
O-carboxymethyl chitosan	*Staphylococcus aureus*	Tetracycline	HEK-293 and THP-1 macrophages	Bacterial inhibition increased sixfold compared to free drug	[369]
Chondroitin sulfate and dextran sulfate	*Salmonella* Paratyphi A	Chloramphenicol	RAW 264.7 cells	Enhanced intracellular uptake and effectively killed intracellular microbes both *in vitro* and *ex vivo*	[370]
Fucodian coated chitosan	*Salmonella* Paratyphi A	Ciprofloxacin	RAW 264.7 cells	Effective in eradicating *Salmonella* infections and effective in dispersing *Salmonella* gallstone biofilms.	[371]

blood cells including macrophages are the first to be infected by the virus and this generally begins with binding of envelop gp 120 to the CD4 receptor on the extra-cellular side, followed by binding of other co-receptors, thereby delivering the viral core to the cytoplasm where there is reverse-transcription of viral RNA genome into DNA [378,379]. As with other intracellular infections, this residency protects the virus against antiretroviral treatment [380].

Recently, Stavudine-loaded chitosan nanoparticles have been developed for treating AIDS [357,363,364]. and Dev et al. designed poly(lactic acid)/chitosan GNPs for lamivudine drug delivery [365]. Stearate-g-chitosan oligosaccharide polymeric micelles were also used to deliver lamivudine and showed high uptake with low cytotoxicity toward viral transfected cells [366]. Azidothymidine-triphosphate, the active form of AZT (Zidovudine), is still important for the treatment of HIV. Chitosan GNPs have been synthesized for the intracellular targeting of triphosphate analogues of Zidovudine for the treatment of HIV with minimal particle size of 200 nm [367]. More recently, saquinavir-loaded chitosan GNPs were reported to be potent anti-HIV therapeutic systems and displayed enhanced inhibition of viral growth [368].

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5.4. Fungal infections

Fungal infections are a global health concern especially regarding management of individuals who have weakened immune systems such as those who have HIV/AIDS or cancer. Candidiasis, aspergillosis and cryptococcosis are some of the opportunistic infections that impact such patients, particularly in hospital settings [387]. Once the fungus reaches the bloodstream, phagocytosing macrophages play a vital role to restrain the fungus or allow it to spread to different organs including brain, lungs and kidneys [388]. The presence of any fungal infection in patients commonly indicates that the host defence systems have been compromised to some extent. The clinical effect of the fungal disease in the immunocompromised host depends on the nature of the underlying disorder and the types of the fungus involved. In general, fungal diseases are very likely to be progressive in nature, and if left untreated, can become life threatening [389].

Many drugs can be used to combat all systemic and superficial fungal infections in humans. Various effective antifungal agents available include polyenes, azoles, allylamines, flucytosine, morpholines, griseofulvin, hydroxyl-stibamine, triphenylmethanes, iodides and imidazole classes of drugs [390,391]. Among them, polyene antibiotics are the most widely used because of their broad spectrum antifungal activity. Amphotericin B (Amp B) is used to treat systemic infections including aspergillosis, candidiasis and histoplasmosis. The major side effects associated with Amp B are its dose-dependent toxicity to the host, particularly in kidneys. Other side effects of Amp B includes fever to severe haemolytic anaemia, headache, chills, hypotension, thrombophlebitis, dyspnoea, nausea and acute nephritis, limiting its complete exploitation as a suitable therapeutic measure [392].

Chemical analogues of Amp B have been prepared to enhance biodistribution and reduce its toxicity but have not led to clinical success. Different drug delivery systems have been demonstrated to deliver Amp B while eliminating its toxic side reactions as well as increasing its therapeutic index. The development of liposomes as vehicles for Amp B has been demonstrated against numerous fungal diseases including candidiasis, histoplasmosis and cryptococcosis. This allows the selective administration of Amp B to phagocytes with higher doses to achieve a sustained drug distribution and systemic trafficking to the sites of active disease, reducing the potential nephrotoxicity of Amp B. However, liposomal formulations have limited shelf life, and high expense per treatment [392]. Therefore, much effort has been spent to produce more affordable Amp B delivery vehicles.

Glyconanoparticles are being developed as better Amp B delivery systems because of their many attributes discussed throughout this review. Tiyaboonchai and co-workers reported uniform spherical shape Amp B-chitosan-dextran sulfate nanoparticles (700–800 nm) made by PEC with efficient drug loading capacity, a rapid release profile and reduced renal toxicity [393]. Recently, Parker et al. reported chitosan and PEG sponges for invasive fungal infection, such as those faced by soldiers in Afghanistan from 2009 to 2010, for delivery of Amp B [387]. They showed the drug Amp B eluted from the blended sponges

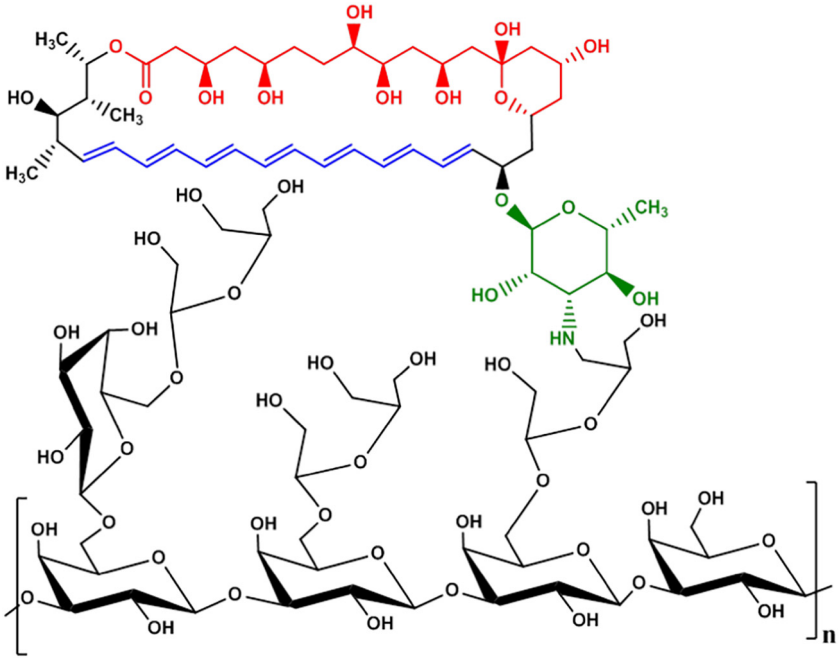

Fig. 26. Schematic illustration of Amp B conjugated arabinogalactan.

within an hour. In a mouse model, they found 100% death of *S. aureus* for the vancomycin-loaded chitosan/PEG 6000 sponges [387,394].

The antifungal activity of Amp B conjugated onto natural polysaccharide chains of arabinogalactan through reductive amination has been reported by Ehrenfreund-Kleinman et al. for efficient inhibition of pathogenic yeast growth (Fig. 26) [395,396]. The conjugates proved less hemolytic (60x) compared to the free drug, and less toxic (40x) in an *in vivo* experiment for acute toxicity. Moreover, the conjugation of Amp B to arabinogalactan neutralizes the toxic effect of cytokine induction in kidneys, and apoptosis in renal tubular cells [392,397]. Vieira and Carmona-Ribeiro reported that cationic nanoparticles prepared from Amp B, cationic lipid and polyelectrolytes display high colloidal stability and excellent fungicidal activity against *C. albicans* [398]. *In vitro* studies suggest the efficient killing of *C. albicans* for the Amp B loaded cationic nanoparticles relative to free drug [398].

The liposomal encapsulation of cyclodextrin and Amp B has been developed providing higher stability and an improved *in vivo* efficacy compared to free drug or traditional Amp B liposomes [399]. It has been found incorporating p-aminophenyl-mannopyranoside in liposomes delivers Amp B to liver and spleen, suggesting that mannopyranoside is a specific ligand for targeting bioactives to the macrophages in these organs while *O*-palmitoyl mannan accumulated the drug in the lungs which preferentially navigates the targeting of bioactives to the alveolar macrophages [400]. Narendra and co-workers developed Amp B loaded muramyl dipeptide conjugated poly(propylene imine) dendrimers for targeting macrophages and caused preferential stimulation of Th1 immunity to increase the safety and efficacy of Amp B [401]. An *in vitro* study revealed very significant reduction of toxicity against erythrocytes and J774A.1 macrophages and an *in vivo* study demonstrated improved antimicrobial activity in Balb/c mice [401].

Apart from Amp B delivery, chitosan-tailored cubic GNPs were developed using the thin film hydration method with Pluronic F127 to deliver clotrimazole antifungal agents and to improve the mucoadhesion properties [402]. The optimum concentration of the polymer mixture in the cubic nanoparticles loaded with clotrimazole showed significantly higher antifungal activity than conventional clotrimazole suspension against *C. albicans* [402]. Low-methoxy amidated pectin (LMAP) and carboxymethylcellulose based formulation was prepared to deliver econazole nitrate against *C. albicans* and *C. krusei* [403]. Finally, Saraf and his group reported cellulose based mucoadhesive gel in a novel ternary mixture of miconazole nitrate with efficient killing of *C. albicans*, *Cryptococcus neoformans* and *Sporothrix schenckii* [404].

6. Future perspective of GNPs

The future success of GNPs in treatment of immune resident infections lies in the development of more efficient approaches towards their preparation while improving their selectivity toward macrophages and/or microorganisms. The potency of the GNPs can be developed *via* control of drug release rate allowing rapid release of payloads from the GNPs at the targeted site. To implement the GNPs clinically, it is not only important for GNPs to target the diseased cells, but they also need to have high drug-loading capability, be non-toxic, cost-effective and potential for industrial manufacturing. Unfortunately, GNPs seldom achieve all of these requirements currently [373,405]. Liposomal formulations of AmpB (discussed in Section 5.2) and doxorubicin (Doxil®) were successfully approved in 1995, and several have been approved since, primarily targeting cancer [406]. Among antibiotics, nebulised liposomal amikacin (Arikace™) completed phase II studies in CF patients recently [407]. Beyond liposomes, more complex drug delivery systems such as the vast majority described herein will require further development and scrutiny.

It is challenging to prepare the GNPs in a uniform, reproducible and scalable manner as the polymer structure such as molecular weight, dispersity, functional group, purity etc. varies depending on their source and batch. In addition, the size of the GNPs is required to be in a range (less than 200 nm) for better macrophage uptake as well as protect them from rapid clearance, particularly the resident macrophages of the liver (Kupffer cells), bone marrow, lung and spleen [408]. At present, it is still somewhat challenging to manufacture a GNP system with suitable properties. The main drawbacks of many GNPs are their ill-defined toxicity profiles as new chemical entities which require additional FDA approval [389]. Greater understanding of the mechanism between GNPs and the targeted living cells are required to optimize these antimicrobial drug delivery systems.

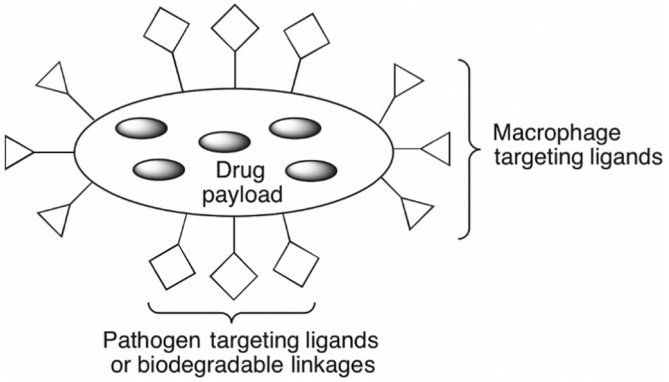

Fig. 27. A model for dual-targeted antimicrobial drug delivery.

This is not meant to imply there is anything but tremendous potential for these systems in drug delivery and more broadly as biological probes. For example, a recent report by Bertozzi highlights the utility of glycopolymer synthesis using *N*-carboxyanhydrides of glycosylated serine residues with different carbohydrate ligands to active antigen-presenting cells through either Dectin-1 or Dectin-2 [409]. This facile glycopeptide synthetic method has been developed by Lecommandoux and others for application to cancer DDS [410] redox-triggered drug release [5] and interaction with macrophage lectins [411].

What have we learned about application of GNP's for macrophage drug delivery to date? From a carbohydrate standpoint, it is clear that mannose and to a similar extent *N*-acetylglucosamine promote significant uptake by macrophages [204]. Chitosan has been used frequently for construction of macrophage-targeting GNPs and the *N*-acetylglucosamine residues may play a role in enhancing uptake. Fructose-coated systems have little affinity for macrophages but can target cancer cells via GLUT5, a fructose-specific transporter [412]. Galactose can target the liver and improve accumulation in lysosomes provided it is linked via its anomeric carbon [212]. Little attention has been paid to potential synergies possible by using multiple carbohydrate types on the surface of GNP's, but this may allow dual targeting toward both the macrophage and microbial cell-surface.

Perhaps such dual targeting will be facilitated by structures that closely mimic the shape of microorganisms described in this review. Bacterial pathogens like mycobacteria and salmonella have rod-like structures that are accessible by modern polymer chemistry. For example, block copolymers can be engineered to form cylindrical rod-shaped micelles. It has been noted that rod-shaped filamentous bacteria are best phagocytized at their ends in a manner that has been similarly proposed for GNP rods [337]. There is evidence pathogenic bacteria possess morphologic plasticity and actually elongate to avoid immune consumption [413]. Successful macrophage uptake of *E. coli* has been shown to require access to bacterial filament termini and as a bacterial cell elongates this becomes more difficult [414]. This may inform the design of rod-shaped GNP's where it might be ideal to have the macrophage targeting ligands on the caps leaving the core structure available for ligands to interact with the microorganism whether this be secondary targeting ligands or linkers that are biodegradable by pathogen-specific enzymes (Fig. 27).

7. Concluding remarks

Carbohydrates have been a crucial component behind development of novel drug targeting methods for several decades [28–33,415]. This review has focused mainly upon development of carbohydrate-based nanoparticles (GNPs) toward macrophage targeting and their potential application in antimicrobial drug delivery systems. The clinical and commercial impact of the antimicrobial drug delivery system based on GNPs has significantly advanced over recent decades directly enabled by synthetic polymer chemistry, material science and bioengineering technology. Particularly, the introduction of new powerful polymerization methods has afforded glycopolymers of diverse architectures that have been exploited to produce well-defined and unique properties of GNPs with better targeting capability towards macrophages as well as high loading content of antimicrobial drugs [232,325]. Despite current progress, many factors need to be considered for the application of GNPs in clinical use including well-defined toxicity profiles, high drug loading and releasing efficiency, and reproducibility. Furthermore, macrophage targeting could be improved by identifying the precise interactions of lectin receptors, which are present exclusively on macrophages, for various types of GNPs to facilitate drug targeting to various macrophage types generated from different parts, organs and/or cells of the body. It is important to note it took 30 years from discovery of liposomes in 1965 until FDA approval of liposomal drug formulations.

Author contributions

Tamim Mosaiab, Dylan C. Farr, Milton J. Kiefel and Todd A. Houston contributed to the writing of the manuscript.

Declaration of competing interests

The authors declare no conflict of interest.

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