EXPERT OPINION

Dextran conjugates in drug delivery

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Introduction: Dextran is a family of natural polysaccharides that is widely under investigation for use as polymeric carriers in novel drug delivery systems. The optimal drug delivery (and consequently maximum therapeutic effect) will be accomplished when carrier systems are used mainly for drugs with antitumoral activity, as they increase their blood permanence time, taking advantage of the increased mass that reduces kidney ultrafiltration.
Areas covered: This review summarizes the attempts that have been made in the development of dextran conjugates and their application. The manuscript describes dextran hydrogels, the use of conjugates of dextran in bioadhesive oral delivery systems, colon drug delivery, reduction of ulcerogenicity of drugs, production of micelles, solubilization, long-circulating pharmaceutical carriers as anticancer drug carriers, non-viral vectors, stabilization of enzymes, functionalization of nanomaterials, diagnosis of solid tumors and hyperthermic treatment and liver targeting.
Expert opinion: Dextran conjugation has aided the design of new tailor-made polymers with different molecular weights, shapes, structures and with the functional groups needed for coupling at the desired positions in the chain. Dextran prodrugs are very useful systems for achieving controlled drug release and drug targeting. In particular, various dextran-antitumor drug conjugates enhance the effectiveness and improve the cytotoxic effects of chemotherapeutic agents. Future studies should concentrate on barriers for their clinical use and safety as a drug carrier.

Keywords: anticancer drug, biopolymer, conjugation, copolymer, dextran, drug delivery, micelles, prodrug

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1. Introduction

New classes of pharmaceuticals and biologics (peptides, proteins, and DNA-based therapeutics) have caused rapid evolution of drug delivery technology. These new drugs typically cannot be effectively delivered by conventional means. Additionally, it has been determined that, for many conventional pharmaceutical therapies, the efficacy may be improved and the side effects reduced if the therapy is administered continuously, rather than through conventional burst release techniques.

The benefits from targeted, localized delivery of certain therapeutic agents are another driving force in drug market. Areas that are being targeted for improvements through device development include: improved efficacy, reduced side effects, continuous dosing (sustained release), reduced pain from administration, increased ease of use, and increased use compliance. To provide these benefits, a number of approaches are being (or in some cases have been) developed. The common thread running through the approaches is the concept of targeted and sustained release with increased bioavailability. During the last two decades, significant advances have been made in the development of biocompatible and biodegradable polymers for biomedical applications. A wildly used biopolymer in drug delivery is dextran.

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Article highlights.

- Some dextran conjugates show bioadhesive properties.
- Prodrugs of dextran are specially useful in colon-targeted drug delivery. Liver-targeted delivery is also reported for dextran conjugates.
- Dextran-based micelles are useful carriers for anticancer drugs.
- Dextran-coated nanocarriers have long-circulating times due to prevention of particles being opsonized.
- Solubilization of poorly soluble drugs may be achieved by their conjugation to dextran.
- Dextran conjugation with cationic polymers reduces toxicity of these polymers while enhances their serum stability.

This box summarizes key points contained in the article.

Dextran is a bacterial polysaccharide synthesized from sucrose by certain lactic-acid bacteria and is consisting of main chains from α-(1→6) linked D-glucose units with different ratios of linkages and branches, depending on the bacterial strains [1]. This polymeric chain of glucosyl units may also be synthesized using dextransucrase by the transfer of D-glucosyl unit from sucrose to acceptor molecules [2]. The chemical structure of dextran (**Figure 1**) includes α-(1→6) linkages that can vary from 97 to 50% of total glucosidic bonds. The branching is made in position α-(1→2), α-(1→3), and/or α-(1→4). The hydroxyl groups in dextran are preferred for most derivatization. The C-2 hydroxyl groups appear to be the first to react because the hydroxyl groups of C-6 are concerned in α-1,6 linkages [1]. Different types of dextrans of varying size and structure are synthesized depending on the dextransucrase produced by the strain. The low molecular weight fractions of dextrans are used as a plasma expander. Furthermore, dextrans are widely under investigation as polymeric carriers in novel drug delivery systems [3]. The solubility of dextrans depends upon the branched linkage pattern. In fact, dextrans with > 43% branching through 1,3-α linkages have been considered water insoluble. Presence of 95% linear linkages makes it water-soluble, which is suitable for various applications [2].

2. Some popular synthesis methods of dextran conjugates

2.1 Direct esterification

Many ester prodrugs of dextran have been developed by its conjugation with acidic drugs to prolong drug release like most non-steroidal anti-inflammatory (NSAIDs) drugs. This type of linkage is formed by conjugation of hydroxyl groups of dextran in the presence of *N*,*N*′-dicyclohexylcarbodiimide with carboxylic acid drugs [4]. Another type of dextran ester is dextran ester-olefin compound copolymer. Multifunctional dextran esters with varying degrees of substitution by furoyl-, pyroglutamyl-, propyl-, and acetyl moieties are able to self-assemble into regular nanospheres.

2.2 Carbonyldiimidazole activation method

Activation of dextran hydroxy groups may be done with carbonyldiimidazole then amino groups are introduced by attaching ethylenediamine, and reacting amino groups with a succinimidyl-activated derivative of other hydroxyl containing substances like PEG [5]. Another example of use of this type of activation is in conjugation of cromoglycic acid with dextran [6].

2.3 Carbonate or carbamate ester method

Drugs containing a hydroxyl or amine group can be coupled to dextran in the form of carbonate or carbamate ester linkage, respectively. First of all hydroxyl groups of dextran are activated by phosgene then the alcoholic or amine drug is added to the activated dextran [7].

2.4 Periodate oxidation method

Enzymes and proteins are attached to dextrans and other polysaccharides by periodate oxidation of dextran which produces dialdehyde dextran. Then Schiff bases are produced from its condensation with amino compounds. The conjugate is then stabilized subsequently by reduction with sodium borohydride [8].

2.5 Cyanogens bromide activation method

Amine containing drugs and proteins may be attached to dextran or other polysaccharides by the cyanogens bromide activation of dextran [9].

2.6 Etherification of dextran

Ethers of dextran are made by irreversible nucleophilic substitution using aliphatic or aromatic halides, sulfates or epoxides, whereas reversible etherification is achieved via Michael addition of α,β-unsaturated reagents such as acrylonitrile, acrylamide, and methyl vinyl sulfone [10].

3. Drug carrier systems based on dextran conjugates

3.1 Dextran hydrogels

Hydrogels form a specific class of polymeric biomaterials. Precise definition of this term is not obvious. Hydrogels are defined as two- or multicomponent systems consisting of a three-dimensional network of polymer chains and water that fills the space between macromolecules. Hydrogels are becoming increasingly important in the biomedical, pharmaceutical specially in controlled release of drugs, biotechnological, and environmental fields. Dextran is a suitable polymer used for the preparation of hydrogels. Dextran hydrogels can be obtained by several different approaches, different chemical compositions, and cross-linking agents: chemical incorporation of glycidyl acrylate into dextran in aqueous phase, followed by free radical polymerization of the dextran derivatives in the presence of *N*,*N*′-methylenebisacrylamide as an additional cross-linker [11], cross-linking of

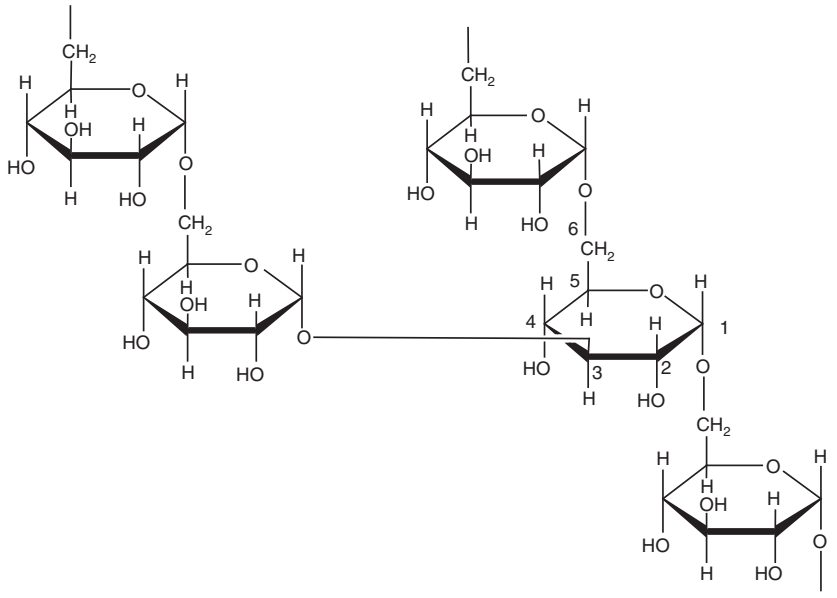


Figure 1. Chemical structure of dextran.

dextran with 1,6-hexanediisocyanate in DMSO [12] and cross-linking of dextran with epichlorohydrin [13]. Kim *et al.* [14,15] also reported the synthesis of methacrylated and acrylated dextrans by reacting dextran with methacrylic anhydride, and with bromoacetyl bromide and sodium acrylate, respectively. Allyl isocyanate dextran and lactide diacrylate were used for preparation of biodegradable dextran–polylactide hydrogel networks. This hydrogel was used in controlled release of indomethacin [16]. Phosphate diesters of waxy maize starch were prepared by cross-bonding reaction using phosphorus oxychloride. Cross-linked dextran is applied as a packing material for gel filtration columns [17].

Enzymatic cross-linking of dextran-tyramine (Dex-TA) conjugates in the presence of horseradish peroxidase and hydrogen peroxide was successively applied in the preparation of hydrogels used for encapsulation of chondrocytes. The Dex-TA hydrogels are promising 3D scaffolds for cartilage tissue engineering applications [18]. The swelling/degradation studies showed that under physiological conditions, Dex-TA linked by a urethane bond hydrogels are rather stable with less than 25% loss of gel weight in 5 months, whereas DG-TA hydrogels with ester-containing diglycolic group are completely degraded within 4 – 10 days [19]. These dextran-based hydrogels are promising for use as injectable systems for biomedical applications including tissue engineering and protein delivery.

Dextran hydrogels containing non-steroidal anti-inflammatory drugs (NSAIDs) as pendant agents, through ultraviolet irradiation of solutions of dextran functionalized with methacrylic groups in the presence of the drug derivatized in the same way have been prepared [20]. Release studies of different drugs from this system have demonstrated that it is strictly related to the concentration of the polymer in the solution submitted to irradiation as well as to its derivatization degree.

3.2 Bioadhesive oral delivery systems

The bioadhesive properties of poly(methyl vinyl ether-co-maleic anhydride) (Gantrez AN) nanoparticles (NP) associated with two hydroxyl-functionalized dextrans and one amino-derivative of dextran have been shown by Porfire *et al.* [21] The *in vivo* bioadhesion study has demonstrated significantly higher adhesive interactions with the gastrointestinal tract of rats for all types of dextran-associated NP compared with control NP. These results encourage us for further use of these systems for oral delivery of drugs.

3.3 Conjugates of dextran in production of micelles

Polymeric micelles using amphiphilic macromolecules are promising vehicles for antitumor targeting. A block copolymer composed of dextran and poly (DL-lactide-co-glycolide) (PLGA) (**Figure 2**) was prepared by Jeong *et al.* [22] for antitumor drug delivery of doxorubicin (DOX). In an antiproliferation study, the polymeric micelles showed higher cytotoxicity to doxorubicin-resistant HuCC-T1 cells than free doxorubicin, indicating that the polymeric micelles were effectively engulfed by tumor cells, while free doxorubicin hardly penetrated the tumor cell membrane.

Since aggregation states of amphotericin B (AmpB) are related to intrinsic cytotoxicity, prevention of AmpB aggregation in aqueous solution will provide low cytotoxicity and increased antimicrobial activity for the infectious disease. For this reason, AmpB was encapsulated in polymeric micelle of PLGA-grafted dextran copolymer [23]. AmpB-incorporated

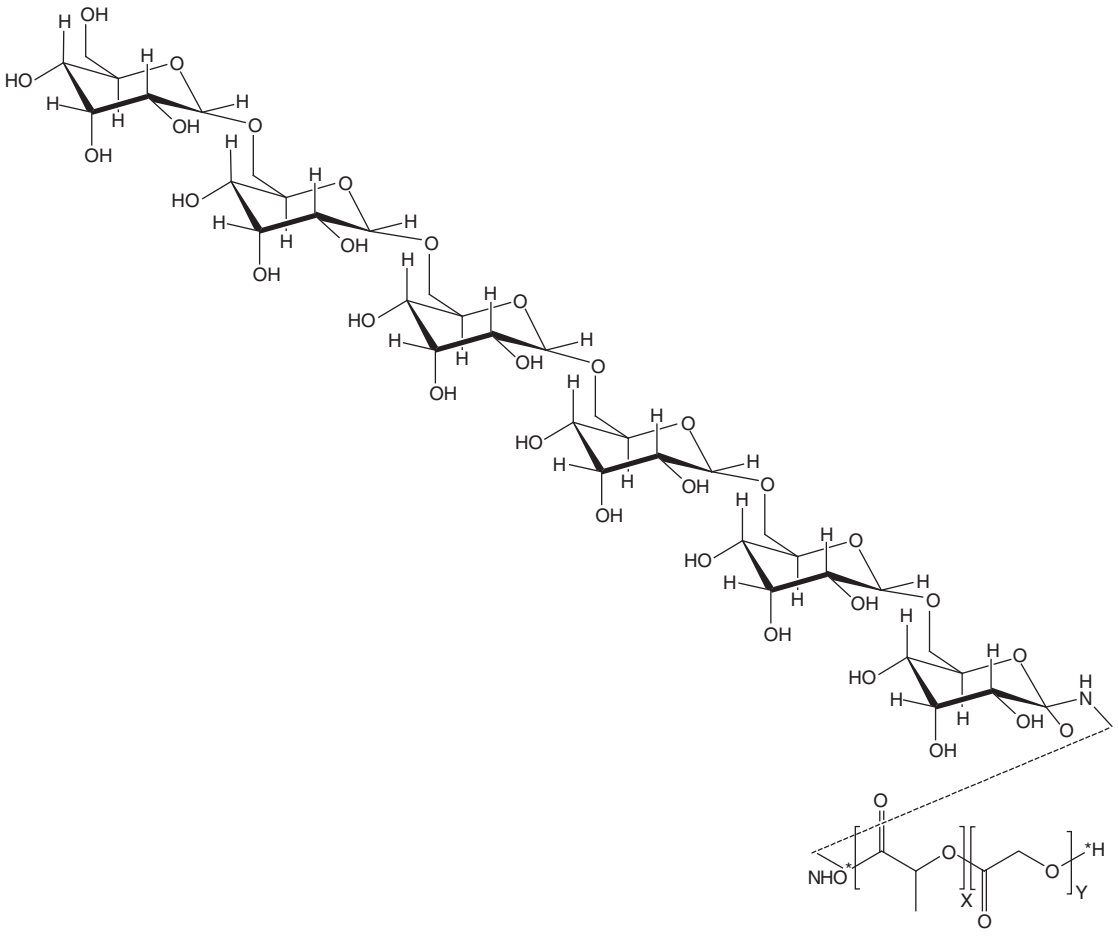


Figure 2. Schematic representation of dextran-poly(DL-lactide-co-glycolide) block copolymer.

polymeric micelle prepared from methanol/water mixture showed low cytotoxicity and favorable antimicrobial activity.

Another type of micelle obtained from conjugation of dextran is stearate-*g*-dextran (Dex-SA) that was synthesized via an esterification reaction between the carboxyl group of stearic acid and hydroxyl group of dextran [24]. Dex-SA could self-assemble to form nanoscaled micelles in aqueous medium. Tumor cellular uptake test indicated that Dex-SA micelles had excellent internalization ability, which could deliver DOX into tumor cells and could prolong *in vitro* drug release to 48 h. *In vivo* antitumor activity results showed that Dex-SA/DOX micelles treatments effectively suppressed the tumor growth and reduced the toxicity against animal body compared with commercial DOX injection.

Enhancement of drug loading and controlled drug release may be achieved by production of interpenetrating micellar networks. The strong associative network between cholesterol-modified dextran and short and long polyoxyethylene cholesteryl ether micelles was prepared [25]. The resulting network was constituted by polymeric chains connected by micellar aggregates through hydrophobic interactions between the micellar cholesterol cores and the pendent cholesterol moieties of the polymer.

Stimuli responsive micelles are another type of copolymers of dextran which can control drug release by the environmental stimuli. One of these systems is reduction-responsive biodegradable micelles that were developed from disulfide-linked dextran-b-poly(ε-caprolactone) diblock copolymer (Dex-SS-PCL) and applied for triggering release of DOX *in vitro* and inside cells [26]. DOX could be efficiently loaded into the micelles with a drug loading efficiency of about 70%. Notably, the *in vitro* release studies revealed that Dex-SS-PCL micelles released DOX quantitatively in 10 h.

Amphiphilic Dex-*g*-PCL micelles were also used as carriers for particle encapsulation and stabilization in the aqueous phase [27]. Multiple supramagnetic nanoparticles were self-assembled together with the help of Dex-*g*-PCL during phase transfer from chloroform to water.

Micelles based on Dex-b-PCL (**Figure 3**), with a series of well-defined chain lengths of each block were also prepared by conjugating a dextran chain with a PCL block via aza-Michael addition reaction under mild conditions [28].

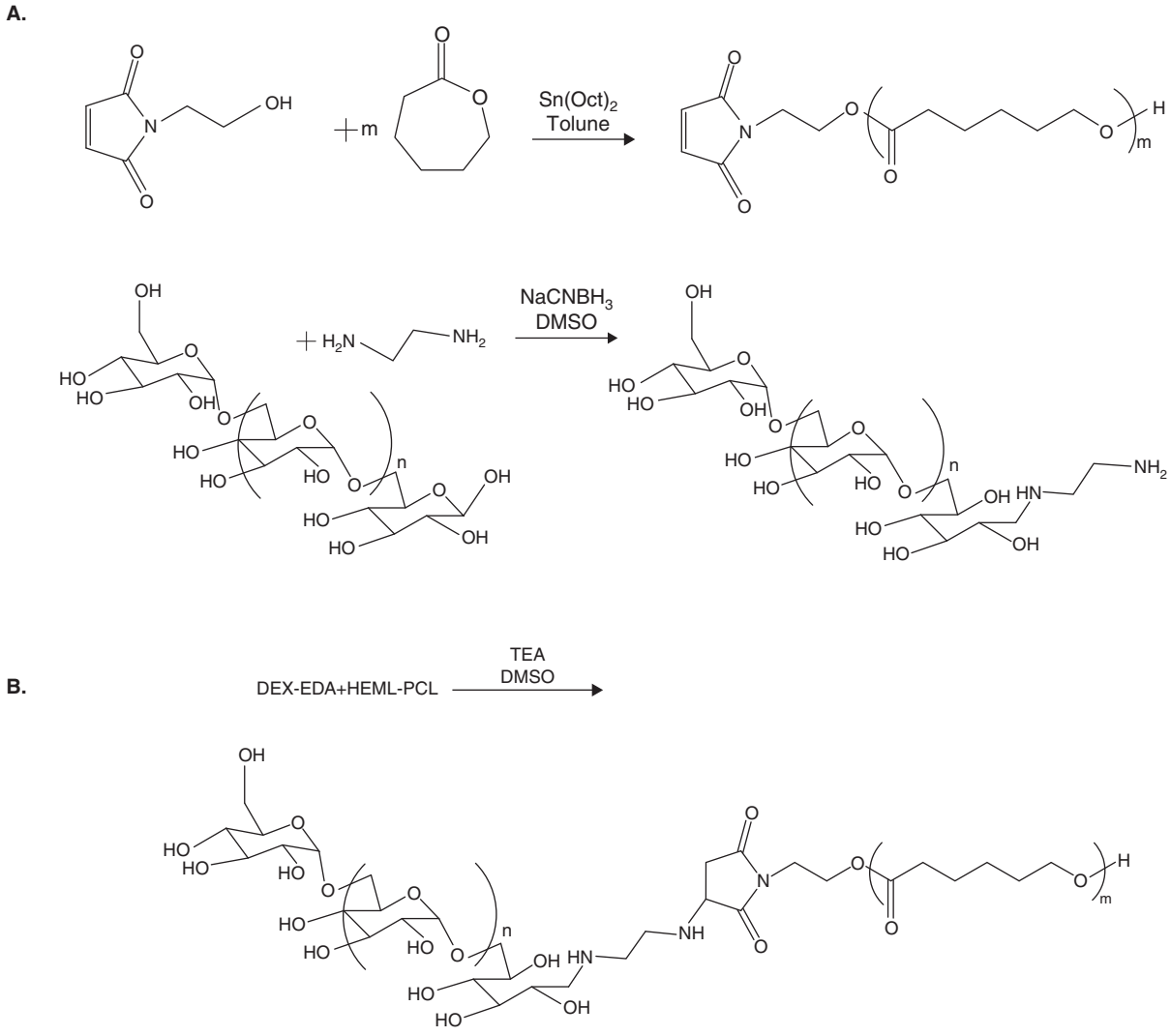


Figure 3. Synthetic route for amphiphilic diblock copolymer DEX-*b*-PCL.
Reproduced with permission from eXPRESS Polymer Letters [28].

The morphology of the copolymer assembly changed from spherical micelles to worm-like micelles and eventually to polymersomes, together with an increase in particle sizes.

A series of amphiphilic copolymers of dextran-*graft*-methoxy-polyethylene glycol/poly(ε-caprolactone) (Dex-*g*-mPEG/PCL) with great potential as drug carriers in biomedical fields were also synthesized by grafting both PCL and mPEG chains to dextran [29]. The prepared copolymers self-assembled into nano-sized spherical micelles in aqueous solution and the critical micellar concentration (CMC) of the graft copolymers could be adjusted by controlling the degree of substitution of mPEG and PCL, and these micelles may find.

Deoxycholic acid (DA)-conjugated dextran (DexDA) micelles (**Figure 4**) are another type of dextran conjugates which was synthesized for DOX delivery to DOX-resistant CT26 colon carcinoma cells [30]. The higher substitution degree of DA and higher drug feeding ratio resulted in increased particle size. Drug release was decreased by increase of substitution degree value of DA and increase of drug feeding ratio. At *in vitro* cytotoxicity test, higher antitumor activity was obtained with DOX-incorporated nanoparticles compared to free DOX.

Targeted micelles of dextran are also prepared for active drug delivery to malignant cells. These micelles are promising in reduction of resistance to cytotoxic drugs. A novel folate (FA)-targeted amphiphilic derivative of all-trans retinoic acid-dextran (ATRA-grafted Dex) was synthesized successfully using carbonyldiimidazole and dimethylaminopyridine for tumor-targeted drug delivery [31]. The degree of substitution of FA was 20% and for ATRA was 5.54% according to the weight of the polymer. The CMC of the micelle was found to be 12.5 μg/mL which is very low than that of the most surfactant micelles. Self-assembly of FA/Dex/ATRA copolymer produced micelles in PBS. Zeta potential of these

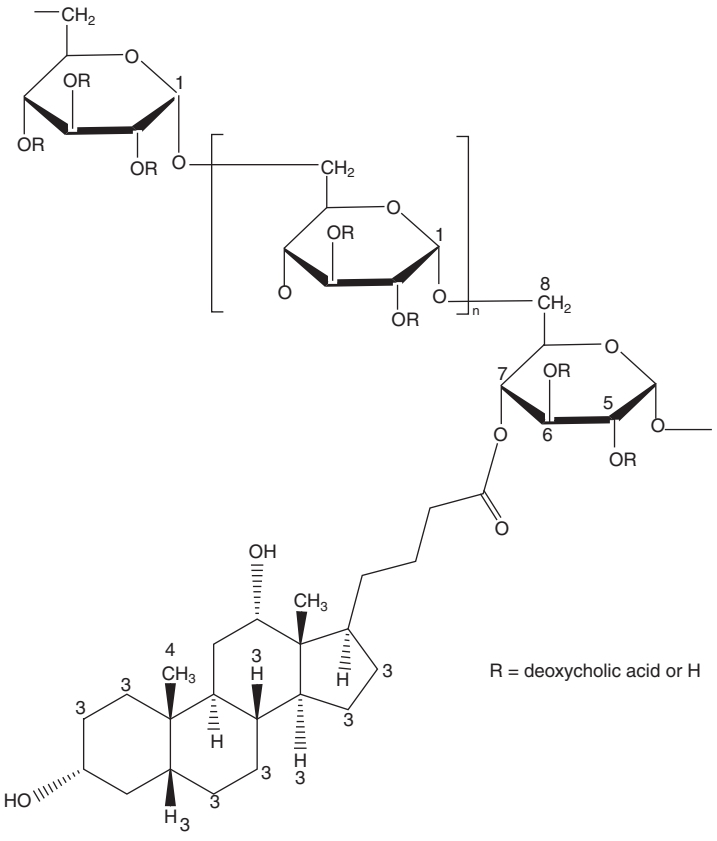


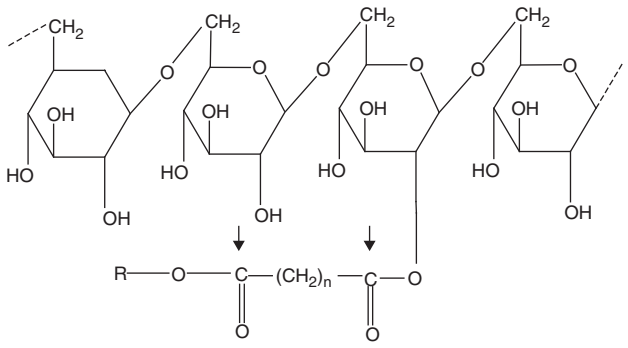
Figure 4. Schematic representation of dextran–deoxycholic acid conjugate.

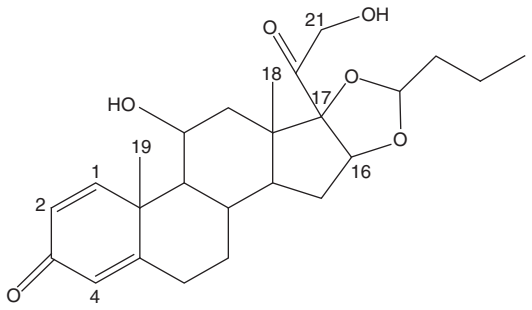
nanomicelles was −15.9 mV indicating good stability of the micelles. The polymeric micelles showed no toxicity on HeLa cells even at 50 μg/ml concentration and at 100 μg/ml about 90% of the cell survived. Then DOX was loaded in the micelles by dissolving method. Then the mixture was prob-sonicated for about 2 min. The cytotoxicity of micelles was evaluated by MTT assay on KG-1 cell line in different concentrations of DOX. The folate-targeted micelles of DOX were cytotoxic on KG-1 cell line (acute leukemia) in half concentration of DOX and seem promising in reducing the dose of this drug in acute leukemia [32].

Polymeric micelles of dextran have not only found their place in targeted drug delivery but they have become popular in food industries. For example β-casein is a good emulsifier in food industry but because of the acidic isoelectric point of casein, its solubility and functional properties are worse in acidic range. It is almost insoluble at around pH 4.6, which is its isoelectric point (pI). This is a significant limitation on the utility of casein in food industry because most foods are acidic. Therefore, the grafting of casein with suitable monomers has been extensively studied in order to improve the properties of casein. However, the graft copolymers produced by casein and synthetic polymers are not suitable in many food applications. Recently to solve this problem β-casein is grafted to dextran copolymer through Maillard reaction which has shown acidic solution properties with good stability in the presence of other acidic foods [33]. Purification of the protein–dextran conjugate is done after dilution and adjusting the pH at 5 that causes precipitation of the un-reacted protein and separation is done by centrifugation. At the end using a cation exchange resin can separate the dextran conjugated to protein [34].

3.4 Long-circulating pharmaceutical carrier

To exert its activity, a drug must reach its pharmacological site (s) of action(s) within the body. One of the current approaches to achieve site specific delivery is the use of nanocarriers. Such systems are able to bypass the normal physiological defense processes occurring after the intravenous injection of particulates and, depending on the particle size and hydrophobicity of the outer layer of carrier properties, it remains for a prolonged period of time in the systemic circulation, or have a degree of selectivity for sites of deposition within the body. Inhibiting the uptake of nanoparticulate drug carriers by the major organ of the reticuloendothelial system, the liver gives greater chance to the drug to penetrate into the affected organs. Both the small size and the long-circulation lifetime suggest their potential application as a pharmaceutical carrier to enhance the delivery of various agents to their targets by the enhanced permeability and





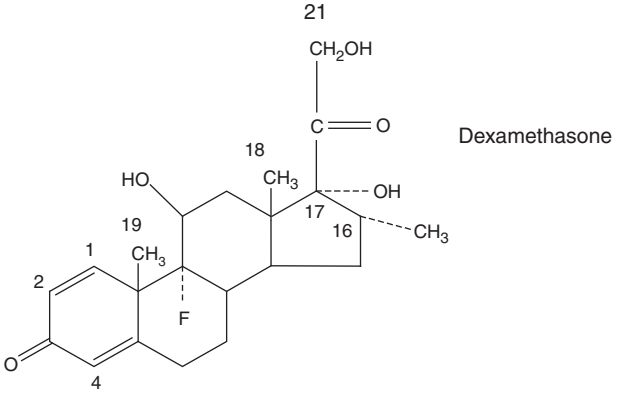


Figure 5. Conjugation of dextran with budesonide or dexamethasone.

retention (EPR) effect. Large molecular weight polysaccharides with molecular mass greater or equal to 40 kD have low clearance and relatively long plasma half-life, resulting in accumulation in tumor tissues [35]. Long-circulating dextran-coated iron oxide nanoparticles have been extensively used as an experimental magnetic label for magnetic resonance (MR) imaging, and some preparations are currently being used in clinical trials [36]. These nanoparticles have extended circulation times because of their dense coating, which prevents opsonization, and their small size.

Due to its hydrophilicity, dextran itself may also be conjugated to other drugs for enhancing circulation time. One of these is uricase (UC) which is conjugated with dextran, cationic diethylaminoethyl-dextran (DEAED), and anionic carboxymethyl-dextran (CMD) giving a molecular weight of 10,000 by the periodate oxidation method [37]. After i.v. injection, 111In-UC was slowly eliminated from the circulation and gradually accumulated in the liver, spleen, and kidney. Conjugation with neutral dextran slightly enhanced the uptake of 111In-UC by the liver and spleen, while DEAED and CMD conjugation resulted in significant enhancement and reduction of hepatic uptake, respectively.

The efficacy of a number of therapeutically active proteins and peptides is severely limited due to their instability in circulation. A successful approach is covalent modification of the protein or enzyme with some hydrophilic polymers such as dextran or PEG. These conjugates are more stable than the native protein both *in vitro* as well as *in vivo*. They exhibit enhanced resistant to proteolytic degradation, have a long-life in circulation and exhibit reduced immunogenicity. The therapeutic efficacy of these conjugates is also greatly enhanced compared to the native protein or enzyme [38]. One of these stabilized peptides is mouse epidermal growth factor (mEGF, 6 kDa). By reductive amination, mEGF was coupled to 13 and 46 kDa dextran [39]. In conclusion, dextranation affects the biodistribution of mEGF *in vivo* giving a prolonged circulation time, a decreased uptake in kidney, and an increased spleen accumulation.

3.5 Non-viral vectors

More than 300 different polycations have been prepared starting from various natural polysaccharides and oligoamines having two to four amino groups. Dextran–spermine cationic polysaccharide was one of them prepared by means of reductive amination between oxidized dextran and the natural oligoamine spermine. Although most of these cationic conjugates formed stable complexes with plasmid DNAs, only the

dextran–spermine-based polycations were found to be highly effective in transfecting cells *in vitro*. Polyethylenimine (PEI) is another cationic polymer that is an efficient transfection reagent with high toxicity and a susceptibility to aggregate in the presence of serum. Dextran can reduce the toxicity of PEI and increase its stability in the presence of serum. Dextran-polyethylenimine conjugates are believed to have greater potential for translational applications because of lower cytotoxicity characteristics and improved stability in serum-containing environments [40].

3.6 Functionalization of nanomaterials

Nanomaterials like single-walled carbon nanotubes, gold nanoparticles and gold nanorods have gained great attentions for biological applications, but they require appropriate functionalization to provide biocompatibility in biological environments. Conjugates of dextran and a phospholipid (dextran-DSPE) have been prepared as a general surfactant material that provides stable coatings for these nanomaterials [41].

3.7 Diagnosis of solid tumors and hyperthermic treatment

Magnetic nanoparticles have been used to diagnose tumors in the liver and spleen by magnetic resonance imaging (MRI) [42]. These nanoparticles accumulate in specific areas in the body and make possible the hyperthermic treatment with magnetic particles [43-51]. Magnetic nanoparticles convert energy absorbed from an alternating magnetic field into heat and may be useful for the delivery of hyperthermic therapy.

Dextran magnetite is used widely as a liver-specific contrast medium and its safety has been established. It consists of core-shell structure with carboxy-dextran covering the core and the iron-oxide particles of the core. Dextran magnetite was conjugated with the carboxyl group of gelatin and cisplatin. This complex was used in thermal ablation which could slowly release the chemotherapeutic drug and showed potentially maximizing its antitumor effects [52-55].

Another magnetic drug-targeting carrier was prepared by encapsulating of magnetic nanoparticles with a smart polymer. The carrier was consisted of functionalized magnetite and conjugated doxorubicin, which was encapsulated with the thermosensitive polymer of dextran-g-poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide). This polymer exhibited a lower critical solution temperature (LCST) of approximately 38°C. This behavior allowed for an on–off trigger mechanism. At an experimental temperature lower than LCST, the drug release was very low. However, at a temperature greater than LCST, there was an initially rapid drug release followed by a controlled released in the second stage, especially, in the mild acidic buffer solution of pH 5.3 [56].

Superparamagnetic iron oxide (SPIO) nanoparticles are effective contrast agents for enhancement of magnetic resonance imaging at the tissue, cellular, or even molecular levels. Multiple SPIO nanoparticles were self-assembled together with the help of Dex-*g*-PCL during phase transfer from chloroform to water, and diameters of Dex-*g*-PCL/SPIO nanocomposites were 64.22 nm [27]. The time for enhanced-MRI could last at least 12 days and totally recovered after 16 days. This novel sensitive MRI contrast agent may find potential applications in discovering small liver lesions such as early tumor diagnosis.

4. Applications of dextran conjugates in drug delivery

4.1 Prodrugs of dextran used in colon drug delivery

Owing to their low tissue toxicity and high enzymatic degradability at desired sites, dextran prodrugs have been frequently considered as a potential matrix system for colon-specific delivery and/or controlled release of bioactive agents. The activation of dextran will be possible by periodate oxidation, succinoylation and reaction with 4-nitrophenyl chloroformate. Even physical mixtures of drugs in dextran microsphers [57] or tablets [58] are prone for targeted drug delivery to colon. Solid dispersion [59] of budesonide, a potent glucocorticoid with high affinity for the glucocorticoid receptor used for the treatment of inflammatory bowel diseases, with dextran is also reported as an effective strategy in controlled drug delivery to colon.

Current oral formulations of budesonide present low efficacy against ulcerative colitis because of the premature drug release in the upper part of the gastrointestinal tract. A colon-specific delivery system for budesonide to increase the efficacy in the treatment of ulcerative colitis (UC) was developed by conjugating dextran to budesonide in the presence of dimethylaminopyridine (DMAP) using succinate spacer (**Figure 5**) [60]. Rats treated with budesonide–dextran conjugate (equivalent to 300 μg/kg of budesonide) showed huge improvement in macroscopic and histological scores of colitis compared to the negative control group, mesalasine and budesonide suspension [61].

Budesonide conjugates were also prepared using glutarate spacer (**Figure 5**) [62]. The conjugate of budesonide–dextran with glutarate spacer could decrease the macroscopic and microscopic scores of induced colitis compared with mesalasine and budesonide suspension.

Dexamethasone was also attached to dextran using succinate anhydride in an anhydrous environment catalyzed by 4-dimethylaminopyridine and 1,1'-carbonyldiimidazole [63]. The dexamethasone-succinate-dextran (DSD) (**Figure 5**) was stable in rat stomach and small intestine and negligibly absorbed from these tracts. Four to nine hours after the oral administration, most of the prodrug (> 95 %) had moved to the cecum and colon, and was easily hydrolyzed by an endodextranase [64].

Ketoprofen-dextran ester prodrugs showed the average absorption fractions of 100 to 67% compared to the oral solution of an equivalent dose of parent ketoprofen [65].

The colon-specific polymeric conjugates of celecoxib have also been prepared with dextran using succinic acid as linker between the drug and dextran [66].

5-Aminosalicylic acid (5-ASA) conjugates of dextrans were developed with a focus on Crohn's disease applications [67]. Dextrans were oxidized using sodium periodate (NaIO(4)), where the aldehyde groups formed were coupled with the alpha-amino (-NH(2)) group of 5-ASA. The resulting imine bonds were unstable in water and were consequently reduced to secondary amine groups. Dextrans with a maximum degree of oxidation (93%) unsurprisingly gave maximum conjugation of 5-ASA but were resistant to dextranase hydrolysis. Less oxidized dextrans (12%) conjugated proportionally less 5-ASA but were successfully hydrolyzed by dextranase, suggesting their potential applications for the treatment of Crohn's disease in the distal ileum and proximal colon.

Dextran-flufenamic acid ester (Dex-FFA) was prepared by imidazolide method [68]. Upon oral administration of this conjugate (20 mg equivalent of FFA/kg) or FFA (10 mg/kg) to rats, t_{max} for FFA delayed approximately 6h compared with that of free FFA, while C_{max} for FFA was similar. The plasma level for FFA became greater around 6 h after administration of Dex-FFA than free FFA and it was maintained throughout the period of 24-h experiment. Dex-FFA markedly attenuated gastric ulcerogenicity of FFA. Thus these studies show the application of the dextran ester prodrug approach for providing selective colon delivery of drugs possessing a carboxylic acid functional group.

4.2 Reduction of ulcerogenicity of NSAIDs

Dextran conjugates of ketorolac [69] and flurbiprofen [70] were synthesized and characterized to improve ketorolac aqueous solubility and reduce gastrointestinal side effects. An N-acylimidazole derivative of ketorolac or flurbiprofen was condensed with dextran as a carrier polymer. *In vivo* biological screening in mice and rats indicated that conjugates retained analgesic and anti-inflammatory activities with significantly reduced ulcerogenicity compared to the parent drug.

Not only NSAID drugs conjugated to dextran have shown less ulcerogenicity but also drug loading into pH-sensitive hydrogels of dextran has shown no ulcerogenic effect. For example pH-sensitive hydrogels of dextran were synthesized by photochemical cross-linking reaction of methacrylate dextran (DEX-MA) at different derivatization degree, functionalized with acidic residues through reaction with phthalic anhydride [71]. Ibuprofen was loaded into the polymeric matrices. *In vivo* studies verified the biocompatibility of the materials. Moreover, when the matrix loaded with ibuprofen was administered to rats, it was able to protect them from the ulcerogenic effects of the drug.

4.3 Solubilization of poorly water-soluble drugs

Most anticancer and antivirus drugs are water insoluble and their passive or active targeting is impossible until they are solubilized. Another application of dextran conjugates is solubilization of the poorly water-soluble drugs. Micellar solubilization is a powerful alternative for dissolving hydrophobic drugs in aqueous environments. The length of the hydrophilic part as well as the content and chemical nature of the hydrophobic substituents has an important effect on the ability of polymeric micelles to solubilize poorly water-soluble drugs. Cyclosporin A (CsA) is an example which is solubilized in aqueous dispersions of dextran-grafted-polyethyleneglycolalkyl ether (DEX-g-PEG-C_n) polymeric micelles [72]. Copolymers with longer polysaccharide chain showed larger CMC and mean diameter. The percentage of CsA loading into micelles was significantly larger in polymeric micelles compared to unmodified dextrans. It increased with increasing number of PEG-C_n units grafted per dextran chain and decreasing dextran molecular weight. The cytotoxicity of DEX-g-PEG-C_{16} polymeric micelles toward Caco-2 cells was significantly lower than that of free PEG-C_{16} molecules.

Acyclovir, the antivirus drug with good *in vitro* activity against hepatitis B virus, is another example of low-soluble drugs which has low distribution in liver. The clinical application of this drug in hepatitis B is limited for this reason. To increase the solubility and the distribution in liver, acyclovir–dextran conjugate was synthesized by formation of Schiff's base [73]. The solubility of obtained conjugate was 12 times greater than free acyclovir. Acyclovir will be slowly released from the obtained conjugate. Relatively higher distribution of acyclovir in liver was observed when i.v. acyclovir–dextran conjugate was administered in mice compared to i.v. free acyclovir.

Paclitaxel (taxol) is a very effective anticancer drug. However, the solution used to enhance the water solubility of paclitaxel, a mixture of polyoxyethylene castor oil (Cremphor EL) and dehydrated ethanol, causes irritation. Taxol conjugation with aminated dextran (Dex-TXL) was synthesized for the water-solubilization of taxol and folic acid was conjugated to it. Dex-TXL showed two to three times greater anticancer effect when conjugated with FA [74].

4.4 Dextran conjugates as anticancer drug carriers

Macromolecular drug carrier systems have been developed in an attempt to enhance the selectivity of action of cytotoxic drugs by coupling them to carriers with expected affinity for the target tissue. Some advantages of dextrans as drug carriers may be summarized as: i) polymeric chemical structure with repetitive monomers, ii) highly water solubility, iii) high stability to acidic or alkaline conditions due to stable glucosidic bonds that are not hydrolyzed easily except under extreme pH ranges, iv) the possibility of derivatization on numerous reactive hydroxyl groups present in its structure, v) availability of different molecular weights, vi) inert nature due to low toxicity and pharmacological activity, vii) protection of conjugated drugs from biodegradation, and viii) an apparent passive targeting of this soluble macromolecules to solid tumors due to EPR effect.

Thus, much effort has been made to target DOX to cancer tissues, improving its efficacy and safety [75]. Daunorubicin and DOX were covalently coupled to dextrans and were found to reduce the toxicity in mice [76,77]. Various other anticancer agents, such as methotrexate [78,61] and mitomycin C [79], 5-fluorouracil [80] or cisplatin [81] have been covalently coupled to dextrans.

It has been shown that dextran–DOX conjugate can inhibit P-glycoprotein (P-gp) pump overexpressed in multidrug-resistant cells and consequently superior antitumor activity to the free drug [82]. Conjugatation of adriamycin to dextran has been done by peptide spacer of Gly–Leu–Gly too and galactosamine also has been anchored to it as a targeting moiety [83]. This conjugate generated the best therapeutic effect with the presence of long-term survival on day 50 against CT-26 mice colon cells implanted subcutaneously in Balb-C mice.

4.5 Liver targeting

It is demonstrated that dextrans may be of great value in targeting therapeutic agents to the liver [84]. The plasma and tissue disposition of two novel dextran prodrugs of methylprednisolone (MP) containing one or five amino acids as linkers were studied in rats [85]. These data suggest that conjugates with one amino acid may be more suitable than five for targeting immunosuppression to the liver and spleen. Molten *et al.* [86,87] worked on carboxypeptidase G2 conjugated to soluble dextrans. They found a pronounced uptake of both CNBr-activated dextran and dextran–enzyme conjugate by the liver. Dextran conjugate of glutathion has also shown transport to hepatic cells, intracellularly hydrolyzed to free form and protects mice from hepatotoxicity of acetaminophen [88].

Positively charged radiolabelled dextrans are rapidly eliminated from the plasma of tumor-bearing mice and accumulate in tissues like the liver [89]. However, negatively charged dextrans persist for a long time in the systemic circulation and have negligible tissue accumulation [89-91]. It is proposed that dextrans enter cells through fluid-phase endocytosis [92] which is a passive phenomenon. However, efforts have been made to chemically modify dextrans for active targeting to specific cells in the liver. Vansteenkiste *et al.* [93] prepared dextrans glycosylated with mono- or tri-D-galactose for asialoglycoprotein receptor-mediated delivery to the liver. In another study [94], carboxy-methyl dextran (CMD) modified with galactose and mannose residues accumulated mostly in the parenchymal and non-parenchymal cells of the mouse liver, respectively. However, non-modified CMD did not accumulate in either type of cells. Schechte *et al.* [95] reported conjugation of 5-fluorouridine to high molecular weight carrier CMD which was charged with two to four biotinyl groups for complexing to trinitrophenyl (TNP)-modified streptavidin (St). Specific liver accumulation occurred following administration of the conjugate only when complexed to TNP-St.

When conjugation of a drug to dextran leads to its undesirable accumulation in the liver at a low dose, an appropriate modification of dextran such as carboxymethylation would be required in such cases [96].

4.6 Targeting to other routes

Passive targeting is also reported for some conjugates of dextran. Pyrimethamine is an anti-leishmanial drug, although this effect *in vivo* appears only in relatively high concentrations. To reach the parasites inside macrophage cells, where they are sheltered, targeted drugs of pyrimethamine, carboxymethyldextran-thiomannopyranoside-pyrimethamine (CMD-P) was synthesized which showed a destruction of approximately 50% of the intracellular amastigotes of *L.(L.) amazonensis*, with no detectable toxicity to macrophage cells [97].

Human interferon β (IFNβ) was passively targeted to choroidal neovascularization (CNV) by combining it with dextran, based on metal (Zn^{2+}) coordination, and an enhanced antiangiogenic effect was achieved. This conjugate could prolong the plasma half-life of IFNβ, enhance the accumulation of IFNβ in CNV lesions, and inhibit progression of CNV in rabbits [98].

Long-term antibiotic treatment is required to cure tuberculosis. Targeted antibiotics should improve the efficacy of treatment by concentrating the drugs close to the bacteria. Dextran was used as the polymer bearing mannose and norfloxacin. Different peptide spacer arms were used to link norfloxacin to dextran. Thus, norfloxacin, which is inactive against mycobacteria in its native form *in vivo*, can be transformed into an active drug by targeting [99].

5. Conclusion

Among the different drug delivery systems, macromolecule conjugates have been widely explored; this review collects and summarizes the therapeutic applications of conjugates of dextran. The insight that will be gained is knowledge about the progress in the development of polymeric conjugates of dextran especially in drug delivery systems and targeted delivery of anticancer drugs. This review also aims to introduce the different conjugates of polymers with natural and modified dextran polysaccharides used in production of micellar nanocarrier systems. The highly versatile nature of the dextran conjugates can overcome many practical difficulties in delivering chemotherapeutics, genes and other drugs due to the surface nature including biocompatibility, degradability and size/dimension are all adjustable. Furthermore, the simple and inexpensive nature of this polymer can also satisfy strict demands from an economic point of view.

6. Expert opinion

The advent of new research on drug delivery in cancer chemotherapy has outlined new strategies for therapeutic

intervention. Conjugation of natural and synthetic polymers, proteins and polysaccharides that have been covalently coupled with cytotoxic and other types of drugs is one of the progressive approaches. Dextran conjugates can be synthesized either by direct conjugation or by spacer arm technique. The advances in the field of targeted drug delivery by dextran conjugates especially targeted micelles of dextran can result in more efficient strategies for cancer treatment. Like many works so far done on stable liposomes, lipid and polymeric nanoparticles as nanocarriers, polymeric and especially dextran-based micelles are colloidally stable and present enormous opportunities for loading chemotherapeutic agents. These dextran-based delivery systems offer such a great versatility that can be used both for parentral, oral and for local drug delivery, with huge possible applications in different clinical areas. Prodrugs of dextran satisfy the requirements for being colon-specific and a potential strategy to circumvent obstacles in developing efficient colon-specific prodrugs. The prodrugs of dextran also have great potency in reduction of ulcerogenicity of non-steroidal anti-inflammatory (NSAID) drugs. Not only NSAID drugs chemically conjugated to dextran but also physically loaded in pH-sensitive dextran conjugates show less ulcerogenicity than parent drug. Solubilization of poorly soluble drugs is another important feature in drug delivery systems that is achieved by dextran conjugation. Conjugation of anticancer drugs to this soluble carbohydrate produces long-circulating carriers which provide the chance of escaping from reticuloendothelial system and nanocarriers will have greater time for permeation and retention by the leaky tumor vasculature. The choice of macromolecule, the spacer, and the chemistry of the linkage with cytotoxic drugs are key points to obtain effective conjugates with higher activity than that of the free drug and reducing its side effects. The clinical usefulness of non-viral methods is still hindered by their relatively low gene delivery/transgene expression efficiencies. Dextran conjugates have shown to be a useful non-viral vector with reduction of toxicity and enough efficiency in delivery of plasmid DNA to cells.

The main advantages of this polymeric drug conjugate include: increased water solubility of low-soluble or insoluble drugs and therefore enhancement of drug bioavailability, improvement in pharmacokinetics, the ability to provide passive or active targeting of drugs to the site of their action and the possibility to form an advanced complex drug delivery system. The most promising techniques in production of its conjugates are specially production of prodrugs and also micellar-targeted carriers for anticancer drugs due to their biocompatibility and natural origin.

Although dextran is a natural polymer and is expected to be the safest platform, the results of clinical Phase I trial of dextran-conjugated doxorubicin has shown some unexpected toxicity including thrombocytopenia and hepatotoxicity possibly due to the uptake of the polysaccharide by the reticuloendothelial system [100]. Therefore, more clinical studies should be performed to remove the question mark on clinical safety of dextran conjugates. Further preclinical and clinical studies are needed to evaluate the safety and potential significance of dextran conjugates in targeting of chemotherapeutics to cancer cells resistant to the therapy. Despite the remarkable potential and extensive research being conducted on dextran conjugates for use in drug delivery, commercialization and large-scale production are limited by the cost and difficulty of chemical reactions needed for their production. A continuing challenge in the field is to work on more feasible chemical procedures for scaling up the production of dextran conjugates.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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