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Dahiya, D., & Singh - Nee Nigam, P. (2024). Dextran Used in Blood Transfusion, Hematology, and Pharmaceuticals: Biosynthesis of Diverse Molecular-Specification-Dextrans in Enzyme-Catalyzed Reactions. *Frontiers in Bioscience-Elite*, 16(2), 17. Article fbe1602017. Advance online publication. <https://doi.org/10.31083/j.fbe1602017>

[Link to publication record in Ulster University Research Portal](#)

Published in:
Frontiers in Bioscience-Elite

Publication Status:
Published online: 03/06/2024

DOI:
[10.31083/j.fbe1602017](https://doi.org/10.31083/j.fbe1602017)

Document Version
Publisher's PDF, also known as Version of record

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Review

Dextran Used in Blood Transfusion, Hematology, and Pharmaceuticals: Biosynthesis of Diverse Molecular-Specification-Dextrans in Enzyme-Catalyzed Reactions

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Academic Editor: Muthu Thiruvengadam

Submitted: 15 August 2023 Revised: 26 March 2024 Accepted: 25 April 2024 Published: 3 June 2024

Abstract

Dextran is an exopolysaccharide synthesized in reactions catalyzed by enzymes obtained from microbial agents of specific species and strains. Products of dextran polysaccharides with different molecular weights are suitable for diverse pharmaceutical and clinical uses. Dextran solutions have multiple characteristics, including viscosity, solubility, rheological, and thermal properties; hence, dextran has been studied for its commercial applications in several sectors. Certain bacteria can produce extracellular polysaccharide dextran of different molecular weights and configurations. Dextran products of diverse molecular weights have been used in several industries, including medicine, cosmetics, and food. This article aims to provide an overview of the reports on dextran applications in blood transfusion and clinical studies and its biosynthesis. Information has been summarized on enzyme-catalyzed reactions for dextran biosynthesis from sucrose and on the bio-transformation process of high molecular weight dextran molecules to obtain preparations of diverse molecular weights and configurations.

Keywords: biomolecule; blood; clinical; dextran; dextran-sucrase; dextranase; enzymes; glucon-sucrase; pharmaceutical; sucrose; transfusion

1. Introduction

Dextrans are exopolysaccharide biomolecules synthesized by bacterial species. Dextran is a polysaccharide of glucose units that are α -1,6-glucans. Dextran is a neutral polymer that can be dissolved to prepare solutions with relatively low viscosity. This property is useful for dextran's applications in various areas, compared to other high-molecular-weight polysaccharides, which do not produce colloidal solutions of desired viscosity, particularly for clinical purposes. Dextran preparations have been previously used to regulate blood circulation in conditions of shock and reperfusion injury, as the activity of dextran was functional in reducing the damage to endothelial cells by protecting activated leukocytes. Dextrans of high molecular weight have been investigated for rheology and their bioactivity; these dextrans were synthesized by lactic acid bacteria [1].

Dextrans, particularly those with low molecular weights (MWs), are required for clinical use and as products for research analytical studies [2]. Fluids prepared using dextran of specific MWs are used in blood transfusions, where they function as an anticoagulant, osmotic agent, volume extender, and antithrombotic and intravenous plasma-lubricant. Dextran-40 solution is used to develop blood volume by injecting it through a vein directly into the bloodstream. Specifically, it is used when blood transfusions of specific matching types are not immediately available, and

there is a deficit in circulating blood volume, for instance, in the condition of shock initiated by burns, surgery, and hemorrhage. In such cases of blood deficit, hemoglobin concentration is not considered the only therapeutic guide, the treatment is focussed on restoring the intravascular volume and adequate hemodynamic parameters [3].

In addition, functional polymers based on dextran are used as cryo-preserved agents for vaccines and organs [4]. Dextran has also been used in the cosmetic industry as a moisturizing and thickening ingredient in some cosmetic products. In pharmaceutical applications, the reducing property of dextran allows its use in products formulated as an anti-aging agent. In the research and development sector, dextran is used for its convenience in creating matrices for chromatography, immobilization of entities on biosensors, generating nanoparticles, and preparing different emulsions. The adaptability of dextran, due to its multi-functional contributions to medicine, cosmetics, and food, has been the subject of research for decades [5].

This article aims to review reports published on the uses of dextran for clinical and pharmaceutical applications and then on the synthesis of dextrans of different MWs. Information has been presented on enzyme-catalyzed biosynthesis and the bio-transformation of high-MW dextrans to yield low-MW molecules with different branching configuration ratios.



2. Dextran Properties and Applications

Dextran polysaccharides contain α -(1,6)-linked glucans and side chains attached to the C-3 position of the glucose chain. Dextran preparations have a range of molecular weights, as described in the following subsections. Dextran molecules have a high capacity for water-binding; for instance, 1.0 g of dextran-40 can retain up to 30 mL of water, although 1.0 g of dextran-70 holds less water, about 20 to 25 mL. The unique property of dextran is that when it is dispersed in normal saline at a 6% w/v concentration, it demonstrates viscosity and colloidal osmotic pressure, identical to blood. The isotonic types of dextran saline solutions are 6 or 10%, w/v. Dextran is soluble in water and organic solvents, and this property of dextran solubility is used to formulate special structures by combining dextran with hydrophobic polymers or bioactive agents. The benefit of dextran hydrogels has increased for soft tissue-engineering applications because of their great biocompatibility and ability to lower the adsorption of nonspecific proteins and attachment of cells. Yet, these dextran properties are not enough to fulfill their function of accomplishing a tissue-engineering scaffold. The conjugation of Arginylglycyl-aspartic acid (RGD, a cell adhesion motif) peptide bioactive moieties on dextran might enable tissue growth and regeneration. Additionally, chemically modified dextran can be used to form spherical, tubular, and 3D network structures [1–6].

2.1 Dextran Used In Blood Transfusions

Dextran has been used as an expander of plasma volume for several years. Dextran-70 and 40 preparations, with molecular weights of 70 and 40 kDa, were recommended to manage shock or impending shock caused by hemorrhage, burns, and trauma [2,3,6]. Kam *et al.* [7] used dextran-40 *in vitro* to evaluate the effect of hemodilution on the coagulation profile, where the thromboelastometry and multiple electrode aggregometry methods measured the test samples. The use of albumin as an alternative might be beneficial in patients suffering from septic shock; however, the cost of clinical-grade albumin is high. Therefore, Bentzer *et al.* [8] investigated the effects of using dextran-70 on organ failure or mortality in patients suffering from severe sepsis or septic shock. Researchers performed their study using a group of patients with severe sepsis or septic shock admitted to a hospital intensive care unit between 2007 and 2015 and administered dextran-70 for resuscitation. The report concluded that no evidence could be detected to support an unfavorable effect of the use of dextran-70 on organ failures and or mortality in patients with septic shock or severe sepsis [8].

For plasma expansion, alternatives to albumin include crystalloids (normal saline 0.9% sodium chloride and Ringer's lactate), plasma protein fraction (alternate protein colloids), and dextran (nonprotein colloids). Although non-protein colloids and crystalloids have not exhibited a bene-

fit over using albumin, these are low-cost options. Dextrans are added to normal saline as an isotonic medium when used as an element in colloid solutions. Winkler mentioned in a previous article on albumin and related products that Rescueflow, a hypertonic mixture, is limited to its prehospital use in treating hypotension caused by bleeding, although its benefit remains uncertain [9]. Warden discussed in his article on fluid resuscitation and early management that in young pediatric burn patients with major burn injuries, colloid replacement is frequently required; thus, the serum protein concentration decreases rapidly during burn shock. In such cases, dextran colloid is routinely used during the resuscitation of children with major burn injuries [10]. Important types of dextran have been summarized in Table 1 (Ref. [11,12]), indicating their molecular weights and applications in blood transfusions.

Dextrans are used as volume expanders, as they have an effect of inhibition on the aggregation of thrombocyte and coagulation factors. The dextrans infusion can direct to anaphylactic reactions in mothers, which can make the embryo vulnerable. It has been suggested that the anaphylactic reactions can be lowered by administering Hapten–Dextran (Dextran-1 of a low molecular weight preparation of specifically 1.0 kDa) immediately before an infusion using main dextran. The binding of dextran-reactive antibodies to dextran-1 prevents the occurrence of large immune complexes and, subsequently, an immune response [13].

2.2 Dextran Used in Hematology

Researchers have investigated the characteristics of dextran polysaccharides in studies relevant to hematology. Dextran-40 has been tested for use in hemodilution compared with normal saline. Kam *et al.* [7] reported the *in vitro* effect of hemodilution evaluation on the coagulation profile by dextran-40, which was determined by thromboelastometry and multiple-electrode aggregometry. Researchers used blood samples taken from the veins of 20 volunteers who were in good health. Samples were diluted using dextran-40, or 5%, 10%, and 15% saline solutions; the results of this study for the coagulation profile did not show any platelet dysfunction. Clot formation was significantly impaired by hemodilution with dextran-40 compared to hemodilution with saline and in blood samples without dilution. At these concentrations of hemodilution performed *in vitro* to exhibit the clinical use of dextran infusions, no considerable fibrinolysis or platelet inhibitions were observed [7].

Studies have been performed to compare the effect of dextran and albumin on blood coagulation in patients undergoing gynecological surgeries. Their platelet count, standard coagulation tests based on plasma, and whole blood viscoelastic clot structure were reported to be highly affected by dextran-70 (6%) compared to albumin (5%); however, the aggregation of platelets did not change. Sigurjonsson *et al.* [14] reported that the Von Willebrand function

Table 1. Dextran products and their application in blood transfusions [11,12].

Product	Application	Product Molecular Weight (MW, Dalton, Da)
Dextran-70	(1) a plasma substitute (2) to prevent deep venous thrombosis	Average: 70,000
Dextran-40 (D-40)	(1) Plasma expander (2) It is used to enhance blood flow in ischemic limbs (3) D-40 improves the micro-circulatory flow by decreasing red cell aggregation	Average: 40,000
Macrodex, Dextran-70 (6%)	Expands plasma to the same volume as the infused amount; solution exists in the plasma for up to 4 hours	Average: 70,000
Dextran-70 (32%)	Sometimes administered intraperitoneally to reduce the adhesions after reproductive surgery	Average: 70,000
Rheomacrodex, 10% Dextran-40	This product is used for its excellent rheologic properties during vascular surgeries. It has efficacy of a larger plasma volume expansion with a shorter half-life than that of 6% Dextran-70	Average: 40,000
Hapten, Dextran-1—a low-MW dextran	Applied as a desensitizer to avoid allergic reactions to large molecular weight dextrans, before the main dextran solution is infused	A fraction of dextran polysaccharide with a low molecular weight of 1000 Da

was not deranged by isovolumic substitution of dextran-70 more than by albumin (5%) because dextran is hyperoncotic compared to the 5% solution of albumin and, therefore, it induces a greater expansion in plasma volume and produces a higher dilutional coagulopathy.

A study on dextran deposition in tissues revealed that infused dextran was mainly unchanged when eliminated at a rate of 50% by the kidney within 24 hours of infusion and another 20% in the next 48 hours. Some of the residual 30% dextrans are metabolized by dextranase (6- α -D-glucan 6-glucanohydrolase) from the splenic and hepatic sources, while some are eliminated by the gastrointestinal tract after its hydrolysis by coliform bacteria [11]. In a clinical project, biopsy and autopsy studies were conducted using 32 patients treated with regular hemodialysis for about 61 months. These patients had also received plasma expanders in the form of dextran-40 because of the hypotension caused during the hemodialysis process.

The clinical performance of dextran was studied in a control test group of 11 hemodialyzed patients receiving alternative plasma expanders instead of dextran. In the other 11 patients in the dextran test group, who were given the maximum dosage of 0.38 g/kg per week of dextran-40, particles were detected in the macrophage cytoplasm of their various organs. These particles presented positive results in the periodic acid-Schiff (PAS) staining method, which detects dextran. None of the intracellular dextran particles were tested in the control group patients (receiver of an alternative for dextran), while no inclusions were also found in those patients who received a lower dose of dextran-40 below 0.08 g/kg per week. A linear relation was observed between the dextran-40 dosage and the number of inclusion particles. This study demonstrated that the material verified in the macrophages was dextran, structurally modified

by macrophage activity to a water-insoluble particle form. Hence, dextran-40 at a lower dose is equally effective without its particle inclusion as other plasma-extender options [11].

2.3 Use of Dextran in Pharmaceuticals

Products of dextran polysaccharides with different molecular specifications have established several applications in the pharmaceutical industry. Dextrans of analytical quality are available commercially as active pharmaceutical ingredients (API). They are applied as excipients for the final formulation of clinical drug products, for medical devices, and for the production of solutions used in injections and infusions. Dextran is an inert material formulated with an active drug ingredient for the long-term stabilization of a medication. Dextran is also used as a bulking agent to increase the mass of those specific solid medicine formulations that contain the main active ingredients in very small measures in the ensemble weight of the product [15]. The role of dextran in pharmaceutical products is to act as a diluent—a filler—and to deliberate a medicinal improvement in the final dosage form of an active component in a pharmaceutical preparation.

Dextran is used as a critical constituent of hydrogels for biomedical applications, including in biosensor materials, drug delivery devices, and tissue engineering scaffolds. Dextran has applications as a pro-drug and in many classes of drug delivery vehicles, such as microspheres and nanocarriers. Injectable hydrophilic dextran/AgNP nanocomposite products have been prepared as white light-active biomolecules for their application as an antitumor agent [16].

Dextrans have established their varied applications for analytical purposes, e.g., in the gel filtration process used to

separate pharmaceutical compounds [5,17]. Dextran polymers can be easily cross-linked and fabricated to generate beads, which are required for their use in columns prepared for gel filtration. A commercialized filtration gel based on dextran is Sephadex®, which is available in many bead sizes and porosities, possessing characteristic ranges for molecular weight fractionation. Such filtration gels have multiple applications in analytical examinations, e.g., Sephadex® G-200, with the highest porosity, is suitable for fractionating proteins in the molecular weight range of 4.0 kDa to 80 kDa. In contrast, Sephadex G-25 is specifically useful for separating peptides with molecular weights lower than 5 kDa. Other than neutral dextran gels, some dextran derivatives, such as quaternized and carboxymethyl dextrans, are also commercially available, which are required for anion and cation-exchange chromatography [17].

2.4 Use of Dextran in Clinical Drug Delivery

Dextrans, with their hydrophilic features, have been applied in the conjugation of bioactive substances (such as enzymes, drugs, antibodies, and hormones) to extend their circulation lifetime, increase stability *in vivo*, or depress their antigenicity. Dextran nanoparticles have been applied in conjugation with insulin for oral insulin administration. Dextran nanocarriers protect insulin from degradation in the gut and modulate its release profiles. In addition to being a hydrophilic and functional polymer, dextrans are extensively used to modify surfaces to fabricate a biosensor. A dextran layer on sensor chips helps minimize the nonspecific adsorption of analytes and facilitates surface immobilization of ligands, thereby successively improving the biosensors' sensitivity.

Derivatives of different polymer lengths of dextran [18] have many biological applications, such as an antithrombotic agent, in MRI contrast components and drug delivery systems due to its unique benefits of solubility and non-immunogenicity. Several dextran-based drug delivery systems with required design properties, such as nanocarriers and self-assembled micelles, have been created. Because of the high solubility of dextran nanocarriers in water, the solubilization and permeation of drugs are facilitated across the gastrointestinal membrane. Dextran polysaccharide molecules also protect drug molecules against their chemical or enzymatic degradation in the gastrointestinal tract, meaning they can only be depolymerized by a specific enzyme, dextranase. The neutral nature of dextran proves favorable in its protection from the mucus layer, which is negatively charged [19].

Two commonly co-administered drugs for chemotherapy in a wide range of cancers are doxorubicin (DOX) and cisplatin (CIS). Dextran-based self-assembled nanovesicles were prepared to conjugate anticancer drugs DOX and CIS in their core and layer [20]. Further, responsive biopolymer-based microgels/nanogels have been suggested for drug delivery applications [21]. The stability of

nanovesicles against the glutathione detoxification was due to dextran vesicular geometry. These had adequate entrapment efficiency and were submitted for breakdown by lysosomal esterase enzyme for the delivery of drugs. In another study, dextran was modified with a 3-pentadecyl phenol to add stimuli-responsive characteristics for pH and enzyme. The anticancer drug doxorubicin could be effectively delivered under acidic pH conditions with the assistance of self-assembled and dual-responsive characteristics of dextran nanovesicles. A different type of derivative, curcumin-functionalized poly (lactic-co-glycolic acid)-dextran nanomicelles, has been synthesized, which exhibited the self-assembled behavior and natural antibacterial activity of curcumin [22]. Table 2 summarizes some commercially available dextrans as active pharmaceutical ingredients for human vaccine applications, lyophilization, organ preservation, and blood volume expanders.

Dextran has many applications in nanomedicine. Dextran nanoparticles have better water solubility, higher load capacity, and inherent viscosity. Thus, these features of dextran made it a favorable polysaccharide material for applications in nano-drug carriers, cell imaging systems, and the fabrication of nano biosensors [23]. For several *in vivo* applications, dextran is one of the most effectively used polysaccharide-based polymers. Dextran-coated superparamagnetic iron oxide nanoparticles are clinically applied as contrast agents in magnetic resonance imaging, and they also possess cancer nodal staging capabilities. The introduction of a carboxymethyl group can upgrade the functionality and stability of dextran-coated magnetic particles cross-linked to epichlorohydrin to obtain cross-linked iron oxide particles, which have better stability than dextran-coated superparamagnetic iron oxide nanoparticles of the same dimensions [24].

Dextran of different molecular weights and branching configurations has become of commercial and pharmaceutical importance for such a wide range of applications. Therefore, several researchers have studied its biosynthesis using enzymes obtained from specifically selected microbial agents. Some of the methods studied for its enzymatic biosynthesis are discussed in Sections 4 and 5.

3. Characterization of Dextran Polymers

Dextran is a generic name given to a few types of glucans, which are formed by the polymerization of the α -D-glucopyranosyl part of sucrose molecules. The reaction is catalyzed by an enzyme called dextransucrase (Fig. 1).

Dextran polysaccharides contain α -(1,6)-linked glucans, and its side chains are attached to the C-3 position of the polymer chain. The periodate and methylation analyses revealed the degree of branching to be nearly 5%. Around 40% of the side chains are formed of single α -D-glucopyranosyl units; 45% of the side chains are two units long, while there are more than two units in 15% of the side chains. Hence, the side chains predominantly have one or

Table 2. List of Commercially Available Dextrans with Diverse MWs: from High to Low MWs*.

Pharmaceutical dextran	Product specification	Product molecular weight (Da)
Dextran-500	European Pharmacopoeia (EP), United States Pharmacopoeia (USP)	500,000
Dextran-250	EP; USP	250,000
Dextran-150	EP; USP	150,000
Dextran-110	EP; USP	110,000
Dextran-70	EP, USP, Japanese Pharmacopoeia (JP)	70,000
Dextran-60	EP; USP	60,000
Dextran-40	EP, USP, Japanese Pharmacopoeia (JP)	40,000
Dextran-25	EP, USP	25,000
Dextran-20	EP, USP	20,000
Dextran-10	EP, USP	10,000
Dextran-5	EP, USP	5000
Dextran-3.5	EP; USP	3500
Dextran-1.5	EP; USP	1500
Dextran-1	EP; USP	1000

* Information sourced from <https://www.dextran.com/>; accessed on 22/07/2023.

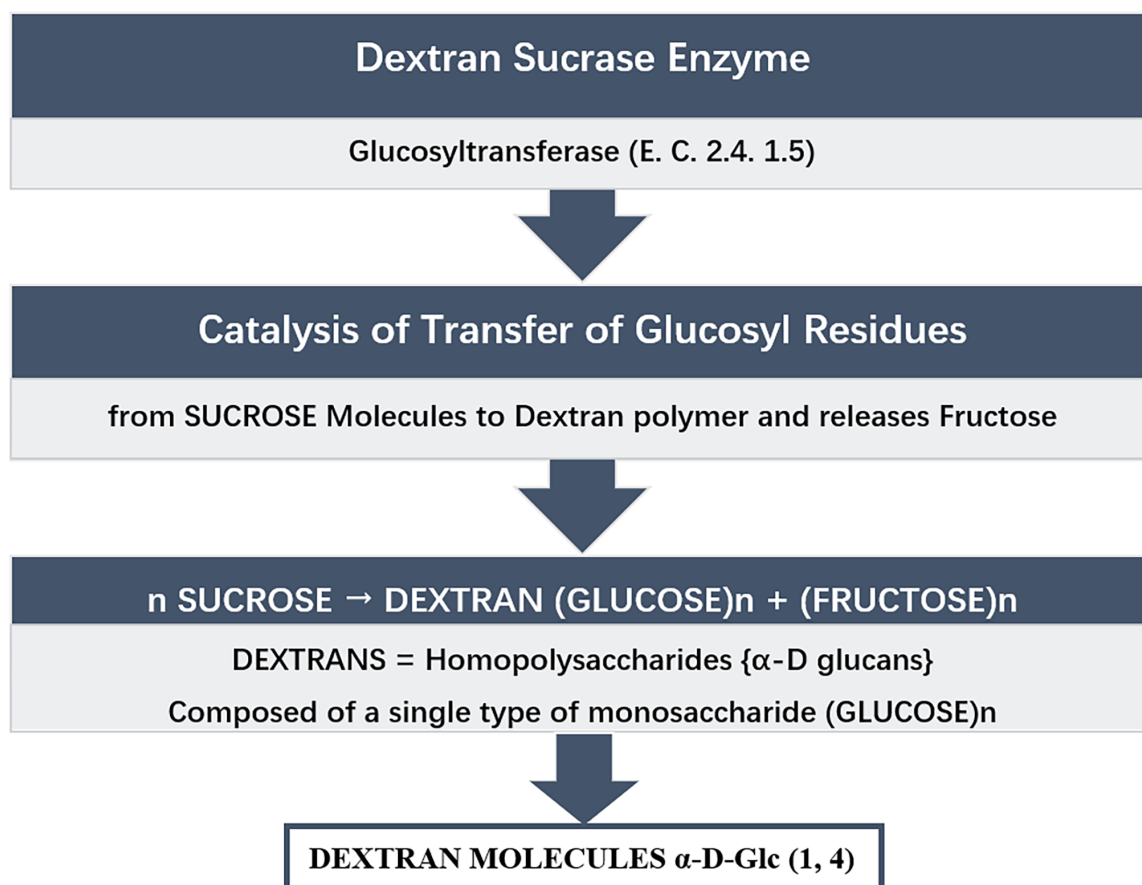


Fig. 1. Synthesis of dextran from sucrose catalysed by enzyme dextran sucrose.

two units of glucose [25]. The molecular weight of dextran produced by a commercial strain *Leuconostoc mesenteroides* NRRL B-512 can range widely from 9 million to 500 million Da. Dextran in solution shows an extendable coil structure, mainly due to its flexible $\alpha\text{-(1,6)}$ -glycosidic linkages in the polymer. It has a good level of solubil-

ity in water in addition to its solubilization in several organic solvents, for example, ethylene glycol, glycerol, formamide, methyl sulfoxide, hexa-methyl-phosphoramide, and 4-methylmorpholine-4-oxide [19,20].

Table 3. Dextran products of varied molecular specifications are synthesized by dextran–sucrase and glucan–sucrase.

Synthesized product specification	Substrate and mixture of substrates used in enzyme-catalytic synthesis of product	Enzymes from original, engineered, or mutated strains used as biocatalyst in reaction	Enzyme sourced from a bioagent	Reference
178 kDa 97% α -(1→6) 3% α -(1→3)	5%, w/v sucrose	Dextranucrase WcCab3 from original strain	<i>Weissella confusa</i> Cab3	[29]
10–20 kDa	10%, w/v sucrose	Dextranucrase (DE3)/pET28- dexYG-dextranase from engineered strains	<i>Escherichia coli</i> , <i>Penicillium aculeatum</i> BL21	[30]
5 kDa	10%, w/v sucrose	Dextranucrase (DE3)/pET28- dexYG from engineered strains	<i>Escherichia coli</i> BL21	[30]
~ 92 kDa 98% α -(1→6) 2% α -(1→2)	400 mM sucrose	Dextranucrase FT045B-dextranase from original strains	<i>Leuconostoc mesenteroides</i> , <i>Penicillium FT045Bsp.</i>	[31]
1645 kDa	1000 mM sucrose	Dextranucrase B-512FMC from mutated strains	<i>Leuconostoc mesenteroides</i> B-512FMC	[32]
126–787 kDa	200 mM sucrose	Dextranucrase B-512FMC from mutated strains	<i>Leuconostoc mesenteroides</i> B-512FMC	[32]
63–514 kDa	100 mM sucrose	Dextranucrase B-512FMC from mutated strain	<i>Leuconostoc mesenteroides</i> B-512FMC	[32]
49–431 kDa	50 mM sucrose	Dextranucrase B-512FMC from mutated strain	<i>Leuconostoc mesenteroides</i> B-512FMC	[32]
20–341 kDa	20 mM sucrose	Dextranucrase B-512FMC from mutated strain	<i>Leuconostoc mesenteroides</i> B-512FMC	[32]
~ 6 MDa 100% of α -(1→6)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940W from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]

Table 3. Continued.

Synthesized product specification	Substrate and mixture of substrates used in enzyme-catalytic synthesis of product	Enzymes from original, engineered, or mutated strains used as biocatalyst in reaction	Enzyme sourced from a bioagent	Reference
~ 20 MDa 93% α -(1→6) 7% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940F from mutated strains	<i>Leuconostoc reuteri</i> 180	[33]
~ 19 MDa 73% α -(1→6) 27% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940E from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]
~ 19 MDa 72% α -(1→6) 28% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940M from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]
~ 20 MDa 84% α -(1→6) 16% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940S from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]
~ 19 MDa 84% α -(1→6) 16% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940A from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]
~ 17 MDa 74% α -(1→6) 26% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940C from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]
~ 17 MDa 85% α -(1→6) 15% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase L940G from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]
~ 23 MDa 78% α -(1→6) 22% α -(1→3)	Maltose 100 mM + sucrose 100 mM	Glucansucrase GTF180 from mutated strain	<i>Leuconostoc reuteri</i> 180	[33]

Table 4. Dextran of different MWs and configurations are synthesized by the enzymatic transformation of dextran and sucrose.

MW of products synthesized	Product configuration– glycosidic linkages	Substrates used for bio-transformation	Enzymes used in the reaction	Reference
2000 kDa	64% of α -(1→6) 36% of α -(1→2)	70 kDa dextran + 292 mM sucrose	Transglucosidase GBD–CD2 cloned	[36]
528 kDa	Not applicable (NA)	892 kDa high molecular weight dextran α -(1→6) and α -(1→3) branching	Dextranase produced by <i>Leuconostoc mesenteroides</i> KIBGE-IB26	[37]
70 kDa	81–88% of α -(1→6) 12–19% of α -(1→2) 62–67% of α -(1→6) 33–38% of α -(1→2)	70 kDa dextran + 292 mM sucrose	Transglucosidase GBD–CD2 cloned	[36]
40 kDa	63% of α -(1→6) 37% of α -(1→2)	70 kDa dextran + 292 mM sucrose	Transglucosidase GBD–CD2 cloned	[36]
10 kDa	62% of α -(1→6) 38% of α -(1→2)	70 kDa dextran + 292 mM sucrose	Transglucosidase GBD–CD2 cloned	[36]
1.0 kDa	68% of α -(1→6) 32% of α -(1→2)	70 kDa dextran	Engineered α -1,2 transglucosidase	[38]
0.5 kDa	75% of α -(1→6) 25% of α -(1→2)	70 kDa dextran	Engineered α -1,2 transglucosidase	[38]
5–8 kDa	NA	40 kDa dextran	Dextranase original from <i>Penicillium</i> Sp	[39]
Low MW fractions	NA	Dextran fractions with high molecular masses of 1500 to 2800 kDa	Dextranase (Sugazym DX L, SternEnzym) from a non-genetically modified strain <i>Chaetomium gracile</i>	[40]
Low molar mass dextran L-Dextran, 3000–5000 Da	Average MW of 3951 Da, 86.0% α -(1→6) 14.0% α -(1→4)	20%, w/v sucrose in sodium acetate buffer (50 mM)	Dextransucrase enzyme DSR-M Δ 2 Q634A and its variants	[41]
Three different fractions of oligodextran	NMWCO of 10 kDa	Substrates (20–50 g/liter) and enzyme (6250–62,500 Units/liter)	Endo-dextranase (1,6-(α)-D-glucan-6-glucan hydrolase from <i>Penicillium lilacinum</i>	[42]
Low-molecular weight dextran (LMWD)	<10(5) Da branching 5% to 16.60%	0.1–4.0 M sucrose	dextransucrase from <i>Leuconostoc mesenteroides</i> B-512FMCM	[43]

4. Biosynthesis of Dextran in Enzyme-Catalyzed Reactions

A commercial strain, *Leuconostoc mesenteroides* NRRL B-512, is used for dextran production. Since the enzyme catalysis is a very effective method for the synthesis of bioactive molecules for their applications in the pharmaceutical industry [26], dextran also can be synthesized in an enzyme-catalyzed process, which is free from the direct cultivation of microorganisms. Several such molecules prepared from microbial strains have been studied for medicinal and therapeutic applications [27]. Biomolecules with special characteristics for industrial biotechnological applications have been prepared using enzymes obtained from purposely selected microbial sources [28]. Considering the productive biosynthesis process of suitable enzyme catalysts, a similar strategy was applied to dextran synthesis in enzyme-catalyzed reactions.

Table 3 (Ref. [29–33]) summarizes some of the processes where dextran has been synthesized from sugars by enzymes dextran–sucrase and glucan–sucrase. These reactions were catalyzed by natural, mutated, or engineered bacterial enzymes.

5. Biotransformation of Dextran and Sucrose to Dextran of Different Configurations

Water-soluble dextran fractions of low molecular weight have multiple applications in pharmaceuticals, including being a carrier for drug delivery. The enzymatic transformation was used to obtain such dextran preparations since the enzymes as biocatalysts have proved useful in the biotransformation of compounds into their pharmaceutically active isomers [34]. Similarly, enzymatic transformation studies produced dextrans of different configurations and MWs. Enzymatic synthesis of dextran was conducted under controlled conditions to produce clinically suitable molecular weight products [35]. The biotransformation of dextran into several molecular weight products has been performed using trans-glucosidase and dextranase enzymes (Table 4, Ref. [36–43]).

A synergistic catalytic process performed by two enzymes, dextranase and dextransucrase, was applied to synthesize oligo dextrans of different molecular weights [30]. A new dextran was structurally characterized as having a low branching produced by a dextran–sucrase enzyme sourced from *Leuconostoc mesenteroides* FT045B [31]. In another study, the main parameter affecting the enzymatic biosynthesis of dextrans was optimized by varying concentrations of enzyme dextransucrase, which was sourced from a different strain B-512FMC of *L. mesenteroides*, with two other factors—the concentration of sucrose used as the main carbon source in the process and the reaction temperature [32]. The biosynthesis of dextran molecules with exact ratios of alpha-1,2 linkages using transglucosidase GBD-CD2 has been studied by Brison *et al.* [36]. Low molecular weight dextran molecules with alpha-1,2 branching were

prepared using an engineered alpha-1,2 transglucosidase enzyme [38]. The method of directing filtration to narrow the molecular weight distribution of oligo-dextran has been tried by Su *et al.* [39] in an enzymatic membrane reactor.

6. Future Prospects

The prospects for dextran applications have increased since the clinical importance of dextran biomolecules was first identified a few decades previous in an early report where a dextran with a low molecular weight was used in 85 cases of vascular surgery to prevent early thrombosis after arterial reconstruction [44]. As a result of ongoing research, dextran polymers of different MWs are now commercially available for use in studies researching drug development [15]. Drug delivery products are prepared as bioparticles made of acid, aldehyde, amine, thiol, sulfate, and vinyl sulfone groups modified dextran polymer [45]. Dextran use is widely accepted as an important component of an aqueous two-phase system, which is a decisive technique for extracting and filtration biomolecules, including proteins, membranes, viruses, enzymes, nucleic acids, and others. Hence, the role of dextrans as an important component in aqueous two-phase systems has established its ever-increasing prospects in the pharmaceutical industry [46]. Therefore, researchers focused on the biosynthesis of dextran for large-scale production using bacterial strains of *Leuconostoc*, *Lactobacillus*, and *Weissella*, which secrete extracellular metabolites in the culture medium in the form of a polysaccharide characterized as dextran [47,48].

Consequently, in the last decade, different methods have been reported to produce various dextran products, either low or higher MW dextrans, as required for specific applications. Such possibilities have increased their wider applications in several industries, including pharmaceutical, cosmetics, and food, as well as dextran as a polysaccharide, which is also used in analytical materials and procedures for research. Owing to various important applications of dextran in pharmaceutical industries, a draft document on dextrans by the European Medicines Agency supported the revision of the annex to the guideline on “Excipients in the labelling and package leaflet of medicinal products for human use” concerning the applications of dextrans [49].

7. Conclusions

The detailed characterization of each type of prepared dextran is important so that any new dextran obtained from a biocatalytic process [50,51] could be as useful as a commercial dextran synthesized through a microbial process. However, dextran products produced via enzyme-catalyzed reactions could be of clinical importance for specific applications compared to those produced in microbial fermentation employing actively growing bacterial cells. Enzymatically produced dextran molecules will be free from any contamination of microorganisms and can be easily characterized for their chemical configurations. Although, low MW

fractions of high MW dextrans could also be prepared in a shorter time using a chemical process of acid hydrolysis compared to longer enzymatic hydrolysis. However, low MW fractions obtained in the acid process would require further steps for their purification, which would increase the overall cost of their production process. Therefore, a cost-effective method is preferred; for that, there is the prospect of optimizing enzymatic hydrolysis to obtain the required MW dextran molecules.

Author Contributions

DD and PSN conceptualized the design of this review article, drafted and wrote the manuscript for first submission. Both authors contributed to editorial revisions and changes suggested by reviewers in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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