Dextrans and dextran derivatives as polyelectrolytes in layer-by-layer processing materials – A review

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Dextrans and dextran derivatives as polyelectrolytes in layer-by-layer processing materials – a review

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ABSTRACT

The layer-by-layer technique (LbL) using polysaccharides is receiving increasing interest as the preparation of nano- and micro- multilayer objects composed by natural materials is a promising alternative for actual systems. The use of bacterial polysaccharides and more particularly, dextrans and dextran derivatives, in LbL assemblies allows the simple formation of biodegradable and biocompatible multilayers with engineered functionalities. The choice of dextrans and derivatives along with the assembly conditions can indeed control internal structure and physical, chemical and biological properties. In this review, we describe the use of dextrans and dextran derivatives into multilayers presented in literature, from the method and principles to the key parameters that need to be considered in their formations. We present their valorisation into nanoobjects with specific and stimuli-responsive properties that are mainly exploited for biomedical applications as drug delivery devices.

KEYWORDS

Dextrans, layer-by-layer, thin films, dextran derivatives, capsules, multilayers, nanomaterials

ABBREVIATIONS

LbL, layer-by-layer ; HIV, humain immunodeficiency virus ; DexS, dextran sulfate ; CHI, chitosan ; QCM, quartz crystal microbalance ; PEI, polyethylenimine ; DEAE-Dex, diethylaminoethyl dextran/2-(diethylamino) ethyl dextran ; IEP, isoelectric point ; Dex-HEMA, hydroxyethylmethacrylate-derivatised dextran ; MF, melamine formaldehyde ; HF, hydrofluoric acid ; PLL, poly-L-lysine ; Cat, catalase ; Ins, insulin ; Apr, aprotinin ;

1. INTRODUCTION

Developing alternative materials and systems based on natural polymers is currently challenging and yet, one of the key issues in material chemistry and nanotechnology in reason mainly of current environmental concerns. In the last decades, the scientific community has started to take an interest in polysaccharides due to their biocompatibility, biodegradability and low toxicity (de Belder, 1996; Hernández-Rivas et al., 2020; J. Liu et al., 2015; Rinaudo, 2008). Polysaccharides are a large family of polymers, obtained from biomass (animal, plant, bacterial, algal and fungal), exhibiting various structures and functionalities. They present a wide variety of structures resulting from the absolute configuration of asymmetric carbons, the stereochemistry of linkages as well as the branching pattern of polymers that differ according to their type and their source (J. Liu et al., 2015). Thus, they have been widely studied and used for their functional properties in the pharmaceutical industry, cosmetic formulation, paper industry, food industry, oil extraction and many other applications fields (J. Liu et al., 2015).

Among all polysaccharides, α-glucans are polymers naturally produced by microorganisms, notably dextrans which are the most widely used bacterial α-glucans in many fields, in both industry and research (Mehvar, 2000; Naessens et al., 2005; Yalpani & Hedman, 1985). Dextran family are D-glucose polysaccharides with a large majority of α-(1 → 6) type glycosidic bonds linkages whose structures are dependent on production due to glucose origin and bacteria involved (Taylor et al., 1985). Those bacterial polysaccharides present a great interest to the scientific community and find numerous applications in various areas, especially in the elaboration of bio-based materials: their wide availability, their diverse structures, their different branching patterns, their ‘clean’ production, as well as the possibility of functionalisation with a large variety of groups or active sites. Charged dextrans in particular have been studied as potential alternatives for many synthetic polyelectrolytes in

66 the elaboration of nanomaterials *i.e.* thin films and coatings, capsules, nanoparticles, etc. The
67 occurrence of chemical groups onto their polymer chain promotes formation of electrostatic
68 interactions and facilitates their inclusion with other charged compounds. Pioneering
69 researches on integration of polysaccharides in multilayered films, by well-known methods
70 such as layer-by-layer (LbL) method, have been begun in the middle 1990s (Lvov et al.,
71 1998). The specific integration of dextrans into those thin films, has started in the early 2000s
72 and their applications are gradually growing since then (Hartley et al., 2002; Serizawa et al.,
73 2000).

74 Polyelectrolyte films have become an unavoidable way to functionalise surfaces and to
75 create ordered nanostructures, that found an application range from biomedical devices to
76 environmental field (Boudou et al., 2010; Gribova et al., 2012; Jaber & Schlenoff, 2006;
77 Joseph et al., 2014). The principle commonly used for polyelectrolyte multilayers is the LbL
78 film formation based on the alternate adsorption of polyanions and polycations from aqueous
79 solutions which was investigated firstly by Decher and Hong in the late 1980s. Revised by
80 Decher *et al.* in the 1990, first research generation in the early 1990s allowed an expansion of
81 the method to polyelectrolyte films with various materials as well as film characterisation
82 (Ariga et al., 1997; Decher, 1997; Decher & Hong, 1991a; Lvov et al., 1995). The
83 polyelectrolyte film construction relies mainly on electrostatic interactions between charged
84 polymers and is highly dependent on the charge balance of polyelectrolytes and experimental
85 conditions (Schoeler et al., 2002; Voigt et al., 2002). Indeed, film properties can be controlled
86 by modulating deposition conditions (deposition time, temperature, etc.), characteristics of
87 polyelectrolytes (charge density, molecular weight, etc.) and parameters of polyelectrolyte
88 solution (concentration, pH, ionic strength, etc.) (Dubas & Schlenoff, 1999; Guzmán et al.,
89 2020). In the last two decades, the interest of the research community for bio-based
90 alternatives for LbL assembly from charged polypeptides and polysaccharides, including

dextran derivatives grew significantly (Crouzier et al., 2010; Elbert et al., 1999; Picart et al., 2001, 2002).

General information on dextrans and dextran derivatives (Figure 1) as well as their versatility for applications in various fields (Figure 2) are reported in this study. This review, more precisely, focuses on the use of dextran derivatives into polyelectrolytes multilayers and the elaboration of dextran-based multilayered structures. Reviewing of the extensive use of dextrans as polyelectrolytes for LbL assembly construction, including the main parameters to be controlled, is proposed in this report. Properties and applications of dextran-based multilayered films and other objects as micro- and nano-capsules may give indications for the elaboration of multilayer structures for future works.

2. DEXTRANS

2.1. Dextrans: sources and structures

The primary reports of dextran focused on the studies of "viscous fermentation" by early chemists when fermentative mechanisms understanding was not related to microorganisms yet (Braconnot, 1813). Later on, observations on "viscous fermentation" (dextrans) were done in the 1800s by Desfosses who explained that sugar was able to form a viscous material with carbonic acid and hydrogen emissions. Further analysis suggested that "sugar water" contained a material able to transform sugar into a viscous substance without any gas emission (Desfosses, 1829). A few years later, Gay-Lussac and Pelouze discovered that mannite and lactic acid compounds were the result of viscous fermentation of sugar beet juice (Gay-Lussac & Pelouze, 1833). In 1861, Pasteur had found that slimes on fermented food with plant origins were caused by microbial action that he reported as "viscous fermentation" or "alcoholic fermentation" (Pasteur, 1861). The term "dextran" was first used to name the segregated carbohydrate found in aging sugar juices in 1874 by Scheibler, who

demonstrated that dextran was a carbohydrate with the formula $(C_6H_{10}O_6)_n$ and with a positive optical rotation (Scheibler, 1874). Back in 1878, Van Tieghem named the bacterium responsible, for that mysterious thickening gum that he called "gomme de sucrerie", *Leuconostoc mesenteroides* (Van Tieghem, 1878). Later studies have shown that this family of α-D-glucans can be produced from sucrose by several bacterial strains, mostly gram-positive cocci, including *Leuconostoc*, *Gluconobacter*, *Streptococcus* and *Lactobacillus* strains (Chludzinski et al., 1974; Hehre, 1956; Jeanes et al., 1954). Out of α-D-glucans, bacterial extracellular enzymes, dextransucrases, can commonly form dextrans with their action on sucrose. Those enzymes are synthesised from different mesophilic and thermophilic bacteria such as genera of *Leuconostoc* and *Streptococcus*.

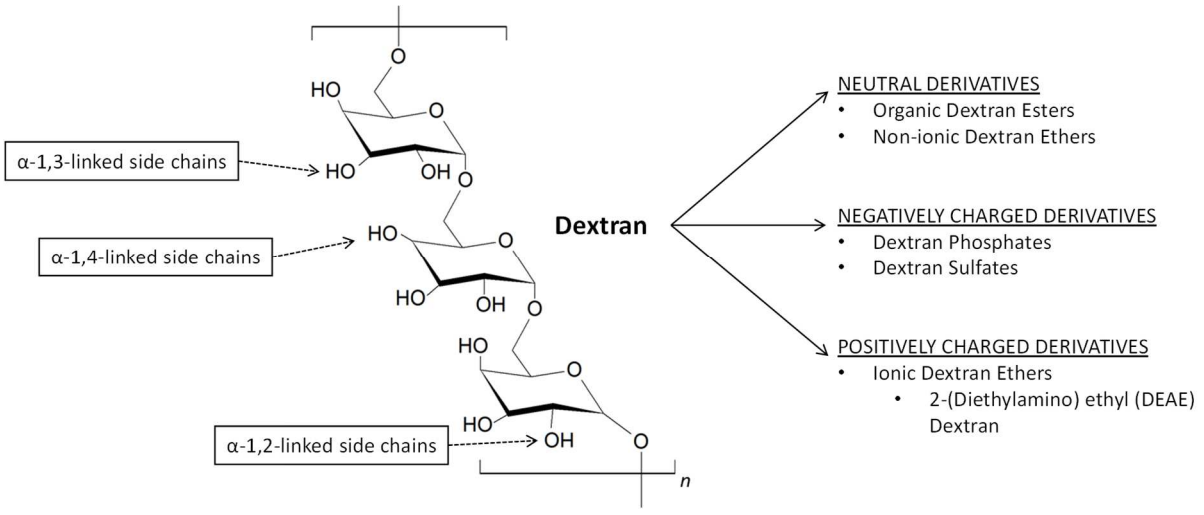


Figure 1. General structure of dextrans with D-glucose main chain linked by α-(1→6) type glycosidic bonds and branches based on α-(1→3), α-(1→4) and α-(1→2) linkages and main derivatives obtained by chemical functionalisation of dextran.

Dextrans are a family of neutral polysaccharides, produced by microorganisms, whose main chain consists of D-glucose units as illustrated by Figure 1. The structure of those α-

glucans is highly dependent on the bacterium strains from which they are produced, which leads to dextrans with various sizes and substitution patterns (Díaz-Montes, 2021). Dextran is a homopolymer of glucose whose backbone chain presents a number of consecutive α-(1→6) linkages that can vary from 50 to 97% of total glycosidic bonds (Leathers, 2002). Side chains of D-glucose units occur in α-(1→3), α-(1→4) and α-(1→2) linkages as indicated on Figure 1. The production of dextran determines the branch density and their nature on polymer backbone as well as its molecular weight (Hehre, 1956; Ruckel & Schuerch, 1967). Dextrans display broad range of average molecular weight (M_w) (10^5 to 10^8 $g.mol^{-1}$) with different polydispersity (M_w/M_n = 1 – 25) that tends to increase with the degree of branching (Antonini et al., 1964; Bovey, 1959; Confer & Logan, 1997; Ioan et al., 2000).

The high content of α-(1→6) linkages leads to important chain mobility as the presence of α-(1→6) linkages between sugar rings provides a considerably wider range of accessible relative orientations of successive sugar rings in dextrans chain (Burton & Brant, 1983; Kadkhodaei et al., 1991). Due to this chain flexibility and occurrence of hydroxyl groups, dextrans display a good solubility in water and most various polar solvents including organic and alcoholic solvents (Heinze et al., 2006; Leathers, 2002; Masuelli, 2013). Most dextrans demonstrate that increasing of the polymer concentration impacts the viscosity of solution that allows the formation of hydrogel (McCurdy, Goff, Stanley, et al., 1994).

2.2. Modification routes of dextrans

Due to the occurrence of hydroxyl groups on the surface of dextrans main chain and branches, the polymer promotes a large possibility of functionalisation to a large variety of neutral and charged dextran derivatives as indicated on Figure 1 (Ahmad et al., 2015; Heinze et al., 2006; Lindenbaum et al., 1977). The two major chemical modifications are esters of dextrans and ethers of dextrans that allow to obtain both neutral and charged dextran

156 derivatives (R. Li et al., 2017). Neutral dextrans represents both organic esters of dextrans and
157 non-ionic ethers. Organic esters of dextrans demonstrate a larger interest as they are used for
158 the coupling with bioactive compounds and for the binding of unsaturated moieties. Among
159 the etherification reactions, about twenty of them are considered as the most frequently used
160 for dextrans modifications and lead to both neutral and charged dextrans (Heinze et al., 2006;
161 Rogovin et al., 1972). Out of the inorganic esters of dextran, mainly negatively charged
162 dextrans, only dextran sulfates (dextran sulfuric acid half esters) and dextran phosphates
163 present a notable interest as they lead to polyelectrolytes presenting interesting biological
164 activity and properties (Bamford et al., 1986; Kagimura et al., 2015; R. Li et al., 2017; Mei et
165 al., 2015). In fact, dextran sulfates have shown anti-inflammatory properties in several
166 studies, anticoagulant capacity as well as anti-viral activity for a few viruses (de Raucourt et
167 al., 1998; Hall & Ricketts, 1952; Jing et al., 2016; Mauzac & Jozefonvicz, 1984; Mitsuya et
168 al., 1988). The introduction of ether-type groups in dextrans structure often results in stable
169 positively charged dextran derivatives such as 2-(diethylamino) ethyl (DEAE) dextrans, with
170 new biological properties such as immunological properties and new physico-chemical
171 properties such as complexing or adhesives properties (Naessens et al., 2005). Even though
172 chemical modifications remained major, cross-linking and grafting are also included in
173 current interest to form esters and ethers of dextrans (R. Li et al., 2017).

174 2.3. Applications of dextrans and its derivatives

175 There is a significant literature on the various uses of dextrans from bacterial origins
176 and their derivatives for medical and industrial applications as summarised on Figure 2.

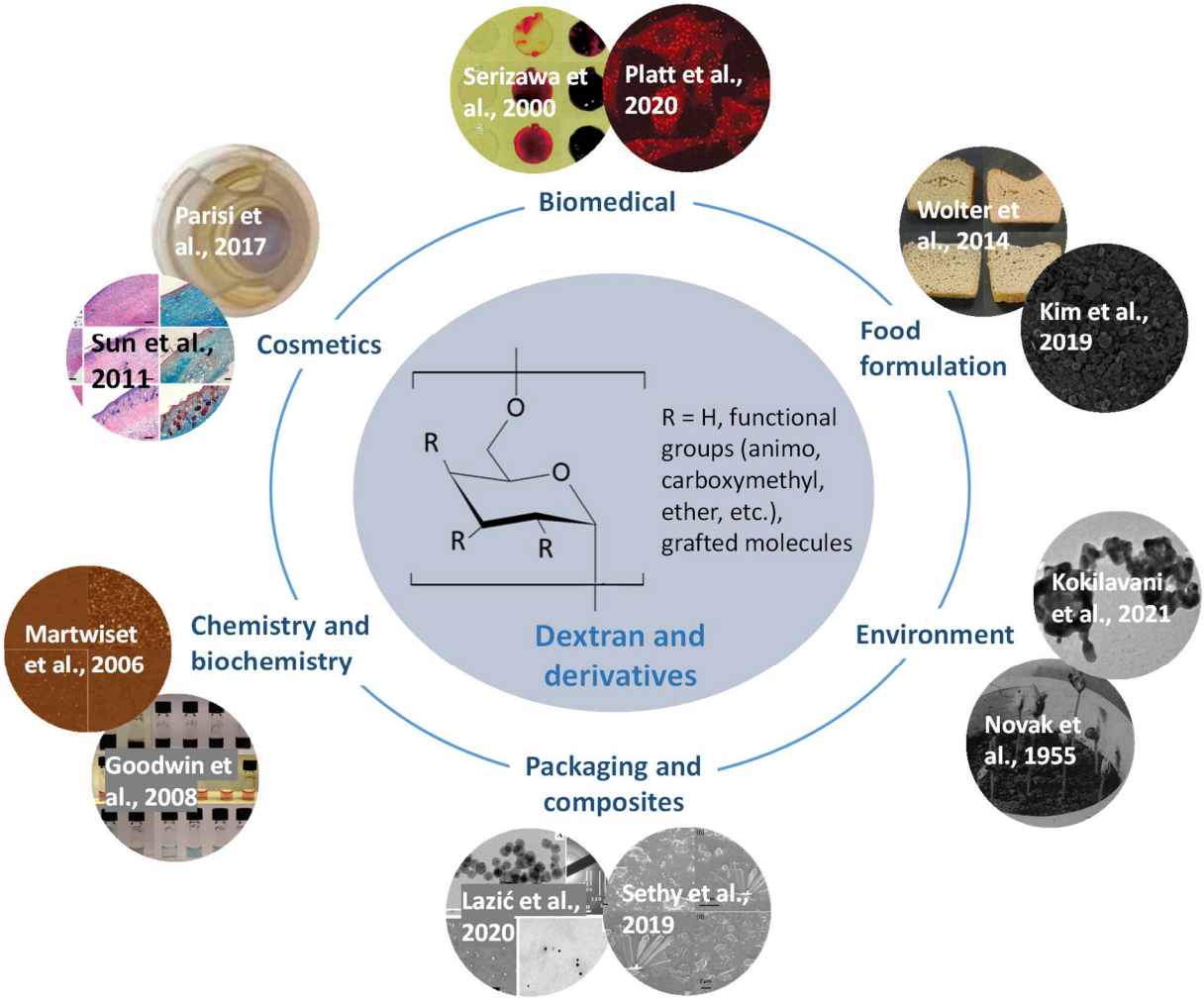


Figure 2. Overview of the most important applications of dextrans and their derivatives in industries. Adapted with permission from (Goodwin et al., 2009), © 2009 American Chemical Society. Adapted with permission from (Martwiset et al., 2006), © 2006 American Chemical Society. Adapted with permission from (Novak et al., 1955), © 1955 American Chemical Society. Adapted with permission from (Serizawa et al., 2000), © 2000 American Chemical Society. Adapted from (Kim et al., 2019; Kokilavani et al., 2021; Lazić et al., 2020; Wolter et al., 2014), with permission from Elsevier. Adapted from (Parisi et al., 2017; Platt et al., 2010; Sethy et al., 2020; Sun et al., 2011).

Dextrans and dextran derivatives have been widely used for years in the biomedical field, as dextrans are physiologically harmless biopolymers. Unlike high molecular weight

native dextran, dextrans with low molecular weight (40 000 – 100 000 Da) are suitable as therapeutic agents in restoring moderate blood volume (Robyt, 1985). The retention of low molecular weight dextrans in plasma is high enough to lead to a volume expansion without causing clogging. In addition, they help to improve blood flow by reducing blood viscosity and inhibiting erythrocyte aggregation (de Belder, 1996). However, sulfate esters of dextrans are mostly used for their anticoagulant properties, similar to the ones of heparin ; by forming complexes with several proteins, dextran sulfates avoid clotting mechanism of blood (de Raucourt et al., 1998; Hall & Ricketts, 1952; Mauzac & Jozefonvicz, 1984; Serizawa et al., 2000). Studies also highlight the use of dextran sulfates as antiviral drugs, laboratory tests showing the possibility of dextrans as anti-HIV (human immunodeficiency virus) agents as well as anti-viral against several other viruses (Mitsuya et al., 1988; Platt et al., 2010).

Beside the medical field, the variety of structures and functionalities found in dextrans and dextran derivatives presents a great interest in numerous industrial domains, mainly in cosmetics formulation and in food formulation. The occurrence of hydroxyl groups and high molecular weights of native dextrans is a source of hydrogen bonds for the formulation of viscous solutions and hydrogels, that are suitable as emulsifiers and as thickening agents (Leemhuis et al., 2013; McCurdy, Goff, & Stanley, 1994). Dextrans and dextran derivatives present a great biocompatibility, moistening properties and excellent solubility, which make them great candidates for the formulation of skin-care products in several cases such as skin regeneration (Sun et al., 2011). In 2017, Parisi *et al.* also highlighted the potential of dextran derivatives as polymeric antioxidants for skin whitening (Parisi et al., 2017).

Moreover, they are often used in the preparation of baked products to improve baking properties and sensory profiles (Lacaze et al., 2007). For instance, dextrans can be used to improve softness, crumb texture and loaf volume in the formulation of gluten-free and wheat breads (Wolter et al., 2014). Dextrans can also find applications as additives to give improved

rheological (gelling, thickening) or physico-chemical (emulsion stabilisation, particle suspension, etc.) properties in several industrial products (Kothari et al., 2014). Recently, more and more studies used dextrans for the elaboration of functional foods such as prebiotics, that can provide health benefits and protection against risk of several diseases (Kim et al., 2019). Since α-(1→6) linkages and α-(1→2) linkages are known to be resistant to human intestinal enzymes, the digestion of dextrans is relatively slow yielding prebiotic activity (Olano-Martin et al., 2000).

Dextran derivatives have potential for the conception of functional materials with great biocompatibility and degradability in the fields of chemistry and biochemistry as they provide a large range of charged or neutral biomacromolecules with different types of substituents, degrees of substitution and molecular weights (Naessens et al., 2005). For example, it was shown that amphiphilic dextrans form stable layers onto surfaces that improve *in vivo* imaging and encapsulation yield (Goodwin et al., 2009). Another study highlighted how grafted dextrans and oxidised dextrans on silicon wafer lead to non-fouling surfaces that can be valorised in the elaboration of biomaterials (Martwiset et al., 2006).

In the environmental applications, charged dextran derivatives are used for separation and detection of particles, soil conditioners, explosives, oil drilling muds, recovery of petroleum or high-viscosity gums. Ionic dextran derivatives have shown potential of flocculants for cleaning of wastewater, as they presented high efficacy for removal of both inorganic and organic particles (Ghimici et al., 2009; Ghimici & Nichifor, 2018). More recently, Kokilavani *et al.* proposed multifunctional materials based on Cu–Ag nanocomposites stabilised with dextrans for selective and sensitive detection of mercury (Kokilavani et al., 2021). Authors also highlighted that this dextran-based nanocomposite presents efficient photocatalytic and anti-microbial behaviour. Dextrans and dextran derivatives also found uses in agriculture as, in the late 1900s, studies proved that inclusion of

238 certain dextrans affects several aspects of soils. Depending on dextran structure, increasing
239 wet-sieve stability of soils studied, percent seedling emergence, rate of plant growth and crop
240 yield for plant used were observed (Novak et al., 1955).

241 Among packaging applications, dextrans and derivatives can be employed in different
242 ways, such as coating for improving compatibility of particles or performance in food
243 packaging as suggested by Lazić *et al.* (Lazić et al., 2020). In this study, dextran used as
244 coating on silver nanoparticles helped to improve barrier properties, *i.e.* oxygen permeability
245 and anti-microbial activity of nanocellulose films. Dextran-composites are also widely studied
246 for elaboration of biocompatible and eco-friendly packaging materials. Sethy *et al.* proposed
247 matrix of dextran-grafted poly(acrylic acid) hybrid nanocomposites and nano-$CaCO_3$ filler to
248 design materials with oxygen barrier, thermal, and antimicrobial properties (Sethy et al.,
249 2020).

250

251 **3. DEXTRAN DERIVATIVES AS POLYELECTROLYTES FOR 2-DIMENSIONAL**
252 **MULTILAYER FILMS**

253 3.1. Principle of layer-by-layer fabrication of multilayers

254 In current technologies, nanostructures and nanomaterials found an important place in
255 the development of ultra-small devices and are mainly prepared by top-down fabrication
256 techniques (Baig et al., 2021; Cheng et al., 2020; Khin et al., 2012; Moon et al., 2011;
257 Pomerantseva et al., 2019; Roduner, 2006; Wang et al., 2021). However due to physical
258 limitations of those techniques, bottom-up techniques are presently gaining in interest and
259 micro- or nano- materials based on self-assembly approaches are becoming more and more
260 present in nanotechnologies (Abid et al., 2022; Lombardo et al., 2020). These methods have

great potential in all fields of research: biomedical (Deng et al., 2010), paper industry (Wu & Farnood, 2014), functional materials (Damasceno Borges et al., 2018), composites (Sher et al., 2010), cosmetics (Yoo et al., 2016), food (Treviño-Garza et al., 2017), electronics (de Oliveira Farias et al., 2015) or even environment (Ma et al., 2011). Among bottom-up approaches, the LbL method is a way to build complex self-assemblies from charged molecules/nanoparticles with controlled architectures. Introduced by Iler in 1966, the LbL method was firstly applied to the alternative deposition of oppositely charged colloidal particles for the electrostatic self-assembly of multilayers (Iler, 1966). In 1991-1992, Decher's group revised the principle for manufacturing polyelectrolyte multilayers on a solid substrate for the first time (Decher et al., 1992; Decher & Hong, 1991a, 1991b). In those studies, the authors presented a simple method to achieve "soft" multilayered films with controlled architectures by adsorption of polyelectrolytes (Decher, 1997). The advantages of the LbL assembly techniques include its simplicity, its versatility but also control of the film architecture (thickness, mass, porosity, etc.) (Figure 3b). The properties of the system are governed to the greatest extent by the choice of polyelectrolytes pair.

Mainly based on Decher group's works, LbL assemblies are traditionally produced by dipping deposition, *i.e.* immersive LbL assembly (Decher et al., 1992; Decher & Hong, 1991a, 1991b; Lvov et al., 1994, 1998). Figure 3a illustrates the formation of LbL films onto a substrate based on the alternate immersion of the substrate in oppositely charged polymer solutions. During immersion, the polymer is adsorbed onto the surface and intermediate rinsing steps allow washing off loosely bound material leading to a layer formation. The dipping procedure is repeated with the opposite charged polymer to form a bilayer. The process is repeated until a multilayer with n bilayers, composed of two layers of polyelectrolytes with opposite charges, is obtained. In addition to the dipping method, there are currently two other deposition processes to form LbL assemblies: spin-coating and

spraying (Richardson et al., 2015). Film fabrication by spin-coating is based on alternative deposition of charged polymer solutions onto a solid substrate immediately followed by a rinsing and drying step, while the substrate undergoes spinning at constant velocity. While polymers are enforced to adsorb during the "classical" spin-coating procedure, spin-assisted LbL assembly of thin films from polyelectrolytes and/or biopolymers have been used in which polymers are allowed to adsorb before spinning steps (Cerclier et al., 2010). During the substrate rotation, the polymer solutions spread onto the surface to obtain layers with complete evaporation of the solvent, generally water. Finally, another alternative of the LbL approach is the consecutive spraying (spray LbL assembly) of polyelectrolytes solutions and rinsing solution on a substrate. This method has been used since the 1970s for the construction of films, but it was introduced into the field of polyelectrolytes in 2000 by Schlenoff, Dubas and Farhat (Félix et al., 2009; Schlenoff et al., 2000).

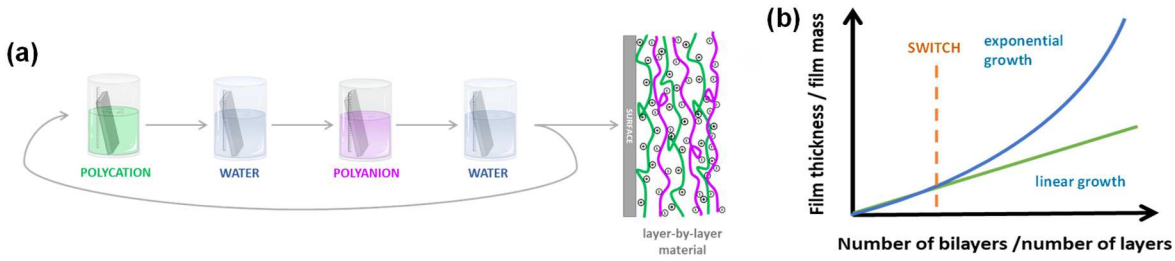


Figure 3. (a) Schematic representation of LbL technique by dipping and (b) graphic representation of film growth behaviour as function of the number of bilayers/layers and the film thickness/film mass.

LbL polyelectrolytes films formation relies on spontaneous adsorption, of at least two species, generally both driven and limited by entropy increase in the system and Coulombic interactions. However, it is important to note that the driving forces involved in multilayers construction are not restricted to electrostatic interactions. More and more multilayer films are exploited for their capacities to form multilayer *via* other interactions than electrostatic ones.

Hydrogen bonds, hydrophobic interactions and van der Waals forces also operate in the formation of the layers and influence the stability of the LbL assemblies (Borges & Mano, 2014; Clark & Hammond, 2000; Kotov, 1999). During deposition, polymers diffuse and adsorb onto the surface and find their equilibrium concentration and configuration. The adsorption process included charge inversion of the surface, indeed adsorption does not yield to surface neutralisation but end with charge overcompensation of the surface that induces repulsive interaction with polymers in solution (Hoogeveen et al., 1996; Schlenoff & Dubas, 2001). The surface charge reversal allows the adsorption of the following layer with composed of oppositely charged polyelectrolyte and thus the growth of the film. From literature, two types of film's growths can be distinguished: linear and non-linear growths. The growth type depends on the polymer couple and experimental conditions and can be identified by the relation between the adsorbed quantity and the number of bilayers differs as presented on Figure 3b (Elzbieciak et al., 2009; Y. Li et al., 2012; Schlenoff & Dubas, 2001). In the first case, polyelectrolyte multilayers growth presents a linear increase of the mass and/or the thickness onto the surface after each bilayer deposition. In the second case, films present a non-linear increase of mass (or thickness) with each adsorbed bilayer, also called supra-linear or exponential growth (Haynie et al., 2011; Picart et al., 2002). Growth mechanisms can be explained by effective charge density of polyelectrolytes, molar mass and are also dependent of characteristics of polymers and the processing parameters (Elzbieciak et al., 2009; Picart et al., 2002; Schlenoff & Dubas, 2001).

More generally, polyelectrolyte multilayer's films and their characteristics are related to the nature of polyelectrolytes and assembly conditions and result in films with different internal structures (morphology, porosity, etc.) and physico-chemical properties (water content, mechanical properties, permeability, etc.) (Borges & Mano, 2014; Dubas & Schlenoff, 1999; Guzmán et al., 2020). Some experimental parameters are crucial for the

assembly of polyelectrolyte multilayers and associated morphologies: physico-chemical characteristics of substrates (roughness, hydrophilicity, charges), physico-chemical characteristics of the polyelectrolytes (charge density, conformation, molecular weight) and the experimental parameters of the deposition procedure (adsorption time, drying step, temperature) and solution parameters (ionic strength, pH, concentration) (Devi et al., 2014; Moreau et al., 2012). The chemistry and structure of polyelectrolytes used in solution have an important role on the formation of LbL films, as they affect the interactions between polymers themselves and with the surface. Charge density of polymer is a key factor that influences the LbL assembly by impacting electrostatic interactions (Calvo et al., 2010; Delvart et al., 2022; Glinel et al., 2002; Schlenoff & Dubas, 2001). While a minimal charge density is necessary to have electrostatic attraction between polyelectrolytes, the adsorption mechanism and the final architecture result from a balance between charge densities of polyelectrolytes employed. An increase or a decrease of charge balance can both evenly lead to complexes formation or absence of LbL assembly (Glinel et al., 2002). Charge density can be tuned by adjusting the pH of the solution for weak polyelectrolytes and charges equilibrium can be switched by further addition of counterions and modification of ionic strength (Dubas & Schlenoff, 2001; Guzmán et al., 2020; Pechenkin et al., 2012). Increasing ionic strength often results in thicker layers due to the screening of charges and changes in polymer conformation (Lundström-Hämälä et al., 2010; McAloney et al., 2001). It can also prevent multilayers formation at some point since it can limit or break the interactions between polyelectrolytes (Dubas & Schlenoff, 2001; Feldötö et al., 2010; Lundström-Hämälä et al., 2010; McAloney et al., 2001). Effects of the counterions types are also of importance: small ions result in lower charge screening and reduced hydration and thickness of the adsorbed layer/film due to weak bonding while larger polarisation of big ions promote thicker layers. Though LbL principle is an easy method,

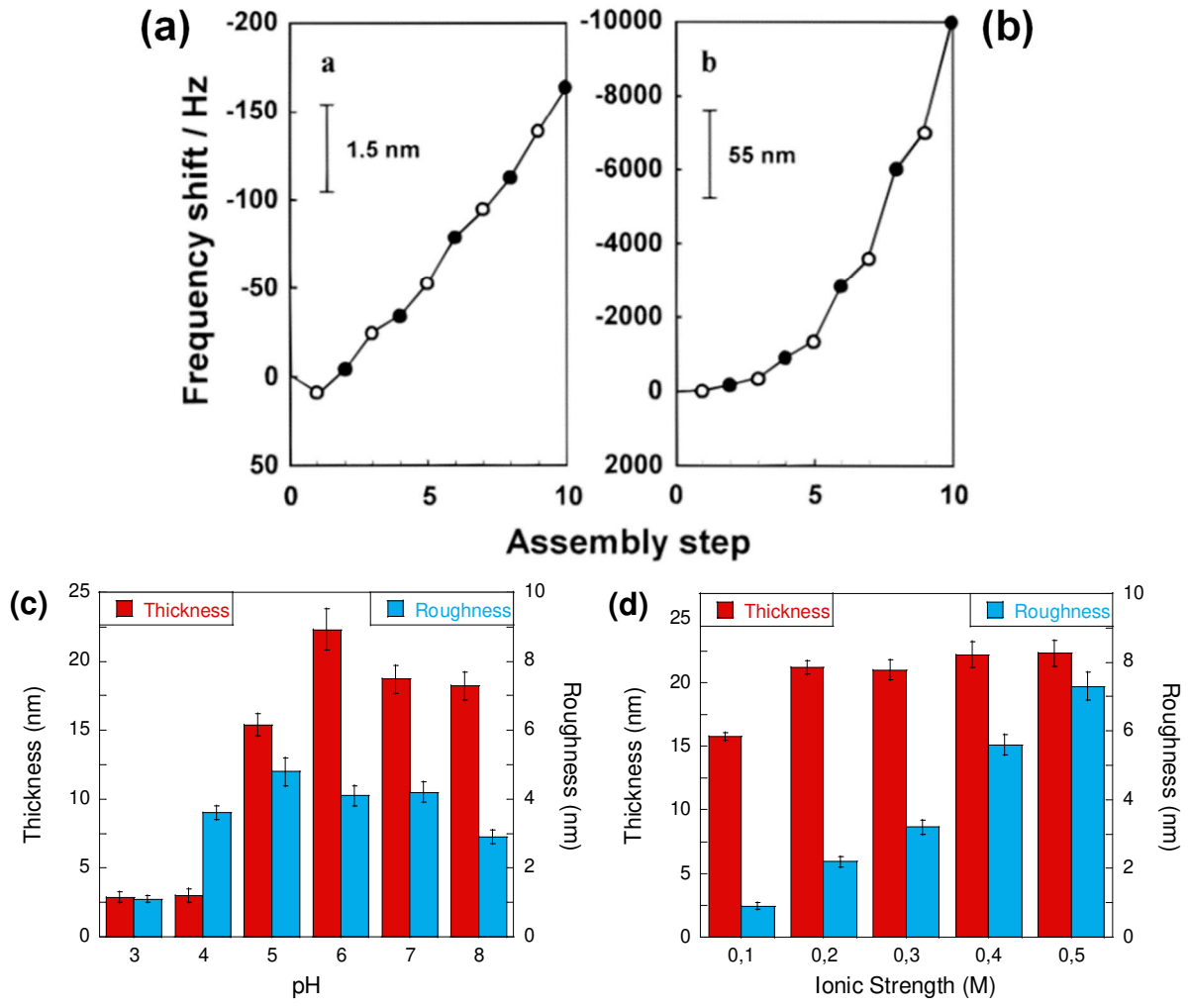
examining all the assembly parameters is critical to control the thickness/growth and the morphology of resulting polyelectrolyte multilayers.

3.2. Dextran sulfates in multilayered films

3.2.1. Dextran sulfates and chitosan multilayered films

Among dextrans used in multilayered materials, dextran sulfates (DexS) are commonly encountered since different molecular weights and sulfate contents are commercially available, expanding the range of materials implementation.

One of the most employed polycation used in combination with DexS is chitosan (CHI), poly[(1→4)-β-linked 2-amino-2-deoxy-D-glucose], a biocompatible and biodegradable anionic biopolymer with NH_2/NH_3^+ groups (pKa between 6 and 7). CHI is prepared by N-deacetylation of chitin extracted from the outer shells of crustaceans or insect wings (Jayakumar et al., 2010; Shukla et al., 2013). The first studies about CHI/DexS based materials were reported by Kikuchi and Fukuda in the 1970s (Fukuda & Kikuchi, 1977, 1978; Kikuchi & Fukuda, 1974). The authors highlight the ability of DexS and CHI to form polyelectrolyte complexes and the water-insoluble complex created was sensitive to the reaction conditions such as pH and concentration of the polyelectrolyte solutions (Fukuda & Kikuchi, 1978). This polyelectrolyte pair was later applied to multilayers for the first time in the 2000s by Serizawa's research group who used LbL principle to build DexS/CHI films (Sakaguchi et al., 2003; Serizawa et al., 2000, 2002, 2003).



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376

377 **Figure 4.** QCM frequency shift as function of adsorbed layer number up to 10 bilayers of
378 (CHI/DexS) films on silver quartz crystal at pH depending on added salt content, (a) 0 M
379 NaCl and (b) 1M NaCl. Frequency shift and the corresponding thickness is indicated.
380 Reprinted with permission from (Serizawa et al., 2000), © 2000 American Chemical Society.
381 Thickness and roughness of 10 bilayers (CHI/DexS) films grown on silica wafer with (c) pH
382 (at 0.5 M ionic strength) and (d) ionic strength (at pH 6) obtained with ellipsometer analysis
383 respectively, data from (Devi et al., 2014).

384 In 2000, Serizawa *et al.* investigated the assembly process of CHI/DexS films and a
385 key parameter of the construction of multilayers: the impact of salt addition on film growth.
386 Using Quartz crystal microbalance (QCM) to investigate films growth, the authors found out

387 that 10 bilayers of CHI/DexS with no salt addition lead to thin films displaying a thickness of
388 3.7 nm (corresponding to quartz frequency shift of Δf = -163 Hz) while adding 1M NaCl to
389 both polymer solutions leads to an increase of the thickness of the films of 227 nm (Δf = -
390 9946 Hz) as reported on Figure 4a. They explained the low thickness value of no salt film by
391 possible incomplete coverage of the surface and non-accurate QCM values due to the very
392 low thickness and uneven repartition of the polymer on the surface. Nevertheless, results
393 showed a shift from linear film growth at 0M NaCl (figure 4a, left) to an exponential film
394 growth at 1M NaCl (figure 4a, right) as well as a six-fold mass/thickness increase with the salt
395 addition. In 2014, Devi *et al.* studied the formation of 10 bilayers DexS/CHI film on silica
396 using dipping method (Devi et al., 2014). Authors observed an exponential growth in
397 thickness of the CHI/DexS film with increasing number of layers at 0.5M NaCl and explained
398 that after the 4^{th} layer, the film growth changes from linear to exponential showing the
399 influence of the substrate on the first adsorbed layers. This observed exponential growth
400 mechanism is related to the ability of the CHI to diffuse in and out of CHI/DexS film and is
401 often observed for CHI-based multilayered films (Salomäki & Kankare, 2009; Z. Song et al.,
402 2009).

403 Devi *et al.* also investigate the impact of ionic strength and pH on the surface
404 morphology of CHI/DexS films (Devi et al., 2014). By increasing ionic strength, *i.e.*
405 increasing NaCl concentration from 0.1M to 0.5M (Figure 4d), the film thickness increased
406 from 15 nm to 25 nm. The presence of ions induces a screening of the polyelectrolyte charges
407 leading to a decrease of the electrostatic repulsion from identical charges on the polymer
408 chain. Thus, polyelectrolytes display random coil conformation if all charges are screened at
409 high ionic charges allowing more adsorption onto a surface due to the highest compaction and
410 decreased repulsion between polymer coils. At low ionic strength polyelectrolytes are in an
411 extended conformation and higher repulsion between chains occurs. Variation of pH from 3 to

8 at fixed ionic strength (Figure 4c) highlighted a clear dependence of the film growth with pH as well which was observed for other multilayers based on chitosan (Guzmán et al., 2011). As displayed on Figure 4c, average thickness of adsorbed layers increases when increasing pH from 1 to 6, then thickness decreases by increasing pH to 8 with an optimum at 23 nm for 10 bilayers at pH 6. In fact, at high pH (> 6), CHI becomes deprotonated and electrostatic-driven LbL assembly cannot occur between CHI and DexS. At low pH (pH<5), amino groups of chitosan are protonated allowing a successful LbL adsorption. However, at very low pH, authors explained that protonation of chitosan leads to an excess of positive charges from DexS and immediate dissolution of multilayers. The variation of charge equilibrium, here ionic strength and pH, also affects morphology of layers as illustrated on Figure 4c, d, by analysing the roughness and the surface morphologies by AFM. Roughness increases from 3.75 nm to 8 nm by increasing ionic strength from 0.1 M NaCl to 0.5 M NaCl and pH variation induces also significant change of both parameters. Similar effects of the modification of charges ratio/ionic equilibrium was observed on the morphology of DexS-based multilayers, by shifting charges density balance between polyelectrolytes (Delvart et al., 2022).

Table 1. Chitosan and dextran sulfate (CHI/DexS) multilayered films reported in literature and their applications.

Application(s)	Films	Targeted properties	Ref
Biomedical	(CHI-DexS)-CHI $(CHI\text{-}DexS)_{1\ to\ 40}$	Alternating anti- vs procoagulant activity, biodegradability	(Serizawa et al., 2000, 2002)
		Control of blood coagulation, antithrombogenic surface	(Sakaguchi et al., 2003; Yu, Jou, et al., 2007; Yu, Lin, et al., 2007)
		Drug delivery	(Xie et al., 2016; F. Zhang et al., 2019)
Tissue engineering	(CHI-DexS)-CHI $(CHI\text{-}DexS)_{1\ to\ 4}$	Bioactivity, fibroblast cell compatibility	(Kulikouskaya et al., 2018; Serizawa et al., 2003)

By considering the physico-chemical properties of chitosan and dextran sulfate and capacity to form films with controlled architecture, (DexS/CHI) multilayers found potential uses in different fields and mainly in biomedical applications. Table 1 outlines applications and main targeted properties of (CHI/DexS) films found in literature. Thanks to the ability of dextran sulfate to prevent blood coagulation, as seen previously in section 2.1, Serizawa's research group highlighted the potential of CHI/DexS multilayers in blood related devices to control blood coagulation (Sakaguchi et al., 2003; Serizawa et al., 2000; Yu, Jou, et al., 2007; Yu, Lin, et al., 2007). Moreover, integration of chitosan into multilayers films allows to block anticoagulation of DexS and open the possibility to form biodegradable films with both anti-coagulation and pro-coagulation properties (Serizawa et al., 2000, 2002). More recently, the interest of the scientific community in CHI/DexS as potential alternatives as multilayered coating for drug nanocarriers increased. In addition of both polyelectrolytes being biocompatible, their use as surface functionalisation can improve their dispersibility in physiological conditions, as it was observed with graphene oxide nanosheets (Xie et al., 2016; F. Zhang et al., 2019). Moreover, DexS/CHI multilayers were proven to be useful for cell attachment and their growth on surfaces (Kulikouskaya et al., 2018; Serizawa et al., 2003). Cell adhesion seems to depend mainly on the stiffness of the multilayers, which can be related to the growth pattern and thus of the choice of polycations and polyanions and the number of bilayers deposited (Kulikouskaya et al., 2018). Kulikouskaya *et al.* demonstrated that multilayered films are formed by alternating adsorption of negatively charged polysaccharides switched from linear to exponential growth by changing the polycation from polyethyleneimine (PEI) to CHI (Kulikouskaya et al., 2018). Authors also showed that those films built with exponential growth had different properties as the surface roughness increased and the mechanical properties change from elastic to viscous by increasing the number of bilayers.

3.2.2. Dextran sulfates and polyelectrolyte- based multilayered films

Apart from chitosan, other polycations were associated with DexS. These include synthetic and natural polyelectrolytes as well as other dextran derivatives allowing building different film structures. In 1995, Elferink et de Koster introduced diethylaminoethyl dextran (DEAE-Dex), polycation derivate from dextran with physiological effects (antibacterial, antifungal, and antitumor) as a good candidate to substitute synthetic polymers in biomedical applications (Elferink & de Koster, 1995). The use of DEAE-Dex into LbL assembly associated with DexS was proposed later by Benni *et al.* to control surface morphology of films to tune protein adsorption and cell adhesion (Benni et al., 2014). The authors studied $(DEAE\text{-}Dex/DexS)_4$ and $(DEAE\text{-}Dex/DexS)_4$-DEAE-Dex films surface morphology and their properties on glass surface depending on the last layer adsorbed (polycation or polyanion). Comparison between multilayers ending with polycation DEAE-Dex layer and multilayers ending with polyanion DexS layer highlighted significant differences in terms of roughness.

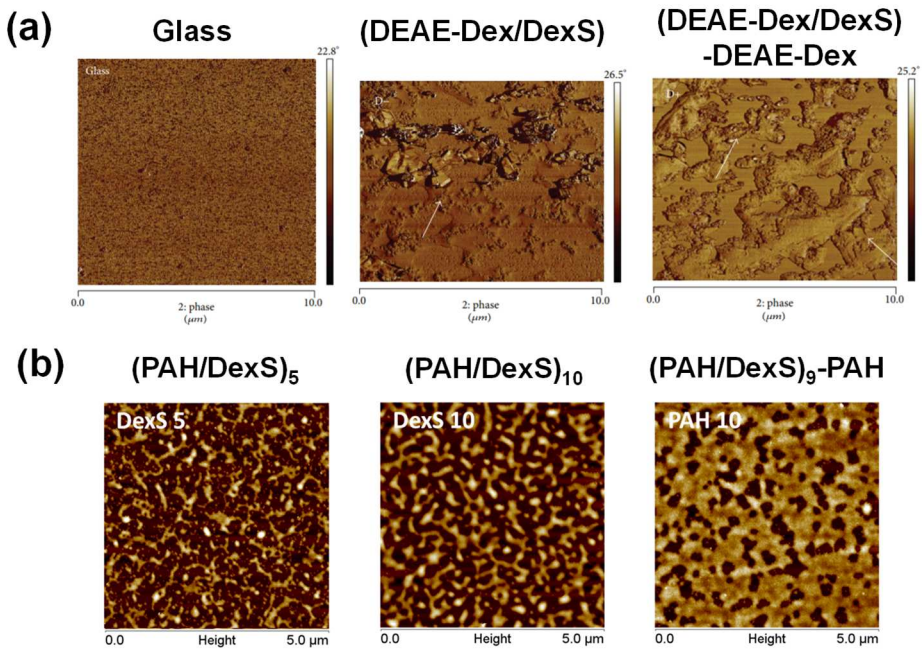

Figure 5. (a) AFM images (10 μm × 10 μm, phase) of bare glass surface, (DEAE-Dex/DexS) multilayer, and (DEAE-Dex/DexS)-DEAE-Dex multilayer adsorbed on glass surfaces (Benni et al., 2014). (b) AFM images (5 μm × 5 μm) of $(PAH/DexS)_5$ multilayer, $(PAH/DexS)_{10}$ multilayer and $(PAH/DexS)_9$-PAH multilayer adsorbed on silica surfaces, reprinted from (Delvart et al., 2022), with permission from Elsevier.

AFM images (Figure 5a) showed that (DEAE-Dex/DexS) and (DEAE-Dex/DexS)-DEAE-Dex multilayers display high coverage of the surface and their topographical morphologies present clusters or granules. Similar morphologies were found with (PAH/DexS) multilayers that are explained by charge equilibrium that led to polyelectrolytes complexes formation and dewatering during adsorption steps (Delvart et al., 2022). Analysis of the multilayers showed an increase of surface roughness with value of 47 nm for (DEAE-Dex/DexS) and 72 nm for (DEAE-Dex/DexS)-DEAE-Dex multilayers while the bare glass roughness range about 3 nm. Advancing contact angles monitoring displays the decrease of hydrophilicity, which may be related to an increase in surface roughness with the number of adsorption steps in general. Also, a higher hydrophobicity of the surface was observed with (DEAE-Dex/DexS)-DEAE-Dex multilayers than for (DEAE-Dex/DexS) multilayers. Consistently, similar surface morphology were obtained with (PAH/DexS) multilayers with also a roughness variation dependent on the last layer as illustrated on Figure 5b (Delvart et al., 2022). In 2019, Jang *et al.* demonstrated similar effect of DEAE-Dex/DexS multilayered coatings on metal stent, both increasing the hydrophilicity and inhibiting cell adhesion of metal stent (Jang et al., 2019). In this study, authors showed an increase of roughness with DEAE-Dex/DexS coating compared to DexS coating. Moreover, water contact angle of (DEAE-Dex/DexS) coated metal stent was significantly higher than water contact angle of the bare metal stent as well, confirming the potential of (DEAE-Dex/DexS) multilayers in tuning surfaces for various applications including protein and cell adhesion.

3.2.3. Dextran sulfates and proteins multilayered films

Proteins were associated with DexS to build multilayers for mainly targeting biomedical applications due to the biocompatibility of dextran sulfates and biological activity of protein. Investigation of interactions between polysaccharides and proteins in multilayers films constitutes a topic of interest in biomedical field in order to build films with controlled organisation of proteins (Brynda & Houska, 1998; J. Zhang et al., 2005). The use of LbL technique and choice of both assembly parameters and nature of polyelectrolyte-protein couple allow building of multilayers structured morphology but also regulation of the conformation of protein within the film (Hong et al., 1993; Lvov et al., 1994, 1995). Similarly to usual encountered polyelectrolytes, processing parameters (pH, salt concentration, compound concentrations, temperature, etc.) are of importance for polyelectrolyte-protein multilayers film construction as well as the nature of protein (Müller et al., 2001; vander Straeten et al., 2018, 2020). Overall, pH was found to be a key parameter in the LbL assembly of proteins with polyelectrolyte to promote interactions between proteins and polyelectrolyte, and pH of the protein solution has to be set apart from the isoelectric point (IEP) (Kayitmazer et al., 2013; Lvov et al., 1995; vander Straeten et al., 2018). In general, proteins may be prone to conformation change according to solution conditions and surface properties, which have an important impact on protein adsorption and multilayer formation.

In 1999, Brynda *et al.* used DexS as a building block to fabricate LbL assembly with human b2-microglobulin antibody cross-linked with glutaraldehyde. The resulting flexible film can be used as immunosensor for b2-microglobulin (Brynda et al., 1999). More recently, Damanik *et al.* investigated the growth of collagen/DexS 4 bilayers on PEI/poly(styrenesulfonate) (PSS) 2 bilayers in order to develop high loading efficiency systems for biomedical applications. This study highlights the effect of collagen/DexS multilayers: collagen at pH 7 leads to linear growth while an exponential growth is obtained

521 with collagen at pH 3. At pH 3, collagen used by authors with basal isoelectric point 7.8 may
522 have more electrostatic interactions with DexS, as well as a compact conformation more
523 likely to lead to exponential film growth. Moreover, they were able to optimise the
524 immobilisation of heparin in such multilayer systems, *i.e.* the bioactivity of heparin is retained
525 on $(PEI/PSS)_2$+$(collagen/DexS)_4$ for 14 days by using collagen in acidic pH and exponential
526 growth of collagen/DexS 4 bilayers (Damanik et al., 2020). He and Hu first reported in 2004 a
527 study on the interactions of hemoglobin or myoglobin with DexS presenting more details on
528 the interactions between proteins and the polyelectrolyte. Authors suggested that localised
529 electrostatic interactions are the driving force in protein/polymer LbL assemblies such as with
530 heme proteins (hemoglobin or myoglobin) that have net positive charges or net negative
531 charges depending on the pH solution (He & Hu, 2004). Houska *et al.* published a report on
532 the influence of polyelectrolyte chain length on the LbL formation with proteins, especially
533 albumin. The authors compared multilayers of albumin/DexS with different molecular
534 weights of DexS and they showed that the assembly of globular proteins and linear strong
535 polyanions at pH below the isoelectric point (IEP) of the protein is affected by the chain
536 length of the polyanion (Houska et al., 2004). The study suggested that at lower molecular
537 weights of DexS, competition with adsorbing protein and absorbed protein might lead to
538 resolubilisation of the polyelectrolyte. Interactions between polysaccharides and proteins in
539 LbL process were further investigated by Jourdain *et al.* using caseinate to understand
540 mechanisms at interfaces for emulsion stabilisation (L. Jourdain et al., 2008; L. S. Jourdain et
541 al., 2009). LbL construction of (Caseinate/DexS) layers displays linear increase of shear
542 viscosity with time explained by strong interactions between caseinate and DexS that produce
543 flat conformation of the layer followed by a slow reorganisation of protein and DexS.

544 3.3. Other dextrans derivatives in multilayered films

In the late 2000s, Lee, Choi and Tsutsumi built polyaniline and carboxydextran multilayer films that present an interesting activity for the oxidation of ascorbic acid but also an excellent electron-transfer mediating capability for oxidation of glucose (Lee et al., 2009). Oxidised dextrans were used to form a bilayer with PEI to immobilise biocatalyst of β-1,4-endoxylanase by surface coating for the production of xylooligosaccharides (Romero-Fernandez et al., 2018). PEI was associated with an amine-substituted dextran, aminodextran (AMD), as well as with oxidised dextrans using dipping technique to build multilayers (Heurich et al., 2011; Romero-Fernandez et al., 2018). Heurich *et al.* proposed the use of biointerfaces for increasing cell compatibility while Romero-Fernandez *et al.* proposed to use them as coating to immobilise biocatalyst of β-1,4-endoxylanase for the production of xylooligosaccharides as well. In order to develop bioink for 3-dimensional printing, another dextran derivative, hydroxyethyl-methacrylate-derivatised dextran (Dex-HEMA), was paired with hyaluronic acid (HA) to produce bio-based hydrogels *i.e.* bioink (Pescosolido et al., 2011). In 2019, boronic derivative (the phenylboronic acid-modified alginate) and a diol biopolymer (a dextran derivative) were applied to the fabrication of H_2O_2-responsive microparticles by Mansour, Joukhar and Belbekhouche (Mansour et al., 2019).

4. DEXTRAN AS POLYELECTROLYTES FOR 3-DIMENSIONAL MULTILAYER STRUCTURES

4.1. Dextran-based multilayer objects: fabrication principle and methods

Polyelectrolyte multilayer objects (films or capsules) form an attractive class of materials which can be designed to achieve multiple functions . Multilayer objects also called shell objects consist of polyelectrolytes layers that are formed in the presence of a template produced by LbL assembly leading to a multilayer of an engineered shape. ‘Hollow’ multilayer objects and capsules are mainly fabricated by coating core particles, which served

as sacrificial templates, with a shell using LbL technique described in *3.1* (Antipov et al., 2003; Bao et al., 2016; Hu et al., 2011; Itoh et al., 2004; Parakhonskiy et al., 2014; G. B. Sukhorukov, Volodkin, et al., 2004). As illustrated in Figure 6a,b, the LbL technique is applied to a core template by sequential adsorption of oppositely charged substances onto the core, followed by removal of the core template by dissolution. However, as presented by Figure 6b, multilayer objects can be built by LbL technique directly onto targeted materials without the need of a dissolution step.

As multilayer films, physical and chemical properties of the multilayered capsules are strongly dependent on chemical nature and structure of the polyelectrolytes used in their fabrication and on the template coated (Gil et al., 2008). The size of the microcapsules can be tuned by varying the size of core template while the thickness of the hollow shell can be controlled by LbL technique conditions, nature of adsorbed molecules and numbers of layers adsorbed (Dubas & Schlenoff, 1999; Shiratori & Rubner, 2000; G. B. Sukhorukov, Shchukin, et al., 2004; G. B. Sukhorukov et al., 2005). Thus, appropriate choice of the template type, of the polyelectrolytes pair and of the LbL deposition parameters should be done to control the morphology of such objects and, as a result, their properties such as permeability (G. B. Sukhorukov et al., 1999; Tong et al., 2005). The choice of polyelectrolytes can also provide interesting properties to capsules such as sensitive permeability, with a stimuli-responsive (pH, ionic strength) character, that is a key property for encapsulation and drug delivery (Delcea et al., 2011; G. Sukhorukov et al., 2001).

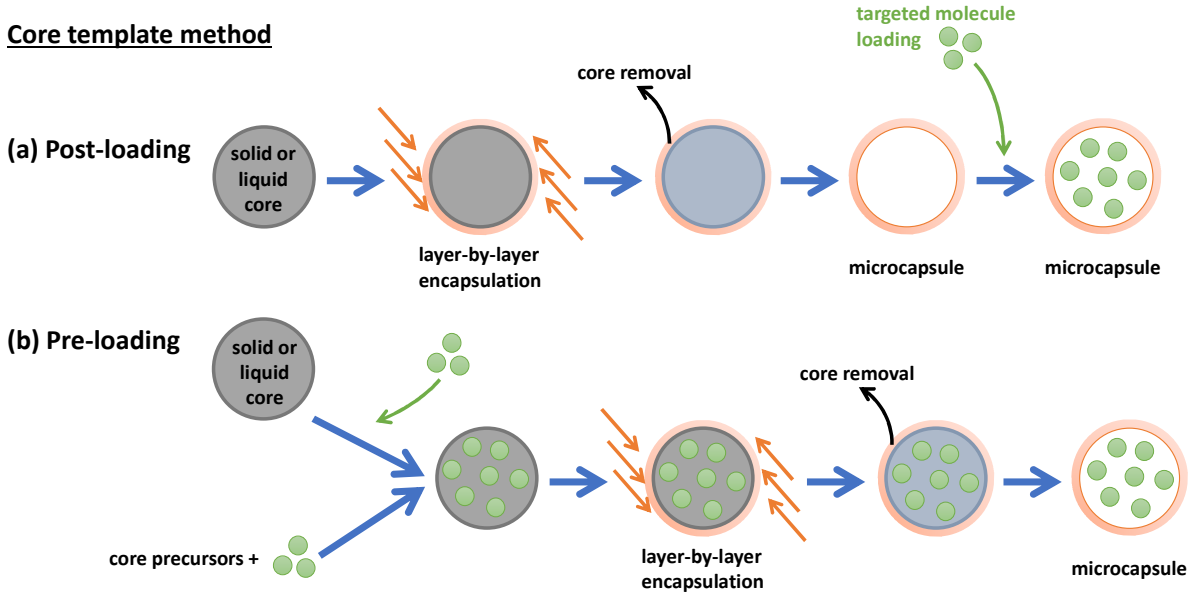

Figure 6. Schematic fabrication of micro- and nano- capsules based on LbL deposition principle onto sacrificial core template with (a) post-loading method and (b) pre-loading method.

Multilayer objects and capsules are mainly used in the biomedical sciences as shown on Table 2 and 3. The scientific community interest is particularly focused on their potential for drug delivery applications that imply loading of active molecules into those objects and their release. The versatility of LbL technique allows the fabrication of micro-objects with various colloid sizes, shapes, compositions and functionalities that answer the problematics of drug delivery devices (Ariga et al., 2011; De Cock et al., 2010; Tong et al., 2012).

A wide range of organic and inorganic molecules/polymers were used as suitable core materials for dextran-based capsules formation and successful formation of microcapsules from the literature is listed in Table 2. Those templates include polymers such as melamine formaldehyde (MF) which has drawbacks concerning production, which involves highly toxic chemicals, and degradation (N. Balabushevich et al., 2005; N. G. Balabushevich & Larionova,

605 2009). In addition to the inherent toxicity of the MF, the dissolution of the MF core at very
606 low pH (< 1.6) or with organic solvent limited their biocompatibility or so their applications.
607 Mineral cores such as SiO_2 or $CaCO_3$ templates are often used for dextran-based capsules
608 (Devi et al., 2015; Gao et al., 2016; Paini et al., 2015; Pawlak et al., 2022; Reibetanz et al.,
609 2011). They have been found to be nontoxic, biocompatible, thermally and mechanically
610 stable (Bao et al., 2016). However, their dissolution step remains a limiting factor since SiO_2
611 cores are dissolved by hydrofluoric acid and carbonates cores are dissolved at low pH (< 3) or
612 with ethylenediaminetetraacetic acid (Antipov et al., 2003; Sudareva et al., 2014; G. B.
613 Sukhorukov, Volodkin, et al., 2004). Moreover, those inorganic cores usually display larger
614 sizes than organic ones (Table 2) which limit their utilisation in some application where
615 capsules with nanometric size are targeted. Dextran microcapsules fabrication can be also
616 formed onto "soft" core templates in order to avoid the removal step (Grigoriev et al., 2008;
617 Tjipto et al., 2006). Preparation of shell capsules are based on emulsions on micro-aggregate
618 procedures of polyelectrolytes and active molecules which act both as the core templates and
619 loaded substances (Averin et al., 2016; Fukui & Fujimoto, 2009, 2011). Less frequent used
620 templates such as metallic silver and gold nanoparticles have also been reported to form
621 'hollow' capsules of dextrans (Anandhakumar et al., 2011, 2012; Livanovich & Shutava,
622 2019).

623 In addition to different sacrificial templates for LbL sequential adsorption, two
624 different approaches for loading active content can be distinguished in literature: pre-loading
625 and post-loading that are illustrated on Figure 6 a and b. With pre-loading procedures, core
626 templates already contain the molecules to encapsulate. It is the case for all the micro-
627 aggregate's precursors, as the first step is the fabrication of the core by complexation of
628 substance of interest with one of the two coating substances (Averin et al., 2016; N. G.
629 Balabushevich et al., 2006, 2016; Crecente-Campo & Jose Alonso, 2019). For example,

630 Averin and co-workers developed doxorubicin containing micro- and nano- particles by
631 preparing insoluble (Doxorubucin-DexS) particles before coating them with
632 $(CHI/DexS/CHI)_1$ (Averin et al., 2016). Pre-loading is also observed with dextran derivatives,
633 using solid templates by adding loaded content directly within the cores during their
634 preparation and keeping/retaining active compounds inside the hollow shell after core
635 dissolution. Selina *et al.* proposed $(DexS/PLL)_3$ biodegradable microcapsules using $CaCO_3$
636 core with entrapped protein (DNA) as template (Selina et al., 2009).

637 4.2. Dextrans and derivatives for multilayer capsules

638 *4.2.1. Overview of dextrans use for micro- and nano- capsules*

639 Table 2 reports the preparation of dextrans-based capsules and their application fields
640 which are mainly dedicated to biomedical, and especially drug delivery. The principal dextran
641 derivatives used, dextran sulfates (DexS) was shown to be suitable for the encapsulation with
642 various macromolecules with control on the quantity and the delivery time of the encapsulate
643 substance. Its availability and its properties in multilayers with various counter-
644 polyelectrolytes opened potential uses for capsules with monitoring capsules releasing and
645 loading by capsule morphology and responsive properties. Although there is a wide of
646 counter-polyelectrolytes, literature overview (Table 2) emphasises that most studies focus on
647 the capsules based on dextrans and bio-based polyelectrolytes (chitosan (CHI), polyarginine
648 including protamine and PLL) for the fabrication of biodegradable and biocompatible objects.

649 **Table 2.** Dextran derivatives as polyelectrolytes for micro– and nano– capsules fabrication
650 reported in literature.

Coating Components	Core Template	Encapsulated species	Size	Applications	Ref
DexS/CHI	SiO_2 cores	FITC-albumin; basic fibroblast	250–350 nm, 3–5 µm	drug delivery	(Devi et al., 2015; Geetha Devi et al.,

		growth factor; vascular endothelial growth factor; rifampicin; ciprofloxacin; ceftriaxone sodium salt; gentamicin sulphate; FITC			2021; Gnanadhas et al., 2013; Itoh et al., 2004, 2006, 2008a, 2008b)
	$CaCO_3$ cores	bovine serum albumin; polyphenol; protein (DNA); antibiotic	3–6 µm	drug delivery	(Ali Said et al., 2020; Ferrari et al., 2017; Paini et al., 2015; Selina et al., 2009)
	Drug-DexS microaggregates	doxorubicin; vitamin E and lecithin	various	drug delivery	(Averin et al., 2016; Crecente-Campo & Jose Alonso, 2019)
	Protein-DexS microaggreagates	N-benzoyl-L-arginine ethyl ester; N-benzoyl-L-tyrosine ethyl ester; insulin	6–12 µm	drug delivery	(N. G. Balabushevich et al., 2006, 2013)
	Emulsion	Phosphate ions; 1-hydroxy pyrene-3,6,8-trisulfonic acid; amphiphilic alendronate; non-ionic glucose	150–250 nm	drug delivery	(Fukui & Fujimoto, 2009, 2011)
	Silver nanoparticles	silver	30–50 nm	catalysis, photonics, pharmaceutics, biotechnology	(Livanovich & Shutava, 2019)
DexS/PAH	Silver nanoparticles	silver	20–50 nm		(Anandhakumar et al., 2011, 2012)
DexS/poly-L-arginine	SiO_2 cores	rhodamine B		drug delivery	(Gao et al., 2016)
	$CaCO_3$ cores	proteins; rhodamine B; messenger RNA; albumin and acid tannic; doxycycline; multikinase inhibitor sorafenib; alpha-2-macroglobulin	4–5 µm, 250–500 nm	drug delivery, cancer therapy, biomedical	(Canova et al., 2015; De Temmerman et al., 2011a, 2011b; Ermakov et al., 2019; Kakran et al., 2015; Karamitros et al., 2013; Kochetkova et al., 2013; W. Liu et al., 2014; Lomova et al., 2015; D. Luo et al., 2016; Novoselova et al., 2020; Poojari et al., 2016)
	Emulsion	acid tannic	150–200 nm	drug delivery	(Kashcooli et al., 2016; Lomova et al., 2010)
DexS/protamine	Melamine formaldehyde core	proteins, enzymes, peroxidases	3–4 µm	food processing, drug delivery, cosmetology	(N. Balabushevich et al., 2005; N. G. Balabushevich & Larionova, 2009)
	SiO_2 cores	kidney cells, various cells	2–4 µm	defoliation, plasmid delivery, drug delivery	(Reibetanz et al., 2006, 2010, 2011)

	$CaCO_3$ cores	proteins, anti-inflammatory, doxorubicin substances	2–5 µm	drug delivery, thermo-induced degradability	(N. G. Balabushevich et al., 2016; Rathmann et al., 2011; Trushina et al., 2018, 2019)
	Insulin-DexS microaggregates	insulin	7–20 µm	drug delivery	(N. Balabushevich & Larionova, 2004)
DexS/PLL	$CaCO_3$ cores	protein (DNA)	2–10 µm	biomedical, DNA vaccines	(Campbell et al., 2021; Selina et al., 2009)
	Erythrocyte carriers	erythrocyte	5–8 µm	drug delivery	(R. Luo, Mutukumaraswamy, et al., 2012)
	Poly(DL-lactide-co-glycolide) nanoparticles	poly(DL-lactide-co-glycolide)	50–100 nm	drug delivery	(R. Luo, Neu, et al., 2012)
	Fe_3O_4 nanoparticles	curcumin	10–20 µm	drug delivery	(Mancarella et al., 2015)
	Emulsion	bioactive compounds	100–200 µm	drug delivery	(Pan & Nitin, 2015)
DexS/DEAE-Dex	$CaCO_3$ cores			antimicrobial agents	(Pawlak et al., 2022)
Animated dextran/ carboxylated nanocellulose	Modified graphene oxide	curcumin	150–200nm	drug delivery, biomedicine, cancer therapy	(Anirudhan et al., 2019)
Carboxymethyldextran/ PLL	CdSe-ZnS cores	quantum dots	150–250nm	drug delivery, biomedicine	(Chen et al., 2003)
Diol dextran/ modified alginate	$CaCO_3$ cores	rhodamine b		drug delivery	(Mansour et al., 2019)

Similarly, for the construction of LbL films, (DexS/CHI) is a common polyelectrolytes couple for the fabrication of micro- and nano- capsules, as reported in Table 2. Since they are biocompatible, biodegradable and pH responsive, (CHI/DexS) capsules present different advantages for drug delivery systems, especially for release control since they offer different possibilities for drug release that can be triggered either by chemical or enzymatic action (Itoh et al., 2004, 2006, 2008a, 2008b).

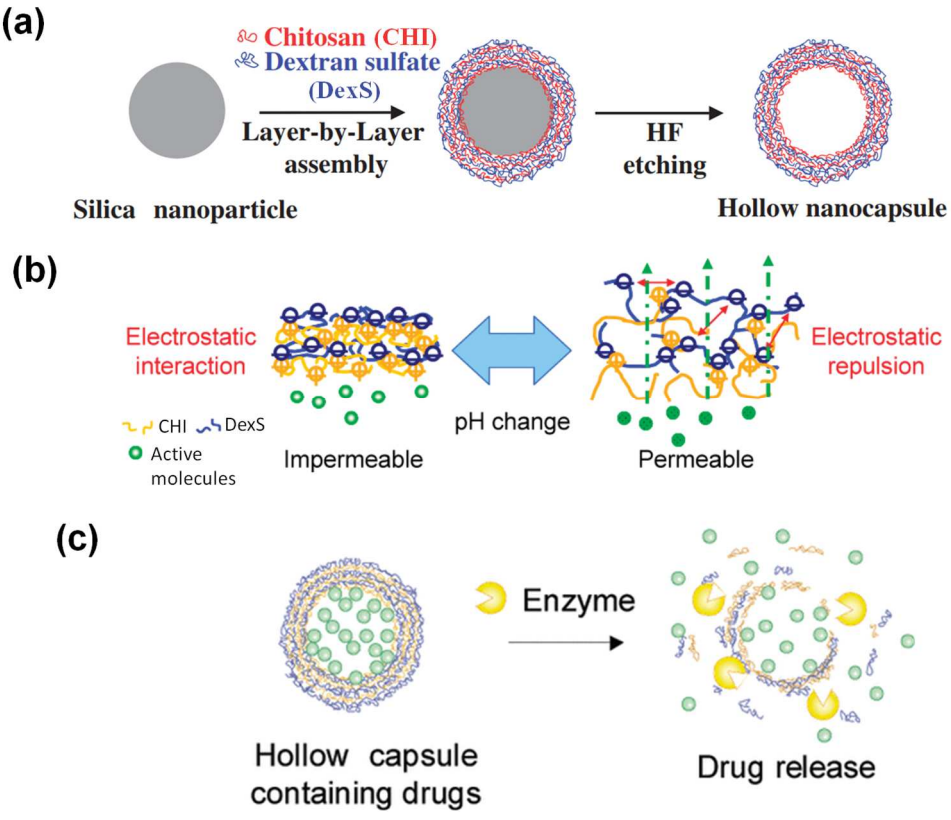

Figure 7. Schematic representations of (a) the fabrication principle of (CHI/DexS) capsules onto SiO_2 cores with dissolution by hydrofluoric acid (HF) (Itoh et al., 2004); (b) sensitive (CHI/DexS) multilayer based on pH changes with the impact on multilayer permeability, reprinted with permission from (Itoh et al., 2008b), © 2008 American Chemical Society; and (c) (CHI/DexS)-based release system of encapsulated drug with enzymatic degradation, adapted with permission from (Itoh et al., 2006), © 2006 American Chemical Society..

Authors designed (CHI/DexS) hollow capsules by LbL assembly on SiO_2 cores before core dissolution, as illustrated by Figure 7a, and obtained capsules with pH-dependent morphology and permeability (Itoh et al., 2008b). They observed a significant change in the permeability of the capsules between pH 6.8 and 8.0. Capsules (CHI/DexS) are impermeable with small pores under pH 6.8 and permeable with larger pores over pH 8.0 due to the pKa of CHI due to the deprotonation of the amine groups of CHI at basic pH as described in Figure 7b. The pH-responsive property of (CHI/DexS) capsules allowed an effective loading of

673 fluorescein isothiocyanate-labelled dextran by switching environmental pH from 8.0 to 5.6
674 but also a release of active molecules triggered by pH change. The advantage of choosing
675 polysaccharides for polyelectrolytes-based structures is their sensitivity to enzymes that allow
676 the elaboration of enzyme-responsive devices (Itoh et al., 2006, 2008a). In those systems, the
677 release is controlled by the selection of the type and amount of enzymes, as illustrated on
678 Figure 7c. Itoh research group demonstrated the biodegradability of (CHI/DexS) capsules by
679 using chitosanase that hydrolysed CHI leading to capsules deformation and degradation (Itoh
680 et al., 2006). Later on, authors also proposed to tune the degradation by building composites
681 multilayer containing other enzyme-sensitive polyelectrolytes such as PLL that can be
682 degraded by α-chymotrypsin. The formation of (CHI/DexS/PLL) allowed the stepwise release
683 of multiple proteins at different time from i) degradation of PLL in a first step and then ii)
684 degradation of CHI. More combinations for a controlled release can be designed based on the
685 choice of polyelectrolyte/enzyme couple and on the characterises of multilayer obtained.

686 Efficiency of dextran sulfates-based capsules and of their release capacity is also
687 dependent on the quantity of targeted molecules encapsulated into the devices. In 2016,
688 Balabushevich *et al.* studied the loading of model proteins: catalase (Cat), insulin (Ins) and
689 aprotinin (Apr) into $(DexS/protamine)_2$-DexS multilayer capsules considering the three
690 approaches (N. G. Balabushevich et al., 2016). 3) Sorption of protein into shell capsules after
691 capsule formation and core dissolution (post-loading), 2) adsorption of protein solution onto
692 pre-made $CaCO_3$ cores before capsule formation (pre-loading and adsorption), 3) co-synthesis
693 of protein with $CaCO_3$ cores before capsule formation (pre-loading and co-synthesis).

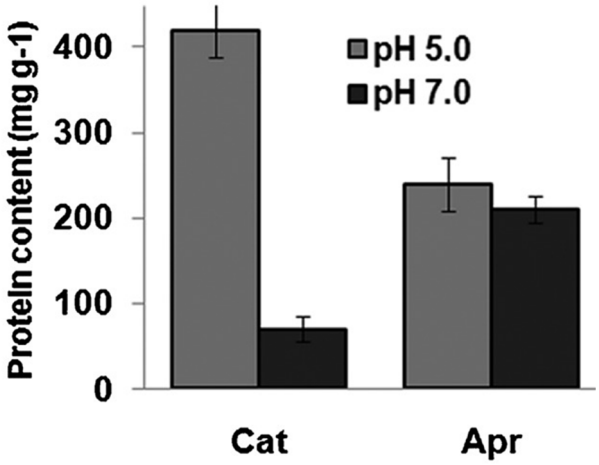

Figure 8. Proteins catalase (Cat) and aprotinin (Apr) contents of (DexS/protamine) capsules obtained by post-loading approach (N. G. Balabushevich et al., 2016).

Pre-loading by adsorption of protein onto $CaCO_3$ cores or by co-synthesis is only based on the electrostatic interaction between proteins and cores at chosen pH while post-loading approach is based on the affinity between proteins and cores. In the post-loading case, it was shown that catalase and aprotinin can be adsorbed into $(DexS/protamine)_2$-DexS capsules at both pH 5 and pH 7 with different efficiency, as illustrated on Figure 8. $(DexS/protamine)_2$-DexS microcapsules have negative charges due to the uncompensated charged groups of DexS, since DexS is a stronger polyelectrolyte than protamine. So, catalase is preferably incorporated at pH 5 (40% by mass) than at pH 7 (7% by mass) as a result of the occurrence of positive charge on catalase at pH 5. For aprotinin, no difference was observed as protein content corresponds to 20 – 25% whatever the pH since the protein is negatively charged at both pH. Those results confirm that loading is mainly driven by electrostatic interactions between loaded molecules and multilayer capsules. Thus, the choice of polyelectrolyte used (charge equilibrium) for multilayers and conditions (pH, ionic strength) are important parameters to consider for controlled loading.

The use of other dextran derivatives remains low compared to dextran sulfates. However, the use of cationic dextrans can increase potential applications for dextran in biomedical due to their use with other polyanion, but it can also add properties to multilayers. In 2019, Anirudhan *et al.* proposed the use of an aminated dextran to create multilayer capsules with stimuli responsive property due to pH sensitivity of both polyanion (oxidised nanocellulose) and polycation (aminated dextran) (Anirudhan et al., 2019). As dextran sulfate is a weak polyanion with high stability in water (pKa ~ 2), the employment of anionic dextran derivatives with a higher pKa can also be useful for the elaboration of stimuli-responsive objects. Dextran derivatives can also be used to substitute synthetic polyelectrolytes in specific applications such as reactive oxygen multilayers. Mansour *et al.* proposed for example the formation of multilayer capsules with hydrogen peroxide sensitivity based on a diol-dextran (Mansour et al., 2019).

5. CONCLUSION

Nanomaterials based on dextran and dextran derivatives built by LbL method present promising applications in biomedical fields due to their biocompatibility and their biodegradability. Dextrans and dextran derivatives have been successfully introduced into multilayer films and structures with control on film growth and characteristics by tuning the processing parameters. Their great compatibility with other polysaccharides (chitosan, cellulose, etc.), polyarginines (poly-L-lysine (PLL), etc.) and proteins (insulin, etc.), allows to form biodegradable multilayers useful for drug delivery systems in particular. Moreover, the versatility and availability of dextrans and derivatives as well as their water-solubility, are key advantages for the exploration of assemblies formed by combining two polysaccharides compared to cellulosic materials (Šimkovic, 2013). The use of different dextrans make possible the formation of LbL films with control over different types of properties (bioactivity, chemical, mechanical) and control over different morphologies to design

736 assemblies and surfaces with specific functionalities (Crouzier et al., 2010). Among
737 derivatives, dextran sulfate seems to present the greater interest for the research community
738 for its many biological properties such as anticoagulant, anti-inflammatory and anti-viral
739 properties.

740 Although studies on the applicability of dextrans and dextran derivatives into
741 multilayers and multilayer objects can be found with various polyelectrolytes, there is a need
742 of deeper understanding of most dextran-based LbL assemblies beside well studied DexS.
743 Works considering other dextran derivatives, such as carboxylmethyl dextran,
744 diethylaminoethyl dextran (DEAE-Dex) or other aminated dextrans, are seldom and dedicated
745 to specific applications so that it is difficult to determine the key parameters controlling the
746 film growth. Commercially available dextran derivatives are still restricted and the chemical
747 functionalisation of dextrans limit the employment of dextran derivatives in the development
748 of innovative structures. Development of new routes of functionalisation of dextrans is
749 promising to extend the panel of dextran derivatives, with a better environmental impact and
750 diversified functional properties. One of them is to explore an enzymatic approach to the
751 custom synthesis of polyelectrolytes based on microbial polysaccharides such as dextrans. In
752 addition to finely controlled structures and molar masses of dextrans, designed enzymes may
753 improve the properties of α-glucans with charged groups (Moulis et al., 2021).

754 Moreover, apart from extensive research on (CHI/DexS) multilayer films and
755 structures, only a few studies have reported LbL assemblies with other polyelectrolyte
756 counterpart than chitosan. Functional groups in dextran derivatives as well as chemical
757 structures provide opening for adsorption. A wider range of other biocompatible and
758 biodegradable functional species from mineral nanoparticles to polypeptides has to be

759 explored in the next years and will open opportunities for controlled elaboration of dextran-
760 based multilayer nanoobjects.

761 Finally, studies and applications mostly focused on biomedical fields with drug
762 delivery applications. The possibility to control the film morphology and the surface pattern
763 of dextran-based multilayer opens opportunities to create specific surfaces or specific objects
764 that can be used in wider application fields. LbL assemblies in general still have room for
765 development in nanoarchitectonics or organized-nanostructures technology from energy
766 applications to life science (Ariga, 2021; Ariga et al., 2022). This includes nano-printing and
767 nano-lithography processes used to fabricate patterns of nanometre scales (Vigneswaran et al.,
768 2014) but also, the possibility to obtain super-hydrophobic coating by tuning hydrophobicity
769 found and developed for cell adhesion and proliferation (Jafari et al., 2019; Sethi & Manik,
770 2018; W. Song et al., 2010).

AUTHOR INFORMATION

Credit authorship contribution statement

Aurore Delvart: Conceptualisation, Investigation, Writing – original draft & editing, Visualisation. **Céline Moreau:** Conceptualisation, Writing – review & editing, Supervision. **Bernard Cathala:** Conceptualisation, Writing – review & editing, Project administration, Funding acquisition.

All authors have given approval to the final version of the manuscript.

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Declaration of Competing Interest

The authors declare no competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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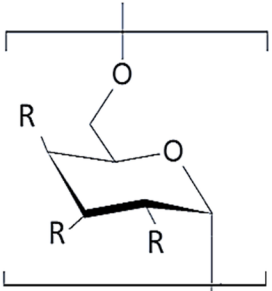
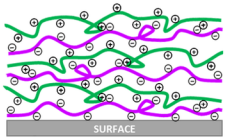
1612

DEXTRAN AND DERIVATIVES

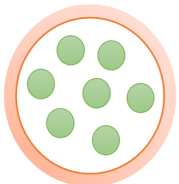


R = H, functional groups (animo, carboxymethyl, ether, etc.), grafted molecules

MULTILAYERS FILMS



MULTILAYERS CAPSULES



APPLICATIONS

pharmaceutics

biodegradable objects

antimicrobial agents

vaccines

photonics

drug delivery

food processing

cell adhesion

hydrophobic surfaces

protein organisation

cancer therapy