

# Polymer-free cyclodextrin and natural polymer-cyclodextrin electrospun nanofibers: A comprehensive review on current applications and future perspectives

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1 Polymer-free Cyclodextrin and Natural Polymer-Cyclodextrin Electrospun Nanofibers: A 2 **Comprehensive Review on Current Applications and Future Perspectives** 3 Andrea Dodero<sup>1</sup>, Guy Schlatter<sup>2\*</sup>, Anne Hébraud<sup>2</sup>, Silvia Vicini<sup>1</sup>, Maila Castellano<sup>1\*</sup> 4 5 6 <sup>1</sup> Department of Chemistry and Industrial Chemistry, University of Genoa, Via Dodecaneso 31, 16146 Genoa, 7 Italy 8 <sup>2</sup> Institute of Chemistry and Processes for Energy, Environment and Health (ICPEES), CNRS UMR 7515, 9 ECPM – University of Strasbourg, 25 rue Becquerel, 67087, Strasbourg, France 10 11 \*corresponding authors: maila.castellano@unige.it 12 guy.schlatter@unistra.fr 13 14 **Abstract** 15 The present review discusses the use of cyclodextrins and their derivatives to prepare electrospun nanofibers 16 with specific features. Cyclodextrins, owing to their unique capability to form inclusion complexes with 17 hydrophobic and volatile molecules, can indeed facilitate the encapsulation of bioactive compounds in 18 electrospun nanofibers allowing fast-dissolving products for food, biomedical, and pharmaceutical purposes, 19 filtering materials for wastewater and air purification, as well as a variety of other technological applications. 20 Additionally, cyclodextrins can improve the processability of naturally occurring biopolymers helping the 21 fabrication of "green" materials with a strong industrial relevance. Hence, this review provides a 22 comprehensive state-of-the-art of different cyclodextrins-based nanofibers including those made of pure 23 cyclodextrins, of polycyclodextrins, and those made of natural biopolymer functionalized with cyclodextrins. 24 To this end, the advantages and disadvantages of such approaches and their possible applications are 25 investigated along with the current limitations in the exploitation of electrospinning at the industrial level. 26 27 **Keywords** 

- 28 Electrospinning; Cyclodextrins; Natural biopolymers; Functionalized nanofibers; Inclusion complexes;
- 29 Polycyclodextrins.

#### 1 Introduction

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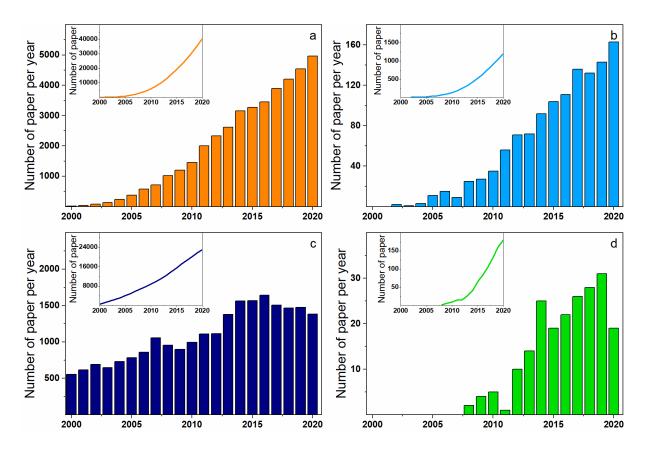
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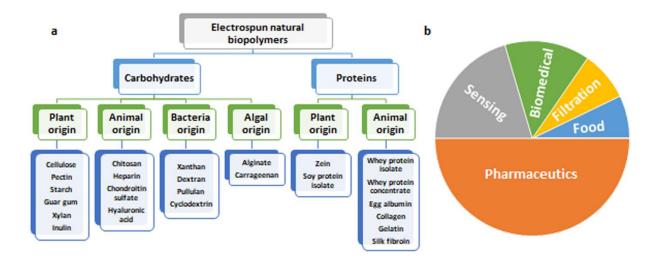
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Electrospinning is a simple, versatile, and cost-effective technique that allows the fabrication of polymeric nano- and microfibers starting from a polymer solution or polymer melt (J. Xue et al., 2019). Demonstrated in 1934 by A. Formhals (Anton, 1934), electrospinning started to gain considerable interest from the 2000s and it is nowadays one of the most employed fiber-forming approaches for several purposes (Ahmed et al., 2015; Dodero, Alloisio, Castellano, et al., 2020; Dodero, Brunengo, Castellano, et al., 2020; Dodero, Vicini, Lova, et al., 2020; Tebyetekerwa & Ramakrishna, 2020; Thenmozhi et al., 2017). Among others, electrospun nanofibers can be efficiently used to encapsulate a great variety of molecules, such as drugs, bioactive compounds and nanoparticles (Castellano et al., 2019; Figueiredo et al., 2020; Quirós et al., 2016; Torres-Giner et al., 2016; Wen et al., 2017). In this sense, cyclodextrins (CDs) offer the chance to obtain functionalized nanofibers with high encapsulation efficiency, enhanced thermal stability, water-solubility, and bioavailability of the encapsulated molecules (Costoya et al., 2017; Senthil Muthu Kumar et al., 2019; Topuz & Uyar, 2019). However, cyclodextrin-functionalized nanofibers remain a barely explored research field and, to the best of our knowledge, no commercial products currently exist besides an increasing number of original research work has being recently published. To this regard, Costoya et al. (Costoya et al., 2017) recently reviewed the fabrication of cyclodextrin functional nanofibers, whereas Topuz et al. (Topuz & Uyar, 2019) and Vidal et al. (Patiño Vidal et al., 2021) focused the attention on their pharmaceutical and food packaging applications, respectively. By way of example, Figure 1 reports the number of publications per year in the last two decades (i.e., 2000-2020) concerning electrospinning (Figure 1a), functionalized nanofibrous membranes (Figure 1b), cyclodextrins (Figure 1c) and cyclodextrin-functionalized nanofibrous membranes (Figure 1d).



**Figure 1.** Annual trend of publications regarding (a) electrospinning, (b) functionalization of electrospun nanofibers, (c) cyclodextrins, and (d) cyclodextrin-functionalized electrospun nanofibers. Insets represent the cumulative number of publications. Data has been retrieved from Scopus database.

Among the great variety of commercial polymers that can be electrospun, naturally occurring materials represent an attractive alternative to synthetic ones (Ding et al., 2019; Soares et al., 2018). Indeed, biopolymers, such as polysaccharides and proteins, can be used to fabricate nanofibers with superior biocompatibility, biodegradability, and lower environmental impact compared to industrially derived materials. Nonetheless, their processing is usually more difficult and it requires a series of experimental precautions (Bertasa et al., 2020; Ding et al., 2019; Dodero, Pianella, et al., 2019; Kakoria & Sinha-Ray, 2018; Mendes et al., 2017; Noruzi, 2016). A schematic representation of the most common natural biomaterial-based electrospun mats and their applications is reported in Figure 2.



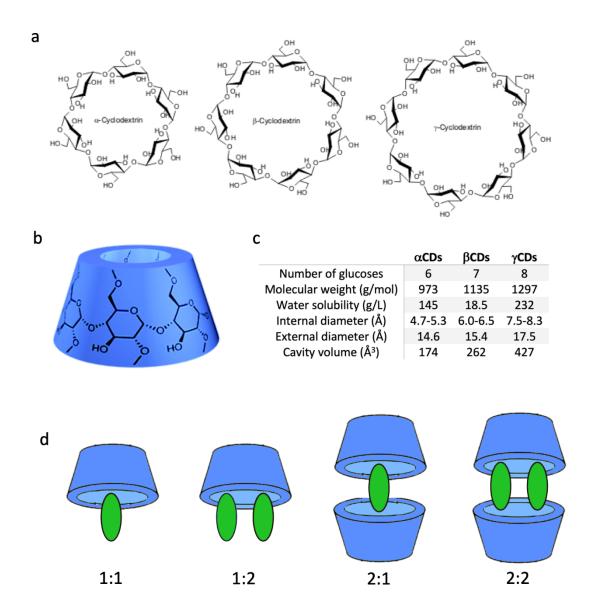
**Figure 2.** (a) Schematic of natural biopolymer-based electrospun membranes depending on the source materials and (b) pie chart representing their main applications according to the Scopus database.

With these premises, aiming to highlight the importance of developing environmentally benign materials, this review aims to provide a comprehensive summary of the recent advances in the preparation of either polymer-free cyclodextrin-based nanofibers, polycyclodextrin-based nanofibers, or natural polymer-based (i.e., polysaccharides and proteins) nanofibers functionalized with cyclodextrins. To this end, after a brief introduction concerning cyclodextrins first and electrospinning then, a critical and complete overview of the current literature is presented and discussed. Finally, a short consideration about the future trends and possibilities is reported together with a conclusion paragraph.

#### 2 Cyclodextrins

#### 2.1 Structure and Properties

Cyclodextrins consist of cyclic oligosaccharides of glucopyranose assuming the structure of a hollow truncated cone (Figure 3b) (Sá Couto et al., 2015). The inner cavity of this three-dimensional structure is partially hydrophobic owing to the -CH and -CH<sub>2</sub> carbons and ether oxygens, whereas the exterior surface is hydrophilic due to the high number of hydroxyl groups (Szejtli, 1998). Although several types of CDs exist, the most common ones consist of 6, 7, and 8 glucopyranose units and are named  $\alpha$ CDs,  $\beta$ CDs, and  $\gamma$ CDs, respectively, with their structure and main properties reported in Figure 3a-c (Del Valle, 2004; Jansook et al., 2018; Kurkov & Loftsson, 2013).



**Figure 3.** (a) Chemical structure of the most common CDs. (b) Three-dimensional conformation taken by CDs. (c) Summary of the main physical properties of CDs depending on the glucose unit number. (d) Schematics of inclusion complex formation with blue and green objects representing cyclodextrins (i.e., host molecules) and small molecules (i.e., guest molecules). For example, inclusion complexes with a molar ratio 1:1 have been prepared between βCDs and racecadotril (Semalty et al., 2014), with a molar ratio 1:2 between βCDs and naproxen (Grandelli et al., 2013), with a molar ratio of 2:1 between βCDs and carvacrol (Bethanis et al., 2013), and with a molar ratio 2:2 between βCDs and linalool (Ceborska, 2016).

Native CDs are highly crystalline and are known to adopt a cage structure with a herringbone arrangement (Saenger et al., 1998). Typically, they present a low solubility that depends on their size, with  $\beta$ CDs being the less soluble ones (Szejtli, 1998). In order to overcome this processing limitation, CDs have been chemically modified to enhance their water solubility mostly by causing a considerable loss of crystallization. Among others, the most studied are randomly methylated- $\beta$ CDs (M $\beta$ CDs), 2-hydroxypropyl- $\beta$ CDs

(HPβCDs) and 2-hydroxypropyl-γCDs (HPγCDs) (Crini, 2014; Landy et al., 2012). Remarkably, an interesting feature of native and modified CDs is represented by their capability to undergo crosslinking/polymerization reactions leading to water-insoluble cyclodextrin-based polymers (polyCDs) with tailor-made properties (Blanchemain et al., 2008; Crini, 2014; Morin-Crini & Crini, 2013; Sherje et al., 2017).

### 2.2 Cyclodextrin Inclusion Complexes

Cyclodextrins are nowadays applied in many industrial sectors (Q. Liu et al., 2020a; Matencio et al., 2020; Wankar et al., 2020; Ying - Ming Zhang et al., 2020). The main reason for CDs success is related to their unique ability to form non-covalent host-guest complexes with a variety of small molecules via inclusion in their hydrophobic cavity (G. Chen & Jiang, 2011; Folch-Cano et al., 2014; Mura, 2015). Depending on both the type of cyclodextrins and hydrophobic molecules, as well as on the formulation conditions, the complexation can occur between a host and a guest molecule, a host and two guest molecules, or two hosts and a guest molecule as represented in Figure 3d (Frömming & Szejtli, 1994; Kim et al., 2006; S. Li & Purdy, 1992; Mohanty et al., 2006; Song et al., 2009). Cyclodextrin inclusion complexes (CD-ICs) are commonly exploited to protect those molecules that are sensitive to light, oxygen, heat, and chemical reactions, as well as to increase the water solubility of hydrophobic compounds and to preserve highly volatile fragrances/flavours. By way of examples, CD-ICs have been widely proposed in food and beverage products (dos Santos et al., 2017; É. Fenyvesi et al., 2016), in the pharmaceutical and (Jansook et al., 2018) cosmetic fields (Crini et al., 2018), in the textile industry (Narayanan et al., 2015; Singh & Sahu, 2018), and in developing filtering materials (Éva Fenyvesi et al., 2020; O. Liu et al., 2020b).

## 3 Electrospinning and its Use as Encapsulation Technique

The electrospinning (ES) technique consists of the application of a high voltage to a polymer solution, or a polymer melt, that is usually extruded from a spinneret at a constant rate. Owing to the presence of free surface charges, the polymeric droplet exiting the spinneret takes the shape of a cone (i.e., Taylor cone) and, when the repulsive electrostatic forces overcome the liquid surface tension, a continuous jet erupts from the

spinneret tip. Hence, solid nano- or microfibers are obtained and generally collected in a pseudo-random manner on a grounded collector (Lukáš et al., 2009). The stability of the polymer jet and the related fiber morphology depend on the spinning system properties, processing parameters and environmental conditions (Amiraliyan et al., 2009; Ismail et al., 2017; Thompson et al., 2007). In this sense, electrospinning represents an easy, versatile, and industrially scalable approach to prepare fibers with tailored properties (Kannan et al., 2016; J. Xue et al., 2019; M. Yu et al., 2017). During the past decades, both synthetic and naturally derived polymers have been electrospun. Synthetic polymers are usually easier to electrospun and allow good reproducibility and superior mechanical performances. Additionally, by using hydrophobic materials, water-resistant mats able to maintain their peculiar structure in contact with aqueous media can be easily obtained without the need for post-production treatments. However, such materials usually require the use of organic hazardous solvents to be processed thereby representing a substantial environmental and health threat. Conversely, the electrospinning of naturally occurring polymers is starting to be broadly investigated as a less impacting and "greener" alternative. Indeed, besides the fact that they can be processed via eco-friendly solvents (e.g., water, slightly acid mixtures, etc), natural biopolymers can be often extracted from food and agricultural wastes hence endowing the interesting possibility to develop circular economy products (Ding et al., 2019; Kakoria & Sinha-Ray, 2018; Mendes et al., 2017; Noruzi, 2016; Schiffman & Schauer, 2008). Moreover, such materials are usually biocompatible, weakly immunogenic, biodegradable, and digestible, and present other peculiar properties that make them extremely promising for the fabrication of biomedical and pharmaceutical products, as well as for food packaging and biosensor applications (Dodero, Lova, Vicini, Castellano, et al., 2020; Galiano et al., 2018). Nevertheless, natural polymers present drawbacks such as poor reproducibility, mechanical properties and thermal resistance, and usually require a post-processing crosslinking reaction to exhibit appropriate stability and performances. Hence, it is not surprising that the electrospinning of such materials is considerably harder compared to synthetic polymers (Valencia et al., 2019; Yi et al., 2020). With these premises, it is not surprising that electrospinning is nowadays widely used to prepare nanofibrous membranes for a broad range of purposes. For example, electrospun mats find several uses as biomedical and pharmaceutical devices (Cheng et al., 2018; Miguel et al., 2018), in filter materials (D. Lv et al., 2018; Snowdon & Liang, 2020), in the packaging sector (Senthil Muthu Kumar et al., 2019; C. Zhang et al., 2020),

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but also for energy-related applications (J. Wang et al., 2020), sensors and biosensors (Han et al., 2019; Rozemarie Manea & Bertea, 2019), and textile products (Mirjalili & Zohoori, 2016). Additionally, electrospinning has proved to be a promising encapsulation technique with several advantages compared to the common industrial approaches, such as spray-drying and solvent evaporation (Becerril et al., 2020; Celli et al., 2015; Lohith Kumar & Sarkar, 2018; Shishir et al., 2018). Specifically, apart from its versatility, the key advantage of electrospinning as an encapsulation technique consists of the absence of heat, which is fundamental to preserve the structure and properties of the entrapped molecules. However, most of the drugs and bioactive compounds of major interest are characterized either by low water solubility, poor thermal stability or a highly volatile nature. Hence, to overcome such limitations and improve the efficiency of electrospinning as an encapsulation technique, the use of cyclodextrins to obtain functionalized nanofibers has recently gained increasing relevance.

#### 4 Polymer-free Electrospun Cyclodextrin – based Membranes

One of the main requirements to obtain defect-free homogenous nanofibers via electrospinning technique is the presence of sufficient intermolecular interactions in the working solutions (or melts). In polymer-based systems, these are usually provided by chain entanglement (Mendes et al., 2017; C. Wang et al., 2016). On the contrary, the electrospinning of low molecular weight molecules is quite a challenge because of the complete lack of entanglements. Hence, only a few can be electrospun alone. Among others, owing to their unique self-assembling behaviour, pure phospholipids (McKee et al., 2006), surfactants (Cashion et al., 2010), tannic acid (Allais et al., 2018), and cyclodextrins (Celebioglu & Uyar, 2010) can be used to prepare polymer-free nanofibers. In this sense, thanks to their unique physical-chemical properties, polymer-free cyclodextrin nanofibers have gained huge interest in recent years. However, their proficient usage in industrial applications remains a challenge and further studies are required to obtain products with effective large-scale applicability (Costoya et al., 2017; Topuz & Uyar, 2019, 2020). In the following, a detailed summary (see Table 1) of the current state-of-the-art is provided by reviewing both proofs of concept and applicative reports.

**Table 1.** Comprehensive summary of polymer-free cyclodextrin electrospun membranes and their main applications. If not indicated (---), the used solvent is only water.

Application	Cyclodextrin	Encapsulated compounds	Solvent	Ref.
	MβCDs		Water, DMF, DMAc, Urea	(Celebioglu & Uyar, 2010, 2012)
-	HPβCDs		Water, DMF, Urea	(Manasco et al., 2012; W. Zhang et al., 2012)
-	HPγCDs		Water, DMF, DMAc, Urea	(Celebioglu & Uyar, 2012)
Fundamental studies	αCDs		Water, DMF, DMAc, DMSO, water – NaOH	(Celebioglu & Uyar, 2013a)
-	βCDs	Compounds   Compounds	(Ahn et al., 2013; Celebioglu & Uyar, 2013a)	
-	HPαCDs		Water, tap water, salty water	(Celebioglu & Uyar, 2020b)
	HPβCDs	Triclosan		(Celebioglu, Umu, et al., 2014; Celebioglu &
				Uyar, 2011)
		Azobenzene		(M. Chen et al., 2013)
		Geraniol		(Aytac, Yildiz, Kayaci-Senirmak, San Keskin,
				Tekinay, et al., 2016)
		Camphor		(Celebioglu, Aytac, et al., 2018)
Drug and bioactive compound delivery systems	ΗΡγCDs	Triclosan		(Celebioglu, Umu, et al., 2014; Celebioglu &
			<del></del>	Uyar, 2011)
		Geraniol		(Aytac, Yildiz, Kayaci-Senirmak, San Keskin,
				Tekinay, et al., 2016)
		Camphor		(Celebioglu, Aytac, et al., 2018)
-	MOCD	Geraniol		(Aytac, Yildiz, Kayaci-Senirmak, San Keskin,
	MβCDs			Tekinay, et al., 2016)
Fast-dissolving nanofibers for the rapid	IIDOCD	Spironolactone	EtOH	(Vigh et al., 2013)
compound administration	HPβCDs	Diclofenac	EtOH	(Balogh et al., 2015)

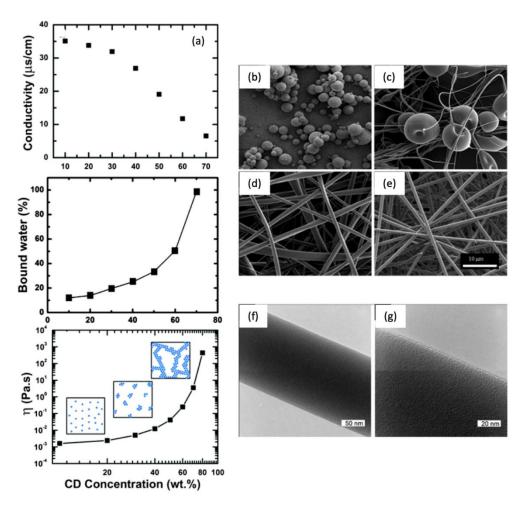
sodium				
Vitamin E	Water – EtOH	(Celebioglu & Uyar, 2017)		
Paracetamol		(Zehra Irem Yildiz & Uyar, 2019)		
α-lipoic acid		(Celebioglu & Uyar, 2019a)		
Ibuprofen		(Celebioglu & Uyar, 2019b)		
Metronidazole		(Celebioglu & Uyar, 2019c)		
Curcumin		(Celebioglu & Uyar, 2020c)		
Hydrocortisone		(Celebioglu & Uyar, 2020d)		
Ferulic acid		(Celebioglu & Uyar, 2020e)		
β-galactosidase		(Vass et al., 2020)		
Doxycycline		(Kiss et al., 2020)		
Thiabendazole		(Gao et al., 2020)		
Vitamin-A		(Calling 1 & H and 2020a)		
acetate	<del></del>	(Celebioglu & Uyar, 2020a)		
Vanillin	Water, DMF, DMAc	(Celebioglu, Kayaci-Senirmak, et al., 2016)		
Limonene		(Aytac, Yildiz, Kayaci-Senirmak, San Keskin,		
Limonene	<del></del>	Kusku, et al., 2016)		
Linalool		(Aytac, Yildiz, et al., 2017)		
Citral		(Aytac, Celebioglu, et al., 2018)		
Carvacrol		(Zehra I. Yildiz et al., 2018)		
Menthol		(Zehra Irem Yildiz et al., 2018)		
Cineole		(Celebioglu, Yildiz, et al., 2018a)		
p-cymene		(Celebioglu, Yildiz, et al., 2018a)		
Eugenol		(Celebioglu, Yildiz, et al., 2018b)		
Thymol		(Celebioglu, Yildiz, et al., 2018c)		
Cinnamaldehyde		(Zehra I. Yildiz et al., 2019)		
	Water – skim milk	(San Keskin et al., 2018)		

Acyclovir		(Celebioglu & Uyar, 2021)
Kanamycin		(Topuz et al., 2021)
Chloramphenicol		(Topuz et al., 2021)
Gentamicin		(Topuz et al., 2021)
Ampicillin		(Topuz et al., 2021)
Sulfisoxazole		(Zehra Irem Yildiz et al., 2017)
Paracetamol		(Zehra Irem Yildiz & Uyar, 2019)
Voriconazole		(Vass et al., 2019)
α-lipoic acid		(Celebioglu & Uyar, 2019a)
Curcumin		(Celebioglu & Uyar, 2020c)
Ferulic acid		(Celebioglu & Uyar, 2020e)
Vanillin	Water, DMF, DMAc	(Celebioglu, Yildiz, et al., 2018b)
		(Aytac, Yildiz, Kayaci-Senirmak, San Keskin
Limonene		Kusku, et al., 2016)
Linalool		(Aytac, Yildiz, et al., 2017)
Citral		(Aytac, Celebioglu, et al., 2018)
Carvacrol		(Zehra I. Yildiz et al., 2018)
Menthol		(Zehra Irem Yildiz et al., 2018)
Cineole		(Celebioglu, Yildiz, et al., 2018a)
p-cymene		(Celebioglu, Yildiz, et al., 2018a)
Eugenol		(Celebioglu, Yildiz, et al., 2018b)
		(Celebioglu, Yildiz, et al., 2018b)
Thymol		(Celebioglu, Yildiz, et al., 2018b) (Celebioglu, Yildiz, et al., 2018c)
		(Celebioglu, Yildiz, et al., 2018b) (Celebioglu, Yildiz, et al., 2018c) (Zehra I. Yildiz et al., 2019)
Thymol Cinnamaldehyde Vitamin-A		(Celebioglu, Yildiz, et al., 2018b) (Celebioglu, Yildiz, et al., 2018c)
Thymol Cinnamaldehyde		(Celebioglu, Yildiz, et al., 2018b) (Celebioglu, Yildiz, et al., 2018c) (Zehra I. Yildiz et al., 2019)
	Kanamycin Chloramphenicol Gentamicin Ampicillin Sulfisoxazole Paracetamol Voriconazole α-lipoic acid Curcumin Ferulic acid Vanillin Limonene Linalool Citral Carvacrol Menthol Cineole	Kanamycin  Chloramphenicol  Gentamicin  Ampicillin  Sulfisoxazole  Paracetamol  Voriconazole  α-lipoic acid  Curcumin  Ferulic acid  Vanillin Water, DMF, DMAc  Limonene  Linalool  Citral  Carvacrol  Menthol  Cineole

				Kusku, et al., 2016)
		Linalool		(Aytac, Yildiz, et al., 2017)
		Citral		(Aytac, Celebioglu, et al., 2018)
		Eugenol		(Celebioglu, Yildiz, et al., 2018b)
		Thymol		(Celebioglu, Yildiz, et al., 2018c)
	γCDs		Water – DMSO	(Celebioglu & Uyar, 2013b)
Air filter materials	HPβCDs		Water – DMF	(Celebioglu, Sen, et al., 2016)
	HPγCDs		Water – DMF	(Celebioglu, Sen, et al., 2016)
Reducing agents for nanoparticle synthesis	HPβCDs	Au-NPs	Water – DMF	(Celebioglu & Uyar, 2013c)
		Ag-NPs	Water – DMF	(Celebioglu, Topuz, Yildiz, et al., 2019b)
		Pd-NPs	Water – DMF	(Celebioglu, Topuz, & Uyar, 2019a)
Sacrificial templates for ceramic hollow	HPβCDs		DMF	(Celebioglu, Vempati, et al., 2014)
nanofibers	MβCDs		DMF	(Celebioglu, Vempati, et al., 2014)
	PolyHPβCDs			(Celebioglu et al., 2017)
		Poly-benzoxazine	DFM	(Dogan et al., 2019)
Woden musiciantian				(Celebioglu, Topuz, Yildiz, et al., 2019a)
Water purification			Water - NaOH	(Celebioglu, Topuz, & Uyar, 2019b)
	Peracetylated βCDs		DMF	(Topuz et al., 2020)
Touris and a bloom of Colde	PolyHPβCDs	Triclosan		(Hamsici et al., 2017)
Implantable scaffolds		Azobenzene	Water – NaOH	(Heydari et al., 2018)

#### 4.1 Fundamental Studies

The first report concerning polymer-free cyclodextrin electrospun nanofibers can be attributed to the group of Uyar ten years ago, which investigated the electrospinning of methyl- $\beta$ -cyclodextrins using water or dimethylformamide (DMF) as solvents with a concentration ranging from 50 wt% to 61 wt% (i.e., 100-160 w/v%) (Celebioglu & Uyar, 2010). A few years later, the same authors extended their studies to three other CD derivatives (i.e., HP $\beta$ CDs, HP $\gamma$ CDs and M $\beta$ CDs) in different solvents (Celebioglu & Uyar, 2012). Similarly to polymer-based systems, the results revealed that CD electrospinning is mainly governed by the solution viscosity, bound water, and conductivity. Comparable findings were also reported by Manasco et al. (Manasco et al., 2012), who investigated the possibility to prepare HP $\beta$ CD-based nanofibers (Figure 4a-g) by using aqueous solutions with a concentration in the range of 10-70 wt%.



**Figure 4.** (a) Effect of HPβCD concentration on the conductivity, bound water and viscosity of aqueous solutions. SEM micrographs of electrospun HPβCD solutions of (b) 50 wt%, (c) 60 wt%, (d) 65 wt%, (e) and 70 wt%. TEM micrographs showing fibers electrospun from a 65 wt% solution at (f) 200000X and (g) 400000X magnifications. Reproduced with permission from Manasco et al., 2012. © The Royal Society of Chemistry 2012.

197 198 In another work, Zhang et al. (W. Zhang et al., 2012) evaluated the influence of HPβCD concentration on the 199 electrospinning process in DMF. By studying the solution viscosity concentration dependence and the 200 concentration regimes, the authors supposed that HPβCDs behave in DMF as neutral polymers in good 201 solvents nevertheless much higher scaling factors were observed compared to the predicted ones (Colby, 202 203 204 205 206 207 208 209 210 211 212 213

2010). Such results were explained by considering the HPβCD tendency to self-aggregate similarly to wormlike micelles (Cashion et al., 2010; Dodero, Vicini, Alloisio, et al., 2020; Rubinstein & Semenov, 2001). Celebioglu et al. (Celebioglu & Uyar, 2013a) also reported on the electrospinning of native αCDs and βCDs from aqueous solutions in the concentration range 55-61 wt% (i.e., 120-160 w/v%). As for their derivatives, the concentration of native cyclodextrin solutions was found to play a fundamental role in conditioning the nanofiber morphology. Interestingly, besides the fact that native CDs are highly crystalline, the authors proved that the resultant CD nanofibers were completely amorphous probably due to the fast solvent evaporation rate. Yet, Ahn et al. (Ahn et al., 2013) presented the preparation of native βCD nanofibers by using an ionic liquid and DMF as solvents and a concentration between 10 wt% and 60 wt%. Only recently, Celebioglu et al. (Celebioglu & Uyar, 2020b) investigated the possibility to prepare nanofibrous membranes by using highly concentrated (i.e., 61-71 wt% or 160-240 w/v%) hydroxypropyl- $\alpha$ CDs (HP $\alpha$ CDs) solutions. Noticeably, the authors also considered industrially relevant aspects by using distilled water, tap water and salty water for preparing the nanofibrous membranes. Furthermore, the effect on the electrospinning process of solution storage over 8 days was investigated due to the tendency of CDs to form aggregates, despite no significant changes were observed neither in the viscosity of the solutions nor in terms of electrospun fiber morphology.

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#### 4.2 **Applicative Studies**

The previously discussed pioneering works demonstrated the possibility to fabricate polymer-free cyclodextrin nanofibers straightforwardly by using different types of CDs and solvents, thereby anticipating the development of a broad number of applicative products.

224 4.2.1 Drug and Bioactive Compound Delivery Systems with Enhanced Release Performances

The ability of CDs to increase the water solubility of several hydrophobic molecules, as well as their thermal resistance, light stability, and bioavailability, has led to the development of polymer-free nanofibers with enhanced drug delivery capabilities hence allowing the development of a new generation of biomedical and pharmaceutical devices.

Encapsulation of Hydrophobic Drugs

Celebioglu et al. (Celebioglu, Umu, et al., 2014; Celebioglu & Uyar, 2011) first prepared HP $\beta$ CD-ICs-triclosan and HP $\gamma$ CD-ICs-triclosan (TCL) electrospun membranes via the electrospinning of polymer-free aqueous solutions achieving defect-free homogeneous nanofibers, with similar morphological results obtained with poly(lactic acid)-based nanofibers in the work of Kayaci et al. (Kayaci, Umu, et al., 2013). The authors investigated the CD-ICs-TCL formation to select the optimal compound concentration to obtain homogeneous nanofibers while avoiding the presence of free triclosan molecules. Both HP $\beta$ CD-ICs-TCL and HP $\gamma$ CD-ICs-TCL nanofibers were tested against E. Coli and S. Aureus bacteria showing enhanced and prolonged antibacterial properties compared to uncomplexed triclosan powder. Remarkably, Chen et al. (M. Chen et al., 2013) reported on the preparation of UV-responsive nanofibers consisting of the inclusion complexes between HP $\beta$ CDs and azobenzene (AAB) molecules. By investigating the effect of UV light in different phases of the electrospinning process, the authors were able to prove the responsive properties of the prepared mats which were pointed out to be extremely promising for the development of stimulicontrolled drug delivery systems.

Encapsulation of Volatile Bioactive Substances

Polymer-free cyclodextrin nanofibers can also be efficiently exploited to avoid the rapid evaporation of highly volatile compounds. For example, Aytac et al. (Aytac, Yildiz, Kayaci-Senirmak, San Keskin, Tekinay, et al., 2016) prepared HP $\beta$ CD, HP $\gamma$ CD, or M $\beta$ CD geraniol inclusion complex nanofibrous mats. The authors proved the capability to encapsulate a higher amount of geraniol in pure CD nanofibers (~11 wt%) compared to polymeric membranes (~5 wt%). After both short-term temperature and long-term open-air release studies,

MβCD-based nanofibers showed the slowest release of geraniol. Moreover, along with strong antibacterial activities, CD-ICs-geraniol mats also displayed efficient antioxidant properties. Yet, Celebioglu et al. (Celebioglu, Aytac, et al., 2018) prepared HPβCD-ICs- and HP $\gamma$ CD-ICs-camphor nanofibers from highly concentrated aqueous solutions obtaining thermally stable and manageable membranes, with HP $\gamma$ CD-ICs-camphor nanofibers showing a slow release of the compound.

- 4.2.2 Fast-dissolving Nanofibers for the Rapid Compound Administration in Food or Pharmaceutical Products
- Polymer-free cyclodextrin nanofibers are highly soluble in water if not subjected to a crosslinking reaction (see Section 5), but such drawback has been efficiently turned into a benefit by exploiting the fast-dissolving nature of these systems for the rapid administration of drugs and bioactive compounds in both food and pharmaceutical products (Balusamy et al., 2020). Owing to their capability to form stable inclusion complexes, cyclodextrins can indeed considerably increase the water-solubility of a wide variety of guest hydrophobic drugs and volatile molecules that can consequently be rapidly released when in contact with a high moisture environment, human saliva or biological fluids (Cheirsilp & Rakmai, 2017; Mura, 2015).

267 Encapsulation for the Fast-dissolution of Hydrophobic Substances

The encapsulation of a hydrophobic drug within polymer-free cyclodextrin membranes has been first demonstrated by Vigh et al. (Vigh et al., 2013). The authors reported on polymer-free HPβCD nanofibers encapsulating spironolactone which were able to completely release the encapsulated drug within a minute, therefore being promising for the rapid oral administration of highly lipophilic compounds. Shortly after, Balogh et al. (Balogh et al., 2015) investigated the possibility to prepare fast-dissolving HPβCD nanofibers containing diclofenac sodium (DCF), a poorly soluble and highly crystalline drug, to avoid the common issues related to its injection delivery methods. Remarkably, the authors implemented the common electrospinning set-up with high-speed blowing air (i.e., electroblowing) able to enhance both productivity rate and fiber morphology. Above all, HPβCD-ICs-DCF nanofibers were completely amorphous and displayed a high solubility in water hence representing a promising alternative to reconstitution injections.

Starting from these preliminary studies, great efforts have been done in preparing fast-dissolving cyclodextrin electrospun nanofibers encapsulating a variety of hydrophobic molecules. For instance, Celebioglu et al. (Celebioglu & Uyar, 2017) reported on the electrospinning of HPβCD inclusion complexes with vitamin E, which consists of a long hydrophobic chain. The authors were able to load and preserve around the 13 wt% of vitamin E in the prepared mats observing only a small loss of the compound during the electrospinning process. The mats showed a fast-dissolving nature and strong antioxidant activities, which were even maintained after UV-irradiation and 3-year storage proving the stability of the formed complexes. Relatedly, Yildiz et al. (Zehra Irem Yildiz et al., 2017) developed first a nanofibrous solid inclusion complex between sulfobutylether-β-cyclodextrins (SEBβCDs) and sulfisoxazole, and then HPβCD-ICs- and SBEβCD-ICs-paracetamol nanofibrous membranes (Zehra Irem Yildiz & Uyar, 2019). The authors demonstrated that the crystalline nature of paracetamol was completely lost owing to the complexation with CDs, thus increasing its water solubility, bioavailability and thermal stability. Recently, Celebioglu et al. (Celebioglu & Uyar, 2019a, 2019b, 2019c, 2020c, 2020d, 2020e) reported on several types of polymer-free cyclodextrin nanofibers encapsulating hydrophobic drugs showing a fast-dissolving nature. For example, the authors demonstrated the possibility to form stable HPβCD-ICs- and HPγCD-ICs-α-lipoic acid nanofibrous membranes. Owing to the absence of crystallinity, the prepared mats displayed a fast-dissolving nature both in water and artificial saliva, and they were characterized by good mechanical resistance. Similarly, the authors prepared free-standing and flexible HPBCD-ICs-ibuprofen nanofibers achieving the complete inclusion of the drug within the host molecules and a much higher loading concentration compared to PVA/CD-ICs-ibuprofen nanofibers investigated in the same work. Again, metronidazole, a poorly watersoluble drug widely used in pharmaceutical formulations, was encapsulated in polymer-free HPBCD nanofibers via the electrospinning of highly concentrated aqueous solutions. Lately, the authors also reported on the preparation of nanofibrous membranes consisting of the inclusion complex between HPBCDs or HPyCDs and curcumin with a remarkable 100% encapsulation efficiency. Specifically, HPyCD-ICscurcumin nanofibers displayed a much higher water solubility and were almost instantaneously dissolved once in contact with water or artificial saliva. Moreover, the authors were able to prove the enhanced antioxidant properties of the prepared mats compared to pristine curcumin, with similar results reported by

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Aytac et al. (Aytac & Uyar, 2017). In an analogous study, the authors prepared electrospun HPβCD-ICshydrocortisone nanofibers to enhance the water solubility and the bioavailability of the drug obtaining selfstanding and flexible defect-free mats able to completely preserve the drug during the electrospinning process. Additionally, the authors investigated the preparation of nanofibrous mats consisting of the inclusion complex between ferulic acid (FA) and HPβCDs or HPγCDs. Despite both systems allowed to reach a compound content of ~11 wt%, HPyCD-ICs-ferulic acid were found to be much more stable thereby making it possible to obtain amorphous nanofibers with enhanced thermal stability and fast-dissolving nature. Lately, Gao et al. (Gao et al., 2020) prepared HPBCD-ICs-thiabendazole (TBZ) nanofibrous mats to exploit the compound antifungal properties, which are usually limited by its poor solubility. Interestingly, owing to the fast-dissolving nature of the mats, the antifungal properties of the compound were considerably enhanced thereby indicating the possibility to use such systems as a novel pesticide formulation. Yet, Celebioglu et al. (Celebioglu & Uyar, 2020a) demonstrated the possibility to prepare HPβCD-ICs- and HPγCD-ICs-vitamin A acetate nanofibers with self-standing and fast-dissolving nature. In detail, the nanofibers were prepared with a loading concentration of around 5 wt% with the complexation between the HPCDs and the bioactive compound ensuring the fast dissolution both in water and artificial saliva media. Only recently, Celebioglu et al. (Celebioglu & Uyar, 2021) also reported on polymer-free HPβCD-ICs-acyclovir nanofibers. In particular, by using PVP-acyclovir nanofibrous mats as a control sample, the authors proved the greater encapsulation efficiency of the hydrophobic compound within the membranes in the presence of the inclusion complexes. Additionally, Topuz et al. (Topuz et al., 2021) also developed polymer-free HPβCD nanofibers with high antibiotic loadings through the electrospinning of cyclodextrin-antibiotic inclusion complexes from water, and the resultant fast-dissolving fibers demonstrated high antibacterial activity towards Gram-negative bacteria. Remarkably, the possibility to prepare polymer-free cyclodextrin nanofibers at an industrial scale has also been explored, despite only a few works are reported in the literature. In this regard, Vass et al. (Vass et al., 2019) investigated the use of a high-speed electrospinning (HSES) setup to process an aqueous solution of SBEβCD-ICs-voriconazole (VOR). The authors were able to achieve an outstanding production rate of 300 mL/h (i.e., 240 g/h of solid material) under ambient conditions and the grounded fibrous powder showed to

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be rapidly dissolvable in water with similar results to Vfend<sup>®</sup> (i.e., reference commercial pharmaceutical product containing VOR), consequently demonstrating the capability of the proposed approach to fulfil the requirements of the pharmaceutical industry. More recently, the authors also reported on the high-speed electrospinning of HPβCD nanofibers containing β-galactosidase, which is a protein-type drug widely used in pharmaceutical formulations, that were subsequently grounded and converted in tablets for oral assumption with β-galactosidase found to maintain its activity over a period of 6 months (Vass et al., 2020). Similarly, Kiss et al. (Kiss et al., 2020) developed a solid HPβCD-ICs-doxycycline (DOX) intravenous formulation using high-speed electrospinning with a production rate of ~80 g/h (i.e., solid material). The authors proved that the explored inclusion complex allowed the preparation of a DOX formulation with a concentration 7 times higher than the commercially available ones, hence suggesting HSES as an alternative to freeze-drying technique.

Encapsulation for the Fast-dissolution of Volatile Substances

Another important advantage of polymer-free cyclodextrin nanofibers is their ability to encapsulate highly volatile compounds hence preserving their bioactivity over a long period while ensuring their fast administration when required. For example, Celebioglu et al. (Celebioglu, Kayaci-Senirmak, et al., 2016) prepared polymer-free electrospun mats by using the inclusion complexes between vanillin and HPβCDs, HPγCDs, and MβCDs in water, DMF or DMA. The authors demonstrated that MβCDs were more stably linked to vanillin leading to a higher encapsulation efficiency (up to ~12 wt%). Remarkably, compared to pure PVA and PVA/CD-ICs-vanillin nanofibers (Kayaci & Uyar, 2012b), the proposed CD-based mats could encapsulate a considerably higher amount of vanillin and showed strong antioxidant activities, high thermal stability and the possibility to tune their dissolving behaviour. Similarly, Aytac et al. (Aytac, Yildiz, et al., 2017; Aytac, Yildiz, Kayaci-Senirmak, San Keskin, Kusku, et al., 2016) proposed the preparation of polymer-free HPβCD-, HPγCD-, and MβCD-based nanofibrous mats encapsulating the highly volatile limonene or linalool compounds. In both cases, the authors proved MβCD nanofibers to be the most efficient in terms of encapsulation capability. Remarkably, short-term (i.e., 3h) and long-term (i.e., 100 days) release studies demonstrated the stability of the encapsulated compounds within the nanofibrous mats, which

showed strong antibacterial activities against both Gram-positive and Gram-negative bacteria, as well as good manageability and fast-dissolving character in water or high humidity environment. In another study, the authors reported on the encapsulation of citral within HPβCD-, HPγCD- and MβCD-based nanofibers obtaining an 80% encapsulation efficiency and the capability to preserve half of the volatile compound after 15 days, as well as increasing both its thermal stability and water solubility (Aytac, Celebioglu, et al., 2018). Comparably, fast-dissolving polymer-free HPBCD-ICs- and HPyCD-ICs-carvacrol nanofibers with potential applications as food or oral care products were reported by Yildiz et al. (Zehra I. Yildiz et al., 2018). Besides the high encapsulation efficiency, the carvacrol complexation enhanced its thermal stability and antioxidant properties for up to three years. In a similar study, the authors explored the preparation of polymer-free CD-ICs-menthol nanofibers by using highly concentrated HPβCD-IC and HPγCD-IC aqueous solutions (Zehra Irem Yildiz et al., 2018). The stable complexation of menthol, a volatile substance with strong antibacterial properties widely used in several applications, led to an increase of the compound solubility and thermal stability while allowing to obtain homogenous and smooth nanofibers with good flexibility and a fastdissolving character. The developed mats endorsed to encapsulate a much higher amount of menthol, which was also stable over a long period, compared to polystyrene (PS)/CD-ICs-menthol (Uyar, Hacaloglu, et al., 2009) and polymethylmethacrylate (PMMA)/CD-ICs-menthol (Uyar, Nur, et al., 2009) nanofibers. Also, Celebioglu et al. (Celebioglu, Yildiz, et al., 2018a) prepared HPβCD-ICs- and HPγCD-ICs-based electrospun mats containing cineole or p-cymene. HPyCD-based nanofibers were able to encapsulate a greater amount of cineole, whereas p-cymene was better preserved by the HPBCD-based ones. However, both mats improved the compound thermal stability consequently representing potential products in food and oral care applications. Yet, the authors investigated the preparation of free-standing nanofibrous mats obtained via the electrospinning of HPβCD-ICs-, HPγCD-ICs-, and MβCD-ICs-eugenol or thymol (THY) systems (Celebioglu, Yildiz, et al., 2018b, 2018c). The complex formation within the nanofibers allowed to reach an encapsulation efficiency considerably higher compared to analogous PVA/CDs-ICs-eugenol nanofibers (Kayaci, Ertas, et al., 2013). Additionally, owing to their fast-dissolving nature, CD-ICs-eugenol and CD-ICs-thymol nanofibers showed much stronger antioxidant properties compared to the pure compounds. In another work, cinnamaldehyde was successfully encapsulated in self-standing HPβCD- and HPγCD-based

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nanofibers by Yildiz et al. (Zehra I. Yildiz et al., 2019). Bead-free and homogeneous nanofibers were obtained with considerably higher efficiency in preserving the volatile cinnamaldehyde compared to analogous PLA-based nanofibers (Y. Liu et al., 2017). Moreover, owing to their fast-dissolving nature, the prepared mats displayed strong antibacterial properties against E. Coli representing a new potential class of materials for applications in both the food, biomedical and pharmaceutical industries.

#### Encapsulation of Living Bacteria

Keskin et al. (San Keskin et al., 2018) demonstrated the possibility to encapsulate living bacteria within electrospun HPβCD-based nanofibers to increase their availability for wastewater bioremediation applications. Despite the encapsulation efficiency was not particularly high, a sufficient amount of bacteria was preserved during the preparation process with the cell viability maintained for 7 days. Remarkably, the used bacteria retained their bioactivity and were proved able to remove Ni(II), Cr(VI) and a commercial reactive dye from aqueous solutions. Such findings indicated the proposed approach as a faster and simpler alternative to the lyophilization procedure commonly applied to preserve organisms for strain collections and applications in dye removal products.

#### 4.2.3 Applications in Air and Water Filtration

The capability of cyclodextrins and their derivatives to form stable non-covalent inclusion complexes with a variety of molecules makes them extremely interesting for the removal of several pollutants from the environment. Furthermore, nanofibrous electrospun membranes represent a class of materials with superior adsorption capabilities owing to their unique structure, which allows exploiting a higher surface of interaction between the adsorbent and the adsorbate. With these premises, in the past decade, intensive research has been carried out to develop efficient filter materials based on polymer-free cyclodextrin nanofibers aiming to maximize the adsorption capability. Celebioglu et al. (Celebioglu & Uyar, 2013b) first reported on the electrospinning of pristine  $\gamma$ CDs in dimethyl sulfoxide (DMSO) aqueous solutions to be used for the entrapment of volatile organic compounds (VOCs). The obtained electrospun mats were completely amorphous and presented, above all, a surface area three times higher than their powder form according to

BET analysis. Aniline and toluene volatile organic compounds were used to test the adsorption ability of  $\gamma$ CD nanofibers that showed a marked complexation capability compared to  $\gamma$ CD powder. Similarly, the authors also investigated the possibility to use HP $\beta$ CD- and HP $\gamma$ CD-based nanofibers as filter materials (Celebioglu, Sen, et al., 2016). Polymer-free electrospinning of CDs was carried out in water and DMF obtaining defect-free mats with a considerably higher surface area with respect to CD powders. DMA characterization was employed to demonstrate the good mechanical properties and integrity of the obtained mats, which were indicated as potentially foldable materials to be inserted in air filter modules. Recently, Topuz et al. (Topuz et al., 2020) reported on hydrophobic water-insoluble nanofibers obtained from the polymer-free electrospinning of peracetylated  $\beta$ -cyclodextrins. Native  $\beta$ CDs were first modified and subsequently electrospun by using a DMF solution, whose minimum concentration to obtain defect-free nanofibers was  $\sim$ 64 wt% (i.e., 180 w/v). The peracetylation procedure drastically boosted the thermal stability and the hydrophobicity of the obtained nanofibers, which were indeed being proved to maintain their nanofibrous structure in water for 24h.

#### 4.2.4 Other Applications

Despite the capability to form inclusion complexes that remains one of the most interesting and exploited properties of cyclodextrins, other promising applications have been considered as well. For example, their use for the easy synthesis of metal nanoparticles have been also investigated (He et al., 2019; Prochowicz et al., 2016, 2017). CDs can indeed directly act as reducing agents for metal ions without the need for toxic chemicals or severe processing conditions, hence allowing the development of environmentally benign materials with unique features and a wide range of possible applications (Celebioglu, Aytac, et al., 2014; Shan Wang, Bai, Li, & Zhang, 2012; Shan Wang, Bai, Li, Zhang, et al., 2012). Celebioglu et al. (Celebioglu & Uyar, 2013c) first proposed the one-step in-situ synthesis of gold nanoparticles (Au-NPs) via the electrospinning of HPβCD solutions containing an appropriate salt precursor. The authors exploited the capability of CDs to act as reducing and stabilizing agents, as well as fibrous matrix supporting material, to synthesize Au-NPs directly during the electrospinning process. Subsequently, the authors reported on the preparation of HPβCD nanofibers containing in-situ synthesized silver nanoparticles (Ag-NPs) produced by

a single-step electrospinning process (Celebioglu, Topuz, Yildiz, et al., 2019b). The authors observed that DMF solution led to thinner nanofibers compared to water, besides an increase of the mean diameter was observed for both solvents by increasing the amount of loaded Ag salt precursor, as similarly reported by Chae et al., (Chae et al., 2011). TEM images revealed that Ag-NPs having a size between 2 and 5 nm were successfully embedded within the nanofibers, with their dimension being a function of the precursor amount and solvent type. Owing to the nanoparticle presence, the prepared nanofibers showed strong antibacterial properties against E. Coli and S. Aureus bacteria over a period of 24h, thus being suitable also for biomedical and food packaging applications. Yet, the authors proposed HPBCD nanofibers loaded with palladium nanoparticles (Pd-NPs) (Celebioglu, Topuz, & Uyar, 2019a). Cyclodextrin solutions in water and DMF containing an appropriate precursor were electrospun leading to bead-free nanofibers. Pd-NPs were homogeneously distributed within the nanofibers and showed a dimension ranging from 3 up to 5 nm that increased with the precursor loading concentration and was bigger for DMF compared to water. Moreover, HPβCD/Pd-NP nanofibers showed strong catalytic performances being able to reduce p-nitrophenol (PNP) in few minutes into p-aminophenol (PAP), thus showing great potentialities for the development of products for catalytic applications. Cyclodextrin-based nanofibers, owing to their fast-dissolving character in water, can be even employed as sacrificial templates for the development of hollow nanofibers. To this purpose, Celebioglu et al. (Celebioglu, Vempati, et al., 2014) reported on polymer-free cyclodextrin nanofibers (i.e., HPβCDs and MβCDs) as a sacrificial pattern for the preparation of metal oxide nanotubes via atomic layer deposition (ALD). The authors proved the possibility to deposit a layer of aluminium oxide (Al<sub>2</sub>O<sub>3</sub>) or zinc oxide (ZnO) on the nanofiber surface to obtain a core-shell structure, subsequently removing the cyclodextrin core by a simple washing process in water. The presence of -OH groups was found to promote the smooth and homogeneous deposition as shown by SEM images, whereas TEM analysis indicated that Al<sub>2</sub>O<sub>3</sub> and ZnO maintained an amorphous and highly crystalline nature with wurtzite structure. Despite such an approach remains at a preliminary stage, the obtained findings indicated that the use of water-soluble CD nanofibers could lead to the simple and cost-effective preparation of metal oxide nanotubes with possible energy storage applications (Yun et al., 2020).

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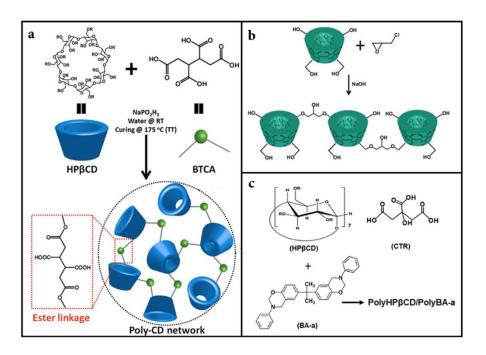
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#### 5 Water-insoluble Crosslinked Polycyclodextrin Nanofibers

The high surface area of cyclodextrin-based electrospun mats and their unique inclusion complexation capability make such systems very promising for wastewater purification applications, as well as for implantable biomedical devices. However, as broadly discussed in the previous Section, their high solubility and fast-dissolving features in aqueous environments represent a limitation to their proficient use for such applications. Therefore, the development of crosslinked cyclodextrin-based systems has started to be explored in the viewpoint to fabricate insoluble and highly performing systems. However, as summarized in Table 1, only a few studies are reported in the literature and further research are needed to investigate eventual toxicity issues related to the crosslinking reaction. Figure 5 depicts some of the most commonly employed crosslinking approaches for cyclodextrins.



**Figure 5.** Schematics of different crosslinking strategies of the cyclodextrin nanofibers. The crosslinking agents are added to the CD solution prior to electrospinning and a curing step initiate the reaction in the final membrane. Reaction of CDs with (a) 1,2,3,4-butanetetracarboxylic acid (BTCA) (reproduced with permission from Celebioglu et al., 2017. © The Author(s) 2017), (b) epichlorohydrin (ECH) (reproduced with permission from Celebioglu, Topuz, & Uyar, 2019b. © 2018 American Chemical Society), and (c) citric acid (CTR) and benzoxazine (BA-a) monomers (reproduced with permission from Dogan et al., 2019. © 2019 Elsevier Ltd.

#### 5.1 Water Purification Applications of polyCD Nanofibers

Celebioglu et al. (Celebioglu et al., 2017) first demonstrated the possibility to prepare crosslinked electrospun poly-cyclodextrin nanofibers as highly efficient molecular filter materials. By using

butanetetracarboxylic acid (BTCA) as crosslinker (Figure 5a), the authors avoided the fast dissolution of the prepared polyHPβCD nanofibers while maintaining their high hydrophilicity. In particular, polyHPβCD nanofibers were characterized by a good affinity with methylene blue (MB) having an extremely high adsorption capacity at dye concentration well above the acceptable limits, showing improved performances compared to an acetate cellulose commercial filter and similar polyacrylonitrile (PAN)/CD nanofibers (W. Zhang et al., 2019). Moreover, the authors were able to prove both their reusability via a simple, fast, and cost-effective washing cycle and their applicability in a real water filtration apparatus. Similarly, Dogan et al. (Dogan et al., 2019) reported on polyHPβCD/poly-benzoxazine (polyBA-a) nanofibers as potential dye adsorbents by using citric acid (CTR) as crosslinker and activating the crosslinking reaction via a simple thermal treatment (Figure 5c). The authors proved that the crosslinked mats were able to withstand several washing cycles with both water and organic solvents showing enhanced thermal stability, hence representing promising products for filtration applications. Noticeably, the obtained mats were tested against a mixture of methylene blue and methyl orange (MO) dyes exhibiting a strong selectivity towards MB being able to nearly completely remove the dye in a period of 6h. Yet, Celebioglu et al. (Celebioglu, Topuz, Yildiz, et al., 2019a) evaluated the possibility to use the polyHPβCD nanofibers crosslinked with BTCA as filter materials for the removal of several polycyclic aromatic hydrocarbons (PHAs) and heavy metals from water obtaining interesting equilibrium adsorption capabilities and the ability to reduce to half the contaminant amount in only 20 minutes. Interestingly, the proposed mats could be recycled four times by a simple treatment with acetonitrile or with a nitric acid solution without showing changes in their morphology and adsorption capability. Also, the authors recently reported on water-insoluble polyHPβCD nanofibers obtained by using epichlorohydrin (ECH) as crosslinker agent (Figure 5b) (Celebioglu, Topuz, & Uyar, 2019b). The rheological investigation of HPβCD/ECH aqueous solutions showed that the reaction partially initiated prior to the electrospinning, despite a post-preparation thermal treatment was the main responsible for the process. The obtained polyHPβCD nanofibers were proved to be highly hydrophilic, nearly completely amorphous, with enhanced thermal stability, and were above all able to maintain their structure after the immersion in water and several organic solvents. The authors investigated the scavenging ability of the crosslinked nanofibers against phenolphthalein and phenanthrene in their aqueous solutions proving that the prepared

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nanofibers showed enhanced adsorption capabilities compared to polyHP $\beta$ CD powder and analogous poly(ethylene terephthalate) (PET)/CD nanofibers (Kayaci, Aytac, et al., 2013).

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#### 5.2 Biomedical Applications of polyCD Nanofibers

Hamsici et al. (Hamsici et al., 2017) proposed water-insoluble HPβCD aligned nanofibers functionalized with bioactive peptides as implantable scaffolds for peripheral nerve regeneration. The highly aligned nanofibers were first prepared and crosslinked via BTCA before being functionalized with IKVAV or KK peptides with a simple impregnation procedure. PolyHP\u00e3CD-ICs-peptide nanofibers did not show toxicity issues and provided the optimal environment to promote cell adhesion, differentiation and proliferation. Specifically, the peptide presence on the nanofiber surface was found to guide the differentiation to PC-12 cells compared to unfunctionalized membranes, whereas the aligned topological arrangement was proven to help the formation of longer neurites compared to the randomly structured samples. In another work, Heydari et al. (Heydari et al., 2018) prepared hydrophobic peracetyl-βCD nanofibers loaded with vitamin B<sub>2</sub> (VB<sub>2</sub>) by the electrospinning of an acetone/DMF solution. HPBCDs were subjected to crosslinking and peracetylation reactions before being electrospun together with VB<sub>2</sub> leading to bead-free homogeneous nanofibers. PolyHPβCD-ICs-VB2 nanofiber release kinetic was studied in simulated gastric and intestinal conditions showing an initial burst release followed by a sustained slow release for 16h. Compared to HPβCD-ICs-VB<sub>2</sub> powder, the prepared mats displayed a considerably slower and more controlled release of vitamin B<sub>2</sub>, thus representing an important advancement in the development of a new class of controlled drug delivery systems.

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# 6 Electrospun Membranes Made of Natural Polymers Functionalized with Cyclodextrins and Their

#### **Inclusion Complexes**

Together with polymer-free CDs and polyCDs nanofibers, electrospun mats containing cyclodextrins have also been prepared from both native CDs and their derivatives in combination with a broad variety of carrier polymers able to provide a good spinnability and very specific properties of the mats depending on the targeted application (Costoya et al., 2017; Topuz & Uyar, 2019). The use of CDs to functionalize nanofibers

offers a wide number of advantages and represents a more and more investigated research field owing to the wide range of possibilities of the obtained products. The ability of CDs to complex hydrophobic compounds and volatile molecules represents the opportunity to enhance their encapsulation efficiency, stability, solubility and bioavailability, as well as provide them with controlled release kinetics. For example, such materials can be used as implantable scaffolds enriched with growth factors and vitamins, pharmaceutical formulations containing poorly soluble drugs, highly performing filters for wastewater and volatile organic compounds, and active food packaging materials with antibacterial and antioxidant properties (Alvarez-Lorenzo et al., 2017; Celebioglu, Sen, et al., 2016; Hall Barrientos et al., 2017; Lin et al., 2017; Moyers-Montoya et al., 2016; Wen, Zhu, Feng, et al., 2016). Several approaches are reported in the literature to prepare cyclodextrin-functionalized electrospun nanofibers with some of them schematically illustrated in Figure 6. The simplest one consists of adding to a proper polymer solution the CDs or the CD-ICs of interest, with the latter usually prepared by precipitation or freeze-drying methods (Beachley & Wen, 2010; Meinel et al., 2012). A faster alternative, which is however less applied owing to the difficulty in accurately control the guest molecule loading concentration, consists of the direct mixing of all the components (i.e., polymer, cyclodextrins, drug or bioactive compound, etc.) (Narayanan et al., 2017). Another possibility is represented by the electrospinning of a polymer-cyclodextrins mixture with the a posteriori loading of the guest molecules of interest usually via a solution impregnation method (Séon-Lutz et al., 2019). Yet, polymer nanofibers can be functionalized by grafting their surface with CDs or CD-ICs via a chemical reaction, therefore obtaining a high surface reactivity (Wu et al., 2015; Yuan et al., 2017). Similarly, CDs and their derivatives can be directly employed as a crosslinker for the polymer chains, thus acting as stabilizing agents and reducing the nanofiber solubility (Boas et al., 2015; L. Li & Hsieh, 2005). Alternatively, CDs and their complexes can be completely embedded within the nanofibers by employing a coaxial set-up producing core-shell nanofibers (Chou et al., 2015). Finally, it should be kept in mind that CDs and CD-ICs, when mixed with a polymer in a liquid solvent, can thread along the polymer chains forming polypseudorotaxanes. These can assemble in supramolecular structures where the interactions between CDs play a fundamental role in conditioning the spinning solution properties (Uyar et al., 2008) and bring grafting sites for nanofiber post-functionalization (M. Oster et al., 2017; Murielle Oster et al., 2015).

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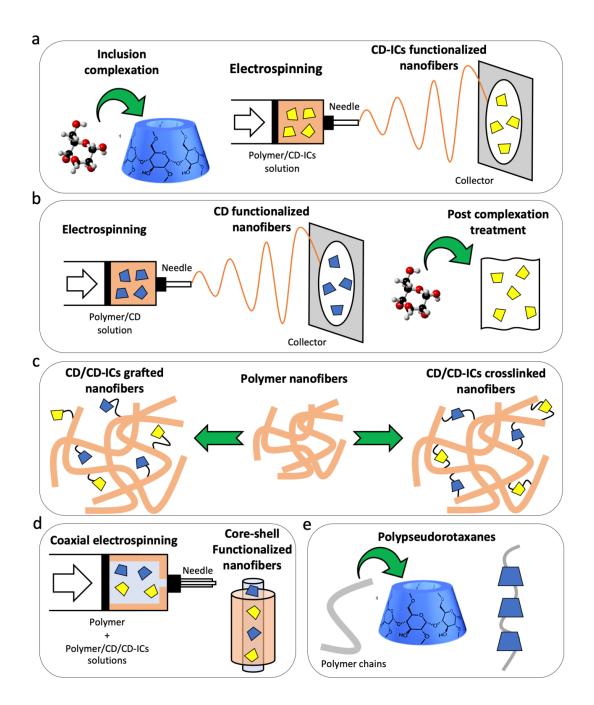
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**Figure 6.** Schematics of preparation methods for cyclodextrin-functionalized nanofibers. (a) Electrospinning of polymer/CD-ICs solutions, (b) electrospinning of polymer/CDs/active compound solutions, (c) CD/CD-ICs grafted or CD/CD-ICs crosslinked nanofibers, (d) coaxial electrospinning of CD/CD-ICs core functionalized nanofibers, and (e) pseudopolyrotaxanes structures.

To date, both synthetic and natural polymer-based nanofibers have been functionalized with cyclodextrins and their derivatives with their advantages and disadvantages. Along with the fact that most natural polymers can be processed in green solvents under mild working conditions, their main advantages are enhanced biocompatibility, biodegradability and the possibility to be obtained from agricultural and food wastes with the development of green and circular economy products. Thereby, it is much likely that natural polymer-

based electrospun membranes functionalized with cyclodextrins will soon represent a new class of environmentally friendly materials with potential applicability in a wide range of markets. In the next two subsections, the current literature about polysaccharide- and protein-based functionalized electrospun membranes is critically discussed by highlighting the recent advances.

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#### 6.1 Electrospun Polysaccharide – Cyclodextrin Based Membranes

Polysaccharides are a family of natural polymers consisting of multiple saccharide units linked together through glycosidic linkages and possess a wide variety of unique properties which make them extremely interesting from an industrial point of view (Cazón et al., 2017; Dodero, Lova, Vicini, Castellano, et al., 2020; Y. Yu et al., 2018). Most polysaccharides can be easily and cheaply recovered from natural sources such as plants, microbes, and animals, with their use being especially profitable when they are by-products of other processes (Dodero, Vicini, & Castellano, 2020; Hamed et al., 2016; Sila et al., 2014). Compared to other natural polymers, polysaccharides are usually more stable and not irreversibly denatured upon heating and can consequently be used as an effective shell to confer enhanced temperature stability to a variety of bioactive compounds. Moreover, polysaccharides show a broad range of interesting properties such as biocompatibility, low toxicity, mucoadhesive behaviour, biodegradability, and ease of functionalization, hence being nowadays widely employed in several industrial fields (Öner et al., 2016). Regardless of their advantages, the electrospinning of polysaccharides remains a challenge due to their tendency to form strong hydrogen bonds that lead to high viscous solutions or even gels, the small number of entanglements formed between the polymer chains, the high solution surface tension, and the poor water stability of the obtained mats (Dodero, Vicini, et al., 2019; Mendes et al., 2017). For example, Dodero et al. reported on the preparation of sodium alginate (SA) (Dodero, Alloisio, Vicini, & Castellano, 2020; Dodero, Donati, et al., 2021; Dodero, Scarfi, Pozzolini, Vicini, et al., 2020) and chitosan (CH) (Dodero, Brunengo, Alloisio, Sionkowska, et al., 2020; Dodero, Scarfi, et al., 2021) crosslinked electrospun membranes by using poly(ethylene oxide) (PEO) as a co-spinning agent, which was then removed by a simple postelectrospinning washing cycle. In another work, Séon-Lutz et al. (Séon-Lutz et al., 2019) proposed the electrospinning of hyaluronic acid (HA)/PVA solutions being able to decrease the co-spinning agent concentration compared to other similar works reported in the literature (J. Li et al., 2006), whereas Vicini et

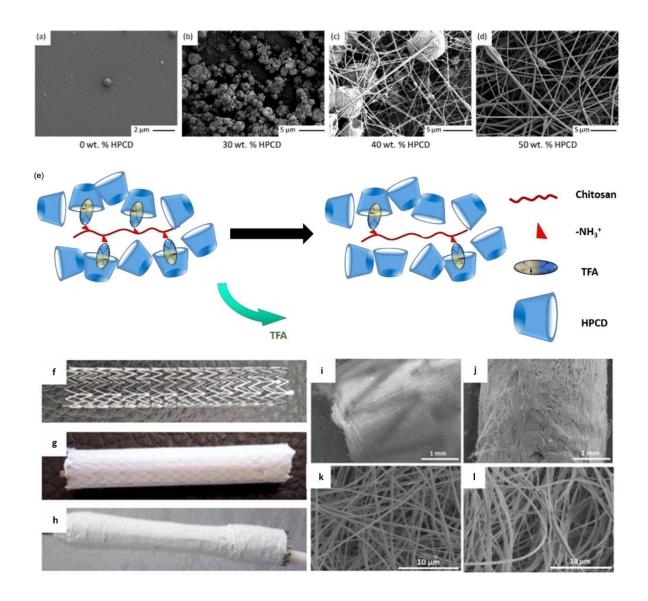
al. (Vicini et al., 2018) used a bath collector electrospinning to obtain crosslinked composite alginate/hyaluronic acid/PEO membranes. Similarly, Ge et al. (Ge et al., 2012) and Huang et al. (X. J. Huang et al., 2007) reported on chitosan/PVA electrospun membranes for the encapsulation of bioactive compounds, whereas pullulan (PUL)/PVA nanofibers with UV-resistant properties were obtained by Qian et al. (Qian et al., 2016). Compared to pure polysaccharide nanofibrous membranes, cyclodextrin-functionalized polysaccharide nanofibers offer several advantages that will be deeply discussed in this section with a complete and up-to-date summary of the literature reported in Table 2.

Table 2. Comprehensive summary of polysaccharide-based electrospun membranes functionalized with CDs or CD-ICs and their main applications.

Polysaccharide	Cyclodextrins	Encapsulated bioactive molecules	Application	Ref.	
			Cyclodextrin grafted nanofibers for effluent dye removal	(Norouzi et al., 2012)	
Chitosan -	βCDs	Cinnamon and oregano essential oils	Nanofibrous membranes with strong antibacterial properties for biomedical and food packaging applications	(Munhuweyi et al., 2018)	
	CMβCDs	Salicylic acid	Cyclodextrin grafted nanofibers as drug delivery systems with tuneable release kinetics	(Bazhban et al., 2013)	
	HPβCDs		Fundamental study of the effect of CDs on chitosan solution spinnability	(Burns et al., 2015; C. Xue & Wilson, 2019)	
	Poly-HPβCDs	Triclosan Poly-HPβCDs		Biomedical and food packaging products with improved water stability, tenable release kinetics and antibacterial properties	(Ouerghemmi et al., 2016)
		-		Simvastatin	Angioplasty bare metal stent covering layer for restenosis prevention
	0CD-	0CD-	Limonene, Perillaldehyde	Edible food packaging products with antibacterial properties, high	(Fuenmayor et al., 2013;
βCDs  Pullulan  γCDs	pCDs	Emionene, remaidenyde	stability and humidity triggered release behaviour	Mascheroni et al., 2013)	
	γCDs	Eugenol	Biomedical and food packaging products with enhanced release and antioxidant properties	(Celebioglu & Uyar, 2020f)	
		N-halamine copolymers	Biomedical and food packaging products with biocidal properties	(R. Li et al., 2014)	
	βCDs	Ag/Fe-NPs	Filter materials embedding in-situ synthesized metal nanoparticles for wastewater purification	(Nthunya et al., 2017)	
Cellulose acetate			Odour adsorbent filter materials for oil and fat derived volatile compounds	(Ghorani et al., 2019)	
			Cyclodextrin grafted nanofibers for the removal of phenanthrene	(Celebioglu, Demirci, et al., 2014)	
			Cyclodextrin grafted nanofibers as filter materials for toluene in wastewater	(Yuan et al., 2017)	
		Tetrafluoroterephthalonitrile	Cyclodextrin grafted nanofibers for the removal of bisphenol pollutants	(Y. Lv et al., 2021)	

		Thymol	Porous nanofibers with antibacterial properties and drug delivery capabilities for biomedical applications	(Yajun Chen et al., 2020)
	αCDs		Cyclodextrin grafted nanofibers as filter materials for toluene in wastewater	(Yuan et al., 2017)
	γCDs		Cyclodextrin grafted nanofibers as filter materials for toluene in wastewater	(Yuan et al., 2017)
Hydroxypropyl cellulose	HPβCDs	Sulfisoxazole	Drug delivery systems with enhanced release abilities	(Aytac et al., 2015)
Almond gum	βCDs	Curcumin	Drug delivery systems with enhanced encapsulation capabilities for oral and gastrointestinal formulation dosages	(Rezaei & Nasirpour, 2019)
Hyaluronic acid	HPβCDs	Naproxen	Wound dressing patches with controlled drug delivery abilities enhanced water-stability	(Séon-Lutz et al., 2019)
Dandelion	βCDs	Litsea Cubeba essential oils	Membranes with strong antibacterial properties for biomedical and food packaging purposes	(Cui et al., 2019)

Chitosan (CH) is a polysaccharide derived from the partial deacetylation of chitin, the second most abundant biopolymer in nature after cellulose and widely present in the exoskeleton of shellfish and fungi organisms. Owing to its unique properties and wide availability, chitosan has been recognized as one of the most promising materials of the future to substitute synthetic polymers (Riaz Rajoka et al., 2019). The first study concerning chitosan nanofibers functionalized with cyclodextrins can be attributed to Norouzi et al. (Norouzi et al., 2012) who reported on chitosan/PVA electrospun membranes grafted with β-cyclodextrins for the efficient dye removal from effluents. After a crosslinking procedure carried out with glutaraldehyde vapours, the prepared samples were able to retain their nanofibrous structure for a long time during which they showed a surprisingly high uptake capacity. Similarly, Bazhban et al. (Bazhban et al., 2013) prepared chitosan/PVA electrospun membranes grafted with carboxymethyl-β-cyclodextrins (CMβCDs) as drug delivery systems demonstrating a slower release compared to the correspondent polymer films. Subsequently, Burns et al. (Burns et al., 2015) tried to understand the effect of HPβCDs on the electrospinning process of chitosan solutions in acetic acid (AA) and trifluoroacetic acid (TFA). The authors observed a strong improvement in the processability of CH solutions enriched with HPβCDs with more homogeneous nanofibers obtained by increasing the cyclodextrin concentration as shown in Figure 7a-d.



**Figure 7.** Fiber morphology of chitosan-based electrospun mats with an increasing HPβCD content: (a) 0 wt%, (b) 30 wt%, (c) 40 wt%, and (d) 50 wt%. Reproduced with permission from Burns et al., 2015. © The Royal Society of Chemistry 2015. (e) Schematic illustration of CH/HPβCD electrospun nanofiber composition. Reproduced with permission from C. Xue & Wilson, 2019. (f) Macroscopic and microscopic images of Nitinol stent covered with CH/polyHPβCD-ICs-simvastatin nanofibers before (g, i, k) and after crimping (h, j, l). Reproduced with permission from Kersani et al., 2020. © 2020 Elsevier B.V.

Such findings were attributed to the formation of a stable inclusion complex between the hydrophobic cavity of cyclodextrins and chitosan amine groups. More recently, Xue et al. (C. Xue & Wilson, 2019) carried out a solid-state spectroscopic and thermal study on CH/HP $\beta$ CD electrospun nanofibers obtained using TFA as solvent. On the contrary to what reported by Burns et al. (Burns et al., 2015), it was suggested that the enhanced processability of chitosan solutions was likewise related to the formation of a ternary complex between CH, HP $\beta$ CDs, and TFA with the solvent molecules acting as bridges, as schematically depicted in Figure 7e. By Raman imaging, the authors were able to prove the absence of direct interactions between

chitosan and cyclodextrins opening the way to the development of new supramolecular structures. Along with these preliminary studies, Ouerghemmi et al. (Ouerghemmi et al., 2016) prepared chitosan electrospun membranes containing the inclusion complexes between polyHPβCDs and triclosan. Compared to pristine HPβCDs, polyHPβCDs provided a higher encapsulation capability and led to the formation of a polyelectrolyte complex with chitosan enhancing the water-resistance to the nanofibers. With respect to chitosan nanofibers functionalized with HPBCD-ICs-TCL or free TCL, CH/polyHPBCD-ICs-TCL mats showed a slower release over a longer period both at pH = 7.4 and pH = 5.5 conditions. Moreover, the authors proved that the mats were embedded with strong antibacterial activities remarkably higher in terms of growth inhibition zone compared to those of similar synthetic products (Kayaci, Umu, et al., 2013; Tonelli, 2008), thus making them suitable candidates for both biomedical and food packaging applications. Yet, Munhuweyi et al. (Munhuweyi et al., 2018) reported on the encapsulation of cinnamon and oregano essential oils in CH/PVA nanofibers embedding βCDs. Owing to the great encapsulation efficiency, which was much higher compared to PLA-, PVA-, and PCL-based nanofibers containing cinnamon oil (Amiri & Rahimi, 2019; Pan et al., 2019; Wen, Zhu, Feng, et al., 2016; Wen, Zhu, Wu, et al., 2016), the proposed CH/PVA/BCD-ICs-cinnamon mats showed particularly marked antibacterial properties against Botrytis sp. bacteria, hence representing interesting materials especially for food packaging applications. Recently, Kersani et al., (Kersani et al., 2020) developed a bare-metal stent for angioplasty covered by an electrospun layer of chitosan/polyHPβCD-ICs-simvastatin (SV) drug as an efficient tool for restenosis prevention represented in Figure 7a. Compared to the nanofibers loaded with free SV or embedding HPBCD-ICs-SV, the use of polyHP\u00e3CDs highly improved the drug loading efficiency leading to a much more prolonged and controlled release from the mats. Additionally, the release of simvastatin was found to be tuneable by simply changing the sample thickness or the initial loading concentration indicating the possibility to accurately personalize the system depending on the patient requirements. Pullulan (PUL) is a water-soluble extracellular polysaccharide obtained from fermentation processes and exploited in the manufacturing of edible films, as well as in several biomedical and pharmaceutical oral care applications (Prajapati et al., 2013). In this regard, Fuenmayor et al. (Fuenmayor et al., 2013) developed edible nanofibrous membranes by single-step electrospinning of a pullulan/βCD aqueous solution containing

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R-(+)-limonene, which was found to be stable over a long time with its release occurring only at high water activity values (a<sub>w</sub>) hence making the prepared mats suitable for fresh food packaging products. Similarly, Mascheroni et al. (Mascheroni et al., 2013) investigated the encapsulation of the volatile compound perillaldehyde, an aroma largely employed in the food industry, within a pullulan electrospun matrix containing BCDs. No evident losses of the aroma compound were observed over several months at ambient conditions with the release occurring exclusively for a<sub>w</sub> > 0.9. Lately, Celebioglu et al. (Celebioglu & Uyar, 2020f) reported on pullulan nanofibers embedding  $\gamma$ CD-ICs-eugenol able to almost preserve the volatile compound with an encapsulation efficiency of ~93%, which was considerably higher with respect to pullulan/eugenol nanofibers (i.e., ~23%). Moreover, the complexation increased the thermal stability of eugenol, whereas its antioxidant properties were substantially enhanced and remained unvaried over a period of 3 months. Cellulose acetate (CA) is one of the most important derivatives of cellulose and it is widely employed as a film base for photography, vapour sensors, optical materials, and to produce synthetic fibers for textile applications owing to its renewable source, biodegradability, non-toxicity and low cost (Candido & Gonçalves, 2016; Lova et al., 2018, 2019; Ummartyotin & Manuspiya, 2015). Li et al. (R. Li et al., 2014) prepared CA nanofibrous membranes embedding βCD inclusion complexes with an ad hoc synthesized Nhalamine copolymer as promising candidates for biomedical and food packaging applications with strong biocidal properties against both Gram-positive and Gram-negative bacteria. Aiming to the efficient removal of bacteria from drinking water, Nthunya et al. (Nthunya et al., 2017) investigated the possibility to prepare cellulose acetate/β-cyclodextrin membranes embedding in-situ synthesized metal nanoparticles. Ag/Fe nanoparticles were here prepared via a green UV photoreduction process under ambient conditions and enriched the mats with strong antibacterial properties against several bacteria strains thus making them a valid alternative for water purification purposes. More recently, Ghorani et al. (Ghorani et al., 2019) developed CA nanofibers embedding βCDs as odour adsorbent filter materials by selecting acetone:DMF (2:1) as the most appropriate solvent system to obtain a considerably high production rate suitable for industrial applications. Above all, the proficiency of the prepared mats to adsorb hexanal molecules, which are a marker for oil and fat oxidation, suggested their suitability for filtration purposes. While the previously mentioned works consist in the direct electrospinning of CA/CD solutions, a different approach was first

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proposed by Celebioglu et al. (Celebioglu, Demirci, et al., 2014) who reported on cellulose acetate nanofibers grafted with βCDs via a simple "click" reaction carried out to avoid leaking issues. The grafted membranes were tested as potential molecular filters for water purification purposes showing greater adsorption capability in removing phenanthrene compared to the pristine CA nanofibers, as well as respect to comparable PET/CD nanofibers (Kayaci, Aytac, et al., 2013). Similarly, Yuan et al. (Yuan et al., 2017) investigated the possibility to use regenerated cellulose (RC) nanofibers functionalized with αCDs, βCDs or γCDs via physical mixing or grafting reaction for the removal of toluene residues from wastewater. Each type of CD led to homogenous nanofibers with the grafting approach enriching the mats with considerably higher adsorption capability compared to the works of Kayaci et al., (Kayaci et al., 2015) and Uyar et al. (Uyar et al., 2010). Yet, Chen et al. (Yajun Chen et al., 2020) reported on the development of hierarchical CA nanofibers embedding the inclusion complex between  $\beta$ CDs and thymol. The proposed membranes showed a prolonged release resulting in marked antibacterial properties, mechanical properties suitable for wound dressing applications, and excellent cytocompatibility. Lately, Lv et al. (Y. Lv et al., 2021) prepared β-cyclodextrin cellulose acetate nanofibers for the removal of bisphenol pollutants from water. The authors first modified native βCDs with tetrafluoroterephthalonitrile (TF) by a simple chemical treatment before grafting them onto the CA mats to enhance the pollutant adsorption efficiency. The obtained products showed a highly porous morphology, a stable crystal structure, and excellent thermal stability, as well as the abundance of surface functional groups. Noticeably, the authors demonstrated the capability of the proposed nanofibers to efficiently act as adsorbent materials in a broad range of conditions for several cycles indicating their suitability for practical applications. Hydroxypropyl cellulose (HPC) is another cellulose derivative showing good solubility in both water and organic solvents and mainly used as an excipient, lubricant and ophthalmic protectant owing to its thermoand pH-responsive properties (Qiu & Hu, 2013; Yang & Li, 2018). In this regard, Aytac et al. (Aytac et al., 2015) presented the preparation of HPC nanofibers functionalized with the inclusion complex between hydroxypropyl-\(\beta\)-cyclodextrin and sulfisoxazole (SFS) for drug delivery applications by developing sandwich-like multilayer materials. Compared to nanofibers containing the free drug, HPC/HPβCD-ICs-SFS

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730 inclusion complexation. 731 Almond gum (ALG) is a natural gum copiously exuded from the trunk, branches, and fruits of Prunus 732 amygdalus trees after mechanical injury and/or infection by microorganisms. Almond gum represents an 733 important waste product in several developing countries and, owing to its antibacterial and antioxidant 734 activities, could be successfully employed as a green alternative to several synthetic materials (Bouaziz et al., 735 2017). The release mechanism of curcumin from almond gum/PVA/βCD-ICs-curcumin electrospun 736 membranes in simulated saliva and gastrointestinal conditions was investigated by Rezaei et al. (Rezaei & 737 Nasirpour, 2019). Compared to the nanofibers loaded with free curcumin, the presence of βCD-curcumin ICs 738 allowed to reach a much higher compound encapsulation efficiency (i.e., > 90%) and enriched the 739 membranes with a greater and faster release, thus proving the possibility to use almond gum-based 740 composite nanofibers as efficient drug delivery systems. 741 Hyaluronic acid (HA) is an anionic polysaccharide present in several human tissues with unique physical-742 chemical properties and a wide range of important biological functions, including cell signalling, wound 743 reparation, tissue regeneration, morphogenesis, matrix organization and pathobiology (Dodero, Williams, et 744 al., 2019; Fallacara et al., 2018). Séon-Lutz et al. (Séon-Lutz et al., 2019) reported on the preparation of HA-745 PVA membranes functionalized with HPβCDs for wound dressing applications using only water as solvent. 746 The membranes were thereafter crosslinked with a carbodiimide and N-hydroxysuccinimide ensuring thus a 747 completely green process of fabrication. The authors proved that the use of HPBCDs stabilized the 748 electrospinning process owing to their capability to establish intermolecular interactions with HA and PVA. 749 thus allowing to noticeably reduce the minimum concentration of co-spinning agent (i.e., PVA). More 750 importantly, naproxen (NAP) drug was a posteriori encapsulated within the prepared nanofibers and 751 presented a sustained release over several days. 752 Dandelion (DP) is an α-type polysaccharide extracted from the roots of a perennial herbaceous plant and 753 currently employed in several food products owing to its antitumor, antioxidant, and anti-complement 754 properties (Guo et al., 2019). Cui et al. (Cui et al., 2019) reported on the preparation of nanofibrous 755 dandelion-based membranes embedding BCD-ICs-Litsea cubeba essential oil (LCEO) as efficient 756 antibacterial agents. The structure of the mats was improved thanks to the addition of the  $\beta$ CD complexes in

mats showed a considerably higher release most likely owing to the enhanced incorporation of SFS through

the spinning solutions owing to the interactions between the components. Interestingly, a sustained release of the encapsulated LCEO was observed over several days resulting in marked antibacterial properties, therefore making the prepared nanofibers suitable to be used for both biomedical and food packaging purposes.

### **6.2** Electrospun Protein – Cyclodextrin Based Membranes

Proteins are biomacromolecules composed of long amino acid chains with an important role in several body functions such as DNA replication, metabolic reactions, stimuli responses, and moieties transportation, as well as in cell viability. Proteins are biocompatible, biodegradable, easily accustomed in the human body, and with interesting isoelectric properties that allow them to interact with a wide variety of molecules (Muiznieks & Keeley, 2017; Sheng Wang et al., 2016; Weisel & Litvinov, 2017). Owing to such properties, it is not surprising that protein-based electrospun membranes are gaining increasing interest for several applications, especially in the food packaging and biomedical industries. However, proteins are known to be infamously difficult to be electrospun because of their complex secondary and ternary structures, with globular properties having too few interactions to form a sufficient number of entanglements (Babitha et al., 2017; DeFrates et al., 2018; Ding et al., 2019; Kakoria & Sinha-Ray, 2018; Zhong et al., 2018).

Protein-based nanofibrous membranes functionalized with cyclodextrins represent an emerging and interesting class of novel materials with the possibility to couple the outstanding properties of both components. However, their investigation remains to an initial stage with only a small number of publications reported in the literature as summarized in Table 3.

**Table 3.** Comprehensive summary of protein-based electrospun membranes functionalized with CDs or CD-ICs and their main applications.

Protein	Cyclodextrins	Encapsulated bioactive molecules	Applications	Ref.
Soy protein isolate	βCDs	Allyl isothiocyanate	Food packaging materials with enhanced encapsulation efficiency and humidity triggered release kinetic	(Vega-Lugo & Lim, 2009)
	αCDs		Fundamental study of the effect of CDs on zein solution spinnability	(Kayaci & Uyar, 2012a)
			Fundamental study of the effect of CDs on zein solution spinnability	(Kayaci & Uyar, 2012a)
	βCDs	Eucalyptus essential oil	Antibacterial food packaging products with enhanced thermal stability	(Dias Antunes et al., 2017)
Zein	_	Quercetin	Antibacterial food packaging products	(Z. Wang et al., 2021)
			Fundamental study of the effect of CDs on zein solution spinnability	(Kayaci & Uyar, 2012a)
	γCDs –	Thymol	Antibacterial food packaging products with enhanced release properties	(Aytac, Ipek, et al., 2017)
		Quercetin	Water-insoluble food packaging materials with fast antioxidant action	(Aytac, Ipek, et al., 2018)
Silk fibroin	HPβCDs	Ds Tamoxifen	Transdermal drug delivery systems with prolonged-release kinetic for the	(W. Liu et al., 2016)
SHK HOTOHI			treatment of breast cancer	
Gelatin			Water-insoluble crosslinked nanofibers as cost-effective water pollutant	(Yu Chen et al., 2018)
	βCDs		removal	
			Respiratory filter media for filtration of aerosols and volatile organic	(Kadam et al., 2021)
		<del></del>	compounds	(Radam et al., 2021)
	-	Galangal root oil	Active food packaging products with antibacterial properties	(Zhou et al., 2020)
	HPβCDs	Ciprofloxacin	Fast-dissolving drug delivery systems for oral formulation dosages	(Aytac et al., 2019)
Gliadin	HPβCDs	HPβCDs Ferulic acid	Biomedical and food products with enhanced thermal stability and fast release	(Sharif et al., 2018)
			properties	(Sharif et al., 2016)
Hordein	8CDs	CDs N,N'-methylene bisacrylamide	Recyclable filter materials for the efficient removal of heavy metals from	(Guan et al., 2019)
Horuelli	ρευς		wastewater	

Soy protein isolate (SPI) is the most refined protein obtained from soybean with several applications in food-related products due to its great abundance and high availability as by-products from industries (Rani & Kumar, 2019; Tian et al., 2018). SPI was the first protein employed to prepare protein-based electrospun nanofibers functionalized with cyclodextrins by Vega-Lugo et al. (Vega-Lugo & Lim, 2009), who reported on SPI nanofibers encapsulating allyl isothiocyanate compound (AITC) by using βCDs as complexation agents and PEO as a co-spinning agent. Beyond the possibility to tune the nanofiber structure by simple changing the mixture composition, AITC release kinetics from the composite nanofibers strongly depended on the environment relative humidity. Specifically, no compound loss was observed at 0% RH, whereas a sustained release for 20h was detected at 75% RH comparably to the results showed by Aytac et al. concerning PVA/βCD-ICs-AITC membranes (Aytac et al., 2014). Zein (ZN) is a clear, odourless, tasteless, water-insoluble and edible prolamin protein derived from corn and broadly employed in several commercial products ranging from the textile fiber market to the food industry (Kasaai, 2017; Turasan & Kokini, 2017; Yong Zhang et al., 2016). Kayaci et al. (Kayaci & Uyar, 2012a) first reported on a fundamental study regarding the preparation of zein nanofibers encapsulating different amount of  $\alpha$ CDs,  $\beta$ CDs, or  $\gamma$ CDs. Comparably to what was reported by other research groups for polysaccharides, the addition of CDs noticeably improved the spinnability of pristine zein solutions leading to bead-free nanofibers, with only a slight morphological dependence on the cyclodextrin type, and enhanced thermal stability. Owing to the abovementioned finding and keeping in mind cyclodextrin complexation capability, the authors indicated that these nanofibrous mats are promising products for biomedical and food packaging applications. Subsequently, Aytac et al. (Aytac, Ipek, et al., 2017) prepared zein nanofibers functionalized with the inclusion complexes between γ-cyclodextrins and thymol, which were able to provide a high encapsulation capability leading to enhanced stability and release kinetic. Moreover, by testing the antibacterial properties toward E. Coli and S. Aureus bacteria in meat simulated storage conditions at T = 4 °C, the prepared mats were suggested as promising antibacterial food packaging materials. Similar work was reported by Antunes et al. (Dias Antunes et al., 2017), who proposed the encapsulation of βcyclodextrin-eucalyptus essential oil complexes in zein electrospun nanofibers by using aqueous ethanol (EtOH) eco-friendly mixture as solvent. SEM images proved the good homogeneity of the obtained nanofibers, which contained around 24% of the formed inclusion complexes. Moreover, the antibacterial

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properties were tested against S. aureus and Listeria monocytogenes (L. monocytogenes) bacteria showing a strong growth reduction and the possibility to use the obtained mats for applications in the food packaging. More recently, Aytac et al. (Aytac, Ipek, et al., 2018) reported on electrospun zein/γCD-ICs-quercetin nanofibers as quick and efficient antioxidant materials, with the encapsulated quercetin showing enhanced thermal stability and water solubility compared to its free form. Similarly, Wang et al. (Z. Wang et al., 2021) prepared homogenous and free-standing zein nanofibers embedding βCD-ICs-quercetin. The encapsulation of the bioactive compound was proved to improve its availability, release time, and thermal stability. Consequently, the obtained mats showed strong antibacterial properties against both E. Coli and S. Aureus bacteria, thus resulting in promising materials for future active food packaging products. Silk fibroin (SF) is an insoluble protein largely produced by the larvae of Bombyx mori and numerous other insects. SF has assumed an increasing interest in biomedical applications owing to its biocompatibility, low immunogenicity, mechanical properties, and ability to remodel in response to the biological environment (Koh et al., 2018; Qi et al., 2017). With this premises, Liu et al. (W. Liu et al., 2016) demonstrated the possibility to prepare regenerated silk fibroin (RSF) nanofibers embedding HPBCD-ICs-tamoxifen (TAM) as potential drug delivery systems by using a simple aqueous mixture. The complex addition strongly increased the spinnability of RSF solutions leading to thinner and more homogenous nanofibers as shown in Figure 8, whereas the encapsulated drug was slowly released over 3 weeks making RSF cyclodextrin-functionalized nanofibers promising products as transdermal drug delivery systems.

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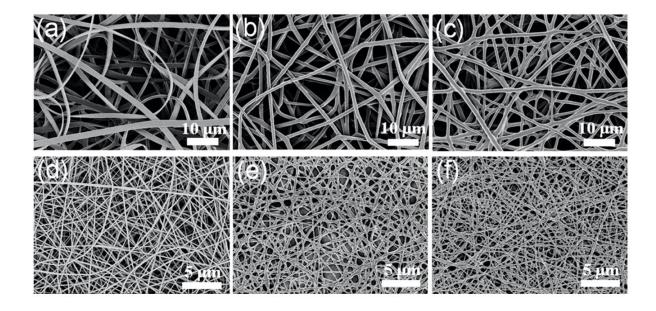
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**Figure 8.** SEM micrographs of (a) as-spun RSF nanofibers, (b) RSF nanofibers after ethanol spraying treatment, (c) RSF nanofibers after acetone immersion treatment, (d) as-spun RSF/HPβCD-ICs-TAM nanofibers, (e) RSF/HPβCD-ICs-TAM nanofibers after ethanol spraying treatment, (f) RSF/HPβCDs-ICs-TAM nanofibers after acetone immersion treatment. Reproduced with permission from W. Liu et al., 2016. © 2016 Elsevier B.V.

Gelatin (GL) is a largely available protein obtained from animal products and broadly employed in manufacturing to prepare foods, cosmetics and medicines owing to its gelling properties and ability to improve product elasticity, consistency and stability (Hosseini & Gómez-Guillén, 2018; Karayannakidis & Zotos, 2016). The use of gelatin/β-cyclodextrins nanofibers for the removal of dyes from wastewater was proposed by Chen et al. (Yu Chen et al., 2018). The authors developed a crosslinking approach with glutaraldehyde vapour both to stabilize the nanofibers and permanently grafting the cyclodextrins to the polymer chains avoiding leaking issues. Remarkably, the prepared mats showed promising adsorption capability towards methylene blue in different experimental conditions and several other common dyes, being above all characterized by good recyclability and reusability, therefore representing cost-effective and promising products for the efficient purification of wastewater. Yet, Aytac et al. (Aytac et al., 2019) investigated the use of gelatin nanofibers loaded with HPβCD and ciprofloxacin (CIP) complexes as fast-dissolving drug delivery systems. The authors were able to prove that the bead-free nanofibers encapsulating HPβCD-ICs-CIP showed to be more rapidly dissolved compared to gelatin/CIP nanofibers, thus pointing out the capability of HPβCDs in increasing the sample wettability and opening the way to the preparation of a broad variety of drug delivery systems able to quickly release high drug dosages. Additionally, Zhou et al.

(Zhou et al., 2020) investigated the preparation of gelatin-based nanofibers containing the inclusion complex between  $\beta$ CDs and galangal root oil (GRO). By using different gelatin sources, the authors evaluated how the composition of the protein amino acids affected the electrospinning process. Remarkably, gelatin/BCD-ICs-GRO showed marked antibacterial properties against E Coli, as well as excellent mechanical and thermal properties, thus being suitable as food packaging materials. Lately, Kadam et al. (Kadam et al., 2021) reported on the preparation of gelatin/BCDs nanofibers to be used as filter materials. In particular, the possibility to easily control the fiber dimension and the mat porosity, coupled with the cyclodextrin inclusion complex capabilities, allowed the prepared materials to show filtration efficiency towards both solid/liquid particles and VOCs. Gliadin (GD) is a prolamin protein largely present in wheat, as well as in other cereals, with a wide range of interesting applications (Jia et al., 2020; Urade et al., 2018). Sharif et al. (Sharif et al., 2018) reported on the encapsulation of HPβCD-ICs-ferulic acid within gliadin electrospun nanofibers. The complexation phenomenon allowed to increase both the thermal and photostability of FA thus preserving its antioxidant properties. Noticeably, compared to the GL nanofibers containing free FA, gliadin/HPBCD-ICs-FA mats showed a superior and faster release of the bioactive compound in artificial media simulating different food or biological conditions. Hordein (HD), likewise gliadin, is a prolamin protein present in barley and other cereals and mainly used for food applications (X. Huang et al., 2017). Guan et al. (Guan et al., 2019) proposed hordein nanofibrous membranes embedding N,N'-methylene bisacrylamide (MBA) molecules and grafted with βCDs for the adsorption of copper ions. The uptake properties of the prepared mats were evaluated at different pH and temperature conditions with the hordein/BCD-ICs-MBA nanofibers showing higher adsorption capability both compared to hordein/MBA and hordein electrospun mats. Additionally, the authors were able to prove the recyclability of the obtained mats via a humble and cost-effective washing procedure hence

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demonstrating their efficient use for the treatment of wastewater.

### 7 Conclusions and Future Perspectives

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Nowadays, electrospinning is worldwide recognized as a simple, flexible, and cost-effective technique for the preparation of nano- and microfibers with applicability in almost any research field and it has become, in the last decade, one of the most promising approaches to improve human quality of life via the production of tailored-made products for biomedical, food, energy harvesting, textile and environmental purposes. In this sense, cyclodextrins may play a very important role and their use in combination with electrospinning has aroused growing interest. Specifically, in most cases, the objective is to prepare polymer-free cyclodextrin nanofibers able to efficiently encapsulate bioactive compounds and accurately control their release. Indeed, the outstanding capability of cyclodextrins to form non-covalent stable complexes with small molecules (e.g., hydrophobic and/or volatile compounds) allows to considerably increase their solubility, stability, and availability, hence leading to a superior encapsulation efficiency that was previously unreachable. However, a variety of innovative applications are recently being evaluated for electrospun nanofibers made of (or containing) cyclodextrins and their derivatives, also creditable to the fact that their preparation allows avoiding the intensive use of toxic solvents and/or hazardous chemicals. For instance, cyclodextrin-based nanofibers can be employed as reducing agents for the in-situ synthesis of metal nanoparticles, as sacrificial templates for the development of conductive hollow structures, as implantable scaffolds for tissue regeneration purposes, as well as to develop high performing filtering materials and food packaging products with antibacterial and antioxidant properties. Additionally, combining the complexation capability of cyclodextrins with naturally occurring biopolymers appears to be the optimal format for the development of mats with unique and tuneable features. For instance, besides biocompatibility and greater biological response, biodegradability and digestibility, the greatest advantage of natural biopolymers is that they can be processed by using water or poorly toxic organic solvents making them extremely interesting from an industrial point of view. Moreover, the continuous advances in the extraction of materials from natural waste sources may lead in the future to the development of environmentally friendly electrospun products in view of a green circular economy. However, the development of these strategies remains at an initial stage and further studies are required since, at present, the electrospinning of natural biopolymers requires appropriate additives to facilitate the processing, as well as post-processing treatments to increase the mat stability and mechanical performances without affecting the

intrinsic biocompatibility. Noticeably, it is noteworthy that cyclodextrins have been demonstrated able to enhance the spinnability of biopolymer-based formulations due to the tendency to create supramolecular structures with the biopolymers, thus reducing, or even eliminating, the amount of required synthetic cospinning agents. Nevertheless, despite the considerable advances recently made at the laboratory scale, the industrial implementation of natural polymer electrospinning has been scarcely explored and remains a great challenge especially in terms of production rate.

In conclusion, in order to ensure the efficient translation between laboratory prototypes and commercial products, workability studies are mandatory to verify the effective applicability of cyclodextrin-based electrospun membranes for the proposed applications and more research-industry collaborations are indispensable to lower the cost and improve the industrialization of such materials.

# **Conflict of Competing Interest**

912 None.

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916 profit sectors.

917	Abbreviations	
918	AA	Acetic acid
919	AAB	Azobenzene
920	AFM	Atomic force microscopy
921	Ag	Silver
922	Ag-NPs	Silver nanoparticles
923	AITC	Allyl isothiocyanate compound
924	Al	Aluminium
925	$Al_2O_3$	Aluminium oxide
926	ALD	Atomic layer deposition
927	ALG	Almond gum
928	Au	Gold
929	Au-NPs	Gold nanoparticles
930	$a_{\rm w}$	Water activity
931	BA	Benzoxazine
932	BET	Brunauer – Emmett – Teller
933	Botrytis sp.	Botrytis species
934	BTCA	Butanetetracarboxylic acid
935	CA	Cellulose acetate
936	CTR	Citric acid
937	CD-ICs	Cyclodextrin inclusion complexes
938	CDs	Cyclodextrins
939	$c_{e}$	Entanglement concentration
940	СН	Chitosan
941	CIP	Ciprofloxacin
942	CMβCDs	Carboxymethyl-β-cyclodextrins
943	COL	Collagen
944	Cr	Chromium

945	Cu	Copper
946	DCF	Diclofenac sodium
947	DDSs	Drug delivery systems
948	DLS	Dynamic light scattering
949	DMA	Dynamic-mechanical analysis
950	DMAc	Dimethylacetamide
951	DMF	Dimethylformamide
952	DMSO	Dimethyl sulfoxide
953	DNA	Deoxyribonucleic acid
954	DOX	Doxycycline
955	DP	Dandelion
956	DSC	Differential scanning calorimetry
957	E. Coli	Escherichia Coli
958	ECH	Epichlorohydrin
959	ECM	Extra-cellular matrix
960	EDS	Energy-dispersive X-ray spectroscopy
961	ES	Electrospinning
962	EtOH	Ethanol
963	FA	Ferulic acid
964	Fe	Iron
965	Fe-NPs	Iron nanoparticles
966	FTIR	Fourier-transform infrared spectroscopy
967	GD	Gliadin
968	GL	Gelatin
969	GRO	Galangal root oil
970	НА	Hyaluronic acid
971	HD	Hordein
972	HPC	Hydroxypropyl cellulose

973	HPαCDs	2-hydroxypropyl-αCDs
974	HPβCDs	2-hydroxypropyl-βCDs
975	HPγCDs	2-hydroxypropyl-γCDs
976	HSES	High speed electrospinning
977	IKAV	Adamantane-6-aminohexanoic acid-GGKIKVAV-Am
978	KK	Adamantane-6-aminohexanoic acid-GGKK-Am
979	L. monocytogenes	Listeria monocytogenes
980	LCEO	Litsea cubeba essential oil
981	MB	Methylene blue
982	MBA	N,N'-methylene bisacrylamide
983	MO	Methyl orange
984	MβCDs	Randomly methylated-βCDs
985	NaOH	Sodium hydroxide
986	NAP	Naproxen
987	Ni	Nickel
988	NMR	Nuclear magnetic resonance spectroscopy
989	NPs	Nanoparticles
990	PAA	Poly(acrylic acid)
991	PAN	Polyacrylonitrile
992	PAP	p-aminophenol
993	PCL	Polycaprolactone
994	Pd	Palladium
995	Pd-NPs	Palladium nanoparticles
996	PEO	Poly(ethylene oxide)
997	PET	Polyethylene terephthalate
998	PHAs	Polycyclic aromatic hydrocarbons
999	PLA	Polylactic acid
1000	PMMA	Polymethylmethacrylate

1001	PNP	p-nitrophenol
1002	PolyBA-a	Poly benzoxazine
1003	PolyCDs	Cyclodextrin-based polymers
1004	PolyHPβCDs	Poly-2-hydroxypropyl-βCDs
1005	PS	Polystyrene
1006	PUL	Pullulan
1007	PVA	Polyvinyl alcohol
1008	PVP	Polyvinylpyrrolidone
1009	RC	Regenerated cellulose
1010	RH	Relative humidity
1011	RSF	Regenerated silk fibroin
1012	S. Aureus	Staphylococcus Aureus
1013	SA	Sodium alginate
1014	SEBβCDs	Sulfobutylether-β-cyclodextrins
1015	SEM	Scanning electron microscopy
1016	SF	Silk fibroin
1017	SFS	Sulfisoxazole
1018	SHP	Sodium hypophosphite
1019	SPI	Soy protein isolate
1020	SV	Simvastatin
1021	SBG	Swim bladder gelatin
1022	TAM	Tamoxifen
1023	TBZ	Thiabendazole
1024	TCL	Triclosan
1025	TEM	Transmission electron microscopy
1026	TF	Tetrafluoroterephthalonitrile
1027	TFA	Trifluoroacetic acid
1028	TGA	Thermogravimetric analysis

1029	THY	Thymol
1030	UV	Ultraviolet
1031	UV-vis	Ultraviolet-visible
1032	$VB_2$	Vitamin B <sub>2</sub>
1033	VOCs	Volatile organic compounds
1034	VOR	Voriconazole
1035	WAXS	Wide-angle X-ray scattering
1036	XPS	X-ray photoelectron spectroscopy
1037	XRD	X-ray diffraction
1038	ZN	Zein
1039	Zn	Zinc
1040	ZnO	Zinc oxide
1041	αCDs	α-cyclodextrins
1042	α-LA	alpha-lipoic acid
1043	βCDs	β-cyclodextrins
1044	γCDs	γ-cyclodextrin

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