chemistry proceedings

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Proceedings Paper

Cyclodextrin-Based Host-Guest Supramolecular Nanofibrous Composite for Biomedical Applications †

Salim Ullah [1,2], Zahid Hussain [1,2,*], Li Wang [1,2], Ismat Ullah [2], Shah Mehmood [1,2], Bingqing Luo [1,2], Yuehu Zhang [1,2], Muhammad Waseem Ghani [1,2], Renjun Pei[1,2,*] and Jine Wang [1,2,*]

[1] School of Nano-Tech and Nano-Bionics, University of Science and Technology of China, Hefei 230026, China; salimbio@mail.ustc.edu.cn (S.U.); liwang2020@sinano.ac.cn (L.W.); shahmehmood@mail.ustc.edu.cn (S.M.); c bqluo2021@sinano.ac.cn (B.L.); yuehuz@mail.ustc.edu.cn (Y.Z.); waseemghani@mail.ustc.edu.cn (M.W.G.)

[2] Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences, Suzhou 215123, China; ullah2020@sinano.ac.cn

* Correspondence: zahid@mail.ustc.edu.cn (Z.H.); rjpei2011@sinano.ac.cn (R.P.); jewang2012@sinano.ac.cn (J.W.)

† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry; Available online: https://ecsoc-26.sciforum.net.

Abstract: Cyclodextrins (CDs) are macrocyclic oligosaccharides, containing six to eight alpha(1→ 4) linked glucopyranose. CDs have a hydrophobic cone-shaped internal cavity and a hydrophilic exterior surface. It forms non-covalent inclusion complexes (ICs) with various drugs by trapping the full or partial inclusion in their cavity. Supramolecular ICs gained interest in engineering entrapped performance due to their potential to protect and modify the physicochemical properties of entrapped lipophilic and volatile drugs. However, the poor structural and mechanical properties of pure CD-ICs could restrict their application and the need for a suitable carrier system. Electrospun nanofibers have been the center of interest for biomedical applications due to their tunable physicochemical properties. Recent studies highlighted that entrapment of drug/CD-based ICs into nanofibers is an active research area since it facilitates high encapsulation, modulate the release profile of guest, integrates multi-type drugs, and leads to a synergistic effect. This mini-review first summarized the potential benefits and shortcomings of drug/CD-ICs and nanofibers and then discussed advancements in fabrication and characteristics of CD-ICs embedded nanofibers, along with some practical suggestions for potential biomedical application.

Keywords: cyclodextrin; inclusion complexes; supramolecular chemistry; electrospun nanofibers; nanocomposite; drug delivery

Citation: Ullah, S.; Hussain, Z.; Wang, L.; Ullah, I.; Mehmood, S.; Luo, B.; Zhang, Y.; Ghani, M.W.; Pei, R.; Wang, J. Cyclodextrin-Based Host-Guest Supramolecular Nanofibrous Composite for Biomedical Applications. **2022**, *4*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s):

Published: 15 November 2022

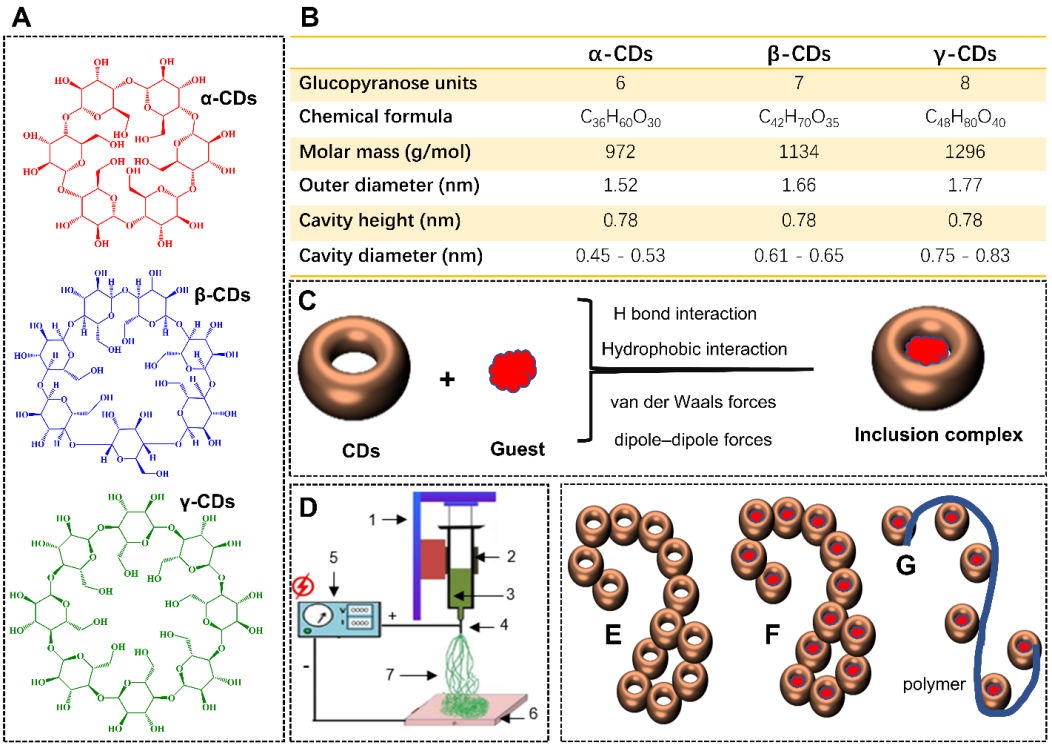
1. Introduction

A supramolecular system comprises two or more molecular entities that are held together using non-covalent binding interactions. Cyclodextrins (CDs) acts as a common host for supramolecular chemistry and rapidly gained interest in biomedical and pharmaceutical applications. CDs are a non-reducing macrocyclic ring-shaped oligomer composed of 6, 7, and 8 alpha(1 → 4) linked glucopyranose units commonly called αCDs, βCDs, and γCDs, respectively. It has attracted interest in engineering pharmacological functionalities because of its cone-shaped structure which possesses a hydrophobic internal cavity (given by the C–H bonds) and a hydrophilic exterior (due to the distribution of free O–H) [1,2]. The internal diameter varies among CDs types and is correlated with the number of glucopyranose units, i.e., internal cavity diameter increases in the following order: γCDs (0.75–0.83 nm) > βCDs (0.61–0.65 nm) > αCDs (0.45–0.53 nm) while the depth of the cavity is the same (~0.78 nm) (Figure 1A,B). CDs with less than six glucose units are not existing (for stoichiometric reasons), while CDs with more than eight glucose units

provide weak complexing properties [3]. Some chemically modified forms of CDs, i.e., hydroxypropyl-βCDs (HPβCDs), hydroxypropyl-γCDs (HPγCDs), methylated-βCDs (MβCDs), sulfobutylether-βCDs (SBE-βCDs), etc., have been introduced to achieve higher solubility, increased drug stability, the potential to undergo polymerization reactions and to extend their practical applications [4,5].

The unique structural properties of CDs offered distinguished physicochemical and encapsulation functionalities due to their potential to form inclusion complexes (ICs) against varieties of solid, liquid, and gaseous compounds with matched polarity, hydrophobicity, and molecular dimension [6,7]. The process of the ''guest'' inclusion into the CD occurs at the molecular level and is attractive for engineering novel functional materials. Some driving forces that support complexation include geometric compatibility, hydrophobic effect, electrostatic interaction, dipole-dipole forces, and charge transfer interactions [8]. It furnishes a suitable microenvironment to guest molecules through non-covalent host-guest ICs and positively modifies their physicochemical properties (Figure 1C). CDs-based ICs are widely used in biomedical, pharmaceutical, food industries, analytical chemistry, water purification, and oilfield application [9,10].

CDs can accommodate and modify the physicochemical properties of many entrapped bioactive drugs, such as antimicrobial agents, peptides, nucleic acid, etc., mainly in a suspension formulation [11]. However, few studies explored these improvements through nanostructured solid formulation for specific biomedical applications. This mini-review first summarized the potential benefits and shortcomings of drug/CD-ICs and nanofibers and then discussed advancements in fabrication and characteristics of CD-ICs embedded supramolecular nanofibers, along with some practical suggestions for potential biomedical application.



	α-CDs	β-CDs	γ-CDs
Glucopyranose units	6	7	8
Chemical formula	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$
Molar mass (g/mol)	972	1134	1296
Outer diameter (nm)	1.52	1.66	1.77
Cavity height (nm)	0.78	0.78	0.78
Cavity diameter (nm)	0.45 - 0.53	0.61 - 0.65	0.75 - 0.83

Figure 1. (**A**) Schematic chemical structure of αCDs, βCDs, and γCDs. (**B**) The main physicochemical properties of αCDs, βCDs, and γCDs. (**C**) Schematics representation of ICs formation between CDs and guest molecules. (**D**) Schematic electrospinning setup. (**E**) Schematic representation of polymer-free CDs nanofiber. (**F**) Schematic representation of drug-entrapped polymer-free CDs nanofiber. (**G**) Schematic representation of drug-entrapped polymer-based nanofiber.

2. Benefits and Shortcomings of CD-ICs in Biomedical Applications

Most drugs and bioactive substances either have poor heat stability, low water solubility, or volatile properties, making it difficult to use these molecules in their natural states [7]. The supramolecular ICs protect and shield guest drugs against devastating environmental effects (heat, moisture, chemical reactions, oxidation) [12]. ICs can improve solubility, bioavailability, photostability, therapeutic index, physicochemical stability, and shelf life of entrapped drugs. It can reduce volatility, modulate the release profile of guest molecules, and limit the unpleasant taste plus smell of some functional compounds [13]. It could decrease local irritation and increase the permeability of poorly soluble drugs across biological membranes [14]. ICs have been administered through different routes (dermal, ophthalmic, nasal, oral, rectal, and intravenous) [5] and hold great potential in pharmaceutical applications. However, the usage of drugs in suspension and tablet forms can cause unfavorable therapeutic effects, uncontrolled drug release, and poor self-healing properties which could limit their practical application. These factors underscore the need for a solid-state nano-carrier system for enhanced biomedical application.

3. Benefits and Shortcomings of Nanofibers in Biomedical Applications

Electrospinning is a simple and affordable technology that uses electrostatic voltage to fabricate continuous nanoscale fibers from various synthetic, natural, and hybrid polymeric materials [15] (Figure 1D). Electrospun fibers offer some benefits including regulated surface chemistry, high drug loading capacity, customizable microporous morphology, nanoscale diameter, huge surface area, and strong mechanical qualities [16,17]. Electrospinning could fabricate tailored nanocomposites that can conform over different surfaces/substrates and can be engineered in multiple shapes [18,19]. Nanofibers could replicate the structural and functional characteristics of extracellular matrix., and their surface properties can be altered with surface conjugated ligands to modulate drug release, bio-adhesive, and cell-instructive properties [17,20]. Electrospun fibers are increasingly recognized in tissue engineering, coating for biomedical implants, wound dressings, sustained medication release, and encapsulation of different bioactive substances for different biomedical applications [21–23]. Since most drugs are water-soluble and volatile, incorporating a considerable drug into fibers while maintaining their biological activity and physicochemical stability can be problematic for drug delivery applications.

4. CD-ICs Incorporated Nanofibrous Membranes in Biomedical Applications

Most medications and bioactive substances exhibit poor heat stability, limited water solubility, or volatility, and these characteristics hinder drugs from reaching therapeutic concentrations for effective treatment. Drugs loading into electrospun fibers by blending in suspension before the electrospinning process or using specific conjugated chemistry cannot overcome these limitations [24]. CDs-ICs offer significant advantages over non-complexed forms of a drug, but their poor structural and mechanical properties restrict could practical application. Recent studies depicted that incorporating CD-IC into electrospun nanofibers has gained significant interest in modifying drug loading capacity, drug release kinetics, and drug performance [25–28] (Figure 1E–G).

Polymer-free (ciprofloxacin/βCDs and dexamethasone/βCDs) and polycaprolactone (PCL)-based ICs embedded supramolecular nanofibers were fabricated in the combined form via electrospinning. The surface of ICs functionalized nanofibers was further modified using adhesive nanofibers using catechol chemistry. The results showed that PCL-based ICs nanofibers possess good mechanical properties, convenient for storage, and integrate dual drugs in amorphous form than polymer-free ICs nanofibers. The designed polymer-based nanocomposite could allow for a single application-based dual drug (antibiotic and anti-inflammatory) delivery to treat otitis externa [24] (Figure 2A). Electrospun PCL nanofibers containing βCD/silver sulfadiazine ICs could be crucial to wound

healing since it reduces the direct contact between silver sulfadiazine with skin and modulates drug release, solubility profile, and distribution properties of drugs [29].

The efficiency of PCL/βCDs nanofibers as wound odor absorbers was studied using a wound odor simulation solution. The results demonstrated that βCD-containing nanofibers were efficient in masking the odor through the formation of ICs with odorants. The nanocomposite could be used for wound odor absorbance and drug delivery purposes [30]. Silver nanoparticles and dimethyloxallyl glycine were used as the drug loading component, cellulose acetate was used as a matrix, and CDs were used as a stabilizer and solubilizer to create the nanofibrous-based wound dressing. The results demonstrated that the nanofibrous composite exhibit sustained-release properties and holds significant antibacterial performance against Gram-positive and Gram-negative bacteria. The nanocomposite is biocompatible and could be a potential diabetic wound dressing material [31]. The combination of chitosan-based electrospun nanofibrous material containing curcumin@βCD/AgNP nanoparticles possessed synergic antibacterial and wound healing potential (in a rat model) [32] (Figure 2B). Silver sulfadiazine (SSD) possesses potent antibacterial properties but is virtually insoluble in water which could limit its widespread use. βCDs/SSD ICs were prepared at various conditions and results demonstrated that such complexation positively modulates the aqueous solubility, bioavailability, and dissolution profile of SSD. The ICs were further embedded in PVA nanofibers via electrospinning. The supramolecular nanofibers improved drug solubility, drug release profile and exhibited strong antibacterial effects against *E. coli* and *S. aureus* [33] (Figure 2C).

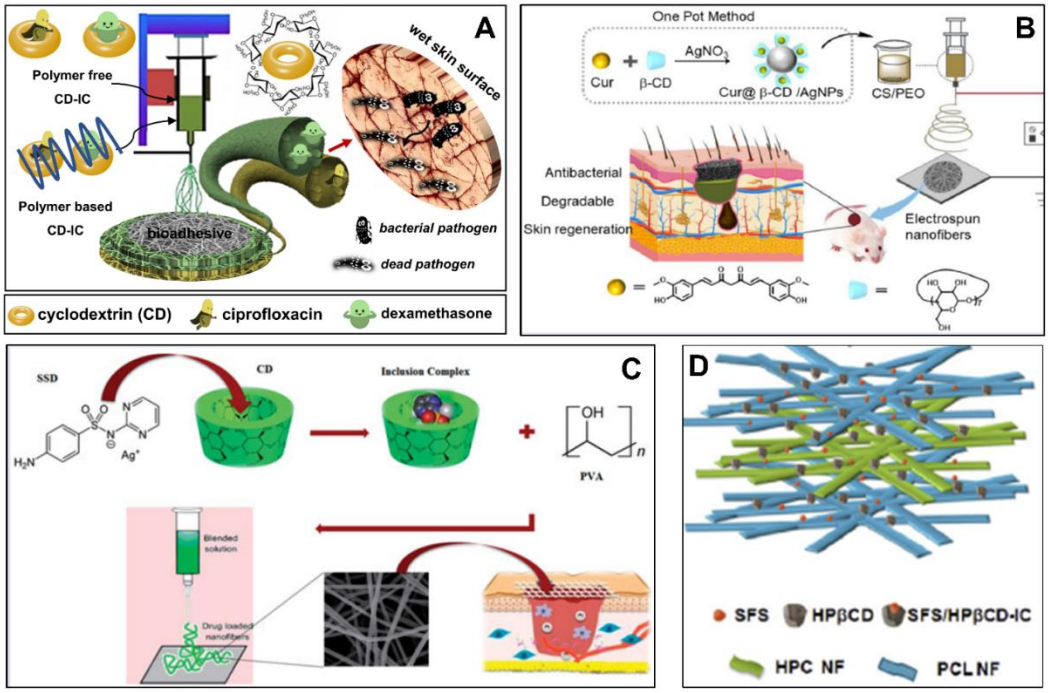


Figure 2. (**A**) The schematic diagram showed releases of dual biocides from IC incorporated nanofibers to inhibit and reduce *S. aureus* growth and inflammatory mediators. Reproduced with permission from [24]. Copyright (2022) Elsevier. (**B**) The chitosan-based nanofibrous material functionalized with curcumin@βCD/AgNPs nanoparticles. Reproduced with permission from [32]. Copyright (2022) Taylor & Francis. (**C**) Schematics representation of ICs formation between CDs/SSD and their incorporation into nanofibers. Reproduced with permission from [33]. Copyright (2019) Taylor & Francis. (**D**) HPβCDs/SFS complex was incorporated in hydroxypropyl cellulose nanofibers via electrospinning to modulate the drug release profile. Reproduced with permission from [34]. Copyright (2015) Elsevier.

HPβCDs based IC with sulfisoxazole was embedded in hydroxypropyl cellulose fibers via electrospinning. The results depicted the fabrication of uniform nanofibers and

the amorphous distribution of ICs in the nanocomposite. A higher amount of drug has been released from the IC-embedded nanofibers than sulfisoxazole-embedded nanofibers. The significant improvement in drug solubility could be attributed to incorporated ICs, which could assist in developing promising delivery systems of hydrophobic drugs [34] (Figure 2D). The ICs between CD and adamantane-conjugated epitope were successfully entrapped in electrospun nanofiber. The nanocomposite scaffold was investigated against peripheral nerve regeneration. The structural properties of nanocomposite promote cell adhesion and proliferation, while bioactive epitopes on nanofibers' surfaces guide cellular differentiation. Both chemical and physical cues were utilized for an effective neuronal differentiation process [35]. The bioactive glass nanoparticles with inherent osteogenic properties are modified with βCDs to enhance their affinity for exogenous estradiol. The estradiol-loaded βCDs functionalized glass nanoparticles were embedded onto silk fibroin-based nanofibers. The localized delivery of estradiol could circumvent the systemic adverse effects and the resultant nanocomposite enhances in vitro apatite formation and sustains the release of estradiol. It significantly enhances osteoblast proliferation, differentiation, and matrix-maturation thus could be crucial in bone reconstruction [36] (Figure 3A). Naproxen has been complexed with βCDs. The pristine drug and ICs were then incorporated into PCL nanofibers. The drug release elucidates that the supramolecular nanofibers have a higher release amount of naproxen than the PCL/naproxen nanofibers due to the solubility enhancement of naproxen by CD-ICs [37].

The electrospinning of hydrocortisone/CDs complex has been introduced to fabricate a rapid-dissolving oral medication delivery system without using an additional polymer matrix. Electrospinning successfully yielded homogenous nanofibrous structures and the resultant complex improved the water solubility and distribution of drugs in an amorphous state. The nanofibrous membrane could rapidly be dissolved in water and artificial saliva, therefore, could be applied as a rapidly-dissolving oral drug delivery system [38]. HPβCDs and tetracycline have been used to form IC. The resultant IC was then blended with pullulan and electrospun to form nanofibers. The electrospinning yielded defect-free fibers with high drug loading in an amorphous state. The supramolecular nanofibers enhanced water solubility and rapid drug release profile in artificial saliva than simple pullulan/tetracycline nanofibers. Furthermore, ICs functionalized fibers exhibited strong antibacterial potential against Gram-positive and Gram-negative bacteria and could be an attractive material for rapid-dissolving oral drug delivery systems [39].

Eucalyptol/βCDs ICs have been embedded in gellan/polyvinyl alcohol nanofibers to eradicate *antifungal* biofilms. The resultant nanocomposite possesses high hydrophilic properties, facilitates rapid drug release, and inhibits the biofilm of *C. albicans* and *C. glabrata*. The introduced fibrous systems enhanced the antibiofilm activity of eucalyptol to treat fungal infections and can be applied as a cost-effective implant coating biomaterial [40]. Electrospinning of polymer-free (acyclovir/HP-βCD) and polymer-based (acyclovir/polyvinylpyrrolidone) has been carried out to form functional nanofibers. Both nanocomposites are embedded with high concentrations of acyclovir. The results showed that polymer-free nanocomposite provided better drug loading efficiency (98%) than polymer-based fibers (66%) and showed faster drug release and disintegration profiles. It could act as a promising strategy for fabricating a rapid-dissolving drug delivery system in good dosage formulation against viral infections [41].

Meloxicam/βCDs functionalized polyvinylpyrrolidone nanofiber was fabricated using an electrospinning process. The results indicated that the resultant supramolecular nanocomposite possesses suitable mechanical properties, incorporated the meloxicam in an amorphous form, and exhibits faster disintegration. Furthermore, nanocomposite membrane exhibit more rapid drug release potential than pure meloxicam powder and commercial meloxicam tablets. Furthermore, nanocomposite remained stable for up to 6 months, could rapidly disintegrate in the mouth, could mask the bitter taste of drugs, and therefore, could be a good candidate for fast dissolving drug delivery systems for bitter medicines [42]. βCDs and thymol were self-assembled to form a water-soluble IC. The

pristine thymol and resultant ICs have separately embedded into cellulose acetate nanofibers via electrospinning. The results demonstrated that ICs functionalized fibrous membranes exhibited sustained thymol release and lasting antibacterial potential against *S. aureus* and showed good cytocompatibility. The IC-embedded nanocomposite could be an attractive candidate for wound dressing material [43].

Poly(L-lactic acid)/gelatin nanofibers were fabricated via electrospinning. The βCDs conjugated hydroxyapatite is coated onto the surface of the nanofiber via specific interaction between βCDs and adamantane. Simvastatin (osteogenic drug) was then loaded into the remaining βCD and overall, results demonstrate that simvastatin-loaded nanocomposite better promotes mineralization, osteogenic gene expression, and bone reconstruction [44] (Figure 3B). The engineering design brings together hyaluronic acid electrospun hydrogel nanofiber segments, functionalized with either adamantane-based guest or βCD-based host supramolecular moieties. The host-guest interaction creates a shear-thinning and self-healing hydrogel fiber network via guest−host complexation [45] (Figure 3C).

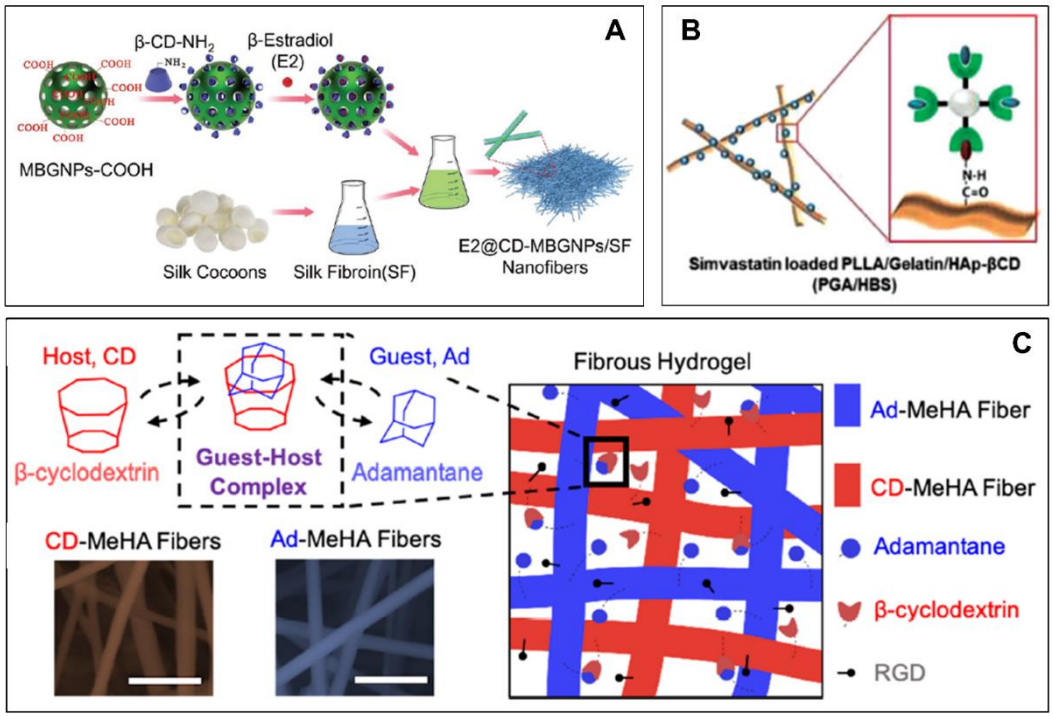


Figure 3. (**A**) The bioactive and osteogenic glass nanoparticles (MBGNPs) are conjugated with βCDs (CD-MBGNPs) to enhance their encapsulation affinity for exogenous estradiol. Reproduced with permission from [36]. Copyright (2018) Royal Society of Chemistry. (**B**) are fabricated via electrospinning. The βCDs conjugated HAp is coated onto the surface of poly(L-lactic acid)/gelatin-based nanofibers through interaction between βCDs and adamantane, and at the latter stage, simvastatin is loaded into the remaining βCD. Reproduced with permission from [44]. Copyright 2016. Wiley-VCH. (**C**) The formation of a macroscale fibrous hydrogel scaffold is brought about as a consequence of interactions involving adamantane and CDs on complimentary bioactive nanofibers. Reproduced with permission from [45]. Copyright (2021) American Chemical Society.

Electrospun nanofibers incorporated with IC of niclosamide and HPβCDs were produced from pH-responsive polymer. The IC-embedded nanocomposite disintegrated at pH values greater than 6 and it had the potential to be utilized for the targeted and regulated release of niclosamide to the colon [46]. Overall, CD-based nanofibers could carry more significant amounts of drugs and are crucial for rapidly-dissolving oral medication delivery systems compared to conventional drug formulations. Furthermore, the structural, mechanical, and functional features of fibrous composite could control drug release properties (according to the desired application) and regulate cell function. The

supramolecular nanocomposite could maximize site-specific drug targeting for tissue engineering, cancer treatment, and other biomedical application.

5. Conclusions and Future Perspectives

There are numerous factors favoring CD-based ICs and electrospun nanofibers in biomedical applications. However, the use of pure CD-IC is unsuited for biomedical applications due to their poor structural plus physicochemical properties, and on the other hand, since most drugs are water-insoluble, the incorporation of high concentrations of drugs into nanofibrous composite while maintaining their functional activity can be problematic for biomedical applications. Considering the properties of CD-ICs and nanofibers, our review highlighted that incorporating CD-ICs into the nanofiber matrix is a simple procedure to engineer drug-encapsulated fibers since distinct properties, and synergistic effects can be obtained. The supramolecular nanocomposite has been investigated as a drug delivery system and is suited for biomedical application because it can assemble into different forms, can engineer diverse assemblies such as nanoparticles, structurally tune the drug release mechanism, could integrate multi-type drugs, can respond to physiological cues, and could maximize the applicability of nanocomposite in a range of biomedical applications. Most of these investigations are still in the proof-of-concept stage, nevertheless, the future for supramolecular nanofiber in the biomedical domain is promising. There is a need to strengthen biodistribution, biodegradability, biosafety, and stimuli-responsive composite design for enhanced biomedical applications.

Author Contributions: Study conception and design, S.U., Z.H. and L.W.; Literature and data collection, S.M., B.L., Y.Z., M.W.G.; review and editing, I.U., R.P. and J.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: Z.H. is grateful to CAS-TWAS President's Ph.D. Fellowship Program.

Conflicts of Interest: The authors declare no conflict of interest.

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