Cyclodextrin-Based Polymers

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Cyclodextrins (CDs) are cyclic oligosaccharide structures that could be used for theranostic applications in personalized medicine. These compounds have been widely utilized not only for enhancing drug solubility, stability, and bioavailability but also for controlled and targeted delivery of small molecules. These compounds can be complexed with various biomolecules, such as peptides or proteins, via host-guest interactions. CDs are amphiphilic compounds with water-hating holes and water-absorbing surfaces. Architectures of CDs allow the drawing and preparation of CD-based polymers (CDbPs) with optimal pharmacokinetic and pharmacodynamic properties. These polymers can be cloaked with protein corona consisting of adsorbed plasma or extracellular proteins to improve nanoparticle biodistribution and half-life. Besides, CDs have become famous in applications ranging from biomedicine to environmental sciences.

cyclodextrin theranostics protein corona

1. Structural Features of Cyclodextrin-Based Polymers

CDbPs are various polymers containing CD-based moieties to improve polymer physicochemical characteristics and functions. The physical properties of a polymer mainly depend on its molecular chain structure giving rise to four categories: linear, branched, cross-linked, and topologic (**Figure 1**) [1][2]. The basic difference between linear and cross-linked polymers is that linear polymers are straight, whereas cross-linked ones have branched molecular topology possessing unique spatial features.

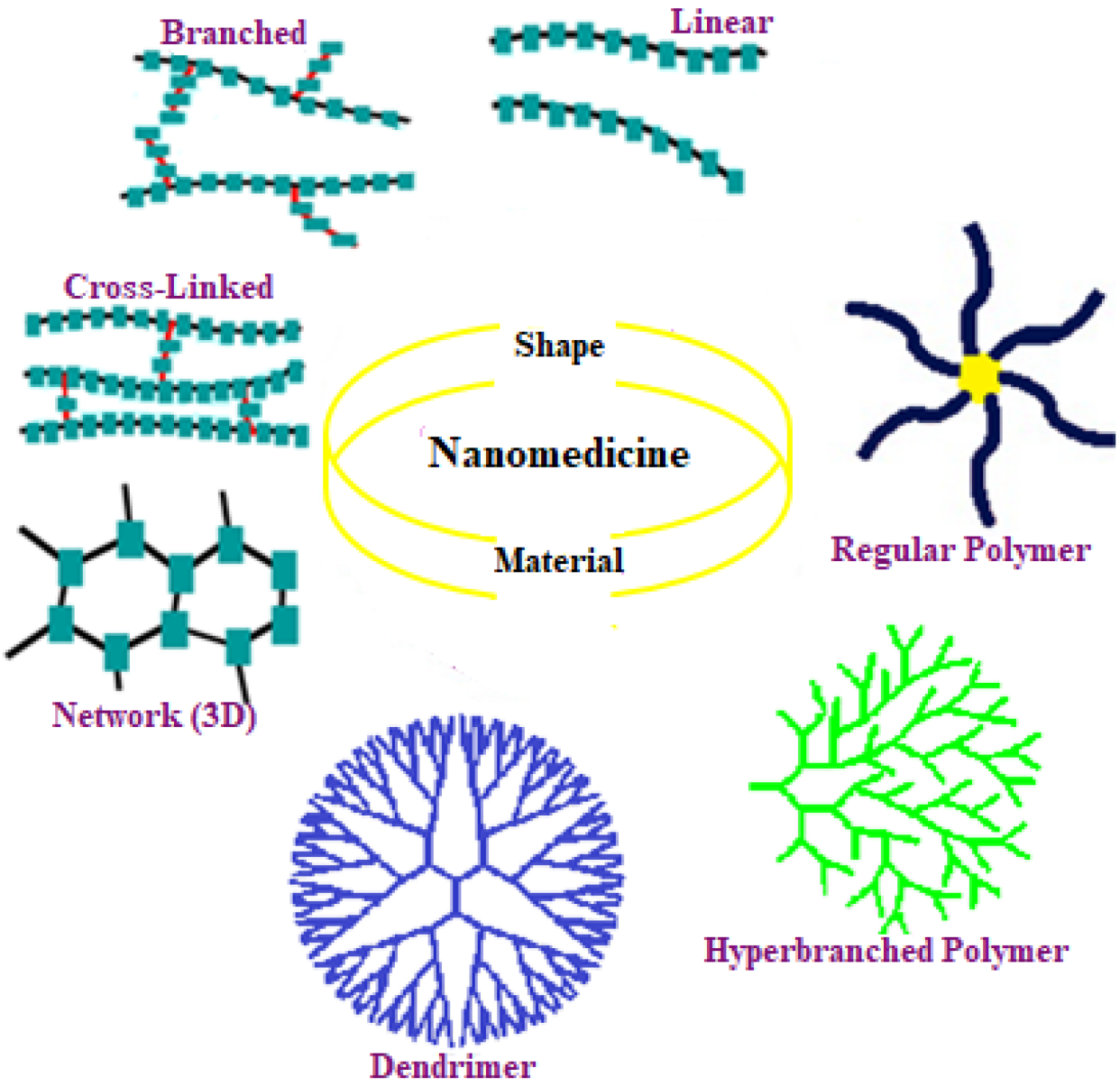

Figure 1. Classification of polymers by molecular topology.

At the beginning of the 1950s, Flory developed a hypothesis to describe the polymer network and the associations between the topology and mechanical properties such as elasticity [3]. In the 1980s, Duplantier developed a hypothesis to demonstrate any polymer network topologies using statistical mechanics, which could assist in determining topology-dependent crucial agents in a polymer network [4]. In the early 2000s, Tezuka and colleagues were the first research group who consistently demonstrated a single molecular chain with topological details [5]. Indeed, supramolecular polymeric molecules would have been regarded to be favorable carriers for biomedical and theranostic applications in cancer and cardiovascular research [6][7].

Due to their large amounts of hydroxyl groups on their external surfaces and hydrophobic cavities, CDs can link to different positions of the polymers. Recently, several interesting CD-based polymeric systems have been developed [8]. The latest progressions in the controlled/living polymerization approaches combined with the highly efficient coupling reactions have offered feasible synthesis methods to prepare complex dendritic polymer

structures. These polymers are highly branched as a 3-D network consisting of at least several subclasses [8]. Now, the CDbPs substances can be categorized depending on their structures: (1) CD-terminated polymers (CDTP), which have two CDs at their ends. To achieve CD-terminated polymers, the homo/block copolymers can be instantly grown from a CD-based large initiator or can be affiliated with a CD-based derivative after polymerization [9][10]; (2) CD-pendant polymers (CDPP), in which they can be classified into two categories. One is accomplished by a replacement reaction between CD derivatives and the target polymers [11][12][13]. The other is produced by the straight polymerization of CD-based monomers alone or with other monomers [14]. Polymers with pendant CD categories on the side chains often possess macromolecular hosts with numerous binding sites. Host-guest polymer assemblies across nano, micro, and macro scales originating from these CD-pendant polymers are attracting more and more interest in nanostructure fabrication, pharmaceutics, and biomedicine [15][16]. CD-centered core polymers (CDCCP), in which CDs function as the core for forming multi-arm polymers, could also be used for rational drug design and discovery [17][18][19]. Due to advances in polymeric science, CDs can be characterized as biomedical agents in these hybrid polymeric systems.

1.1. Cyclodextrin-Centred Core Polymers

Star polymers are composed of several centrally attached linear polymers with many chains and functional groups. The polymer core or center can be atoms, molecules, or macromolecules and chains or arms composed of organic chains of different lengths. Synthesis of star polymers using inexpensive and functional CDs has advantages such as cost efficiency, ease of manipulation, and easy access to multiple functions. Due to the relative order in which the polymer composite arms are made, the synthesis of star polymers using CD cores can be divided into two categories: core-first and arm-first approaches. The core-first approach uses CD-based initiators to grow polymer chains directly synthesizing CD-centric core star polymers. For the arm-first approach, a conjugation reaction is used to synthesize a CD-centred core star polymer, and the synthesized linear polymer is attached to a CD derivative. The advantage of the second method over the previous one is that each arm has the same chain length [20]. As unique structures, star polymers exhibit unique properties that simple linear polymers cannot match. Star polymers are an important group of technological nanostructures used or studied in various nanotechnology applications such as theranostics. The most basic form of the branched polymer is the star-shaped polymer first introduced by Schaefgen and Flory in 1948, who synthesized multiple polymer chains in a star-shaped polyamide [21][22]. A revolutionary breakthrough in star polymers was reported in 1962 by Maurice Morton et al. [23] as they developed the first method of synthesis of the famous star-shaped polymer by anionic polymerization. To date, many studies have focused on the properties, synthesis, and function of star polymers [24].

In this way, linear polymers can be easily defined by obtaining a specific analysis of the arms. Identifying specific compounds in CD-centred core star polymers is a major challenge, as abundant linear polymers need to be increased by enlarging all active sites of cyclodextrins. To achieve high purity for star polymers with CD-centric cores, free linear polymers should be eliminated, often requiring tedious purification processes.

1.2. Cyclodextrin-(Pendant and Terminated) Polymers

CD-capped polymers can be obtained by placing a CD at one or more termini of the polymer. CD-terminated polymers can be synthesized directly using CD-based macro-initiators. These polymers can also be obtained using linear polymer linkages with reactive sites on functionalized CDs.

The CD side-chain polymers are synthesized in two ways: by direct polymerization of a large number of CD monomers or by functionalization of CDs onto the side chains of the polymer. Although it is difficult to synthesize supramolecular polymers with complex structures by conventional covalent routes, these compounds exhibit host-guest interactions in which a polymer with CD side chains and a polymer with a CD terminus act as a host can be obtained [25]. Finally, recent advances in cyclodextrin self-assembly provide the means to design diverse nanomaterials, such as Vesicles, micelles, nanogels, supramolecular hydrogels, complex superstructures, and multifunctional structures, offer a simple combinatorial approach [6][26].

2. Application of Cyclodextrin-Based Polymers in Theranostic Nanomedicine

Key polymers, such as CD-centric core polymers, CD-side polymers, and CD-terminated polymers, have a variety of applications, including materials fabrication for theranostic nanomedicine. Due to this, cyclodextrin-based polymers have been validated as effective scaffolds in nanomedicine [27][28].

CD-based polymers are an attractive platform for theranostic nanomedicine. It is well known that many drug-like molecules have insufficient water solubility. Traditional formulations of insoluble drugs involve a combination of bio-based solvents, surfactants, and extreme pH conditions that often lead to unfavorable and adverse reactions [29]. Therefore, safe CDs might be a perfect choice to stabilize the active pharmaceutical ingredients to reduce volatility, cytotoxicity, or bitterness. For instance, CD-drug formulations can improve not only the water solubility of many poorly water-soluble substances but also their bioavailability and therapeutic efficacy.

The first method for preparing high molecular weight (Mw = 104) water-soluble polymers was described by Solms and Egli in 1965 [30].

Industrial α-, β-, and γ-CD polymers have been investigated for use as eluents in adsorption chromatography (on cellulose thin films) using aqueous solvents. Lederer et al. developed an approach to improve a polymer elution compared to α-CD [31]. Various cleansing active ingredients (especially methylene blue (MB), ethacridine lactate (acrinol), brilliant green (BG), gentian violet (GV), fuchsin acid (FA), cetylpyridinium chloride (CPC)) in CD-based polymers were tested to treat of foot ulcers, infected wounds, and burns [32][33]. The eluents usually contain soluble polymers, while the CD polymers for wound treatments are water-insoluble ones. Therefore, the swelling effect of CD polymers might be an important advantage in wound treatment.

Hyperbranched polymers (HBPs) and hyperbranched polyglycerols (RPGs) are among many dendritic structures that combine excellent functionalization capabilities and stability with low viscosity. Therefore, RPGs are considered promising for theranostic nanomedicine applications for cancer treatment [34].

The rheological properties of star polymers are also important compared to linear polymers. These polymers have a low intrinsic viscosity, a small hydrodynamic radius, a large critical micelle concentration (CMC), and, therefore, low aggregation. Intrinsic viscosity increases with increasing branching functionality and molecular weight. Once the functional efficiency saturates, the viscosity limitation is related only to the molecular weight of the arms. This may be attributed to increased repulsive interactions due to more heterocontacts between different arms [35].

Tang et al. prepared star-shaped polymers via ring-opening polymerization (ROP) followed by reversible addition-fragmentation chain transfer polymerization (RAFT). In this experiment, DOX was used as a standard drug to conjugate the copolymers via an acid-labile hydrazone bond. Analysis of the solution properties of as-prepared DOX conjugates is greatly influenced by the composition and different structures of the polymers. Among the conjugates studied, an eight-arm triblock star polymer related to poly (ethylene glycol) (PEG) and N-2-hydroxyl methacrylamide (PHPMA) showed a poor cell penetration and fragmentary colocalization within lysosomes [36].

A particular star-shaped amphiphilic polymer consisting of a β-CD core with hydrophobic (lactic acid) (PLA) and hydrophilic (ethylene glycol) (PEG) poly arms was prepared for the delivery of anticancer drugs [37].

The study revealed that this star-shaped single-molecule micelle generated from β-CD-PLA-PEG was more efficient than Genexol-PM for cancer treatment [37][38].

Namgung et al. reported a novel nano-assembled drug delivery device fabricated by multifunctional host-visitor interactions between polymer-cyclodextrin and polymer-paclitaxel (PTX) complexes [39].

Furthermore, Badwaik illustrated the production of three Pluronic®-based, cholesterol end-capped cationic polyrotaxanes (PR+) mixed with 2-hydroxypropyl-β-cyclodextrin (HPβCD) for small interfering RNA (siRNA) delivery. The data confirmed 90% of cell viability and a significant silencing effect (>80%) in cell lines such as HeLa-GFP and NIH 3T3-GFP [40]. Gomez-Garcia et al. carried out a manufacturing technique to develop a library of clear-cut multivalent glycoclusters with a showcase of α-mannosyl (α-Man) and β-lactocyl (β-final) antennas using β-CD [41]. Albuzat et al. exhibited that the polyrotaxane PRx2 assembled from a hexatonic α-CD derivative 1 and a cationic polymer I-11 is highly compatible with three cell lines. Additionally, this compound possessed improved transfection potencies in vitro. The molecular mechanism behind it could be explained by the steric hindrance of Coulomb interactions exerted by the natural α-CD rings [42].

Moreover, the hydrophobic tetraphenylethylene (TPE)-AIE (aggregation-induced emission)-active dye (TPE-Ad) was encapsulated inside a hydrophobic core, and the hydrophilic polymer covered the surface of the hydrophobic core and acted as a shell-forming material [43]. TPE-β-CD-PEG copolymers were determined by many types of instruments. The cytocompatibility and cellular uptake behavior of TPE-β-CD-PEG were also considered to evaluate potential biomedical applications. The results showed that TPE-β-CD-PEG copolymers tended to self-assemble into luminescent nanoparticles that exhibited remarkable water-dispersibility, AIE properties, and excellent biocompatibility. Due to this property, TPE-β-CD-PEG has great potential for biomedical applications. Compared to conventional techniques that provide AIE-active copolymers, this technique is very simple for the

following reasons: easy handling (stirring at room temperature without adding catalyst), high atomic economy, short preparation times (<30 s), and high yields. With all such advantages of this technology, conjugating AIE dyes to PEG using β-CD as a bridge is an innovative idea, allowing various multifunctional AIE-activated polymer conjugates for numerous implementations. It was predicted to be a popular technique for further developing the body [43].

3. Application of Cyclodextrin-Protein Corona in Biomedical Approaches

The formation of protein coronas on the surface of nanosized particles endows nanosized particles or polymer systems with novel biological properties, suggesting numerous applications in biomedicine or theranostic nanomedicine. The following subtitles embody the latest advances in nanosized particles and protein corona structures for biotechnological applications.

Yallapu et al. have investigated the sample of human serum protein corona (HSPC) formation with nanosized particles. The change in particle size, zeta potential, hemotoxicity, cellular uptake/cancer cells targeting potential, and MRI characteristics of nanosized magnetic particles were reduced because of the adsorption of human serum. Meanwhile, associated with raised serum and particle concentrations, Apolipoprotein E (APOE = gene, apoE = protein) is absorbed in the surface of nanosized magnetic particles besides serum albumin (HAS) and transferrin (TF). But there existed no conspicuous primary-secondary structural developments noticed in serum proteins by various approaches, including Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and circular dichroism (CDS). Hemolysis evaluation offers nearly no hemolysis at the approved concentrations (up to 1 mg/mL) for nanosized magnetic particles compared with the sodium dodecyl sulfate (positive control). Moreover, the developed internalization and uptake of magnetic nanoparticles through the C4-2B cell line appears to have been confirmed during incubation with human serum (HS). Following the adsorption of serum protein to the surface of nanosized magnetic particles, the immediate proximity within T1 (~1.33–1.73 s) and T2(~12.35–13.43 ms) times of relaxation permitted nanosized magnetic particles to maintain intrinsic magnetic resonance imaging potential even after adsorption of biomolecular protein. All high-level clinical parameters could dictate the translation to clinical practice and the use of this formulation for next-generation nanoscience for drug delivery (DD), cancer targeting, imaging, and theranostics applications [44].

Polymer-based nanocarriers are particularly useful as they offer a high degree of compatibility, and Fluorescence durability correlation spectroscopy (FCS) methods are powerful and functional tools for NCs (nanocarriers) at all levels of nanotechnology processes. In particular, fluorescence correlation spectroscopy (FSC) has been used to investigate the size of NCs and the medical efficacy of post-development loading, the stability of NCs, and possible mediation between the plasmatic and vascular flow. You can run and compute things of drug release in the cytoplasm of target cells [45].

4. Mechanism of Protein Fibrillation

Throughout the first phase, monomers self-associate to form cores or oligomers. Whenever a critical core size is reached, the second stage (the elongation stage) relies on an exponential function around the fibril by successive additions of monomers. At this level, formed protofibrils assemble into fibrils and finally into insoluble mature fibrils (**Figure 2**). Although amyloid fibrils are generally thermodynamically stable, these structures exist in equilibrium between monomeric and oligomeric species [46]. Amyloid aggregation appears to be lineage-specific and may involve similar hydrophobic proteins or different proteins [47]. Protein ongoing amyloid fibrillation and deposition in tissue are discovered in conformational disorders, proteinopathies, or protein misfolding disorders (PMDs) like Alzheimer's (AD), Parkinson's (PD), Huntington's (HD), amyotrophic lateral sclerosis (ALS), and Creutzfeld-Jakob disease (CJD), and so forth. The particular mechanisms at the rear of the fibrillation approach remain elusive, and there is still an absence of peculiar restorative manners for protein fibrillation-related diseases. Researchers are still faced with difficulties in discovering the mechanisms of fibrillation formation and using powerful strategies to inhibit fibrillation in the human body. The particular introduction of nano-scaled materials (NSMs) in nanotechnology applications medicine provides an opportunity to address the existing challenges, as NSMs have been suggested that stop the procedure of fibrillation to a distinct degree [48][49].

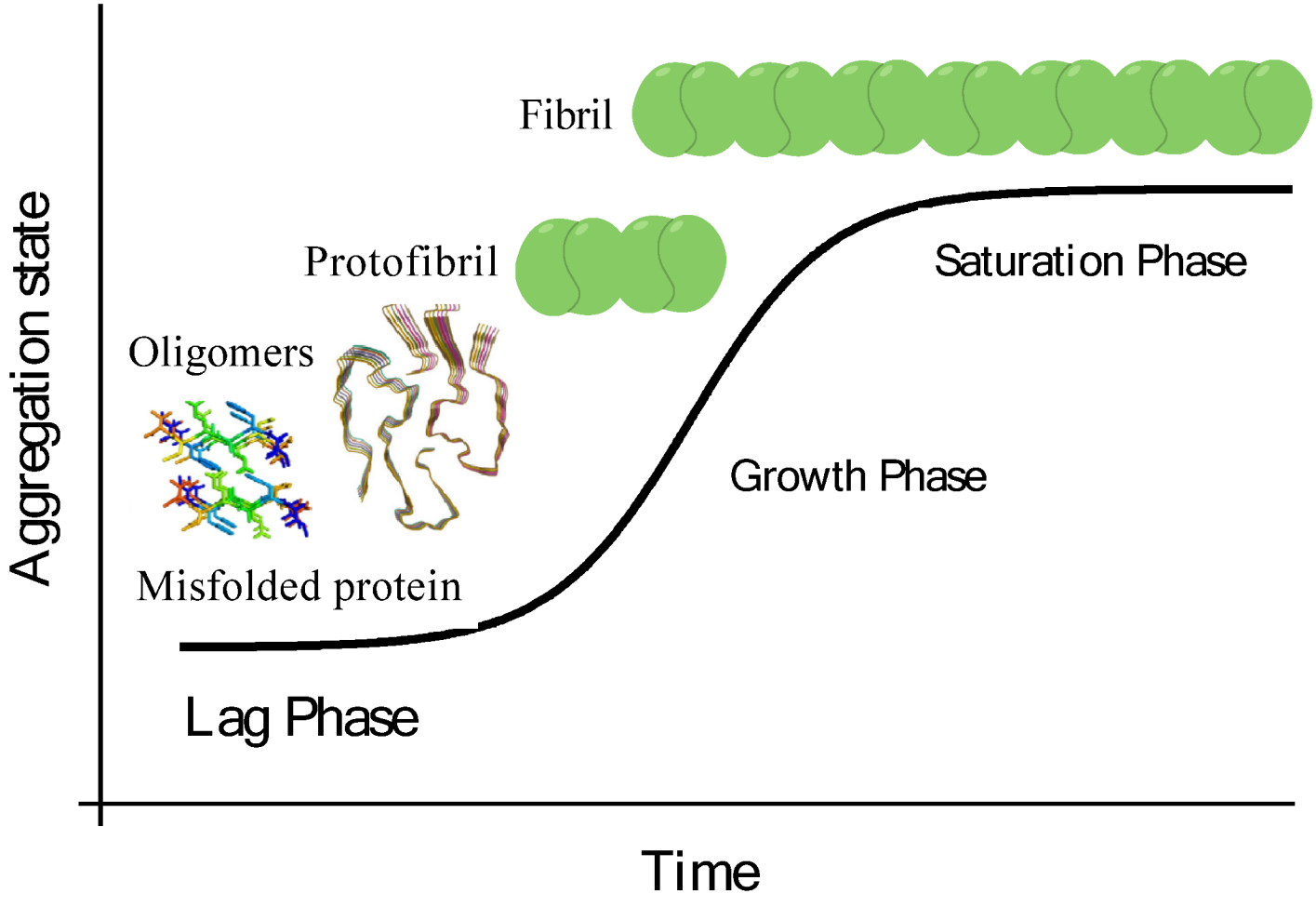

Figure 2. The kinetic proceeding of protein amyloid fibrillation comprising (Lag phase) aggregation of misfolded monomers into tiny intermediate oligomers; (Growth phase) re-arrangement of these oligomers into organized

fibrils containing the cross-beta structure; (Saturation phase) association of beta structured oligomers into proto-fibrils [50].

Amyloid beta fibrils (AβF) are discovered in patients with Alzheimer's disease (AD). The amino acid sequence of 17–24, 30–36, and 38–42 are investigated as hot spot residues of the Aβ peptide and get broadly determined as induce factors for the fibrillation procedure. Bare AuNPs illustrated to reduce the rate of the fibrillation method of Aβ1-42 is impeded by adsorption of the hot spot residue 17–24 to the having a positive charge AuNPs [51]. The inhibitory activities of bare nanoparticles (NPs) were also verified to be dose-dependent. That is, a dense concentration of NPs suggests a greater approachable surface for trapping higher amounts of Aβ1-42 monomers than a minor concentration of NPs, leading to enhanced inhibition activity. Protein corona-coated nanoparticles illustrate fewer inhibitory impacts on fibrillation. PCs give a negatively charged surface on the NPs, and the negatively charged parts of the hot spot residue [52] exhibit less binding tendency of corona-coated nanoparticles, bringing about a reduction of the surfaces of the nanoparticles tend to the Amyloid β (Aβ) monomers. Consequently, protein corona-coated nanoparticles possess less opportunity to trap Amyloid β monomers, assisting the self-assembly of considerable Amyloid β (Aβ) monomers residual in an aqueous solution. Over and above that, the inhibitory activities of corona-coated nanoparticles were confirmed to be protein source and concentration-dependent due to distinctions in the clotting factors of proteins. This demonstrates that a fetal bovine serum (FBS) corona presents a higher inhibitory impact on NPs regarding Amyloid β fibrillation than human plasma (HP) corona, whereas nanostructures with protein corona illustrate a lower inhibitory impact than those from 10% HP/FBS. A thorough study has been carried out on Aβ25-35 with human plasma (HP) or cerebrospinal fluid (CSF) coronas [52]. These inhibitory effects are believed to be related to the Aβ peptide and protein corona. Usually, due to the large capacity for capturing Aβ1-42 monomers, bare NPs represent remarkable inhibitory effects on the Aβ1-42 fibrillation proceeding. Compared to plasma-coated NPs, the NPs surfaces, nevertheless, are not covered by the CSF model. Therefore, CSF-coated NPs have more approachable surfaces for capturing Aβ1-42 monomers and blocking the aggregation of hot spot residues. Hence, plasma-coated gold nanoparticles (AuNPs) and gold nanorods (AuNRs) show less inhibitory activity on the Aβ1-42 fibrillation kinetics than CSF-coated or pristine AuNPs or AuNRs. Concerning the Aβ1-42 peptide, pristine nanostructure accelerates its fibrillation proceeding, while corona-coated nanostructures inhibit the fibrillation proceeding. Multiple hydrophilic residues in the N-terminal (25–30) of Aβ1-42 exist, and multiple hydrophobic amino acids are in the hot spot residue (30–35). The hydrophilic NPs prefer to bind to the hydrophilic region instead of the hot spot residue; Aβ1-42 monomers accumulate within the nanostructured surfaces and have the propensity to form fibrils led by the unbound hot spot residue. Also, to amyloid β peptide, an influence of the nanostructure-protein corona compound on the amyloid fibrillation development of human islet amyloid polypeptide, the fibrillation of which is a hallmark of type 2 diabetes (T2Ds) was further reported [53]. The β-lactoglobulin (BLG) protein is a natural β-sheet-rich protein; its architecture mainly turns into an α-helix after heat treatment. Suggesting BLG and heat-denatured BLG-coated AuNPs to IAPP confirms intercalation of BLG-AuNPs with IAPP is led by β-sheet stacking. The fibrillation development of IAPP can be led to BLG-coated AuNPs since the interactions among the BLG-AuNPs and LAPP block the IAPP self-assembly. It prepares novel evidence for the detection and inhibition of protein fibrillation.

On the other hand, some studies indicated the successful inhibition of Aβ fibrillation by CD-polymer conjugates [54]. In particular, the poly-fluorene-alt-benzothiadiazole loaded with CDs was used to recognize and remove Aβ fibrils to efficiently treat AD. Furthermore, 5[4-(6-O-β-cyclodextrin)-phenyl],10,15,20-tri(4-hydroxyphenyl)-porphyrin and its zinc complex were tested to interact with Aβ and inhibit its fibrillar aggregates [55].

Typically, fluorescence (FL), circular dichroism and *Fourier-transform infrared spectroscopy* (FTIR) spectroscopy, and *atomic force microscopy* (*AFM*) divulge that both approaches to the peptide stored its fibrillation attributes and organized fibrils. Yet, the combined fibrils organized more swiftly than the free peptide, and were long and thin rather than the thick and twisted morphology of the intact peptide. Thus, the limitations presented by the scaffold regulate the structure of the fibrils but do not obstruct the actual fibrillation process. Exploiting fibril-forming peptides (FFPs) in the design of nanomaterial remained a challenge due to the problems in assessing and controlling how amyloid fibrils form [56].

The particular idea of protein corona adsorption adds to new techniques for dwindling potential nano hazards and for using a more logical design of nanoplatforms. It also is a principal program and mechanism for nanostructures to provoke protection from infection. The brand-new fundamental natures are prognosticated to increase the efficacy and bioavailability of nanostructures as possible drug delivery and theranostic factors.

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