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# Self-Assembled Short Peptide Nanostructures: Dipeptides

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**ABSTRACT**

Dipeptides are short peptide molecules formed by the peptide bond between two amino acids, and they play significant roles in various biological processes (such as protein synthesis, nutrient absorption, cellular signaling, immune response). Short peptides have a prominent place in the design of self-assembling materials. In particular, dipeptides have gained considerable attention in the field of biotechnology as a type of self-organizing nanostructure due to their low cost, simplicity of synthesis, biocompatibility, and tunability of functionality. However, there is limited knowledge about peptide and protein-based nanostructures in the literature. Therefore, more information is needed on dipeptide nanostructures, especially in terms of their potential applications for biomedical purposes. This review focuses on dipeptide nanostructures, particularly their potential uses in biomedical applications, and provides a broader perspective on the advantages, challenges, synthesis, interactions, and applications of these nanostructures.

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## 1. Introduction

Self-assembly is a natural conformation of molecules with a specific three-dimensional geometry that occurs spontaneously under certain conditions. This technique is a method in which molecules and self-assembled aggregates are arranged thermodynamically [1,2].

Stable nanostructures with different morphologies may be formed by self-assembly of peptides through non-covalent interactions such as hydrophobic, hydrogen bonding, π-π stacking, and electrostatic interactions [3]. These interactions are known to act in the fabrication of some biological structures such as dendrimers, micelles, liposomes and lipid nanocapsules [4,5].

Peptides are chains of amino acids made up of about < 50 amino acids, easy to produce, and designed to mimic the self-regulation of proteins. Peptides have great superiorities such as chemical versatility, high degree of biocompatibility and biorecognition capacities. In particular, small peptide structures have the ability to translocating cell membranes and cannot induce an immune response [3].

Peptides, and especially short peptides, are very attractive nanomaterials because of their excellent biocompatibility, ease of synthesis, functional and tunable bioactivity, and ability to adjust their structure and function to environmental conditions [6].

In recent years, it has been observed that peptides with very small structures can self-assemble in various nanomorphological structures. Therefore, they have been shown to increase their stability while minimizing the synthesis difficulty and cost. Further research in this context sought to investigate the self-assembly of peptides as small as the dipeptide structure. The first study on the self-assembly of dipeptides belongs to Gazit's group, which researched the mechanism of self-regulation of dipeptide FF [6]. FF dipeptide are highly ordered as nanotubes/microtubes [7,8,9] nanoforests [10] and nanowire [11] structures. One of the desirable properties of FF nanotubes in a material was thermal stability, a matchless property that would be desirable in any biologically inspired material [12].

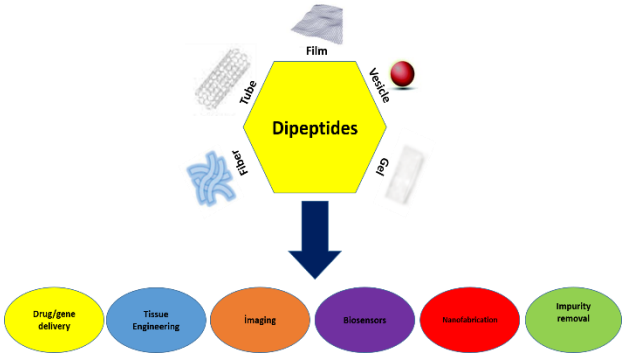


**Figure.1** *Some Applications of Dipeptides*

Peptides have the ability to self-assemble in aqueous solution under different environmental conditions to form different nanostructures. In an experimental study to produce nanofibers in the literature, it has been observed that short peptides dissolve very quickly in a solution at low pH and osmotic pressure. Short peptides have outstanding properties such as versatility and flexibility for the design of self-assembly materials. These properties are convenient for understanding the structures and assembly mechanism of self-assembled peptides for the rational design of some structures [3]. Self-assembled dipeptide nanomaterials may suggest numerous potential implemantations in different fields because of their biocompatibility, easy tunability, and effortless and low-cost fabrication technique [6]. Some *a*pplications of dipeptides is shown in Figure.1. Even if there are many researches on and protein and peptide based nanostructures in literature, there is a need for a detailed review study especially on dipeptide self-assembled nanostructures. This review describes the dipeptide self-assembly mechanism, advantages, and different and important dipeptides.

## 2. Self-Assemble Technique

There are two methods for the fabrication of bio-based nanomaterials, known as bottom-up and top-down. For the top-down technique, nanostructured biomaterials are acquired by controlled removal of components from complex biological structures, i.e. separation of layer [13].

Supramolecular structures may be fabricated by assembling molecules for bottom-up process. It is important to know the method used in nanomaterial synthesis and the structure of each molecule existed the synthesis and the interaction of these molecules with each other. The organization of molecules occurs through weak non-covalent interactions. These interactions are electrostatic interactions, hydrogen bonds, hydrophobic interactions, and aromatic stacking [14]. These kind of interactions are in charge of the structural conformation of all biological molecules and their interaction with other molecules [5,13,14,15].

Self-assembled peptide structures include monomer sequences of short amino acid sequences or amino acid sequences that combine to form nanostructures. Peptides have different physicochemical and biochemical activities with their morphological structure, size and accessibility of surface area from a reactive point of view [16].

Molecular self-assembly defines the spontaneous union of individual molecules with thermodynamic situations into well described and quite stable supramolecule via non-covalent interactions. This case is everywhere in nature [16]. Molecular interactions keep molecules at a stable degree with low-energy status [17].

Secondary structures that allow the self-assembly of peptides are α-helices, β-sheets and β-hairpins [18,19]. α-helix is the basic secondary structure found in proteins [20].

The intrinsic thermodynamic instability phenomenon is that linear peptides with α-helical structure lose their helical structure in solution when separated from their original environment [21]. Although short α-helical peptide structures show ease of chemical synthesis and modification, it is also known that they lack stability in solution. Therefore, the novo design of peptides based on ultra-short α-helix peptides poses a problem [22].

## 3. The Importance of Short Peptides

Recent studies have indicated that short peptide structures have the capability of self-assembly of many different nanostructures, which can minimize the difficulties and cost of fabrication and at the same time increase their stability [23,24]. Self-assembled dipeptide nanostructures continue to be intensively investigated, especially in biomedical applications [25].

Preparation of hydrogel structures by self-assembly with short peptides was reported in one of the related synthesis methods, which self-assembled by intramolecular folding of specific peptide structures. Here, chemical crosslinking processes eliminate the need for toxic crosslinkers that are generally needed to form hydrogels from high molecular weight polymers. Another important point is that peptides with this structure are designed to respond to release. The most important features of drug carriers, such as biocompatibility, robustness and slow release ability during administration, are also expected to trigger release according to treatment needs. Therefore, the synthesis of peptides with improved therapeutic effect, responsiveness to stimuli and controlled release can be designed [26]. Oxaliplatin-peptide conjugate was formed with ultra-short peptides capable of forming hydrogels and tested in the treatment of localized

breast cancer. This conjugate showed tumor growth inhibition [27].

Cell-penetrating peptides act an significant task in drug delivery across cell membranes and translocation of genes within the nucleus. The self-assembly process is key to cell-penetrating peptides penetration mechanisms. Additionally, the self-assembly method may produce a variety of structures convenient for a particular delivery and loading of a wide variety of drugs [28]. Cell-penetrating peptides have been utilized as drug delivery tools because they have cell membrane-replacing properties [29]. Cell-penetrating peptides, which are cationic short peptides of less than 30 amino acids, and oligoarginine-based cell-penetrating peptides, 8-10 arginine residues long, have been demonstrated to have the best membrane penetration [30].

Short peptide structures are a substitute for extracellular matrix proteins. These structures are a substitute for extracellular matrix proteins. They can mimic cell adhesion and remove the complexity of extracellular matrix structural effects in cells [31]. In this sense, peptide ligands have been involved in biomaterials that may be utilized as biomimetic membranes. Examples of these are polyethylene glycol hydrogels, biodegradable polymers and self-assembled monolayers [32]. A large increase is likely to occur in peptide formulations containing polyethylene glycol, cell-penetrating peptides for intracellular delivery, and short sequence peptides as carriers [33].

It has been shown that amyloid fibrils can generally consist of polypeptides of 30-40 amino acids, but may also consist of larger proteins. Nevertheless, recent research has demonstrated the ability of much shorter peptides, namely tetra- to hexapeptides, to form typical amyloid fibrils exhibiting all the typical biophysical and ultrastructural features of amyloid fibrils [34,35].

## 4. Some Special Purpose Dipeptides

In their 2003 study, Gazit and colleagues reported the spontaneous self-assembly of the short dipeptide Phe-Phe. In another study [7], Wangoo et al. demonstrated the self-assembly of aliphatic single amino acids (Ala, Leu, Ile, and Val) [36].

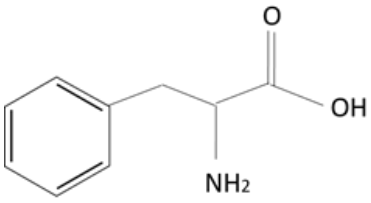


**Figure.2** *Phenylalanine Structure*

Research on phenylalanine (FF), whose molecular structure is given in Figure.2 and plays an important role in the regulation of biological processes, provides new information about the biological effects, synthesis and potential applications of this amino acid. Studies have revealed novel information on FF's biological effects, synthesis, and potential applications in regulating biological processes [37].

This section of the study aims to summarize the existing knowledge on phenylalanine and its derivatives, with a particular focus on phenylalanine amide (FFA) dipeptide nanoparticles and their potential applications. The aromatic rings of FF play a crucial role in the formation of chemical and biochemical supramolecular structures by providing the necessary energetic contribution for aromatic stacking [38]. Studies on FF dipeptide have shown that this peptide can form structures in various shapes, such as spherical or tubular structures, as well as structures in the form of rings, ellipses, disks, and bowls [39].

FF is an attractive option for drug delivery systems due to its simple structure and biocompatibility. FF nanoparticles can encapsulate hydrophobic drugs to a high degree thanks to their anionic character, and drug release can be controlled by pH and glutathione. As such, FF holds great potential as a drug carrier system [40].

A study by Wang et al. on FF dipeptide nanoparticles has shown that they can be used as self-assembled nanotubes for electronic devices on graphene [41]. Liu et al. have used these nanoparticles as drug carriers due to their high biocompatibility and bioactivity [42]. In a different study conducted in 2015, FF dipeptide nanoparticles were used for nanoscale optoelectronic applications [43]. The study stated that FF dipeptide nanoparticles showed high conductivity and their optical properties could be controlled.

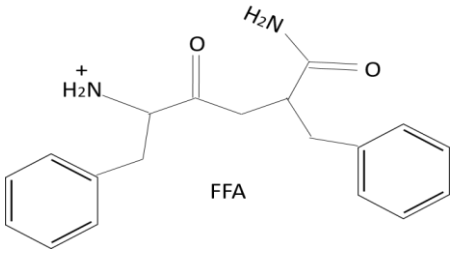


**Figure.3** *Diphenylalanine amide (FFA) Dipeptide Structure*

One of the modifications made to the nanostructures formed by the FF dipeptide is the synthesis of cationic FF (H-Phe-Phe-NH2·HCl) molecules, which are obtained by replacing the -OH group in the carboxyl group with -NH2, to impart different properties [44]. The molecular structure of Diphenylalanine amide (FFA) Dipeptide is given in Figure.3. The study conducted by Yan et al. was the first to

demonstrate the potential application of cationic FF (FFA) molecules as gene and drug carriers by organizing them into nanovesicles at physiological pH [45].
The organization of cationic FF molecules into nanoparticle structures under different stimuli and conditions, and their application as carriers or sensor components, have been the subject of numerous studies [46,47]. However, the common problem in all of these studies is the instability of the resulting peptide nanoparticles, which tend to change shape to adapt to varying environmental conditions [48].

Zhang et al. were the first to develop a stable FF-based nanostructure for drug delivery. This stable nanostructure exhibits high biocompatibility and superior biodegradability properties [49].

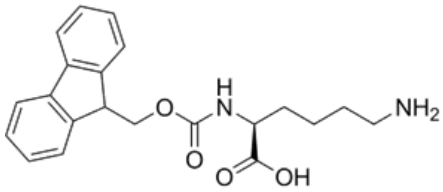


**Figure.4** *Fmoc-Lys Dipeptide Structure*

Another dipeptide gaining importance is fluorenylmethoxycarbonyl lysine (Fmoc-Lys) and its molecular structure is given in Figure.4. Fmoc-Lys is a derivative of the amino acid lysine, protected with a 9-fluorenylmethoxycarbonyl protective group [49]. Lysine is a basic amino acid that is important for many biological functions. Fmoc-Lys contributes to the formation of peptides and proteins by being combined with other amino acids [50]. Typically used in solid-phase peptide synthesis, Fmoc-Lys is attached to solid support by adding an Fmoc protective group to the N-terminus. The protective group is removed with a base, such as piperidine, to extend the amino acid chain [51]. Fmoc-Lys is an important tool used in proteomic and peptidomic research, analyzing biological molecules, and designing new drugs. Additionally, Fmoc-Lys variants can be used to design peptides with increased biological activity by adding specific functions and properties to amino acid chains. Fmoc-Lys contributes to the formation of peptides and proteins by being combined with other amino acids [50,51].

When an amino acid is conjugated with a fluorenylmethoxycarbonyl (Fmoc-) group, the ability of the Fmoc functional group to form thick, tangled fibers facilitates the formation of a gel-like structure that can trap water molecules within it [52]. This property has led to the investigation and use of Fmoc-amino acids in various applications, particularly in potential areas such as drug delivery systems, tissue engineering, and wound healing. Fmoc-based hydrogels are being studied as scaffolds for tissue engineering and drug delivery vehicles [53].

Previous literature reports have shown that various Fmoc-protected amino acids exhibit gel-like properties. For example, it has been reported that amino acids such as Fmoc-F, Fmoc-M, Fmoc-Y, Fmoc-G, Fmoc-W, and Fmoc-I exhibit gel-like properties. However, it has been reported that some amino acids, such as Fmoc-alanine, Fmoc-valine, and Fmoc-leucine, do not exhibit gel-like properties due to their uncertain behaviour [52].

Recent studies by Kundu et al. have examined the self-assembly property of Fmoc-L-lysine in different organic solvents [54]. Additionally, a study by Panda et al. has demonstrated the spherical self-assembly property of Fmoc-cysteine and its applications in drug delivery [55].

## 5. Usage Areas of Dipeptides and Expectations

Dipeptides are widely used, especially in the field of biomedicine, for reasons such as being biocompatible and nontoxic. Dipeptides can also be used for purposes such as the determination of various substances and purification.
The accumulation of various chemicals and drugs in nature and foodstuffs has become a growing problem with the passing years. Nanoparticles are also frequently used for the detection of these residues. It is extremely important that the nanoparticle used is non-toxic. For this purpose, fluorescent nanoparticles were developed by Yan and his group. Biodegradable, tryptophan-phenylalanine dipeptide and sulfadimethoxine aptamer are combined and modified to give fluorescent properties and it has been suggested that it can be used as a reliable method for the determination of sulfadimethoxine [56]. A dipeptide and aptamer-based hybrid fluorescent platform was developed by Jin et al. for the detection of enrofloxacin, a broad-spectrum antibiotic [57].

Dipeptide-based nanocarriers have been synthesized for the release of doxorubicin enzyme-responsive, as an example for dipeptides that are also used in the design of drug delivery systems [58]. The ability to obtain nanoparticles suitable for modification with dipeptides is a feature that increases the potential of the usage areas. Tumor-targeting nanoparticles developed by Panda et al. can be included in this group [59]. In a study published last year, a new dipeptide-based cell imaging probe and tumor targeting agent were brought to the literature [60].

It is known that biocompatible nanoparticles cause fewer side effects compared to their counterparts, and even eliminate the factor that causes side effects in some cases. It has been reported that dipeptide-based nanocarriers, which exhibit antitumor activity and were developed for use in photodynamic therapy, also do not cause weight loss and unwanted immune activity [61].

Since nanoparticles can be modified to suit the preferred

purpose, it is possible to impart various properties to these nanoparticles. For example, photosensitive nanoparticles that are activated in hypoxia and designed for use in breast cancer have been developed. It has been shown that the nanoparticle prepared by combining the photosensitive pheophorbide-diphenylalanine peptide and the hypoxia-activated camptothecin prodrug, performs apoptosis by inducing ROS production after exposure to the 660 nm laser [62]. pH sensitive dipeptide-based systems are also among the systems designed to serve different usage purposes by being developed with modifications [63]. Like pH sensitivity, it is possible to develop solvent-tunable dipeptide-based nanostructures. In this way, different optoelectronic properties have been imparted to nanoparticles in different solvent environments [64]. Among the dipeptide-based nanostructures sensitized to different stimuli, redox-responsive nanostructures developed for targeted cancer therapy can be given as examples. Nanoparticles conjugated with folic acid and loaded with doxorubicin release drugs in the presence of glutathione [65].

Hydrogels are also frequently used for controlled release in drug delivery. In an article published in 2017, a biocompatible, Fmoc protected dipeptide-based hydrogel resistant to proteolysis was introduced. It has been reported that the problem of proteolysis, which is one of the most important disadvantages in the therapeutic use of peptide-based nanoparticles, is also eliminated [66]. Three-dimensional growth and functions of primary liver cells were also supported by dipeptide-based hydrogels [67]. In a recent study, biomineralized dipeptide hydrogels were found to induce bone regeneration [68]. The widespread use of dipeptide-based hydrogels in biomedical applications is due to several advantages. These include biocompatibility, availability for modifications, low cost and high stability [69]. Hydrogels are used in purification as well as biomedical applications. With the increasing importance of wastewater treatment, studies in this field have also increased. The dipeptide superhydrogel developed by Nandi et al. has enabled the removal of various toxic dyes and some heavy metals from wastewater [70].

Another usage area of dipeptide-based nanomaterials is systems in which they act as carriers for nucleic acids. They are known to be effective candidates with advantages such as easy synthesis, enzymatic stability and biocompatibility. Such a system has been designed from cationic dipeptides for gene therapy and has been reported to work successfully without any cytotoxic effect [71]. The transport of siRNAs with these systems is one of the applications that has increased in popularity in recent years. Liver-targeting dipeptide-based siRNA carrier nanoparticles that can be used therapeutically for cirrhosis have been designed. It has been reported that nanoparticles accumulate in the liver and have a therapeutic effect [72].

Due to the various advantages highlighted above, it is seen that the use of dipeptide-based nanomaterials in many areas is becoming increasingly common. It is anticipated that these nanomaterials will be used more frequently in the future, especially in biomedical applications, in the detection of antibiotics and various toxic chemicals, and in wastewater treatment in a wide range.

### 6. Conclusions

The examples we have covered in this review highlight dipeptides and its applications. In the past years, these dipeptide-based systems have advanced from fundamental studies of novel self-assembly principles, to initial results using in vitro systems, to in vivo models for novel therapies especially in cancer.

Peptides can self-assemble into a variety of nanostructures, which can exhibit interesting properties such as high thermostability and mechanical stability, semi-conductivity, and optical properties, which are gaining more and more attention in the biomedical and materials fields.

We believe that dipeptide-based nanostructures will be frequently encountered in the future, especially in biomedical applications, with aspects such as biocompatibility and biodegradability, as well as many other advantages discussed in this review. Its use in both in vitro and in vivo studies will increase if some of its limiting properties such as stability in physiological environments and predictability of their structures are resolved. While many challenges will be encountered in exploring dipeptide self-assembly, the future of peptide-based self-assembly nanomaterials is promising and achievable.

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