

Polydopamine for Biomedical Application and Drug Delivery System

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Abstract

The aim of this paper is to evaluate the properties of polydopamine and its application in medicine and pharmacy. A dark brown-black insoluble biopolymer produced by the autoxidation of dopamine is polydopamine (PDA), also for applications involving surface modifications it is a bioinspired material with tremendous potential. There has been a rapid increase in the synthesis and applications of polydopamine nanostructures in biomedical fields such as drug delivery, cancer diagnosis and etc., however, there are still vague points in its structure and polymerization mechanism. In this review, it can be said that we have provided a general overview of the recent advances in the dopamine-based material which its application is more in the field of drug delivery and cancer diagnosis. The review starts with a summary of the physicochemical properties of dopamine-based materials and nanocomposites in general. Then in the next step, the detailed description is followed on their applications in the fields of cancer diagnosis, drug delivery, and biomolecule immobilization. Through this review, we hope to promote PDA and its role in medicine and pharmacy becomes more prominent.

Keywords: Polydopamine; Biomedical; Cancer diagnosis; Drug carrier

Introduction

A major catechol neurotransmitter in the brain is DA. PDA is a synthetic analog of naturally occurring melanin (eumelanin) [1,2] and also a dark brown-black insoluble biopolymer, manufactured by the autoxidation of its monomer dopamine (DA) is called Polydopamine (PDA). It may be possible to associate the DA function with issues such as the control of movement, as well as the neurobiology and symptoms of Parkinson's disease, schizophrenia, and attention deficit hyperactivity disorder [3] an irregular functional biopolymer and a ubiquitous natural pigment found in different organisms is called melanin [4]. It can be said that in the human body, melanin is primarily responsible for skin color and is generally produced in the epidermal melanocytes. Moreover, melanin can be considered as an antioxidant and photoprotectant and has the ability to increase immunity against the pathogen. In catecholaminergic neurons located at various parts within the midbrain, such as the substantia nigra and the locus coeruleus in the pons, and to the lesser extent in other brainstem nuclei, neuromelanin can be found. Naturally, DA and eumelanin are extracted from tyrosine or 3,4-dihydroxyphenylalanine (L-DOPA). The biosynthetic and synthetic pathway of eumelanin, neuromelanin, and PDA is shown in Figure 1 [1].

One application of the Dopamine-based drugs is to treat Parkinson's disease, schizophrenia and addiction and also dopamine is a catecholamine which acts as an important neurotransmitter in the nervous system [5]. This is important in controlling the rewards and pleasures of the brain [6]. Due to the great importance and direct effect that the discovery of L-DOPA, a precursor of dopamine, has had on Parkinson's disease, won the Nobel Prize in Physiology or Medicine in 2000 [7]. In addition, dopamine can be used to control the growth and metastasis of various types of malignant tumors, including gastric cancer, liver cancer, and breast cancer [8,9]. Specific receptors, such as D2R play a significant role in the antitumor activity of dopamine. An interesting feature of D2R is that, it is responsible for inhibition of insulin-like growth factor-I (IGF-I)-induced cancer cell proliferation [10] and it is also suitable for suppressing cancer cells and migrating through the EGFR/AKT/MMP-13 pathway [11]. In addition, another

feature of D2R is inhibition of angiogenesis via the VEGF receptor 2 [12,13]. In recent years, dopamine has attracted a lot of attention because it is used to make polydopamine, which is a powerful coating. A robust eumelanin-like coating material prepared by oxidative self-polymerization of dopamine in an alkaline aqueous medium was reported by Messersmith and co-workers in 2007, which was the result of an inspiration from the strong adhesion property of mussel adhesive proteins (Figure 2) [14].

Consideration of many phenomena and observation should be made in order to discover new materials and to understand more basic physical processes. The development of ultra-hydrophobic synthetic materials, as well as the construction of periodic microstructures motivated by an examination of the color of butterfly wings, can be considered as an appropriate example in the field of materials science and nanostructures [15-17]. As the mass production and use of polydopamine-based materials have been increasing at a rapid pace in recent years, Figure 3 illustrates its growing trend from 2007 to 2013.

Material Aspects

Dopamine-based materials

As the name indicates, polydopamine can be obtained from polymerization of dopamine. It can be formulated and manufactured in three common methods including enzymatic oxidation, solution oxidation, and electropolymerization methods [2]. It can be mentioned that solution oxidation is the most widely used procedure for PDA

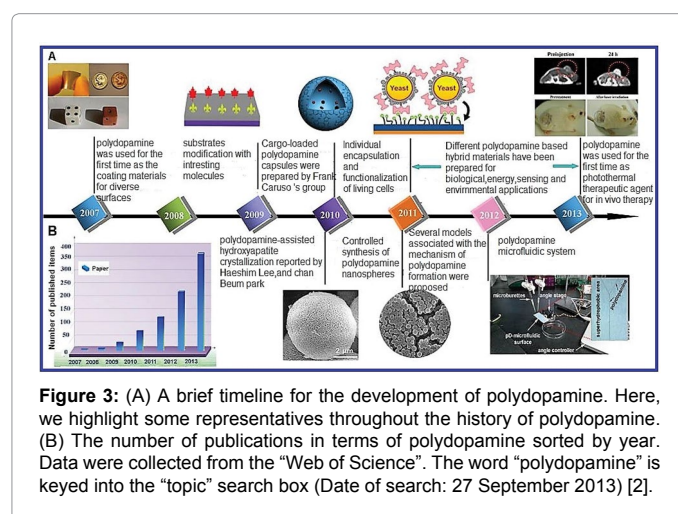
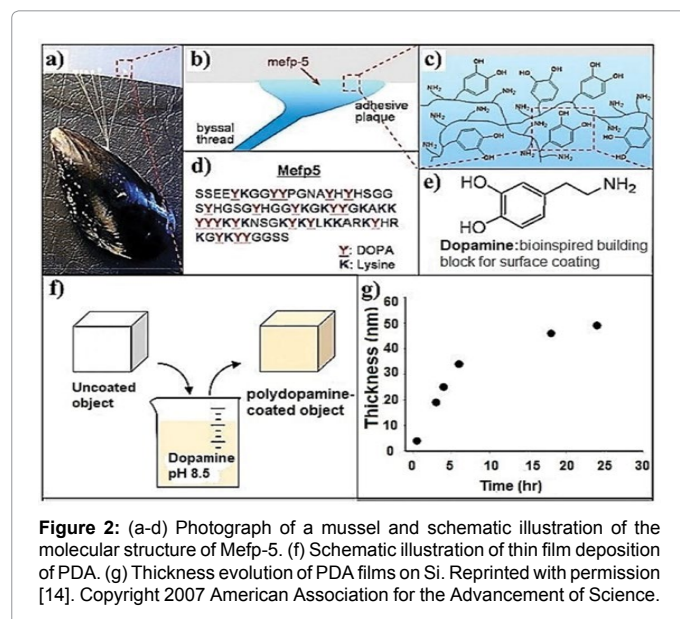
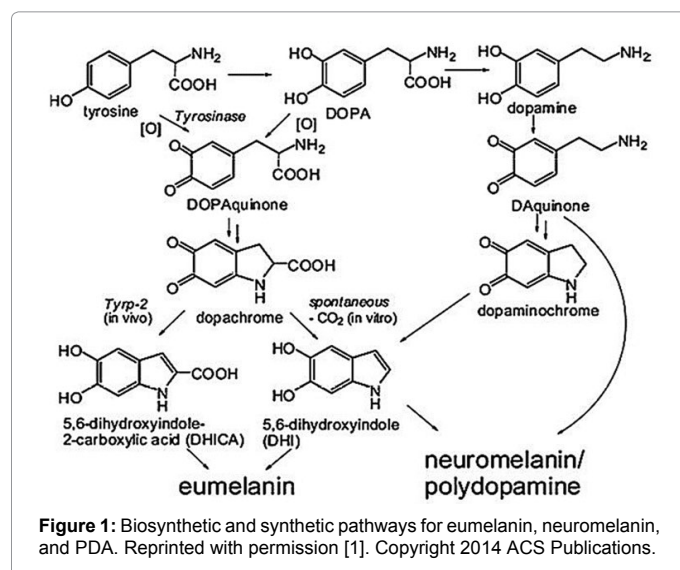
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synthesis, among these methods. One of the positive features of self-polymerization method is that without any need to hard reaction condition or advanced tools, it is also possible, therefore it is a very simple method. By dissolving DA hydrochloride in an alkaline solution in the presence of atmospheric oxygen, the self-polymerization reaction begins quickly. In this reaction, the product color changes from pale yellow to dark brown [18,19]. Here we can refer to various methods and dimensions that PDA synthesizes, including hollow capsules, core-shell structures, thin films and surface coatings [20]. By providing a simple, inexpensive and intelligent method for preparing PDA, one can see an increase in the number of papers on the manufacture and use of dopamine-based materials. Due to the antitumor activity of dopamine, a wide range of nanocomposites, capsules, and films has been made for anticancer applications using self-polymerization or other dopamine-based methods. It can be said that the molecular mechanism of dopamine self-polymerization not completely clear. As a point, it can be said that dopamine is first oxidized into the corresponding quinone through the dissolved oxygen in solution and



also the quinone subsequently changes by intramolecular cyclization to form 5,6-dihydroxyindole. Ultimately, in order to the formation of PDA by covalent polymerization and non-covalent self-assembly, 5,6-dihydroxyindole and the quinone derivative synergistically were used. Since further research on the structure of the PDA is outside the scope of this report, the reader is referred to other articles for more details [21-23].

Nanocomposites

In order to identify and treat various types of cancer and photoacoustic imaging-guided photothermal therapy (PTT) recently, polydopamine (PDA) nanoparticles (NPs) has been shown to be highly effective and can be used as a good candidate to improve the drug delivery process [24]. As already mentioned, these nanoparticles can be obtained from dopamine using different methods (that is, oxidation, enzymatic conversion, and so on) [14]. In general, the PDA is slowly produced by the oxidation process of dopamine and this polymerization involves various advanced steps and also external factors [25]. Although these effects are important for polymerization, yet some of them that determine the size and function of PDA NP is unclear. One of the methods previously introduced for the synthesis of PDA is the oxidation reactions [26]. In order to oxidize and form PDA NPs, Pre-determined conditions (oxidant, H₂O, monomer concentration, pH, stir rate, and reaction time) were used. Important factors that affect this analysis include pH, initial dopamine concentration, ammonium hydroxide/water ratio, alcohol/water ratio, stir rate and reaction time. One of the most important factors and parameters among these factors is water ratio because it has a high ability to distribute PDA NP size. According to Figure 4 and Table 1, it can be understood that pH levels and dopamine concentration can significantly affect particle size.

It can be said that, a dynamic light scattering instrument could confirm the size of the resultant NPs and morphology of these NPs was measured by electron microscopy. In order to write the equation and particle size relations, all the collected data were used and then the most important factor influencing the size of particles was determined [27]. A significant change in biomedicine is due to the rapid development of nanotechnology, especially nanoparticles applied in drug delivery systems. In order to diagnose and treat cancer, nano-platforms can be used to integrate multiple functions onto single-nanocomposites. Therefore, PDA is considered to be an excellent reagent for surface modification and functionalization of nanoparticles because of its strong and non-specific adhesiveness. In order to

fabricate functional nanocomposites for cancer diagnosis and therapy, many types of nanoparticles such as Fe_3O_4 nanoparticles [28,29], Mesoporous Silica Nanoparticles (MSNs) [30,31], polymeric nanoparticles [32,33], Graphene Oxide (GO) [34,35], upconversion nanoparticles [36,37], etc. have been coated with PDA. The ability to modify the surface is one of the wonderful features of PDA. It is accepted that gold-based nanomaterials are a good option for antitumor applications because they are simply synthesized and they have high biocompatibility and unique optical properties also their tunable near-infrared (NIR) localized surface plasmon resonance. The researchers examined that a variety of gold-based nanomaterials including Au Nanoparticles (Au NPs) [38,39], Au Nanorods (Au NRs) [40,41] and Au Nanostars (Au NSs) [42,43] could decorate with PDA. Kumar et al. represent that, for controlled fabrication of plasmonic core-petal nanoparticles with massively branched nanostructures on the surface of PDA-coated spherical Au NPs [44], oxidative nano peeling chemistry of PDA could be used. In their interesting work, they presented two main stages for the synthesis of these new nanoparticles as shown in Figure 5. Essentially as technological advancement progresses, technology progresses intrinsically. It can be said that the synthesis of nanoparticles by metals were managed into two main stapes as (a) nucleation and (b) expansion of nanoparticle. The presence of biological compounds in the chemical reaction blend leads to inhibitory effects on the growth and evaluation of particles [45-47]. Due to their exclusive optical, physiochemical and catalysts properties of AgNPs, they have been used to make considerable and effective applications [48,49]. Because of the high attraction of AgNPs in medicine, industry, and household, its use is increasing these days [50]. Green combination of silver nanoparticles (AgNPs) was accomplished and enhanced, through recovery Ag^+ ions with *Alcea rosea* flower extract. It can be said that some properties such as flower oils, AgNO_3 concentration, and reaction temperature are the main components of this bio reaction. Silver ions, as well as silver-based compounds, due to their powerful antimicrobial effects have been used as antimicrobial agents for a long time [51,52]. Because of the small size of AgNPs, they are exposed to a large fraction of atoms, which can increase the silver's surface that is in connect with microorganisms. This point can be reminded that the germicide characteristics of AgNPs result from the oxidation of silver molecules and Ag^+ ions release from the AgNPs surface [50]. There are bioactive compounds in *Alcea rosea* flower which can influence

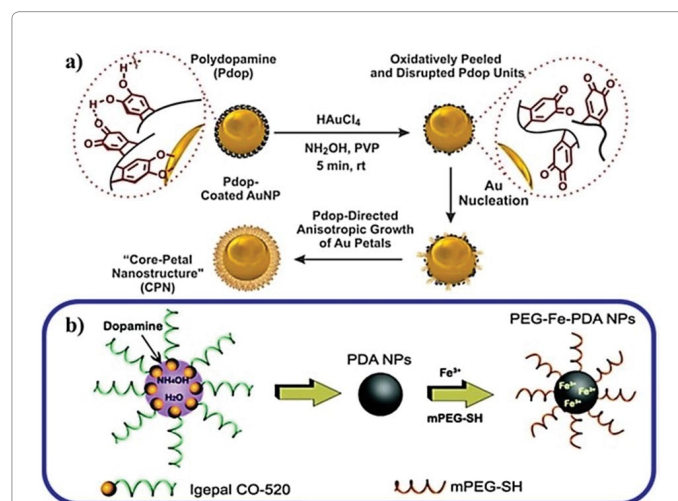


Figure 5: Schematic illustration of the syntheses of (a) plasmonic core-petal nanoparticles via oxidative nano peeling of PDA on Au NPs [48] and (b) PEG-Fe-PDA nanocomposites prepared by a reverse microemulsion method [68]. Reprinted with permissions [44], Copyright 2014 American Chemical Society and [68] Copyright 2015 Royal Society of Chemistry.

bioreduction of Ag^+ ions. So, the AgNPs manufactured are covered by hydrophilic biochemical compounds which have made them colloidal stable. As a matter of fact, the main factors in preparing quality-based AgNPs include silver concentration, flower extract amount and reaction temperature. Thus for making uniform particles these factors must be manipulated and checked [53]. So, in order to the diminution of Ag^+ ions to AgNPs, an optimum quantity of the green source oil is necessitate. For the time of AgNPs biogenesis, a useful diminishing and covering factor was natural carbohydrates existing in average Ephedra [53]. It can be said that absorbed nanoparticles to the outer surface of an organism have the ability to damage cell walls or membranes or release of ions that affect the performance of the organism. As shown in previous studies, the main toxicity of silver nanoparticles in the environment is related to the free ion in the aqueous phase [54,55]. The bacterial activity decreases, as the concentration of AgNPs increase [56,57]. AgNPs were synthesized using bark extracts of *Ficus benghalensis* and *Azadirachta indica* without the use of any external reducing or capping agent *Ficus benghalensis* (family Moraceae) commonly known as 'banyan' is an evergreen tree found all over India. It can be said that, for the silver nanoparticles synthesized by bark extracts of *F. benghalensis* and *A. indica*, the average size of particles was approximately 29 nm and 39 nm. As noted above, various types of nanoparticles have been coated with the PDA to be used to treat cancer and its diagnosis. Therefore, one of the AgNPs' applications can be considered for treating and diagnosing cancer in the future. One of the characteristics of polymer nanocomposites is that it is capable of being used as the carrier of water-soluble chemotherapy drugs such as paclitaxel (PTX) [58] and docetaxel (DTX) [59]. Functional modification and maintaining the original properties can be considered as a challenge for these biodegradable polymeric nanoparticles. Versatile PDA cover can be used to solve this problem. In order to coat DTXloaded star-shaped copolymer nanoparticles based on poly(lactide-co-glycolide) (PLGA)-D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) [59], some researchers used PDA. It can be said that, the outer layer of PDA enabled conjugation of thiol-terminated AS1411 aptamers by Michael addition reaction for targeted drug delivery. As a matter of fact it can be said that, PDA coating can modify Fe_3O_4 nanoparticles. An important point in Wu et al.'s work was the

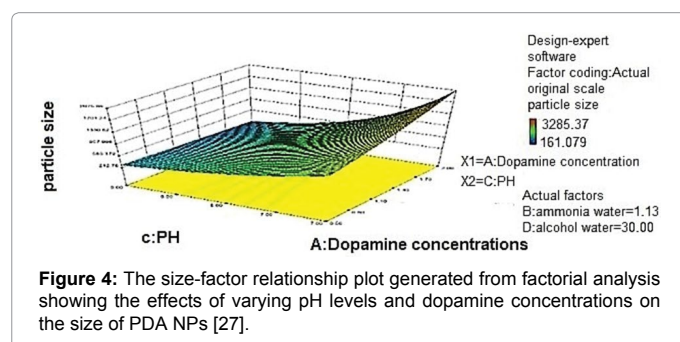


Figure 4: The size-factor relationship plot generated from factorial analysis showing the effects of varying pH levels and dopamine concentrations on the size of PDA NPs [27].

Factor	Relative significance of Factor	Low level	High level	Response Variable
Dopamine(mg/ml)	2	0.5	2	Nanoparticle size
pH	1	7.0	9.0	
Alcohol:Water (0%)	4	10.0	50.0	
Ammonia:Water (0%)	3	0.25	2.00	

Table 1: Data output from Design Expert 8.0 for PDA NP synthesis factorial analysis [27].

production of new clusters of superparamagnetic iron oxide nanoparticles (SPIONs) coated with PDA [60,61]. The SPIONs core was first produced by the emulsification method before being automatically deposited in the PDA shell, and then dispersed in Tris-HCl buffer (pH 8.5). Using an external magnetic field, can increase the accumulation of core-shell nanocomposite which is visible at the site of tumor and this fact has been proven by a darker T2-weighted magnetic resonance imaging (MRI). Another feature of the PDA is that, in addition to modifying the surface, it also plays a major role in nanocomposites. Nowadays, in order to fabricate PDA nanoparticles several methods have been presented and developed. For example, Liu et al. reported the preparation of colloidal nanospheres with a mean diameter of 70 nm using the oxidative self-polymerization process of dopamine in a mixture of water, ethanol and ammonia [19]. Ju et al. used neutralization of dopamine hydrochloride with NaOH in order to prepare melanin-like nanoparticles [62]. One of the characteristics of these nanoparticles was high dispersion in water and biological media. In addition, after testing, it was found that the size of the PDA nanospheres can be measured and controlled by adjusting the molar ratio of ammonia to dopamine. In another interesting research, Zhang et al. were used one-pot oxidation of PDA using hydrogen peroxide (H_2O_2) for making biocompatible fluorescent PDA nanoparticles [63]. Before adding aqueous solution (30% w/w) of H_2O_2 to the solution, dopamine was self-polymerized a pH 10.5 solution for 15 min and finally the fluorescent PDA nanoparticles were obtained. According to the methods mentioned so far, in order to prepare PDA nanoparticles with a simpler and milder method, can refer to the process mentioned in Xie and Wang research, in which a mixture of Tris buffer and isopropyl alcohol was employed [64,65]. Because the above methods are all considered relatively harsh conditions. For specific anticancer cases, it is possible to use a variety of polymers with functional components to form a shell and create useful nanocomposites [66,67]. Liu et al. were presented another new method to fabricate small PDA-based nanocomposites [68]. A reverse microemulsion approach in the blend of ammonia water, oil (cyclohexane) and surfactant (Igepal CO-520) were utilized to manufacture PDA nanoparticles with mean diameters ranging from 25 nm to 43 nm. According to Figure 5b, it can be seen that, these nanoparticles exhibited a high photothermal function and pH activatable MRI contrast for the model of mice when the PDA nanoparticles were combined with Fe^{3+} and modified with Poly(Ethylene Glycol) (PEG).

In a conceptual definition, gene therapy can be considered as the delivery of DNA or RNA to cells, which can be used to cure or to obstruct genetic untidiness. Recently, many approaches and gene-transporter have been advanced to getting better gene transferability. In order to provide a novel approach to cure illnesses and also merging gene therapy and chemotherapy, the usage of Polyethylenimine (PEI) based transfer material is a smart choice [69]. It can be said that, when ketones is exist, improvement methods for the chemoselective reduction of aldehydes are very important and gained notable consideration or even via usage of some additives materials such as thermoplastic thermoplastic, (PET, ABS, SAN) [70-72] nano tube [73,74] resins [75,76] graphene oxide in polymer composite For X-ray radiation shielding [77] and features of nanocomposites, linear low density polyethylene, ethylene-co-vinyl acetate and nano-clay particles through electron rays [78]. Due to the features mentioned, PDA may also be used to do this in future.

Photostability of Polydopamine

Figure 6 demonstrates that PDA is used in a specific and uniform range of absorption that includes ultraviolet to visible light. Perhaps

the point is that polydopamine is the most important melanin color. In fact, the PDA like other ultraviolet absorbers has the ability to absorb between 200 to 400 nm. This positive feature leads to the maintenance to substrate from the accumulation of UV radiation by the PDA. Several experiments have been conducted to verify the stability of the PDA, for example, when the PDA was exposed to ultraviolet light for 48 hours, it was observed that the absorption curve did not alter. This represents the inherent stability of polydopamine. According to the concept definitions, the PDA can be used for photo preservation activities. In order to defeat and degrade polymers, the catechol agent in PDA can trap free radicals that this action is very important. The resent research has investigated the radical anion superoxide performance in order to photodegradation of POD fiber [79].

As shown in Figure 7, the removal ability of PDA for radical superoxide anions were investigated, which is carried out by pyrogallol autoxidation approach [80,81]. It has been accepted that pyrogallol has the ability to oxidize itself in an alkaline solution along with radical propagation and can also create colored products with an absorbance of 320 nm. As a matter of fact, it can be said that the formation of the color product can usually be controlled by the presence of antioxidants. If you notice the curve (a) in Figure 7, it can be seen that color product is continuously created in 240 seconds due to pyrogallol self-oxidization

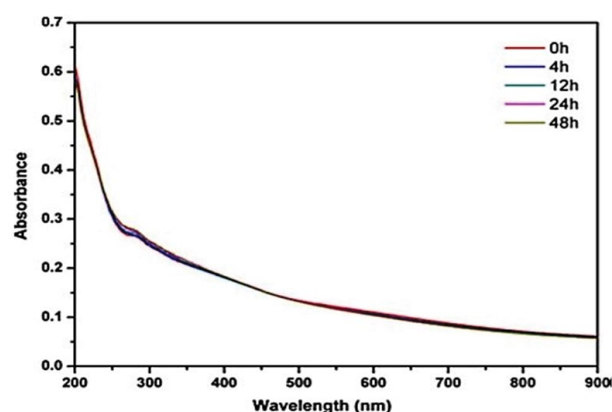


Figure 6: UV-spectra of PDA coating after varied UV exposure durations [80].

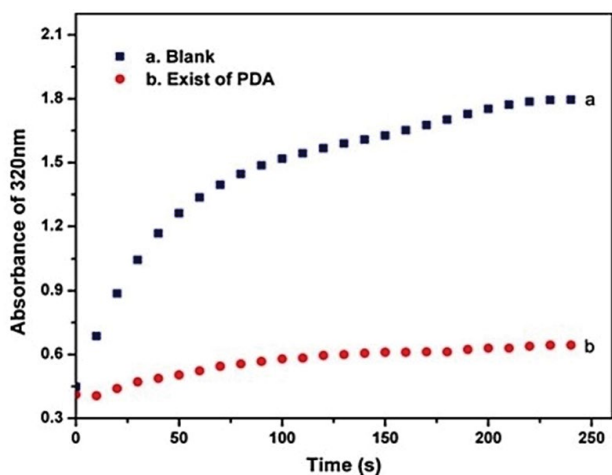


Figure 7: Absorbant changes of colored intermediate product formed by pyrogallol autoxidation with time (a). Blank (b). Exist of PDA [80].

process under the alkaline state. In addition, an agent such as radical anion superoxide manufactured can create a specially designed color product. In accordance with curve b, a PDA may be utilized to inhibit the creation of the colored product. This demonstrates the effective ability of the PDA to eject the superoxide anion radical. All the points presented were due to the presence of the catechol class in PDA construction. Based on the experiments conducted to evaluate the photostability of POD, PDA can be utilized because, in addition to ultraviolet absorption, it can also reject the radical anion superoxide and stop the process.

Polydopamine Applications

Drug delivery

Since polydopamine capsules are highly soluble in water, unique biocompatibility and most importantly cavities on their surface that can contain large amounts of medication, they are considered as a convenient and cost-effective substance for drug delivery systems. One of the characteristics of hydrophobic anticancer drugs is that they are able to place in the polydopamine cavities and are simply converted into the same form. In another interesting study, Zhou et al. said that prepared polydopamine capsules have the ability to absorb drug based on the polydopamine mediated mode [82]. Using the drug rhodamine 6G (Rh6G) have the ability to progress the pharmacodynamics properties of polydopamine. In addition to the loading of Rh6G in the wall of the PDA capsules, it also happened in the inner wall, which is verified through a fluorescent microscope. It has been proved that, by expanding the size of capsules, the amount of Rh6G is also increased as the inner surface becomes larger. The most important parameters affecting the loading of PDA microcapsules can be considered as the pH of the solution and also how to load the molecules. In general, it can be said that methyl orange (MO), Rh6G and alizarin red with cationic or anionic features at various pH content was chosen as the template of molecules. Due to the existence of various functional classes, PDA showed zwitterionicity. When the PDA capsule wall is positively charged, the PH is lower than the isoelectric dopamine point. But even if the PH is the same, MO molecules are in the neutral state, on the other hand with an anionic sulfonate category, and alizarin red can be said that negative loading occurs. Indeed the positive loading of the PDA depends on the electrostatic interactions between them. On the other hand, due to PH-related reasons, there is a very strong repulsive force between PDA capsules and Rh6G molecules. Recently, Wang and coworkers present factors such as pH value and temperature double-flexible capsules using bond arbitrary broom of oligo(ethylene glycol) methacrylate and also 2-(2-methoxy ethoxy)ethyl methacrylate on the exterior level of the PDA. If some agents such as the PH values and temperature of the solution varied in this case, capsules demonstrated governable loading and finally discharged [83]. Despite the great benefits of the loading process it can be said that the system mentioned above still faces a problem like dissatisfaction with drug release in aqueous systems. Caruso and coworkers evaluated a new impulse-flexible drug delivery method through covalently oxidizing the surface of polydopamine capsules with a pH-cleavable poly(methacrylic acid) (PMASH)-doxorubicin (Dox, an anticancer drug) couple [84]. It is accepted that, prominent solubility and good stability in aqueous and buffer conditions associated the Dox discharge following 20% under special PH state more than 12 hours are the main features of new drug delivery system. In fact, by diminishing the pH values, it can be seen a raised Dox discharge, and in next step, almost 85% of the drug was discharged at pH 5.0 across the same time. From the numerous experiments carried out, one can understand that Dox-loaded polydopamine capsules were more beneficial than free Dox for

the elimination of the HeLa cells at the same centralization of Dox. Therefore, using this drug delivery method can improve the therapeutic capability and decrease the toxicity of free drugs, which is very valuable. PDA has especial usage such as Photothermal Therapy (PTT) and chemotherapy when it fabricated in the form of nanocapsules and nanoparticles. In order to improve the anticancer activity of DA-melanin colloidal nanoparticles with the flexible particle, Liu et al. have done a lot of experiments [19]. One of the features of resulted nanoparticles is the ability of the photo thermal changing capability of 40% that is not comparable with PTT factors, for instance, Au nano-rods (22%) previously presented. On the other hand, some researchers have manufactured PDA nanoparticles with flexible particle size and improved the PH value loading and discharge of the anticancer drug Camptothecin (CPT) [85]. Before loading the nanoparticles by present in CPT-methanol solution, nanoparticles were made ready using NaOH-induced polymerization of DA. In comparison with PDA nanoparticles prepared by mesoporous emulsion template (0.08 μmol of CPT / 50 mg of PDA), these prepared nanoparticles showed a better capability of loading (1.46 μmol of CPT / 1 mg PDA). In the same way, Tamanna and Yu have investigated that PDA nanoparticles could act as a sizable nano-reservoir in order to load the antibiotic Rifampicin agent [86]. The stability of these nanoparticles in the acidic condition has been proven for several days. Nevertheless, in order to evaluate some properties of these particles, more detailed study and research is required on them. One of the most important ways to eliminate existing disorders in today's therapies is to integrate chemotherapy and phototherapy. Dong et al. were investigated and presented an interactive nanosystem for the drug-loaded PDA NPs synthesized [87]. Figure 8 illustrated the PDA nanoparticles synthesized using oxidative polymerization of lactosylated DA in one pan [87]. Some features can be considered for these nanoparticles such as, powerful NIR laser

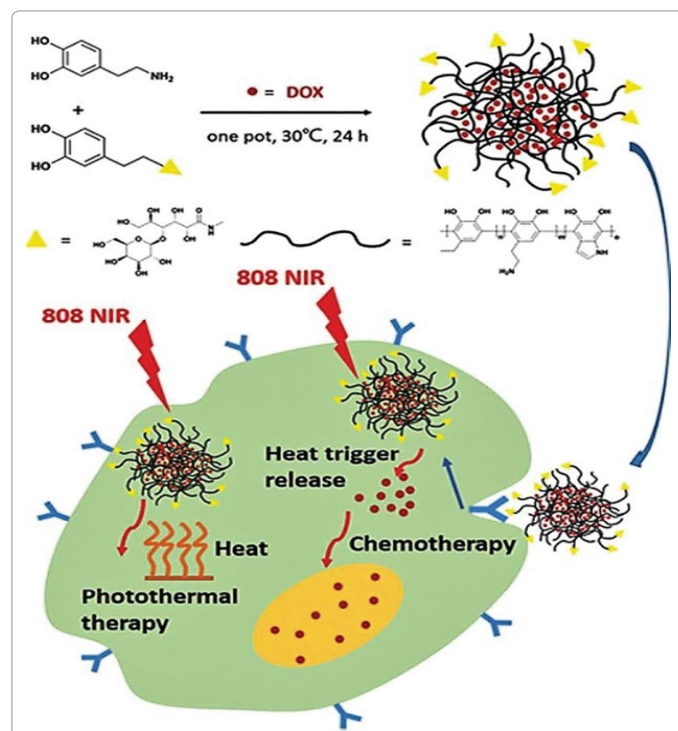


Figure 8: Illustration of the one-pot preparation of the sweet DOX loaded nanoparticles PLDA-DA, the active targeting cellular uptake, and the synergistic combination of chemo-photothermal therapy by NIR light irradiation; reprinted with permission [87]. Copyright 2015 Macromolecular journals.

absorption, excellent photothermal capability and also appropriate photostability. In several experiments the merged photothermal and chemotherapeutic methods of Doxorubicin-loaded nanoparticles were controlled. It is accepted that through revealing the nanoparticles to a NIR laser ray (5 min, 808 nm, 2 W cm⁻²) provide a portion maximal repressive concentration (IC₅₀) of 11.6 µg/mol, that was lower than IC₅₀ resulted after chemotherapy (IC₅₀-43.19 µg/mol) and phototherapy (67.38 µg/mol) alone.

In the same way, in drug delivery systems, different polydopamine coreshell nanostructures have also been presented and tested. Liu et al. in their interesting work, focused on Fe₃O₄@PDA coreshell NPs in order to determine the pH responsive drug delivery of Bortezomib (BTZ) [88]. It can be said that, some properties for instance controlled release rely on the two-sided covalent bond between catechol classes of PDA and boronic acid of BTZ. Because of covalent bonds, drug discharge occurred only in acidic pH gradually and also the transmission of Doxorubicin by PDA covered magnetic NPs had been tested for cancer therapy process [89]. Figure 9 demonstrates theranostic factors for intracellular mRNA diagnosis and MRI, due to the great fluorescence stop capability and powerful NIR laser adsorption features of PDA. It should be noted that research has been carried out by Lin et al. [90].

Recently, due to the unique properties and the ability to handle polymers, many drug/genes delivery based polymer systems have been designed and presented. The use of PDA adhesion properties to modify surfaces and materials, as well as the usage of PDA-coated materials cannot alone affect the solubility of polymeric nanocarriers. On the other hand, it is capable of creating a suitable substrate for secondary reactions of some materials, such as PEG atoms, effective therapeutic parameters and targeting factors [91-93]. It is accepted that, poly(lactic-co-glycolic acid) PLGA nanoparticles based drug delivery process could be manufactured by mussel chemistry and following agglomeration of PEG and TAT peptides [94]. In the next step, some features of the intracellular delivery of an anticancer drug (PTX) and their especial applications were also analyzed. As a result, it can be said that, in comparison with control category, the PLGA nanoparticles revealed great uptake rate in MMP-2 pre-treatment class. For drug delivery applications, the PTX exhibited appropriate ability to eliminate after charging onto PDA controlled biodegradable PLGA nanoparticles. For immobilization of practical polymers and charging drugs for instance DOX and cisplatin for pH-measured drug delivery usages, as reported in recent works, Zhang and co-workers also proved that PDA altered graphene oxide films, carbon nanotubes and silica nanoparticles can be utilized [95-97]. In fact, since PDA-based materials have a unique feature, such as phototherapy, it is possible to introduce these smart drug delivery systems as therapeutic parameters. As it mentioned above, in order to create multitask theranostic organizations, improvement of some features like adhesion capability, great photothermal transmission effect of PDA based nanomaterials and good reactivity for the secondary reaction are required [36,88,90,98-100]. An interesting property of nano-capsules is that they occupy more space than the nanoparticles to load drug molecules so how to manipulate them is very essential [82,101-108]. For instance in order to create the PDA based nanocapsules with various shapes, using emulsion minim as the model is needed [84]. These PDA capsules were utilized for merging the thiol including polymers, which were combined through thiol-maleimide chemistry by thiolated poly(methacrylic acid) (PMASH) and a maleimide hydrazine derivative of doxorubicin. The ability to discharge drug carriers under the acidic condition like endosomes and lysosomes is related to the hydrazone bond which is an acid-labile class but ultimately showed significant sustainability. Figure 10

demonstrated that, by manipulating the PH value, the DOX discharge can be simply checked and also it can be utilized in biological delivery systems significantly. The measured discharge manner of DOX from these PDA capsules was verified through the deconvolution of microscope pictures.

Figure 10c demonstrated this point which, the AF488-labeled PDA capsules have the capability to enter via HeLa cells and also they are predominantly divided into the cytoplasm. But, as shown in the Figure 10b maybe some of DOX entered via cells have the ability to disconnect from the PDA capsules and also penetrate in cell nucleus easily. When the DOX disconnected from the PDA cellular, In comparison with active DOX, the DOX showed better and more comprehensive properties for the elimination of cells. According to the properties presented, PDA capsules can be considered as one of the most suitable drug delivery candidates, moreover, it has the ability to reduce negative effects and also progress the transfer process. Scientists have been able to achieve graphene-based nanocomposites by performing a series of experiments using the powerful and excellent adhesion properties of dopamine [96]. The high ability to load cisplatin and measure the release ration in acidic environments are the most important features of these graphene oxide-based polymer nanocomposites, which is strongly mentioned in their work. Besides, due to their powerful biological property, they are able to utilize for many drug delivery systems. Because dopamine has a unique and strong adhesion, it can be used for stainless applications and ultimately for the steady discharge of siRNA [109].

Cancer detection

One of the most important issues recently addressed by scientists is the introduction of novel and up to date nanotechnology-based approaches to cancer detection and treatment because it is one of the

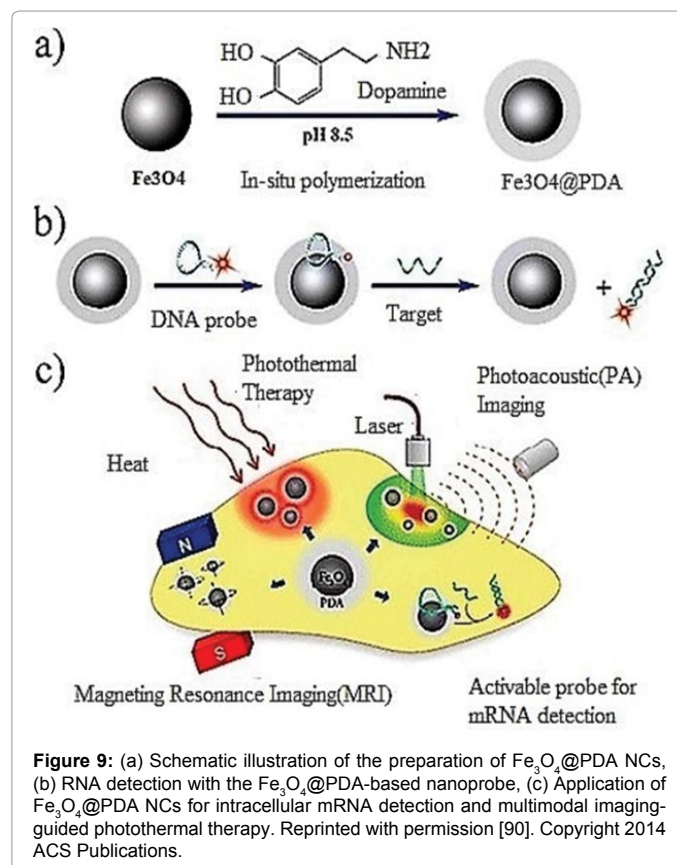
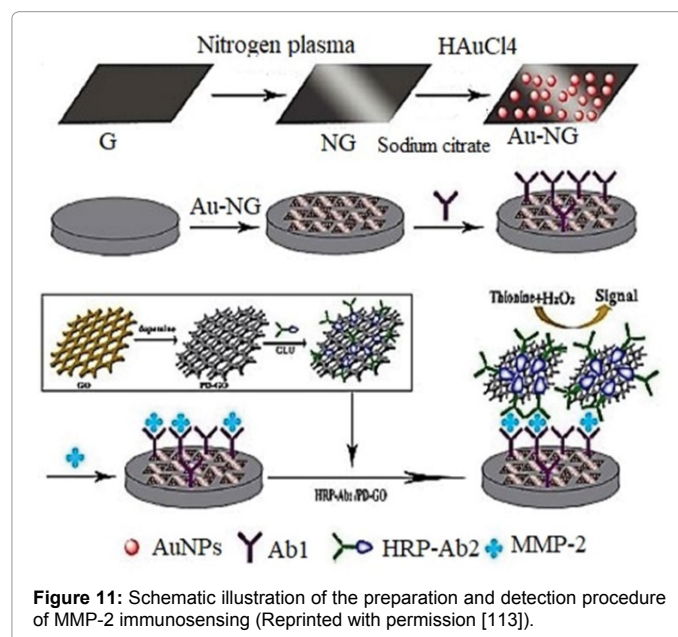


Figure 9: (a) Schematic illustration of the preparation of Fe₃O₄@PDA NCs, (b) RNA detection with the Fe₃O₄@PDA-based nanoprobe, (c) Application of Fe₃O₄@PDA NCs for intracellular mRNA detection and multimodal imaging-guided photothermal therapy. Reprinted with permission [90]. Copyright 2014 ACS Publications.

most important causes of mortality in today's life in cancer [110,111] because cancer is one of the illnesses that endangers human life, methods such as RAMAN technology have been utilized to diagnosis it [112]. Among the methods for identifying cancer, the electrochemical technique can attract a lot of attention due to its powerful sensitivity and comfort. It should also be noted that, the detection and diagnosis of cancer in the first step can lead to timely and effective treatment. Matrix metalloproteinases (MMPs) belong to a group of emitted zinc-dependent endopeptidases, that for matrix-based processes, they are vital and are utilized for a wide variety of cancers. It can be said that basic properties such as the ability to select and powerful sensitivity of these MMPs are very effective in monitoring and controlling the disease. Recently, by utilizing the special properties of graphene oxide and Au nanoparticles, Zhu et al. produced a sensitive electrochemical tool [113]. Au nanoparticles were first fixed on graphene films to create these sensitive tools, and at the next step would attach to the electrode. As shown in Figure 11, by merging two factors such as mussel-inspired chemistry and Michael addition reaction, it can be said that the HRP-Ab2 was fixed on the graphene oxide films. By using the creation of Ab1/MMP-2/HRP-Ab2 fix construction, the HRP-Ab2 limited on the graphene oxide films could be attached on the poles and ultimately can lead to gain of the signal resulted. Thus, considering the above points, we can create sensitive tools for cancer identification that have high accuracy, good quality and significant stability. It is accepted that



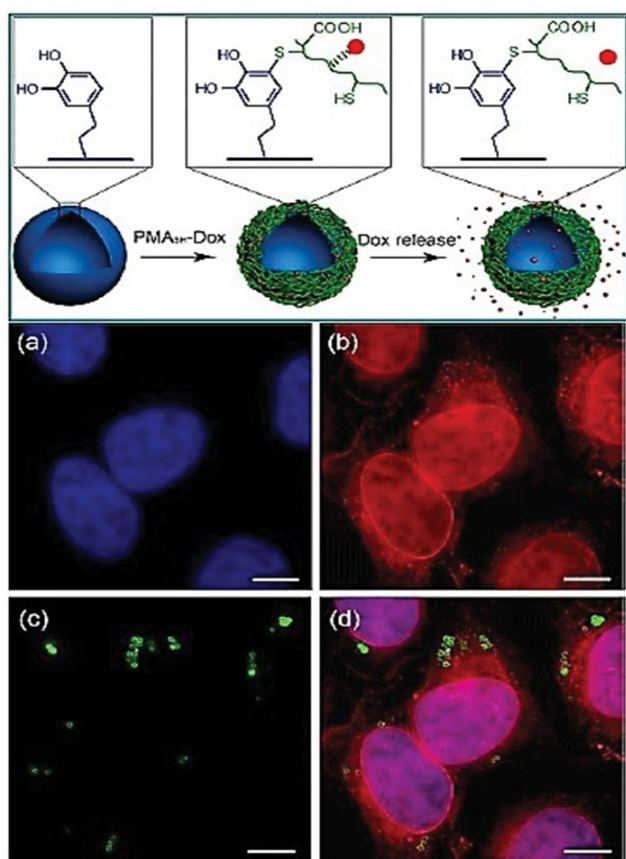
PDA can play a vital role in the immobilization of a large number of antibodies and in the manufacture of sensitive tools [114-118].

In order to identify the familial illnesses, disease-associated pathogens, and other biotic actions, an effortless, immediate, delicate and inexpensive procedure for the diagnosis of especial DNA series is required. It has been proved that the characteristics and manner of absorbing the single ring and two loops of nucleic acids are very dissimilar. For further explanation it can be said that single-loop nucleic acids can simply be absorbed into the surface of the nanomaterials and ultimately lead to the extinguishing of nucleic acid fluorescent. On the other hand, by adding similar nucleic acids, it was possible to create double chain nucleic acids that were isolated from these nanomaterials. Indeed, in order to identify especial nucleic acids, the fluorescence was charged and could be utilized. Today, a certain group of nanoscale materials can be introduced as the fluorescent softener, which includes carbon nanotubes, graphene-based materials, carbon dots, and MoS₂ etc. [119-124]. Sun et al. have investigated that using a relatively simple process that combines alkaline water and ethanol, some properties of PDA nanoparticles such as shape and dimension can be improved (Figure 12). From the results of the experiments it can be seen that the PDA nanoparticles can be introduced as an adaptive stimulus for identifying human immunodeficiency virus (HIV). Factors such as easy preparation, good biocompatibility and high water dispersal are all unique features of the PDA nanoparticles which can be considered as an effective candidate for identification of nucleic acid.

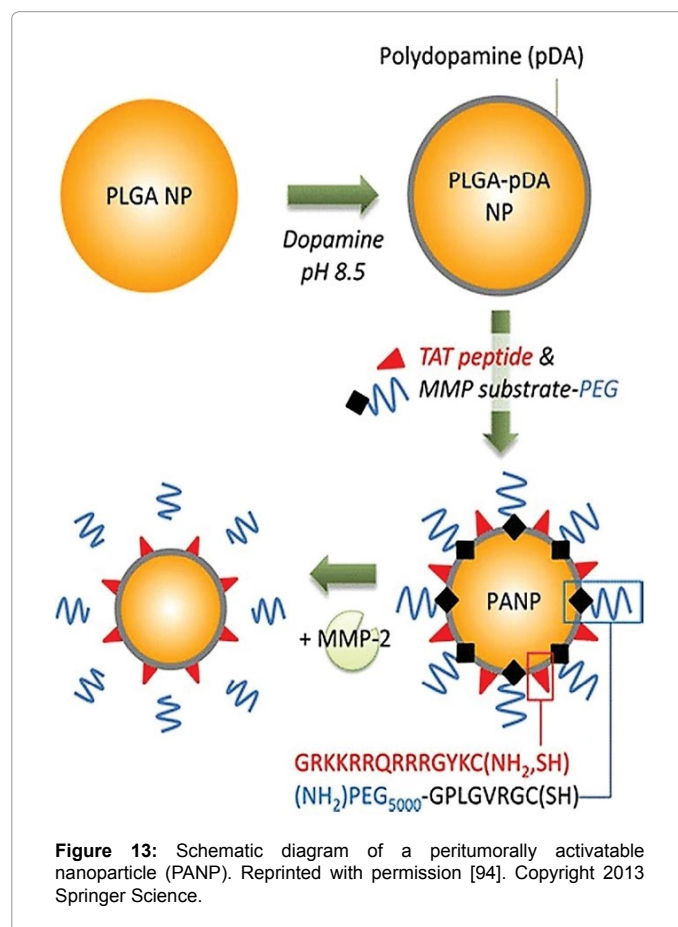
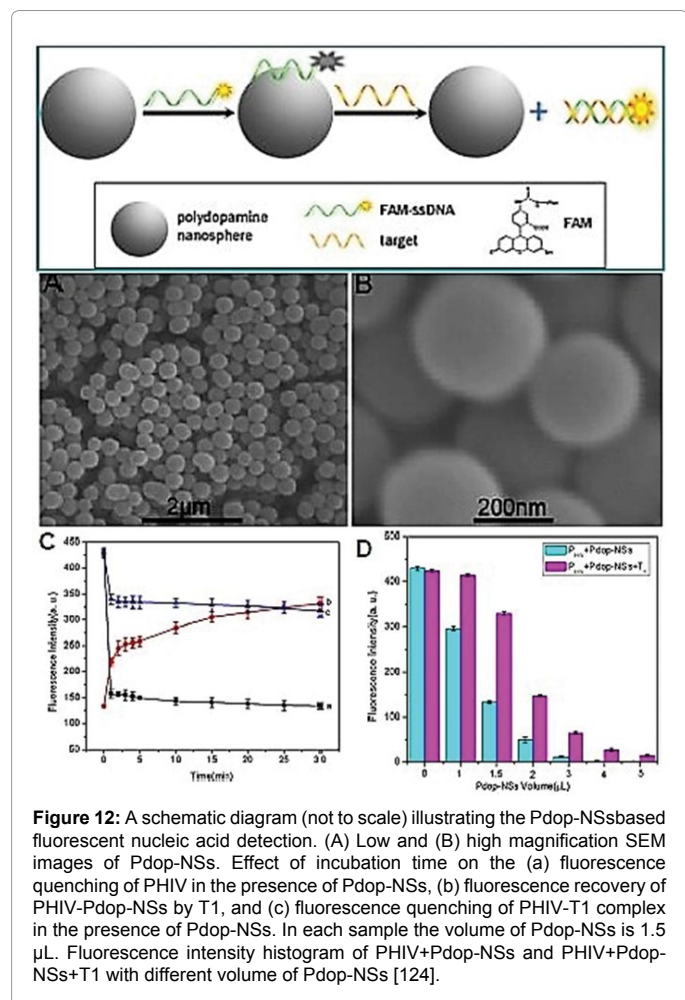
Since the PDA nanoparticles can merge the identification class and the signal reinforcement molecule, therefore it can evaluate as a powerful procedure. Furthermore, some agents, for instance, Fe³⁺-complexed PDA is a favorable factor for MRI. In addition, an important feature that makes the PDA a novel arm for improving Raman scattering (SERS) imaging surface is that it has two similar properties to carbon materials like graphite and graphene.

Other

The sulfoxidation polymerization activity of DA was widely utilized for modification of different surfaces because the PDA molecules have great adhesive feature. One the interesting feature



of this action is that, if new molecules are added to PDA sheets, no problem is created. Indeed, for glycoanalysis, lectins were removed using the PDA [125]. By numerous experiments, scientists presented some issue such as the especial activities of lectin concanavalin A (Con A) and glycoprotein ribonuclease (RNase B), and also the ability to choose Con A to its particular glycoform. The performance of the protein Trypsin on different organic and inorganic surfaces such as polycarbonate, copper, titanium oxide, and cellulose was investigated by Lee et al. [126]. By using a two-step procedure, the modification was done. In addition, after modification it can be said that enzymatic function was maintained as obtained from the transformation of N- α -benzoyl-DL-arginine p-nitroanilide (BAPNA) to a chromophoric product. Besides, Zhang et al. have investigated the improvement of the catalytic performance of mitochondrial enzymes, and functional strength [127,128]. Their goal was to produce capsules that were modified by multi-enzyme procedure. During this production system, several enzymes such as α -amylase, β -amylase, and glucosidase at three various conditions were modified. In addition to all the positive and effective points of this method, it can be said that because of the high adaptability of this process to the test condition, it also can be utilized in areas such as delivery of drugs and genes, catalysts and assays. Gallotti et al. were reported PDA assisted films modification method in order to prepare peritumorally activatable NPs (PANPs) [94]. Figure 13 demonstrated functionalize of poly (lactic-co-glycolic acid) NPs with PDA through immobilization of TAT peptide (a membrane-translocating peptide sequence-GRKKRRQRRRGYKC-NH₂) and a



combination of PEG and matrix metalloproteinases films (MMP-2). In this case PDA played a dual role to immobilize TAT peptide and PEG as well as form combines with MMP-2 substrate peptide. While PEG lets the elimination of PEG upon MMP-2 disposal at the aim. Although this process was very simple and effective in preparation, on the other hand, early medications could easily be released, which is a disadvantage. This problem can be solved by creating a covalent compound form the drug to the nanoparticles with a connector that is subjected to a hydrolysis test for a specific period of time. Recently, for electrochemical immunoassay, PDA-functionalized MSN was presented [129]. Thionine moieties were doped within silica pores as well as onto PDA coating via in situ formations of PDA coating over MSNs. Then human IgG antibodies were labelled on MSNs via Schiff base reaction between amine groups of antibody and catechol quinone groups of PDA to obtain a nanoprobe. Upon exposure to the strongly alkaline environment, Thionine could be easily separated from the nanoprobe and further investigated for electrochemical assay.

In order to evaluate intracellular reactions in polymer-silicate nanocomposites, through modification of clay, by using amplification in epoxy resin, PDA has the ability to handle this action. If oxidative polymerization continues for up to 2 hours, a PDA monomer with a suitable thickness is obtained on pristine montmorillonite clay (Na-MMT). Due to powerful reactions with the matrix, the PDA covering, made easy the reactions and scurf of the D-clay in the epoxy resin. But, in order to achieve a notable move at very low clay loading, the merging of D-clay in epoxy resins was an effecting method to increase the strength of molecules. In addition to the interesting features that have been considered for the PDA so far, scientists have also

considered electronic applications for this material, for example they looked at the properties of PDA-based phototransistors and achieved some wonderful results at relatively low voltages [130]. Additionally, by using copolymerization of DA and 5-Scysteinyldopamine, a photocapacitive sensors were progressed [131]. Different properties of photo-capacitive based materials such as metal-insulator-metal and metal-insulator-semiconductor have been investigated and also it is accepted that, these tools produce possible devices for radiating light. Additionally, according to studies on PDA-modified graphene reduction nanocomposites, it can be said that besides being utilized in electrocatalysts and bio-sensors applications, they have a very good electrochemical activity in comparison with previous models [132,133]. Actually, PDA was found as a carbon predecessor in the creation of a new core shell collection [134]. Fu et al. have investigated the properties of PDA modified decreased graphene oxide silver nanocomposites for the electrochemical reduction of hydrogen peroxide [135]. Fu et al. have concentrated on electrocatalytic features of decreased graphene oxide by knowing this point that PDA has the ability to decrease and modify [136,137]. Many experiments have been carried out for the reduction of graphene oxide (RGO) and at the same time modification with palladium (Pd) NPs. The nanocomposites resulting from this modification have unique characteristics, which have not been detailed due to the purpose of this article.

Conclusion

This review article gives an overview of some of the recent developments in the use of PDA in biomedical fields. Since the discovery of the oxidative self-polymerization of dopamine for preparation of PDA materials, much attention has been paid to the fabrication and applications of PDA materials. Although significant hurdles for their clinical applications still exist, it can be expected that dopamine-based materials will in the future create new solutions for the challenges of cancer diagnosis and drug delivery. The research on dopamine-based materials remains an active subject due to new developments and challenges, and more research efforts should be made to carry forward their clinical applications.

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