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Advances in polyaniline for biomedical applications

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Abstract: Conducting polymers are an outstanding class of materials characterized by electroconducting properties that make them good candidates for applications in several sectors. Among them, polyaniline (PANI) is unique for its extraordinary ability to conduct electricity, biocompatibility and low toxicity. In spite of its surprising features, to date PANI have not yet found application in the practical uses, because of its low solubility and processability. In order to overcome these limitations, different approaches have been developed, such as polymer grafting processes, PANI-based composites and blends preparation. The present review describes the most recent advances on PANI applications in biomedical fields, such as antioxidant, antimicrobial and antivirus activity, drug delivery, cancer therapy, etc. A look to the synthetic procedures is also reported because it is crucial for the realization of more innovative materials in the next future.

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Abbreviations: 2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid (ABTS); bovine serum albumin (BSA); carbon dot (CD); carbon nanotube (CNT); Ce6 ((7S,8S)-3-carboxy-5-(carboxymethyl)-13-ethenyl-18-ethyl-7,8-dihydro-2,8,12,17-tetramethyl-21H,23H-porphine-7-propanoic acid); cetuximab (CET); cholesterol oxidase (ChOx); conducting polymer (CP); deoxyribonucleic acid (DNA); diethylenetriaminepentacetic dianhydride (DTPA-DA); 1,1-diphenyl-2-picrylhydrazyl radical (DPPH); drug-eluting stent (DES); electron paramagnetic resonance (EPR); emeraldine base (EB); emeraldine salt (ES); glassy carbon electrode (GCE); glucose oxidase (GOD); hepatitis B virus (HBV); hepatitis C virus ribonucleic acid (HCV-RNA); hepatitis E virus (HEV); hydrogen atom transfer (HAT); hollow carbon sphere (HCS); immunoglobulin (IgG); International Union of Pure and Applied Chemistry (IUPAC); ionic liquid (IL); limit of detection (LOD); magnetic resonance (MR); metal-organic framework (MOF); montmorillonite (MMT); multiwalled carbon nanotube (MWCNT); *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC); nanoparticle (NP); near infrared (NIR); *p*-toluenesulphonic acid (pTSA); polyaniline (PANI); polycaprolactone (PCL); polydopamine (PDA); polyethylene glycole (PEG); polyethylene glycole diacrylate (PEGDA); polyfuran (PFu); polylactic acid (PLA); polypyrrole (PPy); polythiophene (PTh); polyvinyl alcohol (PVA); reactive oxygen species (ROS); reactive sulfur species (RSS); reduced graphene oxide (r-GO); ring opening polymerization (ROP); saturated calomel electrode (SCE); single electron transfer (SET); smart drug delivery system (SDDS); surface plasmon resonance (SPR); upconversion luminescence (UCL).

1. INTRODUCTION

Owing to the growth and aging of world population the industrial chemistry is continuously involved in new challenges in numerous fields ranging from drugs synthesis to renewable energy sources investigation, passing from environmental remediation and so on. It has been estimated that in 2050 nine billion people will populate the Earth and as a consequence the possibility to count on innovative smart materials is crucial to find possible solutions in many sectors,

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such as technology, energy, medicine, environmental remediation, etc.

Before the 20th century a large number of materials was developed to face the hard and emerging requirements of the world, in particular in the field of biomedicine. Among them ceramics, metals, carbons and alloys have been extensively investigated and utilized [1-3].

Carbon-based materials (nanotubes, graphene, fullerene, etc.) have found applications as sensors for energy storage and conversion in order to replace the use of fossil fuels, as efficient candidates for the production of clean energy by sustainable processes, innovative materials for the degradation of organic pollutants, etc. [4].

Similarly, nanostructured metal oxides have convinced the scientific community for their fascinating optical and electrical properties that make them potentially suitable for application in electronics, optics, photonic and sensors [5].

Probably, after their discovery polymers have been the most employed materials in an extraordinary number of sectors (food packaging [6], biomedicine [7], aerospace [8], energy [9], coatings [10], etc.). Some properties, such as resistivity, dielectric constant, flexibility, lightness have strongly contributed to their success.

More recently, (CPs) have gradually increased the interest of the science thanks to their outstanding properties that make them appealing for numerous applications in many areas ranging from thin film transistor [11, 12] to organic solar cells [13], passing from supercapacitors [14-16], smart adhesive [17], environmental remediation [18, 19] and so on [20, 21, 22].

From the discovery of their good electrical and ionic conductivity, optical properties, high temperature stability and interesting redox abilities the studies on CPs and their composites have skyrocketed. If on the one hand some research groups have addressed their efforts in the development of more environmentally friendly synthetic approaches [23-28], others have driven their work on innovative applications [29, 30].

This new generation of “smart” materials has been recently investigated for application in biomedicine for antimicrobial therapy, drug delivery, tissue engineering, biosensors, actuators, etc. [31].

Most of the CPs features are strongly dependent on the kind of synthetic procedure that can influence morphology, conductivity, processability and all the other properties of these materials. For this reason, part of the present review is dedicated to the description of the most common synthetic methods, underlining the main advantages of each approach. Moreover, the state-of-the-art of the recent application of PANI in biomedicine is described.

2. Conducting Polymers (CPs)

Conducting polymers are an important and innovative class of materials that has represented a real revolution in the field of polymers. They are characterized by the presence of an extensive conjugation along the backbone with alternating single and double bonds [32]. The π electrons in the conjugated chains are responsible of the electric conductivity of these materials thanks to the delocalization into a conduction band that makes them similar to metals. For this reason and for their extraordinary ability to conduct electricity they are also denominated “synthetic metals” [33]. Since the discovery of the highly conducting polyacetylene (PA) in 1977 from Shirakawa and coworkers [34, 35], the interest of the scientific community towards these materials grew with the idea to overcome the limits related to the PA

instability and in order to launch a new class of materials with unique properties. The efforts of the three scientists Shirakawa, Heeger and MacDiarmid were rewarded in 2000 with the Nobel prize in chemistry “for the discovery and development of conductive polymers” [32].

In addition to PA, polypyrrole (PPy), polythiophene (PTh), polyfuran (PFu) and polyaniline (PANI) are representative members of this class (Figure 1).

Figure 1: chemical structure of: a) polyacetylene, b) polypyrrole, c) polythiophene, d) polyfuran, e) polyaniline.

All the CPs are synthesized by two principal approaches: chemical and electrochemical synthesis. The first way generally leads to powders, whereas the former allows to obtain films. If on the one hand the chemical synthesis is the best route for the mass production of CPs, on the other hand the obtained polymers are hard to be processed and structural modifications are necessary to enhance their electronic properties. On the contrary, the control of the polymerization process is easier by the electrochemical way, even though this approach fails for large production quantities [36]. Over the last few years, numerous and various chemical synthetic approaches have been developed to produce CPs in large scale maintaining a fine control of their characteristics. This is determining for real applications where highly performing materials in mass production are required.

Thanks to their multiple applications CPs market is booming. It was evaluated at USD 3.91 Billion in 2016 and is projected to reach USD 6.77 Billion by 2022 [37, 38].

3. Polyaniline

Among the CPs PANI occupies a special role for its diversity of structural forms, high environmental stability, unique doping/dedoping process that allows to quickly switch from insulator to conductor and *viceversa*.

In the family of CPs PANI has a long history. In fact, it is one of the oldest CPs that has continuously attracted attention.

It is known that aniline monomer was isolated as early as 1826 by the pyrolytic indigo distillation [39]. Even though it is not clear the data of the first attempt of aniline polymerization, it is reported that aniline was oxidized for the first time early as 1834 [40] and 1840 [41] by oxidation of indigo distillation by chromic acid.

“Aniline black”, a black precipitated (PANI) part of melanine, was first observed in 1860 [42], whereas the first accurate scientific research dates from Green and Woodhead [43-45]. Only after the demonstration of the conducting properties of PANI by acid doping the interest in this material rose up significantly [46] (Figure 2).

Figure 2: number of published papers on PANI per year.

PANI consists of aniline repeated units. The presence of -NH- groups alternating with aromatic cycles allows the formation of structures characterized by different oxidation states. Among the existing PANI forms, leucoemeraldine, emeraldine and pernigraniline are the three most common ones (Figure 3).

Figure 3: chemical structure of: a) leucoemeraldine, b) emeraldine, c) pernigraniline [47].

However, many other intermediate forms are available, depending on the degree of oxidation of the units.

The most part of the properties and characteristics of the polymer is strictly related to the oxidation state of the backbone. Table 1 summarizes some of this information.

Table 1. Oxidation degree and properties of the different PANI forms [45].

Name	Oxidation degree	properties
Leucoemeraldine	Totally reduced form	<ul style="list-style-type: none"> - Amorphous material, - color from pale brown to white, - high melting point, - insoluble in all the organic solvents, - unstable in air
Protoemeraldine	Partially oxidized form	<ul style="list-style-type: none"> - violet color, after protonation it forms yellowish-green salts - soluble in acetic acid
Emeraldine	Half-oxidized form	<ul style="list-style-type: none"> - partially soluble in pyridine, <i>N,N</i>-dimethylformamide, <i>N</i>-methyl pyrrolidinone - blue color, when protonated it forms dark green salts - insulator when deprotonated, conductor after protonation
nigraniline	Partially reduced form	<ul style="list-style-type: none"> - partially soluble in acetic acid, formic acid and pyridine - blue color, after

		protonation and heating it forms green salts due to the reduction of the backbone to emeraldine form
pernigraniline	Totally oxidized form	- it is not stable in air and solution quickly leading to more reduced forms

Although all these numerous forms, practically only the half-oxidized form (emeraldine) is really interesting, because it is the unique electroconductive form of PANI.

Actually, in its base form emeraldine (emeraldine base) is an insulating material. However, after protonation by organic or most commonly inorganic acid it switches to conductor. This process is known as “doping” and is reversible. The conducting form of PANI is called emeraldine salt (ES) and its conductivity level is related to many factors: kind of dopant, presence/absence of branches in the backbone, level of moisture, etc. [48].

The possibility to tune the electroconductive properties of PANI by several approaches makes the polymer a good candidate for applications in many fields.

3.1. PANI synthesis

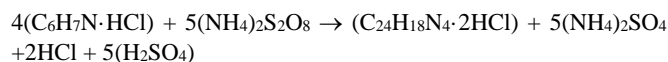
Numerous methods have been developed to produce PANI and its composites. Among them, chemical and electrochemical approaches represent the most common and ease ways. However, in the last years many other uncommon synthetic strategies have been proposed, such as enzyme-catalyzed polymerization, photochemically initiated polymerization and so on [48, 49]. We report below the conventional syntheses of PANI along with some of the most innovative approaches. A glance at some environmentally friendly syntheses is also proposed. Because the features of this polymer are strictly related to the synthetic method employed, knowing the main strategies of synthesis allows you to orient in choosing the best method depending on the required characteristics for each specific application.

3.1.1. Chemical synthesis

Chemical oxidative polymerization represents the oldest and still the most popular way for the preparation of PANI in large scale, even though this approach doesn't allow a fine control of the chemical-physical properties of the final material, because of the fast radical reaction that can lead to side-chain branching and/or overoxidation phenomena into the backbone.

Although in the scientific literature some attempts to produce PANI in organic solvents are reported [50], generally the reaction is carried out in aqueous solution at low pH values, employing many different oxidizing agents: ammonium persulfate [51, 52], metals in high oxidation states, such as gold [53], copper [54], iron [55], etc.

The characteristics of the final polymer (morphology, conductivity, processability, etc.) are strictly related to the kind of oxidant and acid dopant used and their concentration and to the reaction temperature. All these parameters play a key role in the formation of branched structures and on the molecular weight of the polymer. It was demonstrated that low reaction temperatures (about 0°C) inhibit the formation of branches. However, passing from 18°C to -25°C the molecular weight of the polymer gradually decreases [56]. Chemical oxidative polymerization of aniline using HCl as the acid dopant and (NH₄)₂S₂O₈ as the oxidizing agent can be described by the following chemical equation (Equation 1):



As it is possible to observe by the chemical oxidation reaction, PANI is obtained in form of ES along with large amount of inorganic coproducts (e.g., ammonium sulphate) that have to be removed from the polymer at the end of the reaction.

Although, unlike the electrochemical method, the reaction mechanism is not yet fully understood, it has been accepted that the first step of the reaction is the formation of cation radicals (anilinium cations) as depicted in Figure 4.

Figure 4: radical aniline cation formation.

After the formation of these species the radical reaction speeds up leading to PANI in a few hours. However, the “head-to-tail” and “tail-to-tail” free-radical recombination of aniline cation radicals can produce several dimeric species (Figure 5).

Figure 5: chemical structure of: a) *N*-4(aminophenyl)aniline, b) benzidine, c) *trans*-azobenzene.

Among them, *N*-4(aminophenyl)aniline is the unique dimeric species useful to produce PANI, even though the other toxic and carcinogenic dimers (benzidine and *trans*-azobenzene) are inevitably obtained and, as in the case of inorganic coproducts, must be carefully removed from the final

material, especially for applications in medical and biomedical sectors.

Chemical polymerization is still the most popular approach for PANI preparation, thanks to its undeniable advantages, such as large scale polymer production and high level of conductivity of the final material. Nevertheless, for specific applications as in medicine and biomedicine, utmost attention has to be paid to purification steps, averting contamination from traces of toxic byproducts. Moreover, the dramatic low processability of the final powdered product limits its real applications.

3.1.2. Electrochemical method

The first electrochemical preparation of PANI dates back 1962 by Mohilner and coworkers [57].

Instead of chemical oxidation, electrochemical way is not recommended to produce PANI in large quantity. However, it is a useful tool to synthesize small amount of polymer with a fine control of its morphology and conductivity [58]. This represents an interesting advantage to produce thin conducting films, especially required in the field of electrodes.

Electropolymerization is generally carried out in aqueous protonic acidic medium potentiostatically, galvanostatically or by potential scanning (cyclic-voltammetry polymerization).

As for chemical oxidation, the polymerization process is strongly affected by the kind of dopant and solvent used and by the pH value of the reaction medium. However, in this case also the kind of employed electrode can play a role [59]. On the contrary of chemical oxidation, the reaction mechanism of the aniline electropolymerization was completely investigated.

Briefly, the mechanism involves three main steps: initiation, chain propagation and termination (Figure 6).

Figure 6: mechanism of aniline electropolymerization: a) initiation, b) propagation, c) termination [48].

During the first step (initiation) aniline monomer is oxidized at the electrode surface producing aniline radical cations. The formation of radicals was abundantly documented by numerous studies [60]. Depending on the reaction conditions (temperature, solution composition, current density, potential scan rate, kind of anode) the cations can undergo different destinies. Generally, they react by a coupling reaction eliminating two protons and leading to aromatic rings. The subsequent polymerization reaction of the dimeric species is easier and faster, as confirmed by Mohilner *et al.* [58].

During the second step (chain propagation) the previously obtained dimers are oxidized at the electrode surface producing longer chains. At first these latter are in the reduced form of leucoemeraldine; then, during the propagation step they undergo further oxidation leading to totally oxidized unstable chains (pernigraniline) that gradually turn to the more stable emeraldine [61].

Concerning the last step (termination), it is not clear and different hypotheses have been proposed, such as hydrolysis of the terminal amino group, but also gradual decrease of the reactivity of the radical cations owing to steric hindrance and so on.

The described mechanism is only a short simplification of all the reactions involved in the PANI electrochemical synthesis, but it allows to understand the complexity and the difficulty related to the production of this performing material.

Compared to the chemical method, electrochemical synthesis is a much cleaner approach offering incontrovertible advantages. In fact, by this way relatively purer PANI can be achieved with respect to the chemically produced one. Moreover, no additional chemicals such as surfactant, oxidant, and so on are required. The purity of the final polymer, in addition to the high control of the morphology and conductivity, makes the electrochemical polymerization particularly appealing for small-scale PANI production for applications in the field of sensors and films and when traces of contaminants represent a risk [58].

3.1.3. Catalyzed polymerization

As reported above, conventional chemical routes to PANI synthesis are waste-intensive. Moreover, the radical way leading to aniline polymerization inevitably causes the production of toxic and carcinogenic species, such as benzidine and *trans*-azobenzene that represent an important drawback for specific applications of the polymer.

Moreover, this approach is environmentally troublesome, owing to the formation of polluting co-products, e.g., ammonium sulfate in the case of the use of ammonium persulfate and heavy metals in the case of metals in high oxidation state. As previously observed, electrochemical method could represent an alternative. However, it is not suitable for large quantity preparations. The growing interest in eco-friendly processes to produce clean materials and for the environment protection has pushed the scientific community to address its efforts towards alternative approaches.

In this regard, enzymatic reactions are attractive [62]. However, this approach is indicated only for small scale production. Moreover, the catalytic activity of enzymes is strongly depending on the reaction conditions and reaction modifications, such as temperature changes, can compromise the outcome of the process. In addition, the enzyme may remain in the final product forcing further purification steps. Finally, the high cost of enzymes is still an obvious disadvantage.

More conveniently, the possibility to replace strong stoichiometric oxidants with environmentally friendly reagents (especially hydrogen peroxide or molecular oxygen) opens the way to a new era of CPs. From a thermodynamic point of view, H_2O_2 , having a high redox potential (1.77 V vs SCE), should be able to initiate and sustain aniline polymerization. Moreover, on the contrary to what happens using other stoichiometric oxidizing agents, H_2O is the unique reduction co-product allowing to avoid strong post-treatments of the final polymer. However, oxidation reactions by H_2O_2 or molecular oxygen are frequently slow and as a consequence proper catalysts have to be introduced in the reaction. Noble and non-noble metals have been extensively studied as polymerization catalysts [63].

If Pd [64, 65], Ag [64, 66, 67], Au [68-70], Fe [71-73] and Cu [74] can be considered traditional catalysts for aniline oxidative polymerization, more recently selenium [75] and ruthenium-based compounds [76] are emerged as promising alternative.

However, in all these cases if on the one hand the inorganic waste production is strongly reduced, on the other hand the formation of toxic and carcinogenic organic substances remains. A convenient method to overcome this drawback is represented by the bypassing the first step of the reaction: dimers formation.

The possibility to replace aniline monomer with *N*-4(aminophenyl)aniline (its dimer) eliminates the formation of benzidine and *trans*-azobenzene.

Moreover, as reported by Wei *et al.* [77-80], the oxidative polymerization of aniline dimer is thermodynamically more convenient than the monomer, owing to its lower oxidation potential. This means that starting from *N*-4(aminophenyl)aniline PANI synthesis can be carried out more easily replacing strong oxidants with milder ones (H_2O_2 or molecular oxygen) in the presence of catalysts.

Copper [81] and iron ions [22, 82] and nanosized metal oxides (e.g., Fe_3O_4 [68] and $CoFe_2O_4$ [82], TiO_2 [24, 25]) have turned out to be excellent catalysts.

Catalyzed polymerization, in particular using aniline dimer as the reagent, represents a very powerful tool when highly pure PANI in large scale is required for real application, for example in medicine and biomedicine. In fact, it allows to eliminate the production of toxic and carcinogenic co-products and reduces the costs of post-treatment steps.

Furthermore, heterogeneous catalysts, such as metal oxides, if on the one hand open the way to new "green" routes to produce PANI composites with outstanding features, on the other hand act as templates for the polymer growth. In fact, it was observed that both Fe_3O_4 and TiO_2 catalyzed polymerization [71, 24, 25] leads to production of PANI composites in form of nanorods.

Even though the reaction mechanism for the nanorods formation is not clear, some hypotheses have been proposed by the authors.

Nanosized Fe_3O_4 -catalyzed polymerization can be considered as a biphasic method, because the reagents are dissolved in two different phases (magnetic nanoparticles are dispersed in toluene, dopant and oxidant in water, while aniline dimer is partially soluble in both the solvents). More details concerning biphasic polymerization will be discussed below (section 3.1.4). However, it is known that this kind of approach promotes the production of well-organized nanostructures.

Concerning TiO_2 -mediated PANI synthesis, the reaction is described as a two steps process. During the first step, aniline dimer is strongly adsorbed on the TiO_2 surface and PANI oligomers tidily growth on the metal oxide thanks to light irradiation that promotes photocatalytic reactions *via* radicals production. Then, after the addition of the oxidant (H_2O_2), the polymerization reaction rapidly proceeds. More details concerning photo-induced PANI synthesis are reported in the section 3.1.6.

It is interesting to highlight that by these innovative eco-friendly approaches PANI composites having magnetic or photoactive properties (PANI/ Fe_3O_4 and PANI/ TiO_2) can be easily synthesized increasing the inorganic component amount.

For most applications PANI nanocomposites and PANI blends are more suitable than pristine polymer. In fact, they combine the peculiar features of PANI, such as lightness, conductivity, redox activity, etc., with those of the filler (e.g., magnetic [84, 85], photoactive [86, 87], photothermal [88-91] luminescent [90, 92] properties and so on).

The paragraphs 3.1.8. and 3.1.9. are dedicated to innovative syntheses of PANI in form of nanocomposites and blends.

3.1.4 Heterophase polymerization

Heterophase polymerization techniques include different methods ranging from emulsion to suspension, passing from inverse polymerization, etc. All these approaches allow to tune very accurately the chemical-physical properties of the final product.

Some of these methods exploit the low miscibility of aniline in aqueous solution forming spherical droplets whose sizes can be easily controlled by different techniques, such as stirring, ultrasonication, etc.

By this approach, the polymerization reaction takes place on the surface of the organic droplets.

Dispersion polymerization: the first paper describing the preparation of PANI dispersion is dated back 1983 by Armes and Aldissi [93]. Since then numerous works have been published and this method has been deeply investigated because the final materials find application in strategic fields, such as membranes [94, 95], anticorrosion protection metals [96, 97], printable sensors [95, 98], etc.

The reaction consists in the oxidative polymerization of aniline monomer by stoichiometric oxidants (generally ammonium persulfate) in an acidic aqueous medium containing a proper steric stabilizer (typically a water soluble polymer).

Temperature control, level of acidity, kind of oxidant and stabilizer, presence of mediators are key parameters influencing the morphology and the properties of the final product [99].

Stejskal and coworkers proposed a model to explain particles formation (Figure 7) [100].

Figure 7: formation of spheres and coral-like structures during aniline polymerization (orange circles = aniline monomers, small green circles surrounded by blue objects = first PANI aggregates surrounded by surfactant, big green circles = PANI spheres, green rods = PANI in form of coral-like structures).

When all the reagents are mixed (aniline, oxidant, acid dopant and stabilizer), the reaction immediately takes place, and the system consists of a homogeneous phase.

As the sizes of the polymeric chains increase, PANI becomes insoluble in the water medium forming primary PANI nanoparticles, most of which are surrounded by the stabilizer. Subsequently, the nanoparticles aggregate leading to dispersed submicrometer-sized PANI.

Briefly, an increase in the polymerization rate (e.g., by temperature increase or mediator addition) has a negative effect on the PANI morphology passing from spheres to aggregates. Similarly, regular PANI nanospheres are obtained only in the presence of proper amount of stabilizers. Polyaniline hydrogels have been recently prepared stressing the conditions of the dispersion polymerization technique, carrying out the reaction at very low temperature in frozen stabilizer solutions. Hydrogels are obtained after thawing [28, 100].

In this case the water soluble stabilizer acts as a cage inside which a network of ice crystals is formed. Aniline polymerization is forced within the boundaries between ice crystals and stabilizer leading to an interpenetrating network composed of PANI and the second polymer (Figure 8).

Figure 8: a) aniline solution (orange circles = aniline monomers), b) frozen solution (orange circles = aniline monomers, blue objects = ice crystals), c) polymerization (green objects = PANI), d) ice removal.

This latter is responsible for the mechanical properties of the final material.

This novel macroporous soft material showed extraordinary mechanical properties and high hydrophilicity. These features along with appropriate biological properties make hydrogel PANI suitable for application in biomedicine.

Direct and inverse emulsion polymerization: probably the first attempt to prepare PANI by this way was realized by Cao and coworkers in 1993 [101]. Since then, this approach has been fruitfully applied to PANI synthesis, because it allows a strict control on the morphology.

In the direct emulsion polymerization, aniline forms a homogeneous dispersion in the aqueous phase in the presence of a proper surfactant that acts as a stabilizer. The reaction takes place after the addition of an oxidant [102].

In the case of PANI, aniline, oxidant and acid dopant are mixed in a binary aqueous/organic system. Non-polar or weakly polar organic solvents are typically used, such as toluene, chloroform, xylene. In addition, the choice of an organic dopant, such as dodecylbenzene sulfonic acid or camphoric acid, instead of inorganic acids has a positive effect on the emulsion. By this approach, the obtained product must be subjected to numerous purification steps, because it is present in the emulsion along with many co- and by-products.

The inverse emulsion polymerization is alternative to the direct method. An aqueous solution of aniline is emulsified in a non-polar organic solvent (e.g., isooctane, toluene, etc.). The polymerization starts by the addition of an oil-soluble initiator, such as ammonium persulfate, benzoyl peroxide, and so on. Also in this case the final material has to be strongly purified [102, 103].

Interfacial polymerization: by this technique aniline and oxidant are solubilized in two different immiscible phase and then put in contact. Generally, an organic solution of aniline

is produced, whereas oxidant and dopant are used in water medium. The polymerization reaction takes place at the interphase between aqueous/non-polar solvent leading to PANI fibers that can be easily collected by filtration (Figure 9) [104, 105].

Figure 9: scheme of aniline interfacial polymerization.

The strength of the heterophase polymerization lies in the possibility to finely tune the chemical properties of the polymer and its morphology. Moreover, it is suitable for large- and small-scale preparation.

3.1.5. Sonochemical polymerization

The pioneering studies of Jing and coworkers paved the way for the synthesis of PANI nanofibers by this approach [106, 107]. The technique consists in the aniline polymerization by traditional approach but with the aid of ultrasonic irradiation. When an ultrasonic wave passes through a liquid medium a large number of microbubbles are produced. These latter quickly growth and rapidly collapse causing a shock wave. This effect is called ultrasonic cavitation. During the traditional PANI synthesis, the polymer grows in form of fibers or rods. However, if all the reaction parameters are not strictly controlled, especially temperature and reactants concentration, the fibers/rods aggregate leading to irregular agglomerates. Ultrasonic irradiation has a positive effect in this regard, preventing agglomeration phenomena [106].

The advantages of sonochemical polymerization are mainly related to the opportunity to work in absence of chemical initiators and at lower reaction temperatures. Moreover, it leads to faster polymerization rates, higher monomer conversion, reducing aggregate phenomena and guaranteeing the control of the morphology.

3.1.6. Photo-induced polymerization

It is possible distinguishing two types of photo-induced polymerization. The first method consists in the use of photocatalytic systems, the second one in the monomer photoexcitation [108]. In the case of PANI the presence of a photocatalyst is not indispensable. In fact, nanofibers and nanowires were obtained by Tang *et al.* during aniline oxidative polymerization by means of stoichiometric oxidants under UV irradiation [109]. On the other hand, as previously reported, PANI and PANI/TiO₂ composites can be also obtained by TiO₂-photoinduced aniline dimer polymerization [23, 24]. Photo-induced polymerizations are low-energy reactions and represent an interesting alternative to traditional processes, because they are fast, cheap, environmentally friendly and transferable to the industrial scale. However, at despite this, concerning PANI preparation by this technique the research works are very few. Most of

the researcher groups are still focused on the traditional synthetic approach, despite its limitation.

3.1.7. Template synthesis

When PANI with a specific desired shape is required, template synthesis represents a convenient choice. The reaction can be carried out both by chemically and electrochemically methods. In both cases the polymer grows on the surface of the template that at the end of the reaction is removed or destroyed. Among the templates, metal oxides [110-112] and organic polymers are the most employed [113].

This approach is cheap, easy and the templates commonly employed are inexpensive. Moreover, it guarantees large-scale PANI production with a narrow control of the morphology. However, the weak step of the process, the template removal, can cause modification of the final polymer, if it is not properly carried out.

Many other synthetic ways have been developed to produce PANI. However, at the best of our knowledges those reported here are the most investigated in the last years.

3.1.8. PANI nanocomposites synthesis

In the last years, materials combining characteristics and properties of two or more components are constantly required in many sectors.

The synthetic strategies employed to synthesize PANI nanocomposites are crucial, because they affect not only the morphology of the final materials but also their chemical-physical properties.

Two main procedures are generally reported for PANI composites preparation: one-step redox reaction and *in situ* polymerization in the presence of pre-synthesized particles.

One-step redox reaction: the standard reduction potential of numerous metals in high oxidation state is high enough to start aniline oxidative polymerization process. At the same time, metals ions are reduced to zero-valent metal nanoparticles. During the polymerization step metal nanoparticles are embedded in the polymeric matrix leading to nanocomposites. In this regard, noble metals are preferred to others for their properties. By this approach PANI composites with Au [114, 115], Ag [116, 117], Pt [118, 119], Cu [74, 120], etc. were prepared.

In situ polymerization in the presence of pre-synthesized particles: by this approach pre-synthesized nanoparticles are mixed into the monomer solution. Then, the polymerization reaction can be carried out by chemical or electrochemical way. The chemical approach is the most commonly employed because it allows a narrow control of the size and shape of the materials. In some cases, ultrasound application permits to obtain composites with homogeneous dispersion of nanofillers inside the organic matrix.

This strategy allows to produce a large number of PANI nanocomposites including different fillers, such as metal oxides, carbon nanotubes, graphene and so on [121].

Finally, as described above, in the last years it was demonstrated that when aniline dimer is polymerized by H_2O_2 in the presence of Fe_3O_4 , $CoFe_2O_4$ or TiO_2 nanoparticles, these latter act not only as fillers but also as catalysts [24, 25, 71, 83].

3.1.9. PANI blends preparation

Because of its poor mechanical properties, pristine PANI finds few applications in those sectors where flexibility is crucial. Blends of PANI with conventional insulating polymers have received great attention in many fields, especially in medical and biomedical areas.

Synthetic methods for PANI blends roughly include: dispersion polymerization of aniline in the presence of a polymeric matrix, chemical *in situ* aniline polymerization in a polymer, aniline electrochemical polymerization in a matrix covering an anode, polymer grafting to PANI surface, aniline copolymerization with other monomers, aniline modification, etc. [122, 123].

Grafting of conducting polymers represents a particularly advantageous approach, because if on one hand it does not interrupt the conjugation of the backbone of the conducting polymers, on the other hand it improves their properties (mainly electrical conductivity) adding those of the grafted materials (e.g., biocompatibility, solubility, etc.) [124]. The covalent approach is the conventional grafting method that mainly includes three types of strategies: “grafting to”, “grafting from” and “grafting through”. The method “grafting to” involves the reaction of reactive functional groups on the backbone of the polymer with pre-polymerized chains. By the “grafting from” way proper initiators are anchored to the surface of the polymeric backbone and the polymer chains grow *in situ*. Finally, the “grafting through” approach consists in the copolymerization of functionalized macromonomers forming a polymeric backbone in the presence of other polymeric chains [125]. On the basis of this approach Guo *et al.* have recently synthesized an injectable conductive hydrogels based on dextran-graft-aniline tetramer-graft-4-formylbenzoic acid and *N*-carboxyethyl chitosan with potential applications as tissue engineering scaffolds and delivery vehicles for electrical signal sensitive cell therapy [126].

Even though covalent grafting is the most conventional approach, it entails some negative implications (e.g., undesired variations of the polymers, irreversible bonds, etc.) that stimulated the development of alternative strategies, such as non-covalent grafting where the components of the blend interact *via* noncovalent bonding.

However, *in situ* polymerization, where aniline is polymerized inside another polymer, and solution casting method, where prepared PANI is added in another polymer, represent the easiest and most common approaches.

By the first method PANI-covered Nylon 6 fabrics were quickly prepared by Oh and coworkers [127], whereas conducting membrane were obtained by Tishchenko and Elyashevich [128, 129].

More recently, blends of biodegradable polymers and PANI have been successfully employed especially in medical and biomedical field.

In this regard, polylactic acid (PLA), cellulose, polycaprolactone (PCL), gelatin and other biodegradable materials have emerged for PANI modification.

Bortuali *et al.* prepared electroactive and biocompatible fibrous scaffolds based on PANI, PLA and polyethylene glycol (PEG) that are suitable for cardiac tissue engineering applications [130]. Electrodeposited coatings of ginsenoside, PANI and poly(lactic-*co*-glycolic acid) microcapsules were realized by Lukman and Saidin and showed encouraging applications in drug-eluting stents (DES) manufacturing [131]. Xu and coworkers used cellulose hydrogel as template to *in situ* PANI synthesis [132]. The extraordinary mechanical properties, good biocompatibility and guiding capacity for the sciatic nerve regeneration of adult Sprague-Dawley rats of these materials demonstrate their great potential applications in biomedicine. Nanocomposite membranes made of bacterial cellulose/polyaniline/single-walled carbon nanotubes have showed interesting applications as bioelectronics devices [133].

PCL/PANI electroactive scaffolds were recently realized by 3D printing method [134]. The wettability, mechanical and electrical properties of the scaffolds are strongly encouraging for future bone tissue engineering application. In addition, PANI-PCL blended electrospun nanofibers could be potentially used for neural cell culture [135].

Massoumi *et al.* fabricated innovative nanosized highly conductive and electroactive star-shaped polyaniline and polyanisidine through a “core-first” approach from tannic acid opening new perspectives in the realm of conductive scaffolds for neurite outgrowth and nerve regeneration [136]. Monomer modification processes strongly contribute to improve PANI solubility [137-139] with important implications in the context of PANI blends preparation. However, to the best of our knowledge, PANI-based blends prepared by this method are not reported in the literature.

Playing with different components, morphology, porosity, surface area and so on, extraordinary innovative materials can be prepared representing important advances for real and practical applications.

3.2. Properties of PANI

3.2.1. Conductivity

As previously discussed, numerous factors influence the conductivity of the polymer. This topic is actually very complex and not completely explained and is beyond the scope of the present paper. Therefore, below we will just mention only a few aspects.

It has been observed that with the increase in crystallinity the conductivity of PANI is increased. In fact, the structure becomes more organized and facilitates *inter*-chain electron mobility [140].

Moreover, the presence of branching in the PANI structure negatively affects its conductivity stopping the redox process during electrons shift.

In addition, the kind of acid used both during aniline polymerization and emeraldine base (EB) protonation has a crucial effect on the polymer conductivity.

Concerning EB protonation, mineral acids lead to polymers characterized by higher conductivity if compared to that of EB doped by organic acids [141, 142].

Similarly, ES synthesized in aqueous solutions acidified by strong inorganic acids (H_2SO_4 , HCl, etc.) exhibit values of conductivity of the order of units S/cm^{-1} (up to $10 \text{ S}/\text{cm}^{-1}$ when the polymerization reaction is carried out in the presence of sulfuric or hydrochloric acids). On the contrary, when carboxylic acids were used, the values of conductivity fell to 10^{-2} - $10^{-1} \text{ S}/\text{cm}^{-1}$ [143].

The real reason of this difference in conductivity is not known. However, some hypothesis can be proposed. Generally, organic acids are sterically bulkier and less strong than mineral ones. Both these aspects prevent a complete protonation of the polymer.

Finally, moisture positively affects PANI conductivity, promoting the charge transfer along the polyaniline chains and between them. In fact, it has been demonstrated that when PANI is exposed to moisture the resistivity increases by 1 order at pH 0.3 but by more than 2 orders at pH 3.5 [144]. The conduction mechanism proposed by Focke and coworkers allowed a greater understanding of this phenomenon [145].

3.2.2. Mechanical properties

Pristine PANI shows poor mechanical properties (PANI hydrochloride compressed pellets exhibit a value of Young's modulus of $0.9 \pm 0.2 \text{ GPa}$ by pressure of 700 MPa, whereas for PANI base the value is $1.3 \pm 0.2 \text{ GPa}$) [146]. However, significant improvement has been observed in its blends and composites [147, 148].

For medical and biomedical application, the rheological properties of a material are the most important ones.

PANI blends and nanocomposites show promising elasticity and strength, reaching characteristics similar to those of living beings.

For example, PANI/PCL nanofibers exhibit tensile strain of 200%, very comparable to that of native soft tissues of human cells [149]. Moreover, the fabrication of thermoresponsive injectable PANI-based hydrogels with antioxidant and antimicrobial activity is reported [150-152]. These latter are only two examples of PANI blends applications, but they are enough to understand that this polymer represents an extremely fascinating material.

4. Biological activity

4.1. Antioxidant activity

Reactive oxygen species (ROS) play an active role in numerous diseases, such as inflammatory states, aging, premature cancer, tissue damages and so on.

Therefore, materials able to scavenge $\text{OH}\bullet$ and $\text{ROO}\bullet$ radicals are of huge interest for applications in biomedicine.

Among them, CPs have been intensively investigated demonstrating in particular the antioxidant ability of PANI and PPy [153, 154].

It was demonstrated that HCl-doped ES is 1.7 times more active than the corresponding base showing an antioxidant activity similar to that of phenolic antioxidants, such as ascorbic acid and catechin. On the other hand, EB is 5.8 times more efficient than aniline [155].

The superiority of PANI nanofibers respect to bulk material was demonstrated also in the antioxidant activity and it is

strictly related to the diameter of the nanofibers and to the kind of dopant used [156].

Even though the reason of the higher activity of the nanofibers respect bulk PANI is not completely clear, it is probably due to their higher surface area, that make them more active in the scavenging free radicals.

Concerning PANI composites, recently their antioxidant activity has captured the interest of the science.

Composites of PANI and sugars show encouraging results.

For example, the antioxidant activity of PANI/starch materials was investigated in the presence of DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenger and it increases with the PANI amount in the composite [157]. By this test the activity is related to the ability of the material to transfer a hydrogen atom to DPPH, reducing it (Figure 10).

Figure 10: mechanism for PANI antioxidant activity in the presence of DPPH radical scavenger.

Similar results were obtained in the presence of PANI/dextrin nanocomposites synthesized by *in situ* polymerization of aniline in presence of dextrin [158].

More recently, nanocomposites of PANI in combination with carbon, in form of graphene or fullerene, exhibited good antioxidant activity.

PANI/reduced graphene oxide (r-GO) nanocomposites electrosynthesized in the presence of different electrolytes (KCl and *p*TSA) showed an important antioxidant activity towards DPPH and ABTS (2,2-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid) radicals, strongly dependent on the electrolyte amount [159].

Theoretical studies on PANI-functionalized fullerene allowed to investigate the characteristics of the material, such as potential energy surfaces of the reaction between fullerene and PANI by ONIOM method and antioxidant activity [160].

To evaluate the antioxidant activity of the material both HAT (hydrogen atom transfer mechanisms) and SET (single electron transfer) mechanisms were used.

The antioxidant activity of aromatic amines is related to their ability to act as hydrogen donor. Concerning HAT mechanism, PANI and PANI/fullerene composites do not show significant differences.

On the contrary, the effect of the presence of fullerene is extraordinary evident by SET mechanism, involving an electron-donating/-accepting process.

Pur and coworkers investigated the antioxidant activity of PANI modified by ferrofluid magnetic nanoparticles (Fe_3O_4), observing that its ability to remove free radicals is very similar to that of pristine PANI (83.02% PANI/ Fe_3O_4 nanocomposites, 91.18% pristine PANI after 100 minutes in contact with DPPH) [161].

Materials capable to decrease high level of RRS are particularly required. For this reason, PANI and its derivatives can represent an important tool in this sector.

4.2. Antimicrobial activity

Microbial infections are responsible of a huge number of diseases and of failure of several implantations.

In fact, numerous pathogens live for long periods on medical devices, hospital furniture, surgery equipment and many other surfaces that are daily used or touched by health care workers. In addition to the medical sector, other fields are involved in the prevention of microbial contaminations, such as food and pharmaceutical.

The development of innovative advanced materials able to prevent pathogens infections is tremendously necessary.

Among the different materials investigated, polymers occupy an important place both from academic and industrial point of view. [162]. Polymers can be themselves antimicrobial, can be properly chemically modified to acquire antimicrobial activity or can act as matrix holding organic and inorganic antimicrobial agents. This latter is the case of polyaniline.

Pristine PANI shows a certain antimicrobial activity, as demonstrated by the studies of Robertson *et al.* [163]. Even though the mechanism of action of PANI is not clear, it was hypothesized that PANI chains can bind microorganism membranes by $-\text{NH}_3^+$ and $-\text{C}_6\text{H}_5$ groups by electrostatic and hydrophobic interactions. Phenyl groups, responsible of the hydrophobic interactions, should cause membranes disruption leading to serious damage to cells [164].

However, also in this case low PANI processability represents a serious restriction to real application and, as a consequence, PANI-based nanocomposites including noble metals, mainly nanostructured gold and silver, have been investigated as antimicrobial materials with positive results [165-167].

Analogously, PANI composites containing quaternary ammonium compounds, such as chitosan [151], have shown interesting antimicrobial properties.

More recently, metal oxides and nanoceramics have been used as active fillers for antimicrobial PANI nanocomposites. In this regard, nonosized CuO is one of the most investigated agents.

Ansari and coworkers realized PANI/ultrathin nanosheet CuO nanocomposites by a microwave assisted approach and demonstrated their significant antimicrobial activity against *Bacillus subtilis* and *Pseudomonas aeruginosa* [168].

The authors clearly reported the high impact of the materials on the bacterial cell morphology, proposing that this is due to the oxidation of bacterial membranes by CuO leading to

free radicals production, that negatively affects membrane transport system and, as a consequence, the metabolism and growth.

More sophisticated PANI/Zn-doped CuO microparticles composites synthesized using CDs (carbon dots) as the initiators showed remarkable antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* [169].

The mechanism of action based on the production of free radicals was demonstrated by electron paramagnetic resonance (EPR) technique.

PANI/Zn@CuO composites exhibit synergistic effect between PANI and the inorganic part, thanks to the movement of free electrons along the polymer that could be combined with the O_2 in the suspension to enhance the production of radicals.

Remarkable antimicrobial activity was also observed for PANI/ TiO_2 and PANI/ SiO_2 nanocomposites against both gram-positive and gram-negative bacteria [170, 171].

More recently, innovative nanoAu/PANI/Penicillin G nanoconjugates were easily prepared by photopolymerization of aniline in the presence of AuCl_3 , leading to Au/PANI composites, then grafted to the C3 carboxyl group of the β lactam ring of penicillin in the presence of EDAC (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride) able to activate the COOH group of penicillin [172]. The nanoconjugates were tested against penicillin resistant *Staphylococcus aureus* showing a good activity and opening the way towards novel resistant antibiotic bactericidal materials.

Finally, an extraordinary work of Stejskal's group demonstrated a high antibacterial activity against gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* bacteria of printed PANI and Ag/PANI colloids [98].

4.3. Antivirus activity

If on the one hand numerous investigations have been carried out on antimicrobial and antioxidant activities of PANI-based materials, the scientific literature lacks information on antivirus properties of PANI.

Only a few works deal with this aspect and they are discussed here.

The first article dealing with antivirus activity of PANI dates back 2011 [173]. Even though it is not strictly related to biomedical applications it offers an interesting starting point demonstrating the ability of the material to remove influenza viruses A from wastewater [173-175].

More in detail, traditional, one-dimensional, CNT-coated and Ag modified polyanilines were tested as active materials in the adsorption of influenza viruses from aqueous solutions, proving to be more capable than carbon to bind different strains of viruses including infectious of A and B strains of human and avian viruses. The activity of PANI-based materials seems to be independent from their morphology but mainly related to their composition. Doping anions able to improve the hydrophilicity of the polymer positively affect its adsorption properties promoting sorbent/water interactions. A greater effect is played by silver NPs that strongly influence the ability of PANI to interact with viruses participating actively to the process [175].

This ability of PANI and PANI composites was exploited by Isakova and coworkers to develop electrosynthesized PANI and PANI composites films to detect influenza viruses by surface plasmon resonance (SPR) [176].

5. Biomedical applications

5.1. Drug delivery

The necessity to develop innovative and more performing materials able to deliver drugs in target organs and tissues is continuously growing.

One of the most crucial point deals with the necessity to avoid drugs overload or underload to have a constant and controlled drug release within a certain period.

In this regard, smart drug delivery systems (SDDS) represent an interesting tool, combining different disciplines, such as pharmaceuticals, materials science, molecular biology, engineering and so on.

Generally, in this kind of devices drugs are loaded on supports by different strategies.

Roughly, the support can play an active role in the mechanism of drug release or can be not active, working as an inert carrier.

Among the supports, CPs occupy an important place owing to their extraordinary ability mainly related to their unique skills, such as electroconductivity, pH sensitivity, light-sensitivity, etc.

Controlled amoxicillin release was obtained by Castro and coworkers using L-glutamic acid doped PANI nanofibers mixed with polyacrylamide as conducting hydrogel [177].

The drug loaded composite works as an ON-OFF device that releases the antibiotic molecule in response to a cathodic electrical stimulation.

Very recently, nanofibers of chitosan/PANI composites were fabricated by *in situ* chemical polymerization [178]. Thanks to their free volume space ketoprofen was encapsulated within the composites exploiting electrostatic interaction and the hydrophobic effect. It was demonstrated that the drug release is pH dependent increasing by raising the pH of the medium. However, encouraging results were obtained working by simulated biological fluid.

Exploiting the pH sensitivity of PANI-based materials, a pH-electroactive bacterial cellulose/PANI hydrogel for controlled drugs release was prepared by Li *et al.* [179].

Chemotherapy is an emerging treatment for last stage cancer. It consists in the incorporation of a therapeutic agent within a material sensitive to NIR irradiation. This alternative approach to cancer treatment allows to enhance the drug accumulation in a specific target tissue by an accurate release control.

PANI is a promising photothermal converting material and in the last years, numerous research groups have focused their work on this application.

Very recently, an accurately controlled delivery of cisplatin was investigated by You *et al.* developing PANI-mediated polymeric nanoparticles modified by trastuzumab that guarantee cellular uptake owing to its high affinity for tumor cells [88].

The composites (Figure 11) were prepared by a two-steps procedure based on a first synthesis of Pt-loaded

nanoparticles followed by a second nanoparticles modification by trastuzumab.

Figure 11: scheme of polymeric-PtNPs fabricated by You *et al.* [88].

The composite resulted able to load up to 16% (w/w) of drug and showed a cell inhibition efficiency of 93.97% *in vitro* after NIR laser irradiation (808 nm) with the power of 1.54 W for 5 minutes.

Sophisticated smart lipid-modified nanoparticles were developed for the co-delivery of cisplatin and Ce6 by PANI-mediated photothermal conversion [180].

The co-deliver cisplatin and Ce6 leads to a successful synergistic therapy related on the one hand to the typical anticancer activity of cisplatin and on the other hand to the production of ROS by Ce6 after irradiation by NIR light at 670 nm, that enhances the cytotoxicity of the materials inhibiting cell proliferation.

5.2. Cancer therapy

Besides the ability to work as drug carriers, PANI-based materials have shown an outstanding potential in the cancer therapy. Even though to date the scientific literature reports only a few works in this regard, the quality of the results is encouraging for real applications in the photothermal ablation of cancer using NIR light.

Gd(III)-modified PANI particles were successfully realized by Lee and coworkers for simultaneous diagnostic imaging and localized photothermal therapy [91].

Gd/PANI nanocomposites were prepared by a two steps process. During the first step PANI was prepared by the traditional oxidative polymerization reaction. Then, the amine groups of the polymer were chemically conjugated with diethylenetriaminepentaacetic dianhydride (DTPA-DA) in order to chelate and reduce the potential toxicity of Gd(III). The loading of Gd(III) on the modified PANI particles was carried out by mixing $GdCl_3 \cdot 6H_2O$ with the composite in *N*-methyl-pyrrolidinone. Finally, the hydrophilicity of the surface of the Gd/PANI material was improved by modified polyvinyl alcohol (PVA) that allowed the conjugation with cetuximab (CET), an anti-epidermal growth factor receptor, as a targeting moiety.

All the investigations carried out on the material confirmed that the composite shows an enhanced magnetic resonance (MR) diagnostic ability and good efficacy in terms of photothermal ablation of cancer.

Composite materials combining both magnetic and redox properties are particularly investigated, because they can simultaneously act as magnetic resonance imaging contrast agents and as electron transfer mediator. Fe_3O_4 NPs are the most employed magnetic components in these materials owing to their ease of synthesis, high stability and size and shape tunability. Fe_3O_4 /PANI nanohybrids exploit all these aspects and were studied for MR imaging and redox sensing of the cancer cell microenvironment [84]. The synthetic procedure of magnetic PANI nanohybrids is reported in Figure 12.

Figure 12: scheme of magnetic PANI nanohybrids (MPNH) synthesis (MPNHm = MPNH functionalized with maleimidyl-TWEEN 80, MPNHm-P = MPNHm conjugated with a peptide).

Iron (III) acetylacetonate and PANI were dissolved in proper solvents, mixed and thermally decomposed.

Subsequently, magnetic PANI nanohybrids were functionalized with maleimidyl-TWEEN 80 and conjugated with a peptide that can be targeted toward membrane type 1-matrix metalloproteinase that is one of the representative biomarkers of invasive cancer cells. The *in vitro* and *in vivo* tests confirmed the double ability of these materials to act as MR contrast agent and redox sensing agent.

More recently, upconversion NPs covered by a layer of PANI NPs were synthesized by Xin *et al.* The nanocomposites resulted active in photothermal cancer cell ablation after irradiation at 808 nm laser (47.8% thermal conversion efficiency) but also in upconversion luminescence (UCL) process (Figure 13) [90].

Figure 13: scheme of PANI-UCNPs (PANI-coated upconversion nanoparticles) synthesis and application in UCL imaging and photothermal therapy.

Even though the most part of bioactive materials investigated so far contain an active inorganic component, good anticancer activity was also obtained by totally organic compounds. This is the case of polyaniline-b-polyacrylic acid copolymer nanofibrils [181]. The possibility to combine a chemotherapeutic agent with a NIR responsive material leads to synergistic anticancer effects. In this regard, Nguyen and coworkers realized a multifunctional material containing PANI NPs as photothermal agent and methotrexate as an anticancer drug [182]. *In vivo* experiments carried out on mice exhibited higher tumor growth inhibition rate than that obtained by the separated techniques alone. Another innovative approach is based on the fabrication of hybrid nanocomposites combining radio therapeutic agents with photothermal therapy leading to a radiophotothermal treatment. It has been demonstrated that MoS_2 /PANI nanohybrids induce benefits on cancer cell death when compared to photothermal treatment and radiotherapy alone, demonstrating the efficiency of PANI in the fight against cancer thanks to the synergy effect in the radio-photothermal therapy [183].

5.3 Biosensors

The International Union of Pure and Applied Chemistry (IUPAC) defines a biosensor as “a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals” [184]. A general biosensor consists of a biorecognition element, and a transducer element. Biosensors are classified on the basis of the kind of transducer employed that is generally an electrochemical system.

In biosensors CPs work as transducers owing to their extraordinary properties, such as electroconductivity, redox properties, biocompatibility and great sensitivity.

The recent work of Shoaie *et al.* exhaustively displays the state of the art of PANI and PANI composites applications in the field of biosensors [185].

We report below some of the most recent advances in the field of PANI-based biosensors.

5.3.1. Glucose sensing

Diabetes mellitus is a chronic syndrome related to lack or absence of insulin. Among the numerous symptoms, hypertension, kidney failure, heart disease and blindness cause severe complications.

As a consequence, continuous glucose monitoring represents an effective method for diabetic therapy.

The most part of glucose biosensors, as commercial glucose test strips, is based on the use of the enzyme glucose oxidase (GOD) as recognition agent with negative repercussions on costs and durability of the devices.

However, during the years, some researchers have reported interesting results on the development of cheaper non-enzymatic glucose sensors.

The use of PANI and its composites in the glucose sensors has been recently reviewed by Lai *et al.* [186].

We report below the most recent results obtained by the scientific community on the development of enzymatic and non-enzymatic glucose sensors.

A highly selective and stable glucose sensor was obtained by Zheng and coworkers anchoring GOD within a PANI-montmorillonite (MMT)-Pt NPs nanocomposite [187].

The nanocomposite is easily realized by electropolymerization of a solution of aniline in the presence of MMT. Then, starting from a solution of H_2PtCl_6 , Pt NPs are electrodeposited on the obtained PANI-MMT. Finally, GOD was immobilized on the surface of the modified electrode by drop casting (Figure 14).

Figure 14: scheme of the preparation of PANI/MMT/PtNPs-modified electrode.

This electrode exhibits extraordinary properties in terms of selectivity (no interferences were recorded after the addition of substances like glycine, D-galactose, urea, L-phenylalanine, ascorbic acid and L-tyrosine), linearity (from 10 μM to 1.94 mM) and stability (it retains 91.7% of initial current response towards the same concentration of glucose after storage for two months at 4 °C).

Ultra-thin PANI-coated TiO_2 NPs were recently synthesized by Majumdar and Mahanta by vapor polymerization of aniline on the surface of NPs and employed as active materials for glucose sensing [188].

The nanocomposite shows good linearity in the range 20-14 μM glucose concentration and low limit of detection (LOD) of 5.33 μM .

Along with these examples of highly sensitive glucose biosensors based on PANI nanocomposites, innovative non-enzymatic devices have been realized.

An enzyme-free glucose biosensor was realized by Kailasa and coworker by PANI nanosheets/reduced r-GO nanocomposite, easily obtained by mixing traditionally prepared PANI and r-GO [189].

The sensor displays high sensitivity (3448.27 $\mu\text{A}\cdot\text{mM}^{-1}\cdot\text{cm}^{-2}$) and very low LOD (30 nM, S/N= 3).

A surprising paper-based electrical sensor realized by molecularly imprinted glucose recognition sites was developed by Chen *et al.* and tested on the determination of

various glucose concentrations in bovine blood solutions [190].

The recognition sites within the polyaniline was obtained by the addition of glucose as the template in the reaction mixture during the oxidative polymerization step. At the end of the reaction the removal of the template by washing leads to active sites for glucose recognition (Figure 15).

Figure 15: scheme of molecular imprinting process for paper sensor fabrication.

The sensor shows good linearity in the range of glucose concentration 2.2-11.1 mM with a linear correlation coefficient of 0.984.

Non-enzymatic glucose biosensors represent a good alternative to traditional ones based on GOD immobilization and allow to reduce the costs making the devices accessible to poorest communities.

5.3.2. Cholesterol sensing

Cholesterol represents an important biomarker for many diseases. If on the one hand it is an important lipid in the human body (it is part of the cell membrane and contributing to maintain its permeability and fluidity, it is a precursor of numerous biological compounds, such as vitamin D, hormones, etc.), on the other hand high levels of cholesterol in the body are correlated to various diseases, such as hypertension, nephritic syndrome, cirrhosis, atherosclerosis, heart attack, anemia, brain thrombosis, stroke, etc.

Accordingly, the monitoring of cholesterol levels in the body is a key step in disease diagnosis and prevention.

A few years ago, Li and coworkers presented an extraordinary low-cost biosensor able to detect several metabolites simultaneously (uric acid, cholesterol, and triglycerides) with wide linear ranges (uric acid, 0.07–1 mM; cholesterol, 0.3–9 mM; and triglycerides, 0.2–5 mM), high sensitivities, low sensing limits and rapid response times (~3 s) [191]. The biosensor is made of a glassy carbon electrode (GCE) modified with a nanocomposite consisting of Pt NPs homogeneously dispersed in a PANI hydrogel matrix.

Moreover, an innovative paper-based cholesterol biosensor was proposed by Ruecha *et al.* by the immobilization of

cholesterol oxidase (ChOx) enzyme on graphene/polyvinylpyrrolidone/polyaniline nanocomposite as active material [192]. The final sensor results linear in the range of 50 μM -10 mM with a LOD of 1 μM .

Remaining in the field of paper-based sensors, it is worth mentioning the work of Maluin and coworkers, that used a PANI/hematite/Prussian blue nanocomposite with ChOx immobilized on its surface to obtain screen printed paper-based sensors for the detection of cholesterol. The sensor results highly stable in the working conditions and free of interferences. Moreover, it exhibits linearity in the range of 0.6–6.0 mM, a very low LOD of 0.52 mM and good sensitivity of 411.7 $\text{mA}\cdot\text{mM}^{-1}\cdot\text{cm}^{-2}$.

Very recently an innovative sensor for cholesterol detection was presented by the group of Abdi [193]. It consists of a nanocomposite made of crystalline nanocellulose (CNC)/ionic liquid (IL)/PANI deposited on a screen-printed electrode by spin coating technique. Finally, the immobilization of enzyme ChOx was done by drop casting on the modified electrode. The sensor was fast and highly sensitive resulting able to detect cholesterol in the range of 0.001–12 mM with LOD of 0.5 mM.

As previously observed for glucose sensors, also for the detection of cholesterol in biological fluids, non-enzymatic devices have been fabricated.

This is the case of the PANI/multiwalled carbon nanotubes (MWCNTs)/starch modified carbon paste electrode developed by Gautam *et al.* that exhibits wide linear dynamic range (from 0.032 to 5 mM), high sensitivity (800 $\mu\text{A}\cdot\text{mM}^{-1}\cdot\text{cm}^{-2}$), low LOD (0.01 mM) and fast response (within 4–6 s) and results free from interferences [194].

5.3.3. Hepatitis virus sensing

Hepatitis is an inflammation of the liver commonly caused by viral infection, even though other possible causes exist. It can lead to a range of health problems and can be fatal. Five main strains of the hepatitis virus have been identified, named A, B, C, D and E. If on the one hand they all cause liver disease, on the other hand they differ in some aspects, such as transmission modes, severity of the malady, geographical distribution and prevention methods. Among them, types B and C are more aggressive and can lead to chronic diseases.

Also in this sector the outstanding properties of PANI have attracted considerable attention allowing the fabrication of novel biosensors.

Even though only a few papers deal with PANI application for hepatitis virus sensors development, some example is reported below.

Chowdhury *et al.* worked in the realization of a robust pulse-induced electrochemical biosensor for hepatitis E virus (HEV) detection by using a nanocomposite of graphene quantum dots (QDs) and Au NPs embedded into PANI nanowires on which the immunoglobulin (IgG) anti-HEV antibody is immobilized [195]. The material is prepared by interfacial polymerization and self-assembly approach.

The authors demonstrated that by the application of an external electric pulse during the virus accumulation step, the sensitivity of the device towards HEV increases owing to the

expansion of virus surface in addition to the chain length of the antibody-conjugated PANI.

An innovative label-free electrochemical biosensor for the recognition and quantification of hepatitis C virus ribonucleic acid (HCV-RNA) was fabricated by Sheta and coworkers using PANI-modified Ni/metal-organic framework (MOF) nanocomposite [196]. The sensor was layer-by-layer deposited onto a GCE along with deoxyribonucleic acid (DNA) probe and bovine serum albumin (BSA). The device results extraordinary sensitive over the range of 1 fM–100 nM with a LOD of 0.75 fM (at a S/N ratio of 3).

An ultrasensitive electrochemical biosensor made of PANI-decorated hollow carbon spheres (HCS) was recently presented [197]. A thiolated 21-mer oligonucleotide, characteristic of HBV (hepatitis B virus) DNA, was immobilized on the nanocomposite thanks to a thin layer of Au NPs electrodeposited on its surface.

The device exhibits extraordinary sensitivity up to 10 fM and very high selectivity even in real samples.

Other PANI-sensors have been developed for biomedical applications. However, here we wanted to report the more recent obtained results in the major investigated sectors.

5.4 Tissue engineering

The most part of the regulatory mechanisms of human body is modulated by electrical stimuli. As a consequence, electroactive materials have been strongly investigated for application in tissue engineering in order to stimulate cellular responses and enhance tissue regeneration. Pure PANI has not suitable properties for application in tissue engineering. However, it can be converted into a biodegradable and more biocompatible material by combination with natural and biodegradable polymers.

In addition to the typical electroactive characteristics of PANI, the final composites show higher physicochemical and mechanical properties, such as elasticity and flexibility, that make them similar to the tissues of living beings.

Exploring the most recent scientific literature, we found interesting papers dealing with the development of extraordinary innovative materials that report below.

Massoumi *et al.* fabricated a tri-component electrospun nanofibrous scaffold combining the electroactive properties of PANI with those of polydopamine (high biocompatibility, good adhesive feature and conductivity) and with the physicochemical and biological properties of polylactic acid [198]. The composite was easily synthesized by a two steps process consisting in a chemical oxidative copolymerization of aniline and dopamine leading to a PANI-*co*-polydopamine(PDA) composite, followed by grafting of lactide monomer onto PDA segment using a ring opening polymerization (ROP). The final scaffold was realized by electrospinning technique and characterized in terms of conductivity, mechanical properties, electroactivity, biocompatibility, and biodegradability. The presence of the insulating component, polylactic acid, obviously reduces the conductivity of the PANI-*co*-PDA copolymer. However, the value of 0.007 S/cm observed for the scaffold is appropriate for applications in bone tissue engineering as well as those

obtained by mechanical investigations (Young's modulus = 2.56 ± 0.45 GPa, tensile strength = 46 ± 2.5 MPa, elongation at break = 4.6 ± 0.75 %). Cell proliferation assay was carried out for 5 and 7 days demonstrating high cells proliferation performances. Finally, the scaffold exhibits a good potential as biodegradable scaffold in acidic environment that is the typical condition of defective bone.

Novel scaffolds of PANI composites for bone tissue engineering were also realized by 3D printing, as reported by Wibowo and coworkers [132].

The scaffolds were fabricated using screw-assisted extrusion-based 3D printing loading polycaprolactone with different percentage of PANI. 0.1% wt. PANI scaffolds resulted completely cytocompatible for up to 21 days, whereas increasing the PANI load (1-2%) the cytocompatibility of the scaffolds is strongly reduced. Also in terms of conductivity and mechanical properties 0.1% PANI scaffold exhibited outstanding results for bone tissue engineering (compressive strength = 6.45 ± 0.16 MPa, conductivity = $2.46 \pm 0.65 \times 10^{-4}$ S/cm).

Different PANI-based materials have been fabricated for potential application in nerve regeneration. Among the numerous and interesting works reported in the literature, it is worth mentioning that Guarino *et al.* fabricated hybrid PANI/ polyethyleneglycol diacrylate (PEGDA) macroporous hydrogels by crosslinking *via* UV photo-polymerization [199]. The presence of PANI has a positive effect in the biological response of PEGDA, thanks to its electroconductivity that influences cellular activities, such as cell adhesion, survival and nerve differentiation. The possibility to combine the electrical properties of PANI with the fast diffusivity of small molecules and the high degree of hydration of hydrogels makes these materials good candidates to be applied to innovative devices able to respond to external electric fields, paving the way to new routes in the regenerative medicine.

Cardiac tissue engineering is a promising approach to replace or repair injured heart muscle. Thanks to their unique biocompatibility and electroactivity CPs and in particular PANI emerged as good candidates for applications in this sector, as recently demonstrated by Roshanbinfar *et al.* that fabricated electrospun fiber mats containing different percentage of electroconductive PANI, collagen, and/or hyaluronic acid [200]. Nanofibrous mats displayed electrical conductivity similar to that of native human myocardium and higher mechanical properties. The scaffold containing 9.89% of collagen, 1.1% of hyaluronic acid and 1.34% of PANI exhibited the best performances with longer contraction time, higher contractile amplitude, and lower beating rates.

Recently, Qazi *et al.* realized flexible composite cardiac patches by solvent casting method using blends of poly(glycerol-sebacate) and camphorsulfonic acid-doped PANI at different percentage for cardiac tissue engineering applications. The novel patches resulted to be biocompatible revealing good attachment, growth and proliferation of C2C12 myoblasts. Moreover, maintaining good electroconductivity they are good candidates as carrier and delivery vehicles of functional cells to the myocardial infarct [201].

CONCLUSION

This review presents the most recent advances on PANI application in biomedical field. Because the chemical-physical characteristics of the polymer are strongly depending on the synthetic procedure used for its fabrication, a large part has been dedicated to this aspect, highlighting the main advances of each method that typically address the choice of the researchers.

In order to overcome some of the limitations of PANI and PANI-derivatives application into clinical practice, such as cytotoxicity, processability, physicochemical properties, further improvements need to be made in the synthesis procedure. Herein, traditional and innovative approaches have been reported in order to stimulate greater efforts in this regard.

So far, owing to their high biocompatibility, ease of fabrication, tunable morphology and electroconductivity, conductive polyaniline-based nanocomposites represent the most promising materials for practical applications, even though deeper studies are necessary to reach real clinical applications.

However, we are confident that the huge interest of the scientific world on PANI will allow to overcome the limitations that at the present restrain its real utilization.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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