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Conductive Polymers: Photo-Active Tools with Medical and Pharmaceutical Applications

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Abstract

Conductive polymers are well-known unique category of organic compounds with exceptional electrical conductivity. Noble prize for the year 2000 was awarded to the team who firstly described the properties of conductive polymers, appreciating their great contributions. In this mini-review; a concentrated brief of history, chemistry, properties and general applications of conductive polymers is introduced, followed by a short survey focusing mainly on the most important and recent applications of conductive polymers in the medical and pharmaceutical fields including cancer photothermal therapy, antimicrobial photothermal therapy and conductive polymers-based drug delivery systems.

Keywords: Conductive polymers; Polypyrrole; Polythiophene; Polyaniline; Polyacetylene; Photothermal; Drug delivery systems.

1. History

Intrinsic or inherently conductive or conducting polymers are organic polymers having the ability to conduct electricity to extents that may resembles the conductivity of semiconductors or even exceed that of the metallic conductors. [1] Organic molecules, with few exceptions, were previously considered to be insulators that have high resistivity and cannot carry electrical current. The firstly-reported conductive organic materials were the charge-transfer complexes, during the middles of the 20th century. Charge-transfer complexes or electron donor-acceptor (EDA) complexes are usually polycyclic aromatic compounds that can form conductive or semi-conductive charge-transfer complexes with halogens. Great advances in EDA complexes development were achieved since the leading works of Robert Mulliken [2,5] till the first superconductor EDA complex, called tetramethyl selenafulvalene hexafluorophosphate, was introduced.[6] Although EDA complexes are not polymeric in nature, they represented an indication that organic compounds can conduct electricity. On the other side, conductive polymers were firstly described by Prof. McDiarmid and his group in 1974, the efforts for which he and his group was awarded Noble prize of the year 2000 in chemistry. [7] In fact, McDiarmid was not the first scientist reporting the conducting properties of polypyrrole. Earlier, in 1963, the Australian scientists B. A. Bolto, R. McNeill and D. E. Weiss, from the Chemical Research Laboratories of Melbourne in Australia, reported a series of polypyrrole derivatives with high conductivity. They concluded that

polypyrrole “depending on the relative amounts of electron donating or attracting chemisorbed species in relation to the concentration of donor nitrogen atoms in the polypyrrole, the polymer may behave as an intrinsic or extrinsic semiconductor with n- or p-type characteristics”. [8] Yet, conductive polymers were not that very recent discovery. Indeed, the most prominent members of these compounds, polyanilines and polypyrroles, were previously synthesized by electrochemical methods and described for their properties a long time ago, during the nineteenth century. In that age, the “polymer” term was not defined and even the existence of macromolecules was not accepted within the scientific society until the leading works of H. Staudinger, W. Carothers, P. Flory and other scientists by 1920s. During the middle of the nineteenth century, Dr. Henry Letheby (1816-1876); who was a physician and a member in the Board of Health of London, was interested in aniline due to its poisoning effects on workers. He noticed the formation of bluish-green precipitate at the anode during electrolysis which, upon reduction, becomes colorless and regains its color upon re-oxidation.[1] This bluish green precipitate was, actually, a form of polyaniline synthesized unintentionally by electrochemical polymerization. So, despite polyacetylene (CH)_n is considered to be the prototype of conductive polymers [9], polyaniline was an early-discovered member of conductive polymers, yet it had not been well-recognized.

2. Chemistry of Conductive Polymers

However, conductive polymers are a unique series of polymers characterized with attractive electrical properties; mostly due to their exceptional electronic configuration along the polymeric backbone, where π -bonded electrons are delocalized. [10,11] Despite that, this π -conjugation may represent also a major cause for most of their unwanted physical features such as insolubility and bad mechanical properties [12,13].

Conductive polymers could be synthesized by a variety of methods based on oxidative polymerization of the monomer (pyrrole, thiophene, furan...etc.). Oxidative polymerization may be induced chemically, electrochemically or via ultrasonic waves [14-20]. For example, the most applied way for polypyrrole synthesis is the oxidative polymerization of the monomer (pyrrole) using certain oxidants like $K_2Cr_2O_7$ and $FeCl_3$, a reaction that may involve the using of a dopant [21,22]. A similar mechanism was proposed for the chemical oxidative polymerization of aniline [23] (**fig.1**).

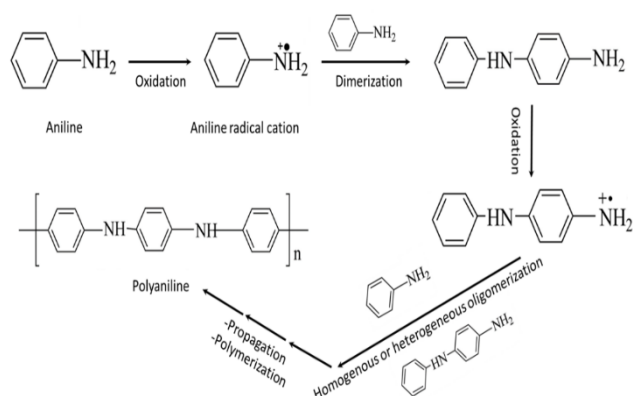


Fig.1. Mechanism of chemical oxidative polymerization of aniline

Electrochemical polymerization is also widely used method for the synthesis of conductive polymers. In this method, the monomers undergo through successive cycles of oxidation/coupling, oxidation/radical polymerization or both until the final step which is termination. Termination is a well-known mechanism in polymer synthesis and carried out in chemical polymerization by the addition of certain compounds [24]. In electrochemical synthesis of conductive polymers, termination usually occur spontaneously as a result of final coupling of the intermediate polymer radicals after the depletion of further radical-attackable monomers. A prominent example is the synthesis of polypyrrole by electrochemical polymerization of pyrrole [25] (**fig. 2**).

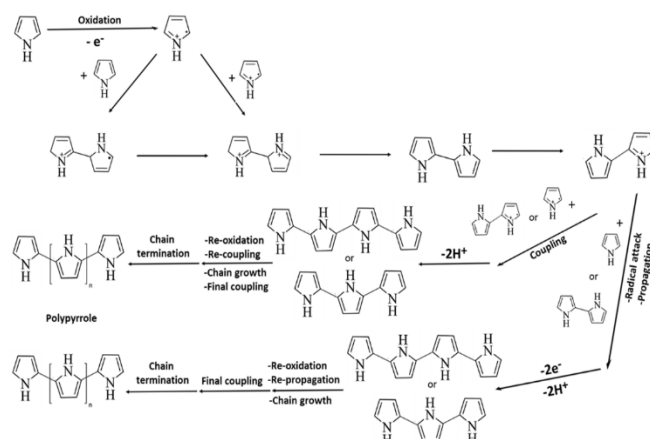


Fig. 2. Mechanism of electrochemical polymerization of pyrrole

As mentioned before, conductive polymers are polymers with delocalized π -bonded electrons along the polymeric backbone. Conductive polymers can be classified according to the nature of the building monomers into aliphatic (like polyacetylene) or aromatic. Aromatic monomer-based conductive polymers, in turn, may be classified into heterocyclic (like polypyrrole and polythiophene) or homocyclic (like polyphenylene). Some conductive polymers may also contain both aliphatic and aromatic units like polyphenylene (**fig.3**). However, the basic principle for the polymer to have conductive properties is the presence of π -bonded delocalized electrons. In such conjugated polymers, where single and double bonds are alternative along the system, three of the four carbon valence electrons form strong sigma bonds with the neighboring carbon and hydrogen, through SP^2 hybridization, where electrons are being strongly localized. The remaining electron in the P_z orbital, which is unpaired, forms a pi bond through overlapping with the neighboring P_z orbital. The pi electrons of these P_z electrons overlap together to form a P_z -electron system extended along the polymer chain through which electrons can move freely (**fig.4**).

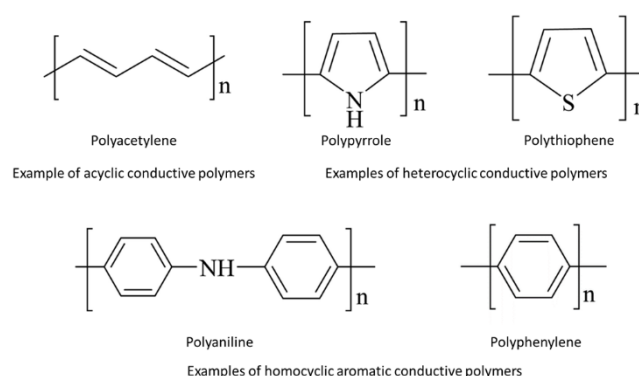


Fig.3. Chemical structures of some conductive polymers

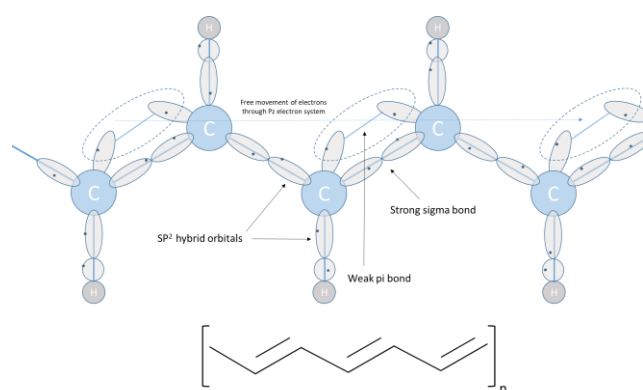


Fig. 4. Delocalization of π -bonded electrons along the polymer chain in polyacetylene

Conductivity of pure conductive polymers is known as intrinsic conductivity. In fact, conductivity of most pure conductive polymers is limited. As in semiconductors, conductivity of conductive polymers can be enhanced by the addition of dopants (extrinsic conductivity).

3. Doping of Conductive Polymers

Conductivity of conductive polymers can be enhanced by what is called “doping”. Doping in conducting polymers involves the introduction of a charged molecule called “dopant” within the polymer backbone to improve its conductivity. The doping process may be achieved by oxidation (p-type) or reduction (n-type), with the introduction of a dopant or counter-ion which may bear a negative charge (p-type) or positive charge (n-type). [12,26-28] However, p-type doping is much more common in conductive polymers due to the instability of the n-type doping. Being the prototype of conductive polymers, as prementioned, polyacetylene (or polyethyne in IUPAC nomenclature) was extensively studied for the doping process more than any other conductive polymer. For example, p-type doping of polyacetylene can be carried out by exposing the polyacetylene films to electron accepting molecules such as halogen molecules like iodine (I_2), chlorine (Cl_2), bromine (Br_2) or fluorine (F). Here, two simultaneous processes occur; firstly, oxidation of the polyacetylene chain leading to leaving positive charges (holes) along the polymer chain and secondly, reduction of the dopants into negatively charged ions which, in turn, get attracted to the positively charged polymer chain.

4. Medical and Pharmaceutical Applications of Conductive Polymers

Applications of conductive polymers cover a wide variety of fields in medicine, pharmacy, industry and agriculture. [29-32] Properties of conducting polymers are affected by numerous factors such as the method of synthesis, the monomer of which the polymer is built, the possible additives and the dopants. [13] Thus, a wide variety of conductive polymers can be engineered to meet the intended function(s). For instance, polypyrrole derivatives were introduced recently in pharmacy and medicine mainly as

versatile drug delivery tools, in bio-sensing and as molds for regeneration of nervous pathways [33-36]. In fact, uses of conductive polymers are not limited to pharmaceutical and medical applications but extend to cover several fields that impact our daily life. In microelectronics, for example, conductive polymers are used in the manufacturing of displays of the intelligent electronic devices, such as smart mobile phones, tablets and computers. Organic light emitting devices or OLEDs are prominent application of conductive polymers in electronics industry [37,38]. Similarly, a new trend in solar cells is based on increasing the energy efficiency and flexibility of such systems by using conductive polymers. [39,40]

4.1. Conductive Polymers in Photothermal Therapy

Photothermal therapy (PTT) is the exploitation of the hyperthermia induced by a photothermal material in treatment of several disorders like tumors and microbial infections. It differs from photodynamic therapy (PDT) in its dependence on the generation of heat not singlet oxygen.[41] The principle of PTT is based on the transformation of electromagnetic radiation (e.g. visible light and NIR light) into heat, a reaction that is mediated by a photothermal material.[41] Therefore, a photothermal material is a material that have the ability to convert the absorbed light into thermal energy or heat. [41] When applied to viable cells, this programmed hyperthermia may initiate and accelerate some hazardous cellular reactions leading cell death. [41,43] Photothermal therapy is also advantageous over photodynamic therapy by the ability of the photothermal materials to be activated via infrared and near infrared light, which allows higher penetration; overcoming one of the most prominent problems limiting the utilization of PDT [44]. Additionally, photothermal therapy induces cell apoptosis rather than cell necrosis, which is known to compromise the antitumor activity through stimulating inflammations⁴³. Mechanisms of action of PTT may include, among others, immunogenic responses and/or heat-related changes such as protein clotting, cytosol evaporation and cell lysis. [45,46] Conductive polymers can absorb light in the far spectrum (i.e. infrared and near infra-red regions) and therefore, they can efficiently convert light into heat, which makes them interesting candidates for use as alternative photothermal tools. For instance, gold nanorods have high photothermal activity but suffer high toxicity and non-biodegradability. On the other side, polypyrroles have comparable photothermal activity but also have the advantage of being non-toxic and biodegradable. [47] The same pattern can be noticed in several polythiophenes and polyanilines. [48,49] Thus, conductive polymers may represent safer and more efficient tools for use in photothermal therapy.

4.2. Conductive Polymers in Antimicrobial PTT

Photothermal and photodynamic therapy treatments of bacterial infections represent a newly emerging trend regarding to their minimal invasiveness, high efficiency and safety. The most important privilege of PTT and PDT over traditional antimicrobials is “their resistance to microbial resistance” [50] ! Being highly photothermal agents,

conductive polymers have attracted great attention in this direction. Light activation of conjugated polymers was promisingly used as an antibacterial approach through different mechanisms.[51] For instance, Behzadpour et al. reported a significant decrement in the bacterial cell viability as a result of the near infrared carbon-polypyrrole nanocomposite-mediated photothermal lysis.[52] Similarly, Jiahui et al. developed a self-healing nanocomposite hydrogel

4.3. Conductive Polymers in Drug Delivery

Being macromolecules, conductive polymers are ideal materials for use as drug delivery systems, regarding their ability to retain drug molecules within their polymeric network. A wide variety of conductive polymers, including polypyrrole, polyaniline, polythiophene...etc., were utilized as effective drug delivery systems in several studies. Conductive polymers don't differ much from usual polymers since both share the unique properties of polymers. Then, what is the advantage of using conductive polymers rather than usual polymers as drug delivery systems?

The main privilege of conductive polymers over other polymeric matrices, lie in their versatility. In pharmaceuticals, conductive polymers are becoming very important flexible and efficient tools, benefiting from their ability to be used as high-capacity drug delivery systems, light-responsive and electric-responsive properties [53-55]. For example, Hathout et al. reported a promising efficiency of dual-stimuli responsive polypyrrole nanoparticles in anticancer therapy. They succeeded to control the release of allicin, which is a compound resulting from the enzymatic hydrolysis of alliin in garlic, via two stimuli; electric field and light stimulation.[56] This model is dependent on that the negatively charged allicin, loaded on the positively charged polypyrrole backbone, is discharged under electric field stimulation, while the photothermal effect of polypyrrole is activated under light irradiation resulting in a dual targetable chemotherapeutic/photothermal anticancer effect. Other studies succeeded to generate dual photodynamic/photothermal effect via loading photosensitizers within conductive polymer matrices. For instance, methylene blue-loaded polypyrrole nanoparticles were used as a photodynamic/photothermal nanosystem, where methylene blue exerts its photodynamic effect while polypyrrole exerts its photothermal effect upon irradiation to NIR light. [57] Another example on the multifunctional properties of conductive polymers is the ability to be used for both therapy and diagnosis. In this context, Phan et al., in 2017, utilized nano-platform based on polypyrrole and methylene blue for both near-infrared photo-therapy and photoacoustic imaging.[58] This great adaptability opens the door for unlimited numbers of hybrid nanomaterials that can be synthesized to achieve several duties concomitantly. Additionally, the features of conductive polymers themselves can be transformed by changing their structures, sizes, stereochemistry, etc. All of this opens great windows for imagination, creativity and inventiveness; giving rise to renewable generations of nanomaterials for smart use in various fields. So, it seems that conductive polymers may

represent promising pharmaceutical tools that can potentially change the game rules.

5. Limitations

Numerous studies based on the exploitation of the versatile nature of conductive polymers were carried out recently. The basic obstructions facing this new trend are the issues of toxicity and bioavailability. Being newly incorporated in medical and pharmaceutical fields, conductive polymers were to be well-recognized for their possible harmful cytotoxic effects. Although several studies were conducted to deal with this concern, more data is still required; especially about their toxicity on normal cells. On the other hand, poor water solubility of conductive polymers [59-62] represents a major problem impeding their wide use in pharmaceutical formulations because it severely affects their bioavailability profiles. In the last few years, this problem began to find a solution through colloidal-dispersion of the polymer particles, but the stability issues of the resulting colloidal solutions are still representing a challenge.

6. Impact of Nanotechnology

Advances in nanotechnology enabled benefiting from numerous materials in radically different ways and opened the gate for exploring totally different uses of the same material, in the nano-scale. In the light of nanotechnology, great uses of conductive polymers have been re-discovered, especially in pharmaceuticals and definitely in featured drug delivery. In the nano-scale, it became easy to formulate different conductive-polymer based nano-systems in several pharmaceutical applicable forms.

7. Conclusion

Conductive polymers represent one of the most promising multifunctional tools in the medical and pharmaceutical fields. These unique materials can be utilized as versatile pharmaceutical drug delivery platforms with unlimited purposes including treatment and diagnosis. The ability of conductive polymers to efficiently transmit electricity, at least in relation to the rest of organic materials, may introduce a basis to link between living and non-living beings in much more compatible way. In our perspectives, without any exaggeration, conductive polymers are the future of multifunctional and stimulus-responsive drug delivery systems.

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