A conjugated polymer-liposome complex: A contiguous water-stable, electronic, and optical interface

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Abstract
The electronic and optical properties of conjugated polymers and conjugated polyelectrolytes have attracted considerable research interest across a broad range of applications. Interfacing them with the lipid bilayer enables the engineering of interfaces with unique characteristics, facilitated by accessing the properties of each constituent material. Research done on these interfaces tap into a broad range of applications. Fundamental studies have been conducted to gain insight into the polymer interaction with a lipid membrane that mimics the biological cell. Bioimaging and biosensing devices have been developed, exploiting optical and superquenching properties of the polymer. Delivery systems based on these complexes were applied in photothermal therapy using the polymer high thermal conversion efficiency. This minireview presents a summary of this research, highlighting that while the field remains in its early development, conjugated polymer/polyelectrolyte interfaces hold huge potential for biomedical applications.

Keywords
complex, conjugated polymer, lipid bilayer, liposome, phospholipid, polyelectrolyte

1 | INTRODUCTION

Inspired by the cell membrane, liposomes were first developed in the 1960s as model systems to understand the structure-function relationships of the biological membrane.[1] Since then, their use has been extended to many bioapplications such as drug delivery, gene therapy, diagnostics, and cosmetics.[2-4] Their widespread use is driven by their ability to adhere to and fuse with the cell membrane, enabling improved therapies by overcoming tissue uptake. Liposomes are made from one or more phospholipid layer. The versatile chemical structure of phospholipids facilitates their complexation with a variety of polymers, improving the long-term stability of liposomes and generating stimuli-responsive systems. More recently, there has been interest in coupling liposomes with conjugated polymers to introduce properties such as high fluorescence and electronic conductivity, otherwise unattainable with conventional lipidome-polymer complexes.

Conjugated polymers are organic macromolecules that have a backbone made from alternating single and double bonds. An overlap between their p-orbitals facilitates
the delocalisation of electrons, giving conjugated polymers their characteristic optical and electronic properties. They also combine mechanical flexibility with electric and ionic conductivity. Their organic nature permits chemical modification such as introducing side chains to enhance their solubility and processability and alter their hydrophilicity/hydrophobicity. These properties made conjugated polymers suitable for a wide range of applications, such as light-emitting diodes and solar cells,[5] tissue engineering,[6,7] biosensors,[8] and bioelectronics.[9]

Coupling conjugated polymers with liposomes allows the engineering of interfaces with unique characteristics, enabled by accessing the properties of each constituent material. The liposome provides a soft template with a versatile surface chemistry, a model for the cell membrane, fusion and uptake by the cell, and drug entrapment and delivery, while conjugated polymers provide optical and electronic properties. Despite their advantages, the research on conjugated polymer-liposome complexes appears to be limited when compared to the application of conjugated polymers in tissue engineering or bioelectronics; however, the studies reported to date indicate that these complexes are poised to make an impact in the biomedical field. Thus, in this minireview, we highlight advancements made in the development of conjugated polymer-liposome complexes. We briefly describe the optical and electronic properties of conjugated polymers. We introduce liposomes and their constituent phospholipids, highlighting the versatility in their chemical structures and mode of assembly. We emphasise the type of interactions between the conjugated polymer and the lipid bilayer, leading to an overview of their applications in the biomedical field. We conclude with a brief future direction highlighting applications that can benefit from these complexes.

2 | OVERVIEW OF CONJUGATED POLYMERS AND LIPOSOMES

The objective of coupling a conjugated polymer with the lipid bilayer has been mainly to exploit the optical properties of the polymer, relevant in applications such as bioimaging, biosensing, and photothermal therapy (PTT).[10–17] However, the advantages of introducing electronic conductivity in liposomes using a conjugated polymer in its doped state has also been demonstrated.[16–23] In addition, a recent research direction explores interfacing supported lipid bilayers (SLBs) with a conductive film based on conjugated polymers with promising results.[24–29] Thus, we present a brief overview on the origin of the electronic and optical properties of these polymers.

2.1 | Conjugated polymers and conjugated polyelectrolytes

The semiconducting properties of conjugated polymers stem from their unique molecular structures featuring a backbone chain formed from five-membered aromatic heterocycles as the repeat units with alternating single and double bonds.[30] Thus, conjugated polymers are inherently hydrophobic unless functionalised with side groups that facilitate their solubility in polar solvents.[31] Conjugated polyelectrolytes (CPEs) are one example of water-soluble conjugated polymers bearing an ionised group within the repeating monomer unit.[31] The chemical structure of CPEs consists of a hydrophobic π-conjugated backbone and flexible hydrophilic side groups. This amphiphilic property provides the polymer with strong absorption/emission properties via the conjugated backbone and solubility in polar solvents via the ionised side group.[31] Additionally, it enables their complexation with liposomes through electrostatic and hydrophobic interactions. Consequently, the bulk of the literature on liposome and conjugated polymers is mainly focussed on CPEs. However, the fluorescent and electronic capabilities of these polymers originate from the rigid hydrophobic aromatic backbone, which is typical of both.[32]

2.1.1 | Electronic properties

The chemical structure of conjugated polymers facilitates the delocalisation of electrons along the backbone, and thus imparts electronic conductivity in the material upon doping. As organic semiconductors, they can be doped chemically or electrochemically. They can be either p-doped or n-doped, depending whether the charge carriers are holes or electrons, respectively.[33] Figure 1 presents the electronic transitions that occur in conjugated polymers upon p-doping. When a π-electron is removed from the polymer neutral state, a free radical and a positive charge called polaron are generated, creating two intermediate band levels in the band gap, with the lower intermediate band level filled with the unpaired electron. Removal of another electron results in the formation of a bipolaron. With increased electron results in the formation of a bipolaron. With increased doping levels, more bipolarons are generated and the bipolaron discrete band levels become continuous band levels. These polaron bands can expand further until they overlap with the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) bands. This creates partially filled bands in which the charge carriers can freely move; this is typical of metallic-like materials.[34] As indicated by the blue arrows in Figure 1, generation of intragap energy levels changes
FIGURE 1  Top row: Chemical structures of polythiophene upon its p-doping: neutral (left), positive polaron (middle), and positive bipolaron (right). $\bullet$ represents the dopant and counterion. Bottom row: Evolution of energy bands as the polymer transitions from its neutral to its doped state; solid black lines in “Polaron” and “Bipolaron” represent intermediate discreet band levels; rectangles in “Bipolaron bands” represent continuous band levels.

the amount of energy required for an electron to jump to an excited state, and consequently also the emissive radiation followed by an electron relaxation. This influences not only the electronic properties of the conjugated polymer but also its chromic and spectroscopic properties.[35] This description is applicable for conjugated polymers in their nondegenerate ground state. For conjugated polymers in their degenerate states, the concept of soliton is introduced and has been extensively explained by Heeger et al.[36]

2.1.2  Optical properties: Fluorescence and phosphorescence

Conjugated polymers can absorb light leading to transitions from low to high electronic energy levels, as illustrated by Jablonski diagram.[30,37] The instant and delayed re-emissions of the absorbed light are called fluorescence and phosphorescence, respectively. In a neutral molecule, electrons with opposite spins are paired in the singlet ground state with a net spin equal to zero. Upon absorption of an external light, an electron transitions to a higher energy level. The molecule is said to be in its singlet excited state if the electron maintains its spin orientation and thus remains paired with the spin of the electron in the ground state. Excited states have several vibrational levels; intermolecular collisions cause the excited electron to lose its energy and subsequently return to the ground state by emitting the radiation related to the energy gap. This phenomenon is called fluorescence and the whole process takes from $10^{-5}$ to $10^{-4}$ s, which can be associated with an instant re-emission of the radiation. The energy of the emitted radiation is always smaller than the absorbed one; in other words, the wavelength ($\lambda$) of the emitted radiation will be always higher than the incident light.[30] In some instances, the light absorbed causes the excitation of one electron with a concurrent spin inversion, forming an excited triplet state. Since pairing electrons with the same spin is unfavourable, the electron takes longer to transition back to the ground state, typically from $10^{-4}$ s to several seconds, and this phenomenon is known as phosphorescence.

Of most interest in regard to CPEs-liposome complexes are the fluorescent properties of the polymer, shown to be modulated by its chain conformation. Changes in the fluorescence spectra of the polymer enabled scientists to gain insights into the interaction of the polymer with the liposome. The fluorescence quantum yield of an extended polymer chain is higher than that of an aggregated polymer chain. Additionally, variations in the chain morphology results in a shift in the emission wavelength.[31] Monitoring these changes has inspired the design of sensing or imaging devices, whereby quenching of the polymer fluorescence upon interaction with other molecules guides the read-out of the device. When a CPE interacts with an oppositely charged quencher, that is an electron acceptor, its fluorescence decreases significantly. This high sensitivity of the polymer is termed “superquenching” and has led to the development of superquenching based biosensors.[38]
2.2 Liposomes

Liposomes, lipid bilayer vesicles formed from phospholipids, can be recognised as the simplest form of artificial biological cells. Phospholipids are naturally occurring amphiphiles that act as the major component of biological membranes. The amphiphilic nature of the phospholipid molecule stems from its composition, consisting of a hydrophobic moiety made of one or two fatty acid chains, and a hydrophilic moiety made of glycerol and a phosphate group. Phospholipids can be either natural or synthetic, with versatile chemical structures. Head groups vary in structure and charge, hydrocarbon tails have different lengths and number of unsaturated bonds, and the type of bonds between the hydrophilic and hydrophobic heads can be either an ester, an ether or an amide bond.

All these structural factors have an immediate impact on the assembly of a liposome and dictate the type of interactions a liposome can undergo with other compounds such as polymers and small molecules.

In an aqueous environment, the hydrophobic tails interact with each other forming a bilayer, with the hydrophilic heads interacting with water on both sides of the bilayer. This results in a liposome with a hollow spherical shape and a size ranging from as small as 30 nm to being as large as a few micrometres. The liposomal suspension, alongside its nano- or microscale size and biocompatibility, shows a favourable method for drug delivery, gene therapy and immunisation. Liposomes are very sensitive to their environment, with the bilayer easily rearranging or even disrupted and rupturing under large deformations. In contact with a surface, several liposomes rupture resulting in large patches of bilayers: these eventually fuse forming a SLB, a two-dimensional bilayer that closely mimics the cell membrane. As a result, SLBs are well suited for studying processes such as protein adsorption, interaction, and function in the biological cell membrane. As will be discussed, conjugated polymers have been interfaced with both liposomal suspensions and SLBs in order to probe various molecular mechanisms occurring at the biological membrane.

2.3 Conjugated polymer/polyelectrolyte-liposome complexes

The amphiphilic nature of phospholipids facilitates their solubilisation or dispersion in both polar or nonpolar solvents. As such, a lipid cake, dried phospholipid, can be either redispersed in organic or aqueous media, enabling the interaction with conjugated polymers or CPEs. Furthermore, by varying the nature and number of charges on the phospholipid headgroup, the nature of the conjugated polymer, number of the side group in CPEs, and the length of the polymer chain itself provide a large spectrum of interaction possibilities between the polymer and phospholipid vesicles. Broadly, these interactions can be classified into hydrophobic interactions resulting in a polymer that is embedded in or very near the bilayer, or electrostatic/hydrophobic interactions leading to the encapsulation of the polymer inside the liposome or its absorption on the surface of the liposome. Figure 2 is a schematic representation of these interactions.

Hydrophobic interactions between conjugated polymers and liposomes have been achieved using CPEs ammonium salt complexes that are organic soluble (Figure 2A-i). Examples include poly(4-(2,3-dihydro
thiophene-(3,4-b)-(1,4)dioxin-2-yl-methoxy)-1-butanesulfonic acid) (PEDOT-S) and poly(6-(thiophene-3-yl)hexane-1-sulfonate) (PHS) with dioctylammonium chloride as the counterion.\cite{13,23} Embedding the polymers in the lipid bilayer enabled monitoring the lipid membrane organisation through changes in absorption and emission spectra of CPE. An alternative approach that exploits hydrophobic interactions is based on conjugated polymer nanoparticles made dispersible in organic solvents by using surfactants (Figure 2A-ii). For instance, using dodecylbenzene sulfonic acid as a dopant and a surfactant during the fabrication of polyaniline (PANI) nanoparticles, aids its dispersion in chloroform and subsequently its interaction with the lipid bilayer.\cite{43} Also, the conjugated polymer-liposome complex can be fabricated by the in situ polymerisation of conjugated monomer precursor in a liposomal suspension. The hydrophobic nature of the aromatic monomer enables its insertion in the lipid bilayer; adding an oxidant results in the synthesis of a conjugated polymer embedded within the lipid bilayer. A conductive polypyrrole-liposome complex was prepared via this approach.\cite{45} Pyrrole was added to an organic solution containing the lipid, lecithin, followed by formation of a pyrrole-lipid bilayer through hydration in an aqueous media. Polypyrrole was then synthesised by adding the oxidant, iron chloride, producing an electronically conductive lipid bilayer characterised by high conductance.

Electrostatic interactions are important in complexes based on water-soluble CPEs. These interactions can be attained either by rehydrating the lipid cake in an aqueous CPE solution (Figure 2B) or by adding the CPE to a prehydrated lipid bilayer (Figure 2C). The approach used determines where the CPE is localised with respect to the lipid bilayer. Rehydrating a lipid cake in a CPE solution results in encapsulation of the polymer within the liposome (Figure 2B-a) as well as its binding to the lipid walls (Figure 2B-b). This indicates that hydrophobic interactions resulting from the CPE backbone are also a contributing factor in its complexation with the liposome; however, suppression of the hydrophobic interactions with the wall can be minimised by tuning the lipid composition. A negatively charged CPE, poly[5-methoxy-2-(3-sulphopropoxy)-1,4-phenylene-vinylene] (MPS-PPV), has been shown to be freely diffusing inside a negatively charged liposome made of 75% anionic dioleoyl phosphatidic acid and 25% zwitterionic 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC).\cite{44} Alternatively, a CPE solution can be added to a hydrated lipid bilayer to form the complex. Here, both electrostatic and hydrophobic interactions should be considered, with the dominant type of interaction dictated by the charge of both the polymer and the lipid.\cite{45} In case the CPE and the lipid have opposite charges, they interact strongly through electrostatic interactions, and the polymer is likely also to embed inside the lipid bilayer through hydrophobic interactions (Figure 2C-1). If they have the same charge, they do not interact, and a complex cannot be formed, indicating that hydrophobic interactions are not enough to override electrostatic repulsions (Figure 2C-2). In case of zwitterionic phospholipids, the charge of the CPE determines the localisation of the polymer with respect to the lipid. The interaction of CPEs bearing cationic, anionic, or zwitterionic charges with the zwitterionic phospholipid, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), has been investigated, elucidating the position of the polymer with respect to the surface or lipid bilayer of the liposome.\cite{46} Among the three polymers, the zwitterionic CPE was found to embed most in the lipid bilayer, as revealed by an observed quenching of the polymer and a large partition coefficient that gives information about the location of the polymer with respect to the lipid and water phases in the liposome. The anionic CPE interacted with the headgroups on the surface of the liposome, increasing their thickness measured by small-angle neutron scattering (Figure 2C-3). The cationic CPE covered the outer surface of the liposome, as revealed by a blue shift in its absorption spectra, indicating a change from aggregated to extended chain conformation.\cite{46} The chain length is another important factor to consider when adding a CPE solution to a hydrated lipid bilayer bearing opposite charges as it can control whether the liposomes fuse together. As discussed, both electrostatic and hydrophobic interactions are favourable in this system, and the CPE will embed in the lipid bilayer, with the CPE having a longer length embedding to a lesser extent than the shorter polymer. The CPE acts as a bridge between liposomes leading to their fusion.

The aforementioned approaches largely entail multistep procedures that require the synthesis and processing of the conjugated polymer or polyelectrolyte before its complexation with the lipid bilayer. Recently, we have introduced a one-step fabrication approach for the development of liposomes decorated with the conjugated polymer PANI.\cite{47} We added the monomer aniline, the dopant phytic acid, and the oxidant ammonium persulfate to the liposomes suspended in water. PANI, in its doped state, was formed around the liposome, thereby producing a conductive conjugated polymer-liposome complex.

3 | APPLICATIONS OF CONJUGATED POLYMER/POYLECTROLYTES-LIPOSOME COMPLEXES

Conjugated polymer/polyelectrolytes-liposome complexes possess the potential for many advantageous applications
in the biomedical field, with bioimaging, biosensing, and PTT being the most practical. These applications are enabled due to the increased light sensitivity of the lipid bilayer when combined with the super-quenchable, fluorescent CPE.\[48\] Bioimaging is a noninvasive process able to visualise biological activity over a specific period of time. CPEs provide a direct link between spectral analysis and the biological process being imaged, due to their photoluminescent and optical properties. Their chemical structure can be altered to achieve tailored conjugated polymers with different emission wavelengths. In addition, their low cytotoxicity and high photostability properties increase their suitability for bioimaging. However, they tend to aggregate in aqueous media due to their relatively hydrophobic chain structure, and therefore their fluorescence signal decreases.\[10,15\] Overcoming this limitation can be achieved by a variety of strategies; a promising approach is via the complexation with lipid bilayers.\[10,13–15,17\] Calver et al interacted the cationic lipid, 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), with the conjugated polyanion MPS-PPV, which was adsorbed onto individual SiO₂ nanoparticles in order to promote deaggregation via the formation of surface-immobilised charging scaffolds.\[17\] Conformational changes in MPS-PPV liposome complex elicited fluorescence intensity enhancements. The interaction with the liposome minimises polymer-polymer interactions. It also extends the CPE backbone leading to an enhanced fluorescent signal. Kahveci et al presented the use of the conjugated cationic polyfluorene, \{[9,9-bis(6'-N,N,N-trimethylammonium)-hexyl][fluorene-phenylene] bromide (HTMA-PFP), as a fluorescent membrane marker when interacted with anionic and zwitterionic phospholipids.\[15,49\] The interaction between the polyelectrolyte HTMA-PFP and anionic lipid vesicles was demonstrated by a blue shift in the fluorescence spectrum and without disruption of the morphology of the lipid bilayer.\[15\] Similarly, the polymer interacted with the zwitterionic membranes but to a lesser extent.\[49\] These studies showed the innate potential for HTMA-PFP for use in the selective detection of pathogenic bacterial cells due to the affinity of the polymer to the cells’ anionic lipids over zwitterionic lipids. The polyfluorene backbone was further modified by replacing the phenylene with naphtho[2,3c]-1,2,5-thiadiazole, extending the wavelength from blue to red.\[10\] A fluorescent probe that emits in the red region is of great interest for in vivo imaging due to the minimal photodamage to the biological samples and minimal interference from autofluorescence. The synthesised copolymer, copoly{-[9,9-bis(6'-N,N,N-trimethylammonium)hexyl]-2,7-(fluorene)-alt-1,4-(naphtho[2,3c]-1,2,5-thiadiazole)} bromine (HTMA-PFNT), was partially inserted into a zwitterionic lipid bilayer formed from DOPC. The complex showed no photobleaching over a storage time of 3 days at a temperature of 4°C, indicating high photostability. Additionally, the complex was shown to interact with human keratinocyte cells, enabling cell visualisation via fluorescence. Furthermore, the HTMA-PFNT polymer was found to label only bacteria cells when added to samples containing both E. coli bacteria and Hela cells.\[50\] This binding selectivity can be potentially exploited as a diagnostic tool for the detection of bacterial infections. A green-emitting cationic CPE, copoly{-[9,9-bis(6'-N,N,N-trimethylammonium)hexyl]-2,7-(fluorene)-alt-4,7-(2-phenyl benzol[d][1,2,3] triazole)} bromide (HTMA-PFBT), was synthesised by Vázquez-Guilló et al.\[12\] The cationic polymer was shown to selectively target anionic membranes of bacteria over zwitterionic mammalian cell membranes. This hints towards their possible use in bioimaging different malignancies and selective recognition of bacteria over mammalian cells. Green fluorescent probes have shorter penetration distances within the tissue compared with red-emitting probes. However, bioimaging of the biological surface is more advantageous in the green band due to their higher fluorescence emission efficiency and ability to differentiate from background autofluorescence.\[12\] These studies demonstrate that CPE liposome complexes are clearly suitable as bioimaging probes, owing to their excellent photostability, high emission rates, tailored emission wavelengths, and cellular uptake/interaction.

The photophysical properties of CPEs are highly influenced by the biological environment. In addition to their environmental sensitivity, CPEs undergo bioconjugation with various recognition elements due to their easily amenable side chains, therefore rendering them useful in biosensing applications. A fluorescence complex based on the cationic polyfluorene, HTMA-PFP, and the phosphatidylglycerol lipid was coupled with the enzyme alkaline phosphatase (ALP). A significant drop in fluorescence was measured within 2 minutes when p-nitrophenyl phosphate (PNPP) was added to the complex. This was attributed to the hydrolysis of PNPP by the enzyme and the generation of p-nitrophenyl (PNP), which is a quencher of the fluorescent CPE. The reported limit of detection was 52 μM, which is significantly lower than physiological concentration of phosphate in human blood. Chemburu et al developed a fluorescence assay based on lipoparticles with cationic derivatives of poly(p-phenylethynylene) (PPE) as the CPE. Borosilicate beads were coated with PPE, which were then subsequently coated with the anionic phospholipid, 1,2-dimyristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] (DMPG).\[51\] The lipoparticles used amplified superquenching with the external electron transfer quencher, 9,10-anthraquinone-2,6-disulfonic acid
Fluorescence quenching increased as the PLA<sub>2</sub> interacted with the lipid. The assay had a detection sensitivity in the nanomolar range comparable to the physiological concentrations in humans. Similarly, notable increases in fluorescence detection sensitivity of microsphere-silica-based assays have been observed when coated with a cationic derivative of PPE. The assay was used to monitor interaction of a model peptide, melittin, with the lipid bilayer DMPG assembled around the PPE microsphere. It was shown that concentrations of melittin lower than 1.6 μM could be detected, a high detection sensitivity not previously achieved. Further studies indicate the high aggregation nature of an anionic PPE derivative, BpPPESO<sub>3</sub>, can be absorbed via complexation with phospholipids, for example, phosphatidylcholine. This was visualised by a blue shift in emission and an enhanced fluorescence intensity indicating that the backbone was extended. The optical changes upon complexation are reversible, inciting the development of a fluorescence turnoff assay when catalysed with lipase enzymes. The fluorescence intensity decreased when the complex was incubated with the enzyme, phospholipase C (PLC). This was attributed to the PLC-catalysed hydrolysis of the phosphatidylcholine that caused structural disruption of the complex, showing effective biosensing targetability. The research to date indicates that CPE-liposome complexes have potential in the development of sensitive assays for diagnostic applications.

PTT employs light-induced heat through near-infrared (NIR) light irradiation for targeted therapy in applications mostly related to chemotherapy. Liposomal formulations have been effective in the targeted delivery of chemotherapy, while reducing toxicity and side effects of the chemotherapeutic agent. Given that liposomes loaded with chemotherapy have improved pharmacokinetics and stability in aqueous media, and conjugated polymers have high photothermal conversion efficiency in response to light, their complexation enables the development of advanced therapeutics. PANI nanoparticles were imbedded into a lipid bilayer, where folic acid was tethered in order to improve cancer selectivity and enhance permeability. These nanoparticle complexes were injected into a tumour in vivo and after 6 hours, via NIR irradiation, the temperature of the tissue increased to 50°C, causing the ablation of tumour cells. By day 10, the cancer was completely eradicated. In another study, the fluorescent probe, cyanine, and the chemotherapeutic agent, rapamycin, were loaded in the liposome-PANI nanoparticle system, developing an imaging guided photothermal drug-delivery nanoparticle. The tumour was completely eradicated by day 20, following the injection of this system and the irradiation with NIR. The utility of PANI-lipid complexes for PTT was further demonstrated by You et al. For example, the authors developed a PANI-lipid complex with a cross-linked core consisting of poly(ethylene glycol-co-caprolactone) (PEG<sub>5K</sub>-PLC<sub>10K</sub>) block-copolymer and the chemotherapeutic agent, cisplatin. The copolymer was incorporated to enhance stability of the complex in body fluid. Additionally, herceptin was tethered on the surface as a targeting ligand for breast cancer cells. The study showed the effective cellular uptake of the carrier and eradication success of cancerous cells when exposed to NIR (95% cell death) as compared to no irradiation (74% cell death). Despite there being only a few studies on PTT using conjugated polymer-liposome complexes, those that have been conducted show promising results for future development.

The above applications were based on the imbedding of the conjugated polymer/polyelectrolyte into the liposome and monitoring the optical changes detected because of changes in morphology of the polymer. A promising new approach that further demonstrates the utility of interfacing conjugated polymers with liposomes is investigating SLBs supported by the conjugated polymer when used as an active channel in an organic electrochemical transistor. Here, the conjugated polymer establishes an electronic communication with the membrane and is an electric read-out, revealing changes in the permeability and morphology of the SLB. This is a promising platform shown to identify bacterial toxins or antibiotic targets that disrupt bacteria and elucidate the interaction of compounds and insertion of proteins with the membrane, monitor ion channel activity in complex biological SLBs and in SLBs incorporating gramicidin channel.

**4  |  CONCLUSION**

Despite the promising studies reported to date on interfacing conjugated polymers or polyelectrolytes with liposome for a variety of bioapplications, the field is yet to see a significant increase in research activity when compared to the application of conjugated polymers in tissue engineering or bioelectronics. The bulk of the literature focuses on CPEs in their semiconducting form, exploiting their photophysical properties. The reported studies largely investigated how the polymer interacts with the lipid bilayer. These fundamental works are guiding our understanding into the development of functional assays based on conjugated polymers, not only for the detection of biomolecules but also enabling the detection of cells with subtle differences based on their cell surface features. Utilising these polymers to establish an intimate electronic
connection with the cell membrane holds great potential, providing the possibility to access and control cell membrane structures via electronic conductivity. By inserting an electronically active CPE-liposome complex in the cell membrane of oocytes, the opening threshold of voltage-gated ion channels was modified. The conductive nature of the polymer in the complex enables a path for communication with redox active proteins in biological systems. Interfacing conjugated polymer or polyelectrolytes with liposomes is in its early development: nevertheless, the research conducted to date indicates that these complexes hold huge potential in the biomedical field. We would like to conclude by highlighting that the conjugated polymer-liposome complexes are injectable, enabling minimally invasive delivery of conjugated polymers to incorporate intimately into electroconductive tissues. This paves the way towards injectable organic bioelectronics currently unavailable.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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