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Prog. Polym. Sci. 30 (2005) 844–857

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Functional polymers: from plastic electronics to polymer-assisted therapeutics

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Accepted 2 February 2005

Abstract

Functional macromolecules once sought almost exclusively for their mechanical or thermal properties are now finding numerous applications in a great variety of areas. In some cases, newly designed functional polymers provide such an array of new properties and functions that they effectively create fields rather than extend or support them. This brief account focusing largely on the work of the author's own laboratory explores recent advances in the design of functional polymers in two seemingly very disparate areas: organic or 'plastic' electronics and polymer therapeutics. While at first glance the requirements for functional polymers appear to be quite different for these two areas, the same general design concepts apply, focusing first on the definition of the key properties to be achieved, followed by the establishment of a synthetic blueprint encompassing these aims, and concluding with proof of concept studies. The examples given in this account illustrate the vibrant nature of research in the area of functional polymers and its great potential impact on to-morrow's technologies.

Keywords: Functional polymer; Organic electronics; Polymer therapeutics; Light emitting diode; Photovoltaics; Organic transistor; Drug delivery; Vaccine carrier

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Contents

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doi:10.1016/j.progpolymsci.2005.06.005

1. Introduction

Functional polymers have garnered much attention over the past four decades as more and more macromolecules find applications beyond their traditional use in commodity plastics and fibers. Three illustrative examples selected from past decades both for their fundamental and their commercial impact include: (i) the crosslinked chloromethylated polystyrene beads developed in the early 1960s by Merrifield [1], which have revolutionized the field of peptide synthesis; (ii) the poly(t-butyloxycarbonyloxystyrene) developed in the early 1980s [2,3] that opened a new era in microelectronics with the introduction of chemically amplified resists [4]; and (iii) the conducting polymer poly(3,4-ethylenedioxythiophene) [5] known as PEDOT, initially developed for use as an antistatic coating in photographic films, but marketed since the early 1990s by Bayer AG for a host of other electronic applications.

While these are only three of a very large number of significant examples of functional polymers, the range of functional polymers available today is enormous: from very simple structures obtained in a single polymerization step, to polymers with complex architectures prepared through multistep syntheses. In most cases, a clear correlation may be established between the complexity of the process used for their preparation and the end-use. In the context of fundamental research, complex designs and precisely elaborated structures may be required to demonstrate a concept or a novel property; in contrast, design simplicity and ease of synthesis are key features for most practical targets. This brief review will therefore explore the broad area of functional polymers emphasizing the relationship between molecular design and ultimate function with a diverse selection of 'case studies' largely taken from work carried out in the author's Laboratories in Berkeley.

2. Designing functional polymers for organic electronics

Since the seminal discovery of the doping of polyacetylene in the late 1970s [6] a large number of electroactive polymers have been developed and have shown enormous potential for a number of technological applications. A particular area of application that has long-term implications for society [7] is the use of polymeric materials in the design and fabrication of low cost organic electronic devices or 'plastic electronics'. Typical targets (Fig. 1) include both two-terminal devices such as plastic photovoltaics (PV) and organic light emitting diodes (OLED), and three-terminal devices such as organic thin film field effect transistors (OTFT), as well as a variety of sensors and radio frequency identification (RF-ID) tags. Since all of these device architectures involve an organic active material confined between two or more electrodes, performance will be a function of the charge carrier mobility through the organic polymer and also across a variety of interfaces involving a multiplicity of dissimilar components. Therefore, obtaining a fundamental understanding and controlling the physical and material properties of the various organic components and interfaces and their impact on mobility is key to improving the performance of all organic electronic devices.

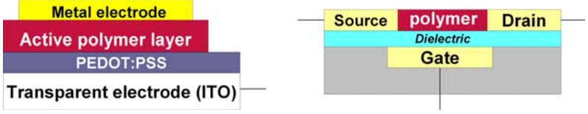


Fig. 1. Schematic representations of a two-terminal photovoltaic device (left) and a three-terminal transistor (right).

2.1. Organic thin film transistors

In recent years, we have focused on the fundamental development of novel families of functional oligo- and poly-thiophenes with structural features that combine their intrinsic electronic properties with enabling processing characteristics for applications such as organic electronics and solar energy conversion.

The solubility of organic semiconducting materials is a particularly important consideration when evaluating candidates for use in low cost electronic devices such as organic thin film transistors, since the desired processing of these materials includes the use of solution-based methods such as spin coating, or printing [7]. These methods have the advantage of being conducted at low temperatures, allowing for the use of a great variety of substrates such as plastic or fabric, and they are also amenable to large area or continuous applications. However, highly conjugated organic materials such as pentacene, oligothiophenes, and most other conjugated oligomers and polymers are notoriously difficult to manipulate due to their low solubility, and functionalization to introduce solubilizing groups is therefore necessary to enable solution processing. However, functionalization may affect the natural π stacking tendency of the molecules, which has a deleterious effect on charge carrier mobility as the latter relies heavily on π-orbital overlap. Indeed it has been observed that soluble organic semiconductors generally provide lower performance than their insoluble counterparts [8]. To minimize this problem, while conferring solubility to the materials, strategically placed substituents that can later be removed by thermal processing may be introduced. The thermal removal of solubilizing groups, key to our design of the now universally used chemically amplified photoresists [2,9], was later used in the Durham polyacetylene [10] and more recently for solution processible pentacene [11]. Removal of the solubilizing groups from an organic semiconductor such as an oligothiophene is beneficial as it gives rise to increased charge carrier mobility through the material, and, with appropriate design [12], it may also endow the materials with enhanced air stability, perhaps through a process in which remote reactive sites performing the function of oxygen traps are introduced as the solubilizing group are removed.

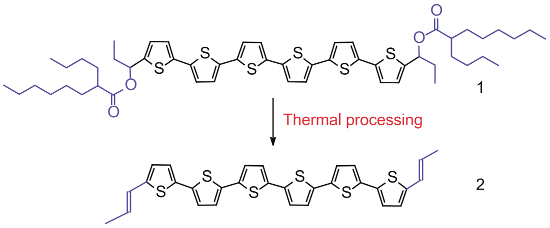


Fig. 2. Solution processible sexithiophene molecule functionalized with thermally removable ester groups.

Using this process with symmetrically α,ω-ester-substituted sexithiophene **1**, (Fig. 2) we have prepared OTFT devices by both spin-coating and ink-jet printing techniques [13]. Once the material has been coated, the material is subjected to a heating cycle to induce thermolytic removal of the ester solubilizing groups. As a result of this removal of bulky substituents, the sexithiophene molecules **2** can re-acquire the preferred π-stacking orientation that leads to high charge carrier mobility through the semiconducting material. Device testing of thin film transistors prepared using the diester **1** pictured in Fig. 2 showed an increase in hole mobility from 1×10^{-5} cm^2/Vs with on/off ratios of $\sim$100 before thermolysis, to 5×10^{-2} cm^2/Vs with on/off ratios $>10^5$ after thermolysis for oligomer **2**. While these values are among the highest ever reported for solution processed thiophene oligomers [12,13], further modifications of the molecular structure of these oligothiophenes and their use in ordered monolayers have led to even higher performances. Oligothiophene **2** also displays enhanced stability to oxygen, a phenomenon that may be associated with the formation of allyl chain-ends during thermolysis as these could conceivably serve as preferential loci for air oxidation, thereby acting to protect the oligothiophene chains themselves. This conjecture will have to be confirmed in comparative experiments involving a variety of oligothiophene structures.

2.2. Non-conjugated bipolar polymers in phosphorescent light emitting diodes

Numerous electroluminescent materials based on conjugated polymers, non-conjugated polymers, and charge-transporting polymers have been used in the design of OLED and several reviews pointing to advances in the field have appeared [14,15].

The use of phosphorescent heavy metal complexes - such as cyclometallated platinum and iridium complexes pioneered by Thompson and Forrest [16, 17] is particularly attractive as the strong spin-orbital coupling of heavy metals facilitates efficient intersystem crossing enabling the complexes to capture both the electrogenerated singlet and triplet excitons. As a result, devices based on these complexes can theoretically approach 100% internal quantum efficiency (IQE). Currently, the highest performing light emitting devices, reaching a peak external quantum efficiency (EQE.) of about 19% [17], have been obtained using vacuum deposited small molecules and emitters based on iridium complexes. However, these materials are not be ideally suited for the low cost production of large area devices and novel systems allowing production via spin-coating or printing techniques are needed. An attractive solution involves the use of solution-processible electroactive polymers doped with phosphorescent emitters. Since most of the polymers used today only transport holes, high percentages of small molecule electron transporting (ET) moieties must usually be blended with the polymer to balance the charges and shift the emission zone from the cathode thus contributing to device efficiency. Therefore, Heeger, Bazan, and their coworkers have achieved 10% EQE by doping tris[9,9-dihexyl-2-(pyridinyl-2′)fluorene]iridium(III) into a blend of 2-tert-butylphenyl-5-biphenyl-1,3,4-oxadiazole (PBD) and poly(vinylcarbazole) [18], while Jiang et al. [19] have reported 12% EQE by doping small molecules and an Ir emitter into a silsesquioxane-terminated poly(9,9-dioctylfluorene).

Using a different approach, we have explored the use of non-conjugated copolymers with bipolar hole and electron transport abilities in combination with phosphorescent emitters for highly efficient light emitting diodes. Such bipolar polymers are very attractive as their use should provide for a good balance of holes and electrons, helping to decrease exciton quenching near the cathode while also suppressing the commonly seen and detrimental phase separation or recrystallization of molecular electron transporting moieties from the blends.

Both random and block copolymers based on styrenic or acrylic monomers containing triarylamine (HT) and oxidiazole (ET) moieties were prepared using living radical polymerization techniques with alkoxyamine initiators [20] as shown in Fig. 3.

The good solubility properties of random copolymers such as **6** enabled their solution processing from chloroform solutions containing 8 wt.% of iridium(III)bis(2-(4-tolyl)pyridinato-N,C2′)acetylacetonate [$(tpy)_2Ir(acac)$] as the phosphorescent emitter [21]. Spin-coated devices based on copolymers with a variety of compositions all showed the same emission centered at a wavelength of 535 nm, which corresponds to the emission of $(tpy)_2Ir(acac)$. In general, styrenic polymers afforded better performance than their acrylate counterparts and performance could be tuned by adjusting the ratio of hole transporting to electron transporting monomer in the random copolymers to better balance the carrier fluxes in the device. With a 2:1 ratio of HT monomer **4** to ET monomer **5**, devices made with polymer **6** and 8 wt.% of $(acac)Ir\ (tpy)_2$ showed a peak EQE of 10.5% (Fig. 4) with a turn-on voltage of 7.5 V and a maximum brightness of 7500 Cd/m^2 [22]. While this performance is among the best reported to date for a solution-processed device, we expect that further improvements are possible with different compositions or through the control of film morphology in block copolymers or novel terpolymers [23] currently under study.

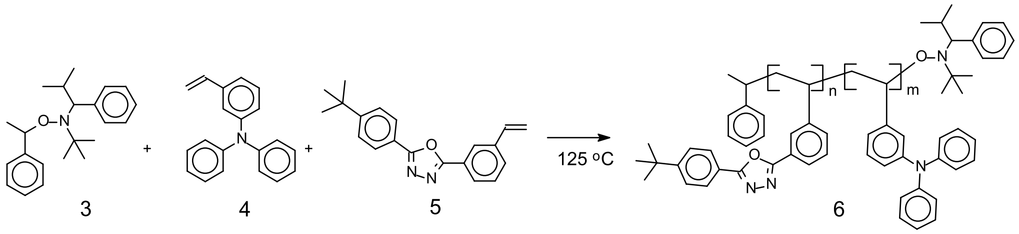


Fig. 3. Preparation of random copolymers of ET and HT monomers **4** and **5**. Block copolymers are prepared similarly via the sequential addition of the same monomers.

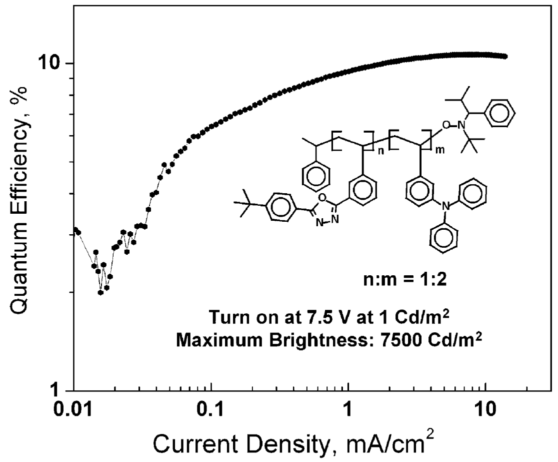


Fig. 4. External quantum efficiency vs. current density for OLEDs made from copolymer **6** with 8 wt.% of (acac)Ir(tpy)$_2$.

The challenge of white light emission from a device made from a single emitter dopant can also be tackled using non-conjugated bipolar polymers [23]. The molecular design of such a device would involve the use of an emitter moiety that can emit light from a combination of monomer and excimer/aggregate states. For example, (2-(4′,6′-difluorophenyl)pyridinato-N,C$^{2'}$)(2,4-pentanedionato)Pt(II) dopant (*FPt*), can produce near-white light from the simultaneous occurrence of blue *FPt* ‘monomer’ emission and red excimer or ‘aggregate’ *FPt* emission, with the ratio of blue to red emission controlled by the total *FPt* concentration, a high concentration favoring aggregate formation and therefore red emission. The excimer lacks a bound ground state, limiting energy transfer between dopants. Since the stability of both emitting species depends on only a single complex, the age-dependent color shifts observed with white light devices based on multiple independent emitters should decrease. To demonstrate this novel design, we have prepared bipolar random terpolymers such as **8** containing various ratios of HT and ET monomers **4** and **5** as well as β-diketonate monomer **7** (Fig. 5). The light-emitting polymer **10** is prepared from its precursor terpolymer **8** by reaction with Pt complex **9**. Since achievement of the goal of white light emission requires that two different forms of the Pt complex be present within the polymer film — the monomeric form for blue monomeric emission, and the aggregate form for orange excimer emission — the composition of copolymer **10** must be adjusted to regulate the extent of *FPt–FPt* interaction within the polymer.

In early studies, a near-white light emitting solution cast device with a notable EQE of 4.6% and a relatively low turn-on voltage of 7.8 V was obtained with polymer **10** having the composition

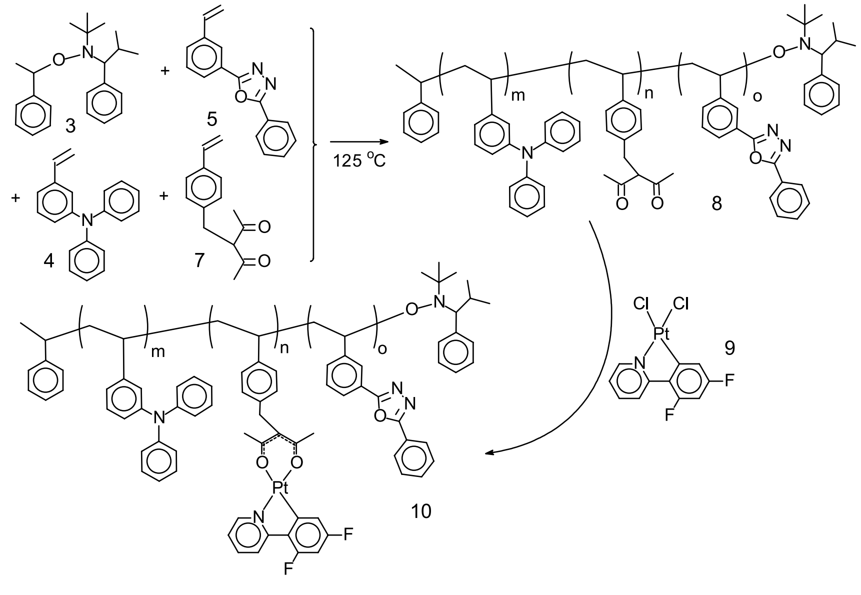


Fig. 5. Preparation of random terpolymer containing HT, ET and emitter moieties.

m:n:o = 10:1:10 (Fig. 5). Devices with significantly higher Pt complex loadings appear to suffer from Förster losses [23].

This and other studies [22–24] demonstrate the great potential of electroactive polymers with phosphorescent emitters for the preparation of highly efficient solution processed OLEDs. The high efficiencies realized to date are such that it is possible to envision the use of these materials in a number of applications, likely including large area lighting. Current studies with block copolymers and block terpolymers containing an emitter block in addition to hole and electron transporting blocks should uncover the role of film morphology and its effect on device performance.

2.3. Polymers in hybrid organic–inorganic photovoltaic devices

The development of photovoltaic (PV) devices relying exclusively on polymeric materials is still in its infancy and the few polymeric devices reported to date lag far behind the inorganics in terms of overall efficiency. The better efficiency of inorganics over their organic counterparts is mainly due to the superior carrier mobilities displayed by inorganic semiconductors, leading to the fast transport of charges to the electrodes and to fewer opportunities for losses via recombination. While polymers display useful hole transport properties, electron mobilities in polymers remain extremely low, due in part to the presence of numerous electron traps such as oxygen. Therefore, until novel polymers with high electron mobilities are designed and introduced, the use of blends of high electron affinity semiconducting inorganic materials with low ionization potential hole transporting polymers will remain a most attractive proposition.

In pioneering studies, Alivisatos and coworkers [25, 26] have demonstrated the use of blends of semiconductor CdSe nanorods with a conducting polymer to fabricate hybrid solar cells with power conversion efficiency of up to 1.6% [26]. In these hybrid organic–inorganic photovoltaic devices, the active layer is a solution-processed mixture of an electron donor phase — a π-conjugated polymer such as regioregular poly(3-hexylthiophene) (P3HT) — and an electron acceptor phase consisting of CdSe nanorods. Therefore, while in these devices holes are transported by a continuous polymer phase, electron transport must occur through a discontinuous array of nanorods. Alivisatos et al. have shown that the length of the nanorods is an important variable for electron transport while the diameter of the nanorods controls the band gap, thereby enabling some optimization of the overlap between the absorption spectrum of the cell and the solar emission spectrum. As is also the case with light emitting diodes, device performance in such photovoltaics is greatly affected not only by the structure and electronic properties of the organic polymers but also by the characteristics of the interfaces they form with the various other device components.

Given the discontinuous nature of the numerous interfaces that exist in hybrid organic–inorganic photovoltaics it is expected that the morphology of the blend could have a dramatic effect on device performance. While these blends consist of a three-dimensional interpenetrating network of the two major components — the nanorods and the polymer — additional species such as insulating surfactant remaining from the preparation of the nanorods are also present. These surfactants facilitate the dispersion of the nanorods in the polymer but their presence may also reduce device efficiency by impeding the transfer of charges between nanorod and polymer, as well as the transport of electrons between adjacent nanorods. Indeed we have shown that the use of the electroactive oligothiophene surfactant **12** in combination with CdSe nanorods and P3HT, **11**, as shown in Fig. 6 led to better 'electronic communication' between the various components of the blend [27].

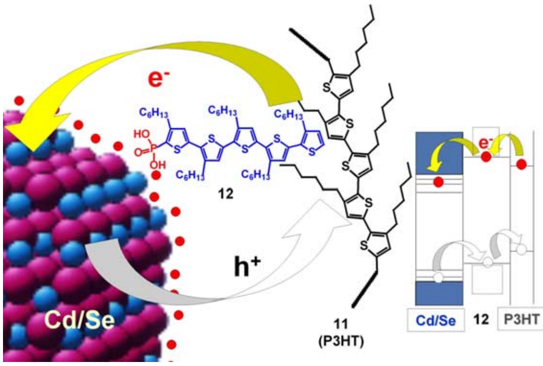


Fig. 6. Schematic representation of the use of electroactive surfactant **12** at the interface between CdSe nanorods and poly(3-hexylthiophene) **11**.

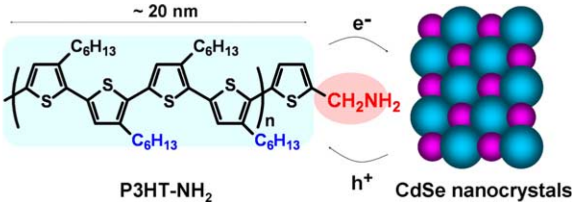


Fig. 7. End-functional polythiophene interacting with the surface of an inorganic CdSe nanorod.

A simpler approach involves the use of end-functional polythiophenes [28] designed for their ability to effectively interact with the surface of the CdSe nanocrystals (Fig. 7) affording intimate nanocomposites with a more dispersed morphology while also ensuring enhanced transfer of charges between the two components. Since both the size of the nanorods [25,26] and the molecular weight of the P3HT [29] affect their electronic properties, the study of the effect of the polymer chain ends on the morphology of the blends and the performance of the PV devices should be carried out using a single batch of nanorods and a series of polymers with the same regioregularity and molecular weight. Therefore, a single batch of bromine terminated regioregular P3HT **13** was prepared and split into several samples, one to be used unmodified and the others to be used after modification of a single chain-end to introduce a moiety capable of interacting with the surface of the nanorods [28]. The preparation of an aminomethyl end-functionalized polymer **14** is shown in Fig. 8. Note that the molecular weight of the polymer remains essentially constant during this transformation, as the only modification of the starting polymer **13** involves the addition of a single cyanothiophene ring, and a local reduction step.

The morphology of composite films prepared from polymers 13 and 14 with CdSe nanorods ca. 7 nm in diameter and 30 nm in length was studied [28] using transmission electron microscopy (TEM). Fig. 9 shows two typical TEM images of thick composite films containing 40 wt.% of CdSe blended with **13** or **14**. It is clear from these TEM images that the use of the end-functional polymer **14** leads to a more homogeneous dispersion of the nanorods in the polymer phase than is the case with the native P3HT **13**.

A correlation between morphology of the blends and PV performance under illumination by solar simulator can be established using polymers **13**, **14**, [28] as well as an additional polymer also prepared from **13** but containing two amino groups on one of its chain-ends. A plot of the AM 1.5 power conversion efficiency *vs.* the volume ratio of CdSe nanorods in the active layer for each type of device is shown in Fig. 10. When the volume ratios of nanorods in the active layer are the same, devices made using **14** or its analog with twin -NH_2 end groups exhibited significant increases in power efficiency when compared to devices made using unfunctionalized polymer **13**. It is clear from these data that the interface between the polymer and the inorganic material plays an important role in determining the ultimate performance of the polymer and that customization of the polymer chain end is a useful approach to ensure better transfer of charge between nanorod and polymer. Whether or not this approach will ultimately be useful for the preparation of highly efficient hybrid polymer-nanorod PV devices remains to be determined in view of the many experimental variables involved with this highly heterogeneous system in which only the polymer phase is continuous. While a benefit in charge transfer between polymer and inorganic may be expected as a result of the better dispersion and concomitant larger interacting surface, more effective electron transport might also be expected to take place in the alternative case where nanorods are aggregated, perhaps counterbalancing the more effective charge transfer. However, as demonstrated in our recent preliminary study of polymer-titania photovoltaic devices [30] it is likely that optimized, 'interacting' interfaces involving

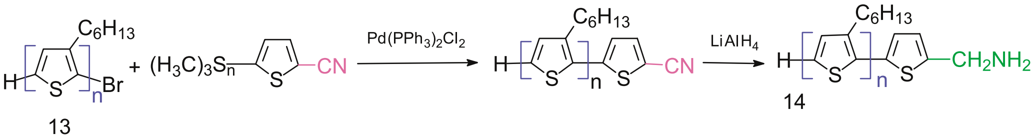
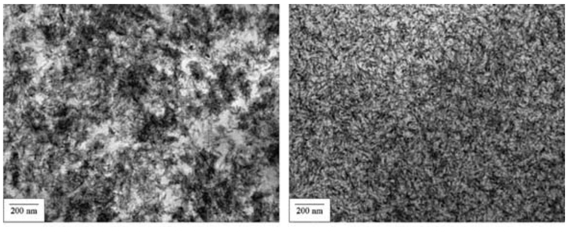


Fig. 8. Preparation of end-functionalized poly(3-hexylthiophene) by chemical modification.



13 / CdSe (40 wt% CdSe) 14 / CdSe (40 wt% CdSe)

Fig. 9. TEM images of 40 wt% blends of CdSe nanorods in polymers **13** (left) and **14** (right).

tailored functional polymers, will play a role in improving the performance of polymer-inorganic PV devices for which the two phases are co-continuous.

3. Designing functional polymers and dendrimers for biomedical applications

Although only a limited number of examples exist to date due to an entrenched belief that only molecules with molecular weights below 500 or so are pharmacologically useful, functional polymers are likely to find more and more applications as key components of therapeutic systems. They can be used not only to encapsulate drugs or assist in time-release formulations, but also to help in targeting and in enhancing the efficacy of a known drug, or as therapeutic agents in their own right. For example poly(ethylene glycol) (PEG) has been used to significantly improve both the bioavailability and the pharmacokinetics of existing drugs [31]. As a result, the conjugation of drugs to PEG ('pegylation') is being aggressively explored by numerous pharmaceutical companies to improve the physical and pharmacological properties of both known and newly developed drugs [32]. In recent years several PEG-protein drug conjugates such as PEG-Neulasta (Amgen) and PEG-Intron (Schering Plough) have been approved by the FDA and successfully introduced on the market. However, unlike the pegylation of small molecule that can be achieved at a unique location, monopegylation of a protein may involve different amino acid residues or locations along the protein chain, potentially leading to several related species with different pharmacological properties [33].

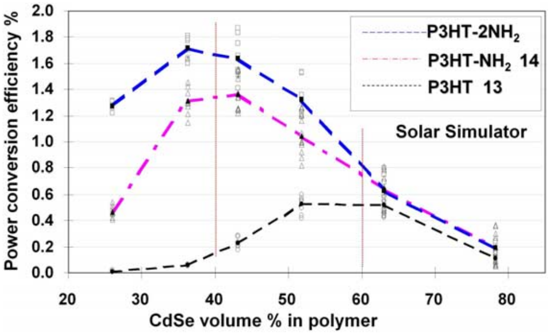


Fig. 10. Performance of PV devices prepared from a single batch of nanorods and polymers differing only in the nature of their end-groups.

In contrast to PEG with its limited functionality, polymers can be used for the conjugation of multiple copies of a drug onto a single polymer chain as demonstrated so well by the work of Kopečeck, Duncan, and others using poly(*N*-2-hydroxypropylmethacrylamide) (HPMA) as the carrier for various drugs [34]. While linear polymers such as HPMA will continue to be exploited successfully, the study of dendritic species [35,36] with a variety of architectures is extremely attractive as they may well offer advantages in the areas of solubility, viscosity, biocompatibility, bioavailability, and plasma residence time, while still providing plurivalency with enhanced access to their numerous reactive sites since these possess identical accessibility.

3.1. Dendritic macromolecules in drug delivery

Interest in dendrimers for drug delivery originally stemmed from their unique monodisperse character, which distinguishes them from all other synthetic polymers. This monodispersity results from the stepwise synthesis used in their preparation and the ability to purify dendrons and dendrimers at each step of growth. While such multistep syntheses are relatively costly and therefore may preclude the use of large dendrimers in some low-end biomedical applications, the knowledge derived from experience with pegylated protein drugs suggests clearly that a strict monodisperse character is not necessary for therapeutic applications. Polymeric drugs should have a low and controlled polydispersity, and the polymer molecules used in their preparation should be free of either very small or very large molecules, which could

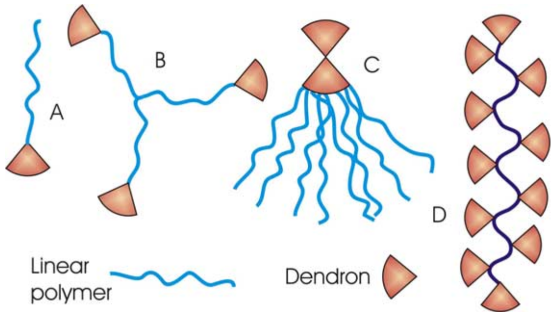


Fig. 11. Dendritic hybrids: (A) linear-dendritic, (B) star-dendritic, (C) bow-tie-linear, (D) dendronized polymer.

exhibit non-uniform pharmacological properties. This requirement is easily met by a number of dendritic macromolecules in existence today. Another feature of dendrimers that is clearly be beneficial in the design of polymeric drugs is their regular branching pattern and plurifunctional character enabling the attachment of multiple copies of a bioactive or other moiety in locations with essentially identical accessibilities. Therefore current trends in the use of dendrimers for medical applications include the use of readily prepared and readily purified biocompatible dendrimers such as the PAMAM dendrimers [36,37], the polylysine dendrimers [38], the aliphatic polyester dendrons and dendrimers [39], or the low polydispersity combinations of dendrons and linear polymers [40] (Fig. 11) such as linear-dendritic hybrids [40–42], bow-tie dendrimers [43,44], and dendronized polymers [40,45–47]. The use of dendrimers and other dendritic polymers in drug delivery has been reviewed recently [48].

As a result of their early commercial availability Tomalia's PAMAM dendrimers [37] are the most widely studied dendrimers for biomedical applications. The native amine-terminated dendrimers have a polycationic surface that leads to toxicity and liver accumulation issues that may be mitigated by a variety of complexation or surface modification processes [36,49]. The polylysine dendrimers originally developed by Denkewalter [38] have also received much attention due to their facile synthesis and have recently been used by Starpharma Holdings Ltd. in the formulation of a microbicidal dendrimer for the prevention of HIV. The aliphatic polyester dendrons and dendrimers derived from 2,2-bis(hydroxymethyl)propionic acid [39] represent an interesting class of neutral, non-toxic plurifunctional macromolecules that are also potentially degradable due to the presence of ester linkages. These dendrons have also been used extensively in the formation of dendritic hybrids and dendronized polymers [42–47] providing access to a variety of molecular architectures that are extremely useful in the determination of structure-activity relationships for polymer therapeutics. A particularly interesting family of dendritic hybrids based on the novel 'bow-tie' dendrimer concept has been developed by Gillies et al. [43,44].

The bow-tie dendrimers (Fig. 12) typically consist of two orthogonally functionalized dendrons that can be used to selectively attach multiple copies of different species on each of the two dendrons or lobes of the bow-tie structure. These dendrimers are prepared [43] by the coupling of dissimilar dendrons or through a combination of convergent and divergent growth step as shown in Fig. 12. In this case convergent dendron **15** was grown first, then grown divergently [39] at its focal point by reaction with anhydride **16**. The orthogonally functionalized dendrimer **17** can then be functionalized on one lobe only to introduce monomethoxyoligo(ethylene oxide) solubilizing groups as shown in structure **18**. The remaining hydroxyls on the other lobe can then be used for the attachment of bioactive or diagnostic moieties.

In order to test the effect of macromolecular architecture and molecular size on biological properties, a library of bow-tie hybrids (i.e. bow-tie dendrimers with solubilizing linear polymer chains attached to one of the dendrons) was prepared in which one of the two dendrons carrying 2, 4, or 8 attachment sites (Fig. 13) was functionalized with solubilizing polyethylene oxide chains of molecular weight 5,000, 10,000, and 20,000 Daltons [41]. This library was then tested for its toxicity, degradability as well as biodistribution and plasma residence time in vivo. This study showed that the bow-tie dendrimer hybrids were both non-toxic and biodegradable in vitro, while biodistribution studies in vivo revealed that the bow-tie hybrids with molecular weight greater than 40,000 g/mol were generally long-circulating with half-lives greater than 24 h. As expected, the more highly branched bow-tie hybrids with 8 arms

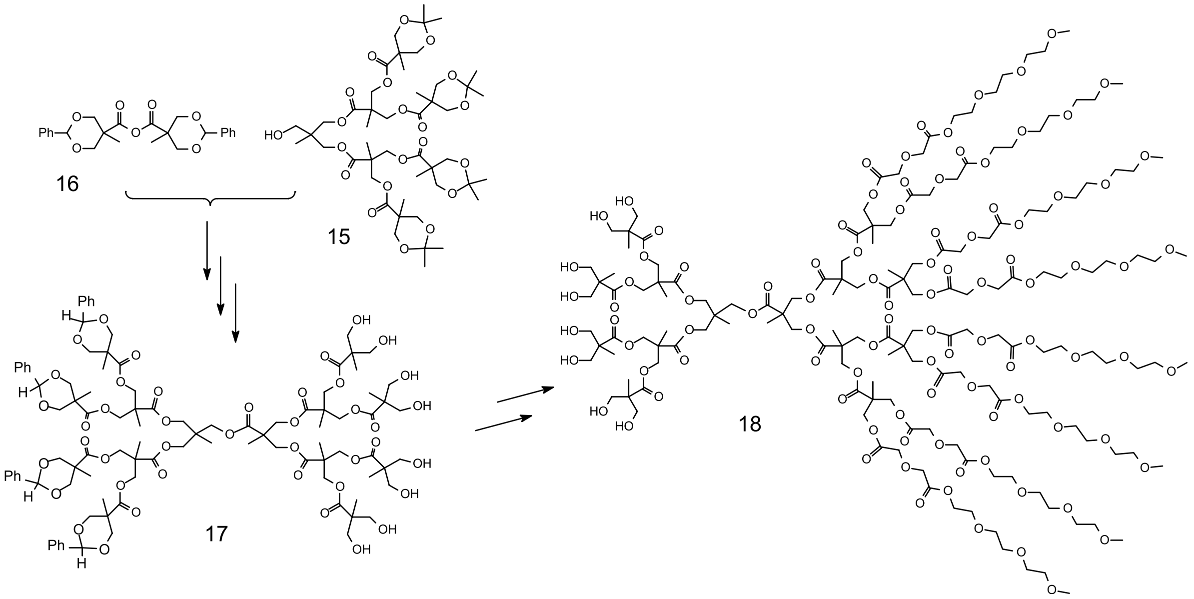


Fig. 12. Preparation of bow-tie dendrimers with two orthogonally functionalized lobes.

were excreted more slowly into the urine than their analogs of equal molecular weight but with only four arms [44]. This reflects the intrinsic ability of the polymer chains to reptate through the pores of the glomerular assembly in the kidneys in order to be eliminated. It is well-known that linear polymers have more flexibility than star polymers and thus the ability of macromolecules with fewer branches to reptate through small pores is expected to be higher than that of more highly branched, less flexible, macromolecules of similar size. This slower reptation translates into a lower rate of elimination, which is advantageous as it results in a longer residence time for the macromolecule in the plasma. Indeed, high levels of the higher molecular weight, long-circulating, bow-tie hybrids were found to accumulate in subcutaneous B16F10 solid tumors via the enhanced permeation and retention (EPR) effect, making these carriers promising for chemotherapy applications [44,48]. It should be noted that the biodegradability of the linkages holding the solubilizing groups onto the core of the bow-tie dendrimer suggests that undesirable long-term accumulation in the body should not be observed since the smaller fragments resulting from in situ slow degradation are readily eliminated [44]. Preliminary studies with similar bow-tie hybrids loaded with an anticancer drug show promising results suggesting that the molecular design of the bow tie dendrimer hybrids incorporating the highly desirable features of degradability, plurivalency, releasable solubilizing groups, and long plasma residence time is suitable for further therapeutic evaluation.

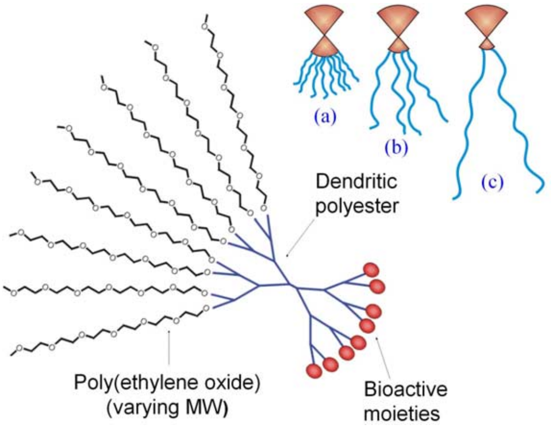


Fig. 13. Schematic representation of bow-tie hybrids with (a) 2 linear polymer chains, (b) 4 linear polymer chains, and (c) 8 linear polymer chains attached to one of the dendrons, and multiple bioactive moieties attached to the other.

3.2. Polymer nanoparticles for vaccine delivery

Macromolecular delivery systems also hold much promise for use in antigen-based vaccines. One example of a macromolecular assembly designed for this purpose involves polymer nano- and micro-particles capable of delivering antigens to antigen presenting cells (APCs) for Class I and II presentation, and providing immunostimulatory signals to APCs to induce the appropriate cytokine release for effective T cell activation. The molecular design of the nanoparticles must take into account the need to encapsulate the payload, protecting it from a hostile environment, while also allowing it to be liberated in the target environment of the cytoplasm of targeted cells (such as dendritic cells and macrophages). Typically, the nanoparticles encapsulating an antigenic payload will be internalized by APCs through the size-selective process of phagocytosis. The functions described to this point could be performed by many fairly ‘standard’ polymer nanoparticles, but the next step requires a special design in order to enable escape of the antigenic payload from the lysosomal compartment before payload degradation can take place. Such a design has been described by Murthy et al. [50] who built the encapsulating polymer with acid-labile components [50,51] that are stable at physiological pH but break down quite rapidly in the acidic environment of the lysosome. This rapid breakdown causes the osmotic pressure to increase within the lysosomal compartment causing water to rush into it, leading to its rupture. As a result, the antigenic payload contained in the degradable nanoparticle escapes its confined environment before being affected by lysosomal action and is liberated intact in the cytoplasm of the cell where it can now fulfill its function [52].

In order to develop suitable acid-sensitive crosslinkers we have studied a great variety of acetals and ketals [51] and their rate of hydrolysis at pH 5.5. Those deemed to have the desired degradation kinetics were then incorporated in novel bifunctional crosslinkers and used in the preparation of micro and nano-beads encapsulating the antigen, for example through a process of inverse emulsion polymerization (Fig. 14). Given the intended use of the nanoparticles special attention must be paid to the polymerization conditions and the components of the polymerization system [50] to avoid the inadvertent incorporation of unwanted species and to optimize the size of the particles for delivery to the appropriate target cells such as macrophages and dendritic cells.

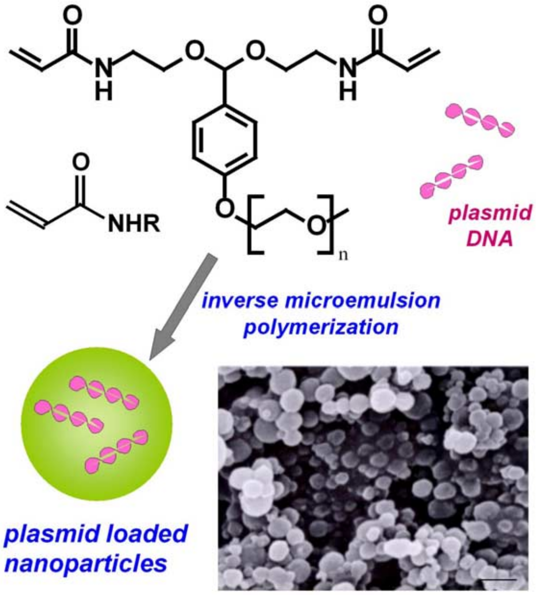


Fig. 14. Encapsulation of a bioactive macromolecule in a degradable nanoparticle, and SEM of a batch of nanoparticles. Both monomers used can contain degradable linkages.

Murthy et al. have carried out a variety of studies, both in vitro and in vivo [52,53], to verify the concept of lysosomal disruption and antigen delivery to APCs with protein loaded acid-degradable nanoparticles. This concept was subsequently extended by Goh et al. [54] to the delivery of plasmid DNA (Fig. 14) in a study that demonstrated that plasmid DNA remained active through the processes of both encapsulation by free radical polymerization and release by acid hydrolysis of the nanoparticles. In addition, the delivery of peptides and oligonucleotides that cannot be encapsulated due to their small sizes can be achieved through their reversible conjugation to the nanoparticles.

Although all of these studies are still in their early stages, this versatile approach to the delivery of biologically active molecules to target cells through appropriately functionalized macromolecular delivery systems is very promising due to its applicability to vaccinations involving a broad spectrum of antigenic macromolecules.

4. Conclusion

This brief account is clearly inadequate to describe the rapidly expanding field of functional polymers, but it illustrates with examples taken from the two diametrically opposed fields of molecular electronics and pharmaceutical science the importance of tuning molecular design to achieve the ultimate function that is desired. It is clear that functional polymers possess the intrinsic versatility needed not only to meet the demands of new and fast developing technologies but also to spur novel concepts and indeed new industries.

Acknowledgements

Support of our research by the US Department of Energy (Basic Energy Sciences under Contract No. DE-AC03-76SF00098), the National Institutes of Health (GM 65361 and EB 002047), the National Science Foundation (DMR), and the Air Force Office of Scientific Research is acknowledged with thanks. In addition I am indebted to my coworkers and collaborators at the University of California, the University of Southern California (Prof. M. Thompson and coworkers) and the University of California at San Francisco (Prof. F. Szoka and coworkers) whose names are cited in the references for their key contributions to the work described in this brief account.

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