REVIEW ARTICLE

Advancement in polymer therapeutics and characterization

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The beauty of the discipline, polymers in drug delivery, is its longevity and self-transforming quality. Polymers have, for decades, performed a valuable function as excipients in tablet and capsule formulations, moving steadily into the parenteral arena as blood circulation time enhancers, and are now capable of offering advanced and sophisticated functions (such as drug targeting) to medicine. Polymers have unique cooperative properties that are not found with low-molecular weight compounds and therein lies the root of their success. Polymers are used as carriers for the delivery of drugs, proteins, targeting moieties, and imaging agents. Several polymers, polyethylene glycol, *N*-(2-hydroxypropyl) methacrylamide, and polylactide-*co*-glycolidecopolymers have been successfully utilized in clinical research. Recently, interest in polymer conjugation with biologically active components has increased remarkably as such conjugates are preferably accumulated in solid tumors and can reduce systemic toxicity. Further, it is essential to elucidate the structure–activity relationshipof a drug when it is conjugated with a polymer using different conjugation sites as this can vary the efficacy and mechanism of action when compared with its free form. This review will discuss the current advancement in drug targeting with polymers, smart polymers and recombinant polymers for drug delivery. Finally, it will also highlight on various methods of polymer characterization, including various techniques for polymer molecular weight measurement.

Key words: *Drug targeting, polymer, polymer characterization, recombinant polymers, smart polymers*

INTRODUCTION

A polymer is a substance composed of molecules with a large molecular massof repeating structural units or monomers connected by covalent chemical bonds. Well known examples of polymers include plastics, DNA, and proteins.

Scientific reports are peppered with polymer-containing systems that:

- Prolong drug action by entrapping the drug within the matrices.
- Shift drug distribution in the direction of the tumors.
- Shunt therapeutic genes or oligonucleotides into the cells.
- Enable drug absorption at optimum gastrointestinal tract absorptive sites.
- Make the drug available only when there is a defined change in temperature or pH or when activated by an enzyme.

Simple manipulation of the water solubility of polymers by increasing their chain length through cross-linking or by hydrophobizing or hydrophilizing them with copolymers and other groups yields a wealth of materials with a wide spectrum of possible applications. The resulting materials are capable of a variety of drug-enhancing functions. Polymers are able to:

- Prolong drug availability if medicines are formulated as hydrogels or microparticles.
- Favorably alter biodistribution if formulated into dense nanoparticles (NP).
- Enable hydrophobic drug administration if formulated as micelles.
- Transport a drug to its usually inaccessible site of action if formulated as gene medicines.
- Make drugs available in response to stimuli.

Natural polymer materials such as shellac and amber have been in use for centuries. Biopolymers such as proteins (e.g., hair, skin, and part of the bone structure) and nucleic acids play crucial roles in biological processes.

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A variety of other natural polymers exist, such as cellulose, which is the main constituent of wood and paper. Typical synthetic polymers are Bakelite, neoprene, nylon, polyvinyl chloride, polystyrene, polyacrylonitrile, polyvinyl butyral, and various cellulose derivatives. Polymers are studied in the fields of polymer chemistry and polymer science and also in the pharmaceutical field.

DRUG TARGETING WITH POLYMERS

While many approved and developmental drugs are well tolerated, numerous drugs need advanced delivery technologies to improve pharmacokinetics, decrease toxicity, increase tolerability, and, ultimately, enhance the therapeutic index. Peripheral toxicity related to the systemic administration of compounds can be dose limiting. However, the application of drug carrier platforms (dendrimers, liposomes, polymers, micelles) can significantly improve the biodistribution while the addition of a targeted ligand (antibodies, peptides, proteins, vitamins) can enhance the selective uptake of the drugs to target tissues or cells, thereby minimizing non-specific binding to non-target tissue. Advances in polymer technologies have enabled delivery specialists to design carriers for targeted delivery either through direct drug conjugates or through polymer formulations.

Polymers at specific cell targeting

The researchers have evaluated the feasibility of biodegradable polymer microspheres of poly L-lactic acid and poly glycolic acid to deliver a substance directly to the retinal pigment epithelial (RPE) cells. The microspheres were encapsulated with a fluorescent dye (rhodamine 6GX) that was used as a drug marker. The dye released from the microspheres was analyzed by spectrofluorophotometry *in vitro*. Microspheres were administered to cultured bovine RPE cells. Phagocytosis of the microspheres by RPE cells was studied by fluorescent microscopy and transmission electron microscopy. Intracellular release of the fluorescent dye was also evaluated after phagocytosis of the microspheres. A suspension of the microspheres was administered into the subretinal space via the transvitreal approach with a glass micropipette inrabbits *in vivo*. The release rate of the fluorescent dye was controllable by changing the molecular weight and the monomer composition of the copolymers *in vitro*. Microspheres were phagocytosed by RPE cells and the dye was released intracellularly during incubation. After subretinal delivery, the microspheres were degraded in the cytoplasm of the RPE but the fragments were observed for up to 4 weeks. The retinal architecture overlying the delivery site was well preserved. These results suggest that it is feasible to deliver substances directly to the RPE cells with the use of polymer microspheres without damaging the neural retinal structure. This drug delivery system may enable the functions of RPE cells to be modified pharmacologically.[1,2]

The efficacy of nucleus-targeted drug or gene-carrying NP may be limited by slow transport through the molecularly crowded cytoplasm following endosome escape. Cytoskeletal elements and cellular organelles may pose steric and/or adhesive obstacles to the efficient intracellular transport of NP. To potentially reduce adhesive interactions of colloids with intracellular components, the surface of model NP was coated with polyethylene glycol (PEG). Subsequently, multiple-particle tracking was used to quantify the cytoplasmic transport rates of particles microinjected into the cytoplasm of live cells. PEGylation increased the average NP diffusivities by 100% as compared withthe unPEGylated particles in live cells. This result adds to an impressive list of positive benefits associated with PEGylation of drug and gene delivery vectors.[3]

Polymers in the treatment of cancer

The two thermally responsive polymers that are discussed here, poly-N-isopropylacrylamide-co-acrylamide (poly(NIPAAm)) and an artificial elastin-like polypeptide (ELP), were designed to exhibit a soluble–insoluble lower critical solution transition in response to increased temperature slightly above 37°C. *In vivo* fluorescent video microscopy and radiolabel distribution studies of ELP delivery to human tumors implanted in nude mice demonstrated that hyperthermic targeting of the thermally responsive ELP for 1 h provides an ~two-fold increase in tumor localization compared with the same polypeptide without hyperthermia. Similar results were also obtained for poly(NIPAAm), although the extent of accumulation was somewhat lesser than that observed for the ELP. The endocytotic uptake of a thermally responsive ELP was also observed to be significantly enhanced by the thermally triggered phase transition of the polypeptide in cell culture for three different tumor cell lines. Preliminary cytotoxicity studies of an ELP–doxorubicin conjugate indicate that the ELP–doxorubicin conjugate has near-equivalent cytotoxicity as free doxorubicin in a cell culture assay.[4-6]

Another example is mucoadhesive anticancer drug delivery system using 70% deacetylated chitin (DAC-70) and cisplatin (CDDP) and 5-fluorouracil (5-FU). The adhesive force between the system and the human colonic mucosa was measured *ex vivo* and a release profile of each drug was examined *in vitro*. Each system demonstrated a stronger mucoadhesive force at 37°C than that at 25°C. The CDDP-loaded system showed a sustained release of the drug while the 5-FU-loaded system exhibited an initial bursting of the agent. We presume that the release profile of CDDP and 5-FU is closely related to both degradability of the chitin and interactions between the chitin and each drug. The DAC-70/CDDP system would be clinically promising in locoregional cancer chemotherapy.[7]

Multiple options for the treatment of lung cancer have often been described in the past, including surgery, chemotherapy, and radiation, but the therapeutic effect is typically

transient and mostly absent with advanced disease. New approaches to the treatment of lung cancer are urgently needed. Gene therapy has been widely proposed as a novel strategy to improve therapy. Although progress has been made using viral vectors, rapid advances in transfection technologies employing non-viral vectors, together with their relatively low toxicity, suggest that non-viral vectors may have a significant potential for clinical applications. Recent research briefly reviews the general principles of gene delivery with emphasis on recent developments in the arena of lung cancer using non-viral vectors (naked DNA, polycationic polymers, cationic liposomes, etc.). Employing gene transfer techniques to achieve therapeutically useful levels of expression of therapeutic genes in the lung could provide a new strategy for the treatment of lung cancer.[8]

Paclitaxel and docetaxel have established themselves as an important class of antitumor drugs currently available to the oncologist. While the great contribution of these drugs to the management of the disease and their effect on the improvement of the patient quality of life could not be overemphasized, a great deal of research is being undertaken to improve two key pharmacologic factors, antitumor activity and systemic toxicity. Both physical and chemical means have been employed toward the enhancement of antitumor activity and, at the same time, lowering the inherent toxicity and side-effects of these drugs. The research compiles the recent reported works on the design and the development of taxane delivery systems through tumor cell surface receptor-targeted delivery mechanisms such as small-molecule peptides and monoclonal antibodies as well as those on non-targeted procedures such as with the help of liposomes, nanostructures, and natural and synthetic polymers.[9]

The presence of lymph node metastases relevantly and significantly impairs disease-specific survival in patients suffering from squamous cell carcinoma of the upper aerodigestive tract. In an animal tumor model, an interstitial translymphatic therapeutic approach using cis-diaminedichloro-platinum(II) (CDDP) conjugated to a polyethylene oxide-block-polylysine (PEO-b-PLys) block copolymer tracking system has been proven to be effective in the successful treatment of lymph node metastases. The systems contained 0.25-0.003 mg/kg/body weight CDDP compared with 1 ml/kg/body weight as usually used for intravenous administration. This approach encourages further and more detailed research of a CDDP-based interstitial translymphatic administration of chemotherapy for lymphogenic metastasizing carcinomas in different body regions.[10,11]

Polymers in brain targeting

Nanoparticulate polymeric systems (Np) have been widely studied for the delivery of drugs to a specific target site. This approach hasrecently been considered for the therapy of brain diseases. The major problem in accessing the central nervous system (CNS) is linked to the presence of the blood–brain barrier. The recent review deals with the different strategies that have been developed in order to allow the entry of Np drug carriersinto the CNS parenchyma. Polymeric Np have been shown to be promising carriers for CNS drug delivery due to their potential both in encapsulating drugs, hence protecting them from excretion and metabolism, and in delivering active agents across the blood–brain barrier without inflicting any damage to the barrier. Different polymers have been used and different strategies have been applied. Among these, the use of specific ligands to enhance the specificity of drugs delivered to the CNS has recently been considered. At present, clinical trials are being conducted for the use of these drug carriers.[12,13]

Polymers and drug eluting stents

Another recent application of polymers includes assessing the feasibility of sustained intracoronary delivery of paclitaxel from a polymer-coated stent. Characterization of the coating morphology and its correlation with the mechanism of drug release is critical for the development and understanding of controlled drug delivery coatings. Three successive layers of drug mixed with biodegradable polymer solutions were applied on SS 316 stents using the air suspension spray coating technique. *In vitro* release of paclitaxel at regular intervals for 38 days from stents was analyzed using high-performance liquid chromatography (HPLC). Scanning electron microscopy (SEM) was used to characterize the mechanism of drug delivery from multilayered biodegradable polymer-based stents, and it was observed that the drug particles were released owing to a swollen polymeric matrix and bulk erosion.[14]

Drug-eluting stents have been proposed as an alternative approach to decrease neointimal hyperplasia. Polymer-coated stents can serve as a reservoir for local drug delivery. In this research work, a novel four-layered biodegradable/ biocompatible polymeric blend (poly L-lactide, poly DL-lactide-co-glycolide, poly L-lactide-cocaprolactone, and polyvinyl pyrrolidone) was utilized for the preparation of the paclitaxel drug-loaded matrix. The air suspension technique was modified and effectively used for coating the coronary stents with the paclitaxel drug and the biodegradable polymeric blends. SEM revealed a consistent coating profile devoid of any irregularities like cracking and delamination after crimping and expansion of the stent. HPLC established the efficiency of the modified air suspension coating technique and controlled release of paclitaxel drug from the four layered coated stent.[15]

Polymers in oral targeted drug delivery

A floating drug delivery system of drugs (e.g., piroxicam) in the form of microspheres was prepared using an enteric polymer (e.g., ethyl cellulose) and emulsification solvent-evaporation method. The microspheres remained buoyant continuously

over the surface of the acidic media containing the surfactant for a period of 8-12 h *in vitro* in the upper gastric region.[16]

A multiparticulate system of chitosan (natural polymer) hydrogel beads exploiting the pH-sensitive property and specific biodegradability for colon-targeted delivery has been developed for satranidazole. Chitosan hydrogel beads were prepared by the cross-linking method followed by enteric coating with Eudragit S100. All formulations were evaluated for particle size, encapsulation efficiency, swellability, and *in vitro* drug release. Degradation of the chitosan hydrogel beads in the presence of extracellular enzymes as compared with rat cecal and colonic enzymes indicates the potential of this multiparticulate system to serve as a carrier to deliver macromolecules specifically to the colon, and can be offered as a substitute *in vitro* system for performing degradation studies. Studies demonstrated that orally administered chitosan hydrogel beads can be used effectively for the delivery of the drug to the colon.[17-19]

Development of a colon-specific delivery system of flurbiprofen using various azo-aromatic polymers and pH-sensitive polymers was also well known. The azo-aromatic polymers were synthesized and characterized for physical appearance, solubility, film-forming properties, and effect of colon microbial flora on the polymers. *In vitro* dissolution studies showed that flurbiprofen bearing hard gelatin capsules coated with these polymers released drug only in simulated gastrointestinal fluid containing human fecal suspension, at pH 7.5. *In vivo* studies revealed that azo-aromatic and pH-sensitive polymer coatings disintegrate only in the colon after 10 h of oral administration. Hence, these polymers can be successfully used to deliver the drug at the colon.[20,21]

SMART POLYMERS IN DRUG DELIVERY

An understanding of the technology in smart polymers, which alters their physicochemical properties in response to minute changes in environmental conditions, advances, challenges to novel concepts for drug delivery, and new fabrication techniques in dosage forms have been introduced and progressed in the last two decades. Most approaches are currently experimental; however, commercial products based on the smart polymer technology are soon anticipated. "Smart polymers" are also known as "intelligent polymers," "sensitive polymers," or "responsive polymers," all terms being used interchangeably. They can be defined as systems of either soluble or cross-linked polymers that undergo a reaction to a small variation in the chemical and physical environmental conditions. These responses include changes in solubility, water swelling, shape, or sol–gel transition and often present clear and relatively sharp transition phenomena.

Application of smart polymers to cancer chemotherapy was proposed by introducing a new pH-sensitive functional group responding to change in pH around the physiological condition. Polymers with a sulfonamide pendant group, which is weak, with its pKa ranging from 3 to 11 based on the chemical structure, open a new application of pH-sensitive polymers for dosage form or drug delivery devices. By selecting proper sulfonamide and polymer composition, the resulting linear polymers or cross-linked network exhibit first-order-like transition in solubility or swelling around pH 7.4.[22]

RECOMBINANT POLYMERS FOR DRUG DELIVERY

There is a significant interest in polymeric biomaterials for drug and gene delivery applications requiring the circumvention of multiple biological barriers. The ability of some polymers to traverse these barriers and deliver bioactive agents without significant toxicity lies primarily in their chemical structure. Although still at an embryonic stage of development, the application of genetically engineered polymers to drug delivery thus far can be divided into two general approaches: Polymers for systemic administration and gel-forming polymers for localized, controlled release applications. Although the application of genetically engineered polymers for the delivery of bioactive molecules is in its infancy, the level of interest is gaining momentum and it is likely that new materials and applications will emerge in the near future.[23]

POLYMER CHARACTERIZATION TECHNIQUES

Molecular variables that control the function include the nature of the monomers and monomer linkers, monomer sequence distribution along the chains, the average molecular weight and the molecular weight distribution, molecular conformation, and molecular architecture. For drug delivery systems, the important polymer bulk properties, which indeed derive from the polymer's molecular properties, are solubility, biocompatibility, biodegradability, and stability. In considering the polymer's functional properties, it is of utmost importance that adequate polymer characterization is available for material selection. Different methods for the determination of polymer molecular weight are end-group assay, cryoscopy (freezing point of dilute polymer solution), ebulliometry (boiling point of dilute polymer solution), vapor-pressure osmometry, membrane osmometry, ultracentrifugation, light scattering (LS), gel permeation chromatography (GPC), GPC/LS, viscometry etc.

Other methods used for polymer characterization include vibrational spectroscopy —infrared and Raman spectroscopy — nuclear magnetic resonance spectroscopy, microscopy (traditional optical microscopy, SEM and transmission electron microscopy, and scanning probe microscopy), thermal analysis (differential scanning calorimetry, thermal gravimetry,and dynamic mechanical analysis, X-ray diffraction methods (wide-angle X-ray scattering and small-angle X-ray scattering, and mechanical and rheological analyses.[24]

CONCLUSION

The successful clinical application of a polymer–protein conjugate and the promising clinical result arising from trials with the polymer–anticancer drug conjugate reflect well for the future design and development of the even more sophisticated bio-nanotechnologies that are needed to realize the full potential of the post-genomic age. The entry of hybrid conjugates that combine synthetic polymers with proteins or drug and polymer micelles that incorporate covalently bound drug inclinical development has established polymer therapeutics as a credible option for medicine development. Guiding sufficient numbers of molecules in a sufficient time directly to their targets is the future. Polymers have helped this endeavor and will continue to enable this effort in the foreseeable future.

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