The Use of Polymers in the Treatment of Neurological Disorders

A Discussion Emphasizing Encapsulated Cell Therapy

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Numerous neurological disorders, including Parkinson's and Alzheimer's diseases, are inadequately served by existing therapies that rely on passage of a drug across the blood–brain barrier. Site-specific drug delivery to the brain can be accomplished with polymeric materials, allowing continuous delivery of lower dosages which may result in increased efficacy with decreased side effects. Polymers of either synthetic or natural origin play an integral role in the delivery device chosen. Encapsulated cell therapy methods are reviewed and pump technology and controlled release systems are introduced. Encapsulated cell therapy relies on immunoisolatory, selectively permeable polymeric membranes and matrices; pumps require polymeric catheters and semipermeable membranes; and controlled release systems rely on either biodegradable or biostable polymeric materials.

Polymers continue to play an increasingly important role in the delivery of agents to treat human diseases. In particular, polymers may provide an appropriate delivery vehicle for treatment of neurological disorders that are inadequately served by standard therapeutic approaches. Neurological diseases represent a broad range of disabling disorders from varied sources, such as genetic mutations or deletions, autoimmunity or infectious agents, that are generally poorly understood and difficult to treat. The blood–brain barrier (BBB) acts like a selectively permeable membrane by rigorously maintaining a well-defined, homeostatic environment; it restricts the transport of most molecules, except that of small neutral amino acids and lipophilic molecules, to prevent entry of potentially damaging substances. Consequently, most traditional drugs cannot cross the BBB; those that do show limited diffusion across the BBB, requiring the administration of large systemic doses. In order to overcome the BBB, both chemical and physical strategies have been designed. While chemical modification of a systemically delivered drug for passage across the BBB

has met with some success, surgical implantation of a delivery device provides the possibility of prolonged, constant delivery[1].

Chemical strategies to achieve passage across the BBB include chemical disruption of the BBB and modification of the drug. By disrupting the BBB, using mannitol, for example[2], additional molecules other than the drug of choice cross into the brain and may result in adverse side effects. Intracarotid infusion of hypertonic solutions is the most characterized method for reversibly disrupting the BBB. Osmotic disruption of the BBB apparently induces shrinkage of endothelial microvasculature which transiently opens the endothelial tight junctions that define the barrier. Chemical modification of a drug to its prodrug form, prior to administration, has been successful in some cases. Parkinson's disease (PD), resulting from a neurological deficiency of dopamine, is treated with its precursor levodopa (L-3,4-dihydroxyphenylalanine or L-dopa) because L-dopa can penetrate the BBB whereas dopamine cannot. However, large systemic doses of L-dopa are required because 95% of L-dopa is decarboxylated to dopamine peripherally. While the dosage can be reduced by co-administering inhibitors of L-dopa decarboxylase (e.g. carbidopa or benserazide), the progressive loss of L-dopa efficacy and the dose-related side effects experienced by PD patients indicate that an alternative therapy for advanced-stage PD is needed[3]. A continuous delivery system that can provide the appropriate therapy is likely to reduce the clinical fluctuations observed in L-dopa levels in plasma.

Recently, a number of technologies have emerged that allow continuous delivery of a given agent directly to the central nervous system (CNS). Relative to systemic delivery, cerebral delivery potentially requires a decreased dosage to alleviate symptoms; consequently, side effects and clinical fluctuations, experienced with systemic therapy, are reduced. Delivery devices used to accomplish continuous release of therapeutic agents to the brain include, among others, pumps, controlled release systems and encapsulated cell or gene therapy.

Polymeric biomaterials provide an integral part of these delivery systems. Pumps require polymeric catheters and semipermeable membranes; controlled release systems use natural or synthetic materials that are biodegradable or biostable; and encapsulated cell therapy relies on immunoisolatory, selectively permeable polymeric membranes and matrices. Erodible drug delivery or depot systems, such as catheters or pumps, have

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advantages stemming from the relative ease of surgical procedure and the high control of dosage over the short term. Encapsulated cell delivery systems may be advantageous over other techniques because of their ability to deliver *de novo* synthesized therapeutics. Macroencapsulated cell delivery systems also allow quick termination of treatment by device retrieval and may provide a safe technique for supplementation with additional or replacement devices. The use of tumor or genetically engineered cell lines, in contrast to fetal or other primary tissues, offers the additional advantages of clonal selection, cell banking, and rigorous cell screening for viral or adventitious agents prior to cellular transplantation (see Glossary). Some of the advantages and disadvantages of implantable delivery systems are summarized in Table 1.

Pumps

Pump technology provides a simple approach to achieving constant drug delivery. Delivery to the CNS is accomplished with a subcutaneous implanted pump and drug reservoir to which a silicone-based polymeric catheter is attached and guided to the lateral ventricle of the brain. Stable drugs requiring only limited penetration into the brain parenchyma can be delivered with pump technology[4]. While in some cases (5–10% of patients) the cerebrospinal fluid leaks around the catheter, resulting in spinal headaches, pumps provide effective drug delivery and are often used in CNS drug therapy studies.

Pumps for drug delivery have evolved from the Ommaya® drug reservoir and the Infusaid® pump to the

Table 1. Some advantages and disadvantages of implantable delivery systems

Pumps	Controlled release	Encapsulated cell therapy
Advantages		
Quick delivery of therapeutic	Good release over short term	Cells constitutively produce active therapeutics
Retrievable	Retrievable[a]	Retrievable[b]
Dosage can be regulated	Single minimally invasive surgical procedure	Minimally invasive surgery
	Biocompatible	Biostable, biocompatible
		Xenogeneic or engineered cells may be used without immunosuppression
Disadvantages		
Therapeutic may degrade in reservoir	Therapeutic may degrade	Potentially inadequate long-term cell viability
Prolonged delivery may be limited	Dosage may be difficult to control[c]	Potentially difficult to regulate cell output
		Complex regulatory issues

[a]Applicable when biostable polymers are used.
[b]Applicable to macrocapsules, not microcapsules.
[c]Applicable when biodegradable polymers are used.

Glossary

Adrenal chromaffin cells: the noradrenaline and adrenaline-secreting cells from the adrenal medulla.

Allogeneic: comprising a different genetic constitution within the same species.

Cell line: a homogeneous cell population that can be propagated indefinitely.

Cerebrospinal fluid: the ionically balanced watery fluid produced by the choroid plexuses that fills the ventricular cavities and surrounds the outer pial-glial surface of the brain.

Cholinergic neurons: nervous system cells and nerve endings that liberate the neurotransmitter acetylcholine.

Endotoxin: toxin produced by gram-negative bacteria that is liberated only when the bacterium is broken down.

Fimbria–fornix: a cholinergic pathway in the brain between the fimbria of the hippocampus and the fornix (structure adjacent to the striatum).

Intrathecal: within the spinal canal.

Intraventricular: within a ventricle (e.g. lateral).

Lateral ventricle: the cavity within each cerebral hemisphere that contains cerebrospinal fluid and leads to the third ventricle.

Noncytotoxic: not destructive to cells.

Nonmutagenic: not causing genetic mutations.

Nonteratogenic: not inducing the development of abnormal structures in an embryo.

Parenchyma: brain tissue.

Striatum: the caudate and the lentiform nuclei of the brain – a striatal dopamine deficiency is observed in Parkinson's disease.

Xenogeneic: comprising a different genetic constitution across different species.

Alzet® mini-pump and the Medtronic battery-operated pump. The Ommaya reservoir, requiring the application of external pressure, provides inconsistent drug delivery[5]. The Infusaid refillable infusion pump relies on the expansion of a fluorocarbon propellant to exert pressure against a collapsible reservoir for drug delivery. Consequently, changes in body temperature or altitude alter the drug's delivery kinetics[6]. The Alzet mini-pump uses an osmotic-pressure-driven system to achieve constant drug delivery for approximately one month[6]. Medtronic's battery-powered pump provides continuous drug delivery for between three and five years and can be reprogrammed from outside the body with a microelectronic control element[6].

Controlled release systems

Controlled release systems involve the encapsulation of a drug in a polymer for either systemic or direct delivery to the CNS. Often, in systemic delivery, there is an initial burst of drug prior to constant delivery and a time-delay in drug effectiveness. For example, for systemically administered Sinemet CR® (delivery of L-dopa and carbidopa against PD), there is a lag time between L-dopa administration and its effectiveness in the brain as a result of its passage across the BBB and the time taken for cerebral decarboxylation to dopamine. However, L-dopa or dopamine can be delivered directly to the brain when encapsulated, for example, in ethylene–vinyl acetate (EVAc) copolymers. Solvent cast disks of the drug and EVAc demonstrate linear release for three months, with decreased amounts released at longer time periods[7]; L-dopa has been delivered from EVAc for 225 d *in vivo* and 600 d *in vitro*[8].

Biostable materials, such as EVAc, and biodegradable materials, such as poly(amino acids) or polyanhydrides, have been used in devices that have been approved by the Food and Drug Administration for use *in vivo*. Some biostable devices may not be easily retrieved. Biodegradable materials, unlike biostable materials, degrade to nontoxic, erodible polymers, obviating the need for their removal. Both biostable and biodegradable delivery vehicles are biocompatible, resulting in a minimal host tissue reaction. While the surgery required is minimally invasive, repeated implantations may be required for chronic, long-term delivery.

Drug delivery from biodegradable controlled release systems is dictated by polymer degradation and drug diffusion. Polyanhydrides and aliphatic polyesters degrade, by ester hydrolysis, to nonmutagenic, noncytotoxic and nonteratogenic products. For poly(lactide-*co*-glycolide), the molar ratio of lactic acid to glycolic acid controls degradation in conjunction with polymer crystallinity, molecular weight, size, shape and implantation site[9]. Poly(lactide-*co*-glycolide) microspheres implanted in rat striatum have released dopamine for prolonged periods. Polyanhydrides have been shown to approximate a zero-order drug-delivery profile. For example, fatty acid dimer–sebacic acid provides delivery for hydrophilic drugs whereas poly[bis-(*p*-carboxyphenoxy propane) sebacic acid] (PCPP–SA) provides delivery of hydrophobic drugs. The ratio of hydrophobic PCPP to hydrophilic SA controls degradation rate (and thus drug delivery) with a greater percentage of SA resulting in faster biodegradation[4]. PCPP–SA-encapsulated carmustine disks have been implanted in the brain for the treatment of malignant gliomas (brain tumors)[10]. Release of carmustine for two to three weeks at the tumor site has been shown, first, to be more effective than systemic delivery in controlling the growth of brain tumors and, second, to increase the survival of patients with glioblastoma at six months by 50%.

Biodegradable polymeric controlled release vehicles can be macroscopic or microscopic. Macroscopic implants, such as that of PCPP–SA–carmustine, are prepared by combining either dry drug and polymer prior to molding or dissolved drug and polymer, removing the solvent and pressing the material into the desired shape (rod, disk or wafer). Microscopic implants, or nanoparticles, are prepared by numerous techniques including physicochemical coacervation, chemical interfacial polycondensation and mechanical spray-coating. The resulting microparticle structure is either that of a reservoir – the drug resides in a cavity surrounded by a membrane through which it diffuses – or that of a matrix through which the drug is dispersed – drug diffuses through polymer mass or through water-filled pores[11].

Encapsulated cell therapy

Cell therapy provides the potential for continuous delivery of *de novo* secretory reagents. Encapsulated cell therapy, an alternative to conventional transplant modalities (i.e. neural transplantation) and pharmacological therapy, has been utilized in the CNS for the site-specific delivery of neuroactive substances produced by primary tissues[12–14] and cell lines of both allogeneic and xenogeneic sources[15–18]. Encapsulated cellular transplants into the CNS may be especially useful in chronic neurodegen-

erative disease states that result from specific neurochemical deficits[19,20]. Animal models of neurodegenerative diseases, such as Parkinson's and Alzheimer's, have been treated by macroencapsulation cell therapy. For example, the motor deficits associated with Parkinson's models in rodents and non-human primates were reduced by treatment with pheochromocytoma (PC12) cells encapsulated in a poly(acrylonitrile-*co*-vinyl chloride) [P(AN–VC)] semipermeable membrane that was implanted in the striatum of the brain[12]. Transplantation of encapsulated cells that secrete nerve growth factor in the fimbria–fornix-lesioned rat[16,17] and non-human primate[21] models have saved cholinergic neurons, whose loss is associated with learning and memory disabilities in Alzheimer's disease, from an otherwise certain death.

Encapsulated cell therapy has recently made the transition from animal models to clinical trials[22]. Bovine adrenal chromaffin cells were encapsulated in a P(AN–VC) hollow fiber membrane, approximately 5 cm in length and 1 mm in diameter. The encapsulated cell transplants were implanted in the subarachnoid spaces of the lumbar spines of eight end-stage cancer patients whose chronic pain could not be adequately treated with narcotic drugs. The encapsulated cell transplants allowed some patients substantially to reduce their morphine intake. In another trial, cells that were genetically engineered to produce ciliary neurotrophic factor were encapsulated in a P(AN–VC) hollow fiber membrane for treatment of amyotrophic lateral sclerosis (also known as Lou Gehrig's disease). The encapsulated cell transplants were implanted in the subarachnoid spaces of the lumbar spines of three patients and have been shown to be safe. While still in the early stages of clinical trials, encapsulated cell transplants offer great therapeutic potential, relying on continued delivery of cellular products to the CNS.

Polymer encapsulation inhibits entry of host immune system proteins and cells while allowing neuroactive substances to diffuse from the transplant. Cell isolation for the treatment of neurological disorders may be accomplished using one of two approaches: first, hollow fiber rods, membrane sheaths or disks – i.e. macrocapsules (used in clinical trials described above) – or, second, spherical dispersions – i.e. microcapsules (see Fig. 1)[23]. Encapsulated cell therapies to treat CNS disorders consist primarily of porous, microreticulated, thermoplastic hollow fiber macrocapsules and hydrogel-based microcapsules. In these applications, the typical dimensions of hollow fiber membrane rods are a diameter of 0.5–3.0 mm with a length of 1–10 cm whereas microcapsules have spherical dispersion diameters of approximately 0.2–2.0 mm.

The essential physical properties of macro- and microencapsulation semipermeable membranes include transport, biocompatibility and mechanical strength. Transport across the membrane permits bidirectional diffusion of neuroactive substances, nutrients and metabolic wastes yet excludes immune system elements that may otherwise destroy the encapsulated cells. Biocompatibility, or bioacceptance, of the membrane with the host tissue is influenced by its outer surface morphology, material composition, presence of residual processing agents, leachables, solvents, monomers and endotoxin levels. Material handling, implantation method and site

affect the host tissue response to the implant. Biocompatibility is important because a fibrotic reaction of the host tissue would be likely to decrease the diffusive flux across the semipermeable membrane, thereby depriving the cells within of essential nutrients. Additionally, host cells in a fibrotic layer may compete with encapsulated cells for nutrients. Membrane strength is influenced by choice of polymer, membrane composition and dimensions. Strength is an essential component for safe insertion and retrieval of the macrocapsule. Transport, outer morphology and strength can be manipulated by membrane processing conditions.

Macrocapsules

A typical macrocapsule consists of cells, suspended in a matrix material, and encapsulated in a hollow fiber membrane rod that is sealed at either end by a biocompatible glue, heat, or by immersion in a heated polymer solution that solidifies upon cooling and precipitates upon immersion in a non-solvent (e.g. water)[24]. The matrix material enhances cellular distribution within the device while the seals ensure device integrity. Other materials used in the device may include radio-opaque markers (for imaging), tethers (for retrievability) and sutures.

The use of a polymer matrix for the immobilization of cells within the device can serve several purposes. For example, calcium-crosslinked alginate immobilizes small tissue clusters and inhibits reaggregation of primary cells such as adult or neonatal-sourced tissues, including adrenal chromaffin cells. In the absence of a polymer matrix, considerable reaggregation of chromaffin cell clusters has been observed; large cell clusters with central necrotic areas form, concomitant with a decrease in the production and release of neuroactive compounds over time. Similar observations have been made with the PC12 cell line. Precipitated chitosan, a partially deacetylated form of the crab exoskeleton chitin, has been shown to be a suitable matrix for the distribution and continued viability of PC12 cells within the device[19]. The matrix may be used to manipulate other cell–biomaterial interactions, which could influence cell attachment, differentiation or proliferation. Cells may also produce their own extracellular matrix, consisting of proteins such as collagen or fibronectin.

A number of membrane materials can be used for cell encapsulation including: polyacrylonitrile (PAN) and PAN copolymers, polysulfone, poly(ether sulfone), poly(vinylidene fluoride), polyamides, polycarbonate, poly(ether imides), polypropylene, polyethylene and cellulosics[21]. The random copolymer of acrylonitrile and vinyl chloride has been used extensively for cell encapsulation because it is biocompatible in numerous implant sites and can be fabricated with the appropriate transport and strength properties for most implantation and explantation procedures. The monomeric content of vinyl chloride typically varies between 40 and 60% while the molecular weight (weight average, M_w) may be between 30 000 and 200 000 g mol^{-1}.

Membrane fabrication

The majority of thermoplastic ultrafiltration (UF) and microfiltration (MF) membranes that are used to encapsulate cells are manufactured from homogeneous polymer solutions by phase inversion[25,26]. UF and MF membranes
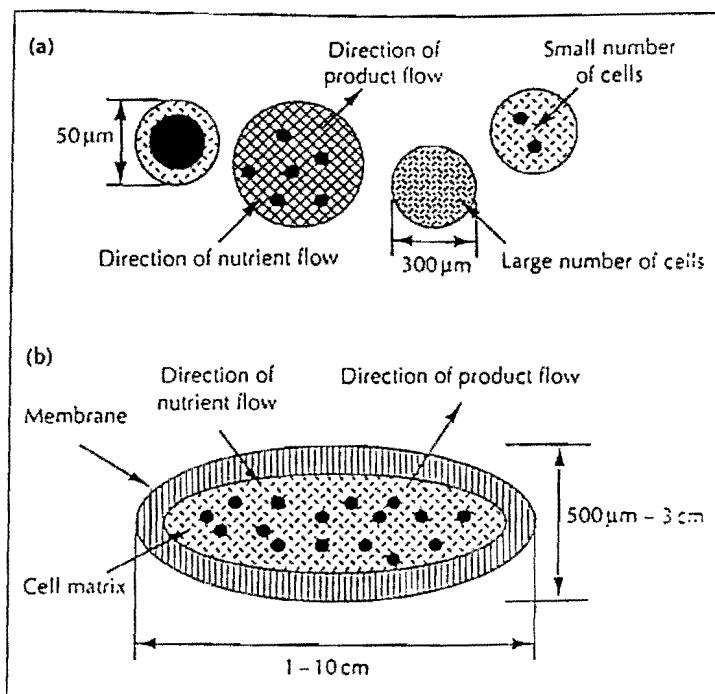

Fig. 1 *Immunoisolatory vehicles for cell encapsulation. (a) Microcapsules have a small number of cells or cell clusters (●) that are surrounded by polymeric hydrogels. Selectivity is achieved by tightly crosslinking the hydrogel or by binding other polymers to the hydrogel surface. (b) Macrocapsules have a large number of cells or cell clusters that are encapsulated within the lumens of hollow fibers or between two flat sheet membranes. Fibers or disks (rods) are implanted directly into tissue or sites bathed with cerebrospinal fluid.*

have pore sizes ranging from 0.006 μm (6 nm) to 0.09 μm and from 0.1 μm to 1 μm, respectively. Phase inversion is a versatile technique that allows membranes to be formed with a variety of nominal molecular weight cut-offs (i.e. 90% retention of transport marker), permeabilities and morphologies[27]. A dissolved polymer can be cast as a flat sheet or extruded as a hollow fiber. During the casting or extrusion procedure, the polymer precipitates by a phase transition, resulting from a change in either temperature or solution composition. Any polymer that forms a homogeneous solution that separates into two or more phases with a change in either temperature or composition can be used. The membrane properties depend on the thermodynamic and kinetic parameters of the process; for example, chemical potential and the free energy of mixing of the components determine phase separation[27]. The process is often described by a polymer–solvent–non-solvent ternary phase diagram.

Membranes can also be manufactured by thermal gelation[28] as in the case of polyethylene and polypropylene, diffusion-induced precipitation[28] and post-treatment of dense films such as PTFE and polycarbonate membranes[29].

Cells can be encapsulated in membranes post-fabrication or by co-extruding a polymer dissolved in a water-miscible organic solvent with cells suspended in tissue culture medium. Polymers, such as PAN, P(AN–VC) and polysulfone, may be co-extruded from organic solvents, dimethylsulfoxide, dimethylacetamide and dimethyl formamide, that are innocuous to encapsulated cells after minimal exposure. In co-extrusion, the conventional

hollow fiber dry-jet, wet-spinning technique[30] is modified to produce discrete cell-containing devices. Both primary adrenal chromaffin cells and PC12 cell lines have been encapsulated by co-extrusion[31]. It is also possible to co-extrude a cell–matrix suspension with the matrix acting as the phase inversion agent.

Membrane properties: morphology, strength, transport

The membrane morphology can be altered during fabrication or afterwards by a post-treatment. Using phase inversion techniques, the outer membrane surface morphology can range in pore size from nanometers to micrometers. Membrane morphology, cross-sectional area and thickness of membrane walls affect membrane strength. To increase strength, the composition, structure and dimensions of the membrane can be manipulated. An inherently strong material has a high molecular weight or a highly ordered molecular structure. Membrane strength is generally inversely proportional to the diffusive transport in a homologous series.

UF membranes retain species 0.01–0.1 μm in diameter[32] whereas MF membranes retain much larger species (≤ 4 μm). Most xenograft cell transplantations require a UF membrane for immunoisolation. However, allograft cell transplantations may be successful in MF membranes because the transplantation is within the same animal species; here, only contact inhibition between host and transplanted cells may be necessary to avoid an immune system response.

Membranes are characterized by both convective and diffusive transport measurements (for example, see Fig. 2). The convective rejection coefficient (R) of a membrane is defined as one minus the concentration (C) ratio of molecular weight species in the filtrate (f) and retentate (r): $R = 1 - C_f/C_r$. A species with a rejection coefficient of one indicates that it does not convectively pass though the membrane, whereas a species with a value of zero indicates complete passage. The mass transfer coefficient of a membrane, k_m, is calculated using a Fick's law analysis. It represents the proportionality constant between the diffusive flux through a membrane, J, driven

by a concentration gradient, DC: $J = k_m DC$ (Ref. 33). In this analysis, the membrane diffusion coefficient, $D_{membrane}$, is equal to k_m multiplied by the membrane thickness, d_m: $D_{membrane} = k_m d_m$.

Figure 2 shows the convective and diffusive transport properties of a membrane that has successfully immunoisolated xenograft tissue; bovine adrenal chromaffin cells were encapsulated in this membrane and transplanted in humans for several months for the treatment of chronic pain[33,34]. Shown are R, k_m, and the ratio of the diffusion coefficient of a marker in the membrane to that in water, $D_{membrane}/D_{water}$, which is indicative of the amount of diffusive resistance that a membrane provides. (The markers used, with their molecular weights, include: glucose, 186 g mol^{-1}; vitamin B_{12}, 1300 g mol^{-1}; cytochrome C, 13 400 g mol^{-1}; bovine serum albumin, 67 000 g mol^{-1}; immunoglobulin G, 155 000 g mol^{-1}; and apoferritin, 440 000 g mol^{-1}.) For the larger species, R is nearly one, whereas the diffusive parameters are non-zero, indicating that large species are able to transport through the membrane, albeit in a very reduced manner. Thus some larger molecular weight species, such as immunoglobulins, may be able to diffuse slowly into the membrane if pore size remains unchanged after exposure to body fluids.

Membrane surface modification

In order to improve the surface properties of a polymeric membrane, the surface can be modified with a second polymer to achieve, for example, lower protein adsorption. Low protein adsorptive membranes may enhance sustained diffusion of cell products and nutrients. In one study[35], preformed P(AN–VC) anisotropic membranes were chemically modified with poly(ethylene oxide) (PEO) by one of two aqueous reactions: (1) acid hydrolysis of the nitrile group to a carboxylic acid with which amine-terminated PEO (PEO-NH₂) reacted, or (2) base reduction of the nitrile group to an amine with which PEO-succinimide (PEO-SC) reacted. Approximately 1.3% of the bulk material was modified with PEO-NH₂ whereas 1.8–3.5% of it was modified with PEO-SC as determined by ¹H-NMR and ATR FTIR. The P(AN–VC)-g-PEO fibers were characterized relative to P(AN–VC). Approximately 50–75% less protein adsorbed to PEO-grafted materials relative to unmodified P(AN–VC). PEO modification is thought to decrease protein adsorption by an excluded volume effect. The transport properties were compared by passive diffusion and convective nominal molecular weight cutoff and hydraulic permeability. Transport properties were unchanged after the surface modification reaction with PEO, indicating that the pore structure was not affected by the chemistry involved in grafting PEO. *In vivo* biocompatibility in the brain was measured by the host's tissue response to the implanted fibers; PEO grafting decreased the number of macrophages and foreign body giant cells present at the P(AN–VC) hollow fiber membrane.

Microcapsules

Most simply, microcapsules differ from macrocapsules by their geometry. Microcapsules typically consist of cells or cell clusters encased in a spherical, selectively permeable membrane. The encapsulating membranes can be formed from either water-insoluble materials, utilized
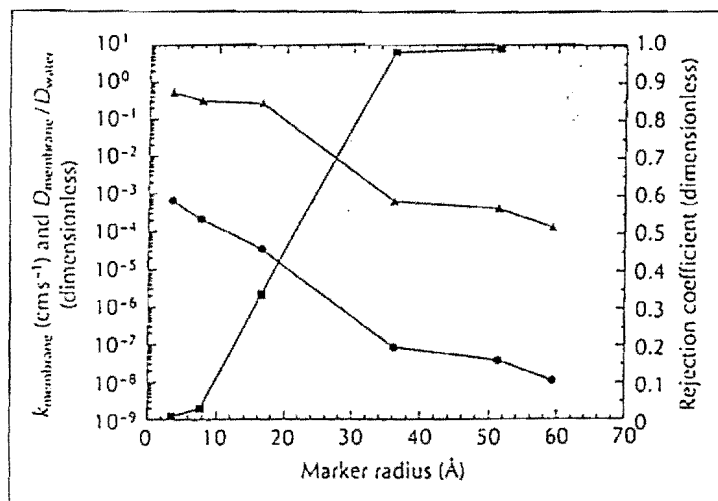
Fig. 2 *Convective rejection coefficient (■), membrane mass transfer coefficient ($k_{membrane}$) (●) and relative membrane diffusivity ($D_{membrane}/D_{water}$) (▲) versus protein molecular size at 37°C (Ref. 31). A P(AN–VC) hollow fiber membrane was used.*

in the co-extrusion process described above, or water-soluble solutions, such as ionic polyelectrolytes, that are crosslinked upon encapsulation. In microencapsulation, as in macroencapsulation, the long-term stability of the material under physiological conditions is essential. The microcapsule must be permselective with a molecular weight cutoff less than approximately 100 000 g mol⁻¹ to allow the passage of nutrients and oxygen without allowing that of host immune elements.

Microcapsules were prepared for the delivery of proteins[36] and later for cell encapsulation[37]. Spherical microencapsulated cells in the anionic acidic polysaccharide, alginic acid, are formed with a coaxial air flow system; microspheres are formed by dispensing cell-containing alginic acid into a physiological solution of calcium chloride. The calcium-crosslinked cell-containing alginate microcapsules are further modified by adsorbing cationic poly(amino acids), such as polylysine or polyornithine, which improve the integrity and stability of the microcapsule. Striatal implantation of calcium-cross-linked alginate microencapsulated PC12 cells has resulted in a reduction of movement disorders in animal models of PD[38]. The biocompatibility of the alginate microcapsules is reportedly improved by exposing crosslinked alginate microspheres to PEG-grafted polylysine[39] or by grafting hydroxyethyl methacrylate (HEMA) to alginate prior to crosslinking it in calcium chloride[40].

In addition to alginate, agar, agarose, carrageenan, chitosan, polyacrylamide, gelatin, fibrinogen and collagen have been used to encapsulate both suspension and anchorage-dependent animal cells, among others[41]. Microbeads may be prepared by dispersing an aqueous solution of polymer and cells in an organic phase as was done with cells suspended in agarose, which was extruded into a cooled bath of paraffin oil[42]. Despite demonstrating good biocompatibility and diffusion properties, agarose fails to isolate cells from the immune system, making it unsuitable for allogeneic and xenogeneic transplants because immune system cells could destroy the cells, rendering them unable to produce therapeutic reagents.

Synthetic polymers, such as acrylate-terminated poly(ethylene glycol) (PEG-acrylate) and poly(hydroxyethyl methacrylate) (PHEMA) and copolymers [i.e. poly(hydroxyethyl methacrylate-co-methyl methacrylate) (PHEMA–MMA)], have been successfully used for microencapsulating cells for transplantation. In the presence of 2,2-dimethoxy-2-phenylacetophenone dissolved in N-vinylpyrrolidinone, PEG-acrylate was polymerized and crosslinked in situ by exposure to UV irradiation[43]. The PEG microbeads were found to be both biocompatible and immunoprotective for encapsulated cells[43]. PHEMA–MMA dissolved in PEG was co-extruded with a PC12 cell suspension into hexadecane in which PHEMA–MMA precipitated, thereby encapsulating the cells within[44].

The microcapsules offer the cells an optimal geometry (i.e. high surface-to-volume ratio) for diffusion of nutrients and oxygen, which enhances cell survivability for most cells. However, the inability to retrieve the majority of microcapsules without significant trauma to the host may limit this technique for CNS applications. In addition, microcapsules may block the flow of cerebrospinal fluid if implanted in the ventricular space of the brain[20].

Conclusions

Transplantation into the adult CNS has shown great potential as a replacement strategy for neurodegenerative disorders characterized by the loss of specific neuronal or glial cells. Neural transplantation of many sources of tissue or cells has been shown to ameliorate the behavioral deficits associated with a number of animal models of neurodegenerative diseases[45]. Adrenal and fetal tissue transplants have been successful in both rodent and primate models of Parkinson's, Huntington's and Alzheimer's diseases; however, obstacles remain concerning adrenal tissue survival following transplantation and the availability of quality-controlled donor fetal tissue. The use of cell lines, especially those genetically modified to produce neurotrophins, is attractive from a homogeneity standpoint, but limited in terms of long-term stability and safety issues related to immunologic rejection in xenografts and tumorigenicity in allografts.

Drug delivery to the CNS can be augmented by polymeric materials. Numerous clinical trials (some of which are mentioned in this review) demonstrate the potential benefits of using polymers in the otherwise limited treatment of neurological disorders. Whether used in pumps, controlled release systems or encapsulated cell therapy, polymers allow continued delivery of therapeutic agents directly to the CNS. Consequently, patients may receive a lower dosage and may have potentially fewer dosage-related side effects. While other approaches, such as autologous gene therapy, are being developed to deliver therapeutic agents without the use of polymers, this technology is in an exploratory phase. Polymers will continue to provide the vehicle for delivery of therapeutic agents, whether that vehicle is a pump, controlled release system or an encapsulated cell transplant.

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Rubber Toughened Engineering Plastics

edited by A.A. Collyer, Chapman & Hall, 1994. £85.00 hbk (xi + 366 pages) ISBN 0 412 53830 1

Rubber toughening of polymers (by addition of relatively small amounts of elastomers to polymeric materials) has led to many diverse engineering materials. Whereas the initially produced materials, high-impact polystyrene and acrylonitrile–butadiene–styrene, have been studied in detail, this is not the case for many other toughened polymers. In particular, for the high-temperature engineering and speciality plastics, difficulties are encountered in the choice of rubber for the dispersed phase, in the synthetic routes involved for obtaining the optimum particle distribution, particle size, particle size distribution and interfacial adhesion, and in the lack of knowledge concerning the toughening mechanism that is operating. The book can give helpful information here, with a collection of ten chapters written by known specialists in the various fields.

The book can be read in two parts: in the first (chapters 1–5), failure and toughening mechanisms, methods of measuring toughness, and toughening agents are reviewed; the second

part of the book (chapters 6–10) is devoted to describing the synthetic routes and toughening strategies involved for various polymer matrices, namely, epoxies, polyamides, polyesters and polycarbonates, polysulphones and polyaryletherketones, and polyimides, respectively.

In the opening chapter, 'Failure mechanisms in polymeric materials', A.M. Donald discusses some fundamentals of the mechanical behaviour of macromolecules, of mechanical properties in general, and of shear deformation and crazing in particular. Whereas the entanglement concept of deformation is discussed in detail, some other possible mechanisms of energy absorption are not mentioned. In chapter 2 ('Rubber toughening mechanisms in polymeric materials' by I. Walker and A.A. Collyer) a good overview is given on some important variables of the matrix, including glass transition temperature, entanglement density and a so-called rigidity parameter, and of the blends, including miscibility and dispersion of the rubber phase, the type of rubber, rubber volume content, rubber particle size, and interfacial strength (adhesion). The main possible toughening mechanisms are also discussed, including energy absorption directly by rubber particles, energy absorption by shear yielding or by crazing, and the role of

cavitation. In chapter 3, 'Fracture and toughening in fibre-reinforced polymer composites' by G.C. McGrath, the rubber toughening of matrix materials used for fibre-reinforced polymers is discussed. Although the increase of toughness of matrix polymers is a question of particular importance, only a few relevant mechanisms of rubber toughening are mentioned. In chapter 4, entitled 'Methods of measurement and interpretation of results', A. Savadori reviews some basic mechanical parameters and traditional techniques of strength evaluation (static, fatigue, impact testing). In particular, an overview is given on fracture mechanics methods, particularly for the determination of toughness (i.e. for systems with energy dissipation). The techniques of studying fracture surfaces (fractography) by optical microscopy, and scanning and transmission electron microscopy are mentioned; however, a somewhat deeper discussion of these techniques seems necessary because of their importance in determination of the relations between microstructure, crack propagation and mechanical parameters, and for understanding the micromechanisms of toughening. Chapter 5 ('Toughening agents for engineering polymers', by H. Keskkula and D.R. Paul) gives an overview on general synthetic