Advanced Drug Delivery Reviews xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Polymers in cell encapsulation from an enveloped cell perspective ☆

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ARTICLE INFO

Article history:
Accepted 13 November 2013
Available online xxxx

Keywords:
Encapsulation
Natural polymers
Synthetic polymers
Insulin
Alginate
PEG
Surface properties
Biocompatibility
Biotolerability

ABSTRACT

In the past two decades, many polymers have been proposed for producing immunoprotective capsules. Examples include the natural polymers alginate, agarose, chitosan, cellulose, collagen, and xanthan and synthetic polymers poly(ethylene glycol), polyvinyl alcohol, polyurethane, poly(ether-sulfone), polypropylene, sodium polystyrene sulfate, and polyacrylate poly(acrylonitrile-sodium methallylsulfonate). The biocompatibility of these polymers is discussed in terms of tissue responses in both the host and matrix to accommodate the functional survival of the cells. Cells should grow and function in the polymer network as adequately as in their natural environment. This is critical when therapeutic cells from scarce cadaveric donors are considered, such as pancreatic islets. Additionally, the cell mass in capsules is discussed from the perspective of emerging new insights into the release of so-called danger-associated molecular pattern molecules by clumps of necrotic therapeutic cells. We conclude that despite two decades of intensive research, drawing conclusions about which polymer is most adequate for clinical application is still difficult. This is because of the lack of documentation on critical information, such as the composition of the polymer, the presence or absence of confounding factors that induce immune responses, toxicity to enveloped cells, and the permeability of the polymer network. Only alginate has been studied extensively and currently qualifies for application.

This review also discusses critical issues that are not directly related to polymers and are not discussed in the other reviews in this issue, such as the functional performance of encapsulated cells in vivo. Physiological endocrine responses may indeed not be expected because of the many barriers that the metabolites encounter when traveling from the blood stream to the enveloped cells and back to circulation. However, despite these diffusion barriers, many studies have shown optimal regulation, allowing us to conclude that encapsulated grafts do not always follow nature's course but are still a possible solution for many endocrine disorders for which the minute-to-minute regulation of metabolites is mandatory.

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☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Cell encapsulation and drug delivery".

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http://dx.doi.org/10.1016/j.addr.2013.11.005

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1. Introduction

Encapsulation involves the envelopment of living cells in polymer membranes to protect the cells from immune destruction. The introduction of this technology dates back to 1933, when Bisceglie et al. [1] studied the effect of encapsulation on the survival of tumor cells in the abdominal cavity of pigs. Bisceglie demonstrated that prolonged cell survival can be achieved by enveloping cells in immunoprotective membranes [1]. To achieve this, Bisceglie applied amnion tissue as a membrane but did not recognize the potential of the technology for the treatment of disease. In 1950, Algire et al. [2] introduced the concept of the "diffusion chamber" to graft therapeutic cells. Algire was also the first to emphasize the importance of the application of biocompatible polymers with constant, predictable properties as a prerequisite for therapeutic application [2]. Since then, many groups have demonstrated the principal applicability of encapsulation technology for the treatment of different types of diseases [3]. The number of diseases for which this technology has been proposed is long and includes hemophilia B [4], anemia [5], dwarfism [6], kidney [7] and liver failure [8], pituitary disorders [9], central nervous system insufficiency [10], and diabetes mellitus [11].

Basically, the encapsulation of living cells is applied in two geometries: macro- and microcapsules. In macrocapsules, living cells are enveloped in relatively large diffusion chambers with semipermeable properties. Diffusion chambers have been produced in the form of flat sheets, hollow fibers, and disks [12]. Macrocapsules can be distinguished in intra- or extravascular devices [13]. In intravascular devices, cells are distributed outside of artificial capillaries and connected to the blood circulation as a shunt. The advantage of these devices is that they are in close proximity to the bloodstream, implying the fast exchange of therapeutic molecules and nutrients, such as oxygen [14]. A major disadvantage of this system is that thrombosis may occur with these kinds of devices. This makes the use of life-long anti-coagulation therapy a requirement. For most endocrine diseases for which encapsulation is proposed, this risk of thrombosis makes it an unacceptable alternative for conventional treatment, in addition to its side-effects [15]. For this reason, most groups currently focus on extravascular devices, in which cells are enveloped within semipermeable diffusion chambers and implanted under the skin or in the peritoneal cavity without direct vascular access. The technology is associated with minor surgery and allows easy replacement in case of failure of the graft or when the transplant has to be substituted for other reasons. The numerous reports on the successful application of macrocapsules in experimental animals and humans [16–19] illustrate the potential of the technique. However, there is also a drawback. Macrocapsules are characterized by a relatively large surface-to-volume ratio. This implies that high amounts of nutrients are required to build an adequate diffusion gradient for ingress of the nutrients. This interferes with optimal nutrition for the cells. Another obstacle is that the cell density in macrocapsules should be quite low to guarantee adequate nutrition [13]. Within most applications, the cell density should not exceed 5–10% of the volume fraction [14]. This suggests that if large numbers of cells are required to cure disease [14], then numerous or large devices must be implanted. Current research on macroencapsulation focuses on the development of techniques that increase nutrition for tissues [20–22].

Microcapsules are not associated with surface-to-volume ratio issues. They allow for the fast exchange of therapeutic molecules and have been shown to closely mimic the release of insulin and glucose. Because of this beneficial property of microcapsules, the majority of research groups have concentrated on the development of microcapsules that provoke low or no inflammatory responses for the cure of endocrine diseases [11,23–25]. During recent years, the technology has reached the human stage [26–30].

Before discussing the advances in polymer research, a number of important items should be discussed that influence the functional survival of encapsulated tissue, regardless of the type of polymer that is being applied. As outlined below, encapsulated grafts have several limitations that cannot be overcome by simply applying better, innovative polymers.

2. Functional performance of encapsulated cells

A prerequisite is that the capsules or their materials should not interfere with cellular viability. Encapsulation procedures and the polymers applied, therefore, should not be associated with toxicity. Toxicity is a phenomenon that is rather cell-specific, and the susceptibility of cells to toxic molecules varies considerably [31,32]. Moreover, cells with high proliferation or regenerative capacities are more susceptible to toxicity than cells that derive from cadaveric donors, such as pancreatic islets [32,33]. In the latter case, minimal or no loss should be associated with the encapsulation procedure. These issues are discussed below with regard to the principal applicability of the procedure for mammalian cells.

In addition to optimal viability, an encapsulation system should allow for optimal function. Viability and function are not always directly related (discussed below). Immunoprotected cells are proposed for the treatment of diseases for which minute-to-minute regulation of a metabolite is required. To illustrate its potential, diabetes is currently being treated with multiple daily doses of exogenous insulin. This therapy is associated with fluctuations in the daily glucose profile, with consequently frequent episodes of hyper- and hypoglycemia. In the long-term, this can lead to diabetic complications [34,35], hypoglycemic unawareness, or even the failure of organs, such as the kidneys [36]. This can only be prevented by using an insulin source that regulates glucose levels on a minute-to-minute basis [34]. Immunoprotected pancreatic islets are proposed to be such a source.

Many studies have shown that immunoprotective capsules do not interfere with the free diffusion of glucose and insulin. Until a size of 1 mm is reached, the capsules do not disturb the normal biphasic release of insulin after a glucose challenge [37]. However, this is very different in vivo, in which the same functional, biphasic serological release patterns of insulin as those seen from islets in the normal pancreas may not be expected [38,39]. This can be explained as follows. Conventionally encapsulated islets are transplanted in the peritoneal cavity where they remain free-floating in the peritoneal fluid without direct vascular access. This implies that a number of barriers have to be overcome before glucose-induced insulin release can be observed in the systemic circulation. Glucose must first pass the basement membranes of the capillaries in the peritoneal cavity. This can take up to 5 min after glucose is increasing in blood [40]. The released insulin then must

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build a sufficiently high diffusion gradient to allow the diffusion of insulin back to the circulation [39]. To study how efficiently this process occurs, we mimicked the release of insulin by a pancreas in the peritoneal cavity [39]. This was achieved by releasing insulin in the same amount as that produced during a test meal via an intraperitoneally implanted catheter in rats. This physiological dose effectively lowered glucose levels, but we were unable to measure any elevation of insulin levels during the experiment. Twice the amount of insulin that is normally released during a test meal was necessary to detect an elevation of insulin levels in the systemic circulation [39]. The explanation for this is simple. The released insulin must build a diffusion gradient that exceeds the basement membrane to be taken up into the circulation. This building up of the diffusion gradient occurs over a relatively large diffusion area. At the same time, the visceral organs and liver [41] adsorb a significant amount of the released insulin to take up the elevated glucose in the portal circuit. Consequently, high, non-physiological amounts of insulin are required to detect an effect on insulin levels in the systemic circulation [39]. Thus, a true measurable biphasic elevation in insulin levels may not be expected in recipients of encapsulated islet grafts.

To quantify the delay in responsiveness of an intraperitoneally implanted encapsulated graft, we subsequently performed an experiment in mice in which we measured graft-derived c-peptides upon a glucose challenge [42]. C-peptide is not adsorbed by visceral organs or metabolized by the liver. This experiment revealed that islets in the peritoneal cavity responded rapidly to a glucose challenge. At 20 min, we observed a significant elevation of c-peptides [42]. Glucose levels were adequately regulated and always remained below 6.8 mM, illustrating the adequate regulation of glucose metabolism. This was also confirmed in other studies that quantified HBac1 levels in rat recipients of encapsulated islet grafts, in which glucose levels were always within the normal range [43], illustrating the adequate regulation of glucose levels in the short and long-term. Fig. 1 illustrates the currently known barriers that glucose and insulin must overcome before reaching the systemic circulation.

The aforementioned issues illustrate an important item. Encapsulated grafts do not always follow nature's course but are still functional. The lack of direct vascular access or transplantation in ectopic sites is responsible for different release patterns caused by barriers that the therapeutic agent must overcome to reach the systemic circulation. However, as outlined above, this does not imply that the graft or regulation is inadequate. It is different when measured in the systemic circulation but still adequately regulates metabolism on a minute-to-minute basis.

3. Longevity of the graft and biotolerability

The optimal function of a graft is a prerequisite, but the longevity of the graft is equally important. For most applications, a survival period of several months is required [44]. This implies that the supply of nutrients for cell survival is essential when choosing a transplantation site for the encapsulated tissue. The cells in the capsules are not vascularized after transplantation, and the lack of direct vascular access is considered a true Achilles heel for encapsulation. The lack of direct vascular access is considered an important issue for the exchange of glucose and insulin and the exchange of nutrients and metabolic waste. Many feel that long-term cell survival cannot be expected [22,45–51]. Considerable attention has been paid to the role of oxygen in the functional survival of encapsulated tissue. Again, many of these studies have focused on encapsulated islets that require high amounts of oxygen for adenosine triphosphate generation and optimal function [22,52]. Oxygen tension in the peritoneal cavity is 40 mm Hg [53], which is considerably lower than the arterial pressure of 120 mm Hg [54]. Normally, every

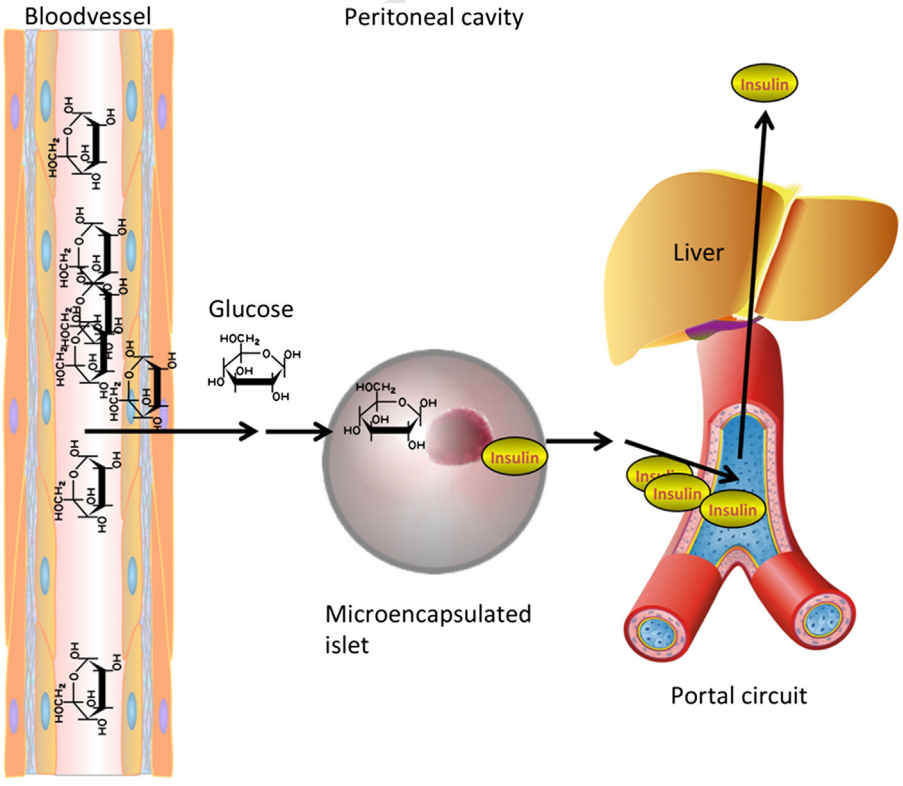

Fig. 1. Barriers that glucose and insulin must overcome to accomplish a glucose-induced insulin response in recipients of an intraperitoneally implanted encapsulated islet graft. After the consumption of a meal, glucose has to build a diffusion gradient across the basement membrane before it can diffuse into the peritoneal cavity. It then has to pass the capsule membrane and diffuse through the non-vascularized islet to induce an insulin response. The released insulin must diffuse out of the capsule through the peritoneal fluid to build a diffusion gradient across the blood vessels in the portal circuit. When entering the portal circulation, it must cross the liver where a significant portion of the insulin is adsorbed. Finally, it reaches the systemic circulation where physicians measure the glucose-induced insulin response.

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islet cell is in contact with a blood vessel and therefore exposed to high oxygen tension. Several studies have shown that lower oxygen tension may result in necrosis in the central part of islets when transplanted in ectopic sites, such as the peritoneal cavity. The size of islets varies between 50 and 350 μm, and they remain in capsules as spherical clumps of cells [43]. Especially larger islets are susceptible to the gradual development of necrosis because of the competition for nutrients that diffuse from the periphery to the core [55]. In rats, we found that islets less than 150 μm were free of necrosis and functional 12 weeks after transplantation. In contrast, islets greater than 150 μm had large necrotic zones with only a rim of living cells remaining at the periphery of the cell clumps [43]. This has important implications for the longevity of the graft because the adequacy of the regulation of glucose metabolism depends on the endocrine volume of a graft [56,57]. Larger islets make a relatively high contribution to this volume because the volume increases by a third power as the diameter of the islets increases [58]. Losing all of the larger islets implies that 60% of the graft volume is lost in the first weeks after transplantation because of nutritional issues that impose a full metabolic load on the remaining 40% of the graft [43]. This issue is still insufficiently recognized in the field but should be considered a major hurdle to improve the longevity of the graft. A conceivable approach to solve this issue is to create grafts with smaller islets (i.e., <150 μm diameter).

The diameter restriction that is necessary to prevent cell death was found for rodent islets. Theoretically, however, the diameter restriction may even be stricter with human islets. Recent observations showed that human beta-cells may dedifferentiate and undergo an epithelial-to-mesenchymal transition under the influence of the hypoxia-mediated activation of hypoxia-inducible factor-1α (HIF-1α) [54]. HIF-1α mediates Twist expression, which contributes to the development of progressive fibrosis. Although still a subject of debate [54], we do not feel this is a substantial issue in encapsulation because we have demonstrated the prolonged survival of encapsulated human islets in the peritoneal cavity in rats with an oxygen tension of 40 mm Hg [59]. This suggests that the epithelial-to-mesenchymal transition does not occur at sufficiently high levels to interfere with the survival of human grafts.

There is another reason to avoid large islets, the production of so-called danger-associated molecular patterns (DAMPs). These DAMPs are molecules that are released by cells that undergo necrosis. Examples of DAMPs are cytosolic proteins, such as heat-shock proteins or pieces of DNA and RNA [60–63]. The mammalian immune system, including the human immune system, has specialized receptors called pattern recognition receptors (PPRs) that recognize these DAMPs. The most well-known PPRs are Toll-like receptors. The immune system, however, also has other DAMP sensors. These include c-type lectins, nucleotide-binding oligomerization domain (NOD) receptors, retinoic acid inducible gene (RIG) receptors, and inflammasomes [62]. The DAMPs released from large islets might be very potent activators of PRRs, which subsequently induce an inflammatory response. This response leads to the release of massive amounts of cytokines that are deleterious to the survival of encapsulated cells [60]. Therefore, it is advisable, if not mandatory, to avoid the application of large tissue clumps in which necrosis may occur. The avoidance of necrosis-induced immune activation by danger signals deserves more attention in encapsulation research (Fig. 2). As outlined above, we know that islets with a size less than 150 μm do not develop necrosis. Because we do not yet know the critical size for the release of DAMPs, we recommend applying islets of 150 μm to avoid necrosis-induced immune responses.

The aforementioned discussion of longevity-interfering factors does not include polymers. They are included in this review to illustrate that not all issues in promoting survival are related to the biomaterials we apply. The size of cell clumps, distance to nutrient-supplying blood vessels, DAMPs, and likely many other factors still to be discovered all contribute to the duration and quality of graft performance. However, the polymer applied is a leading subject in discussions on the crucial

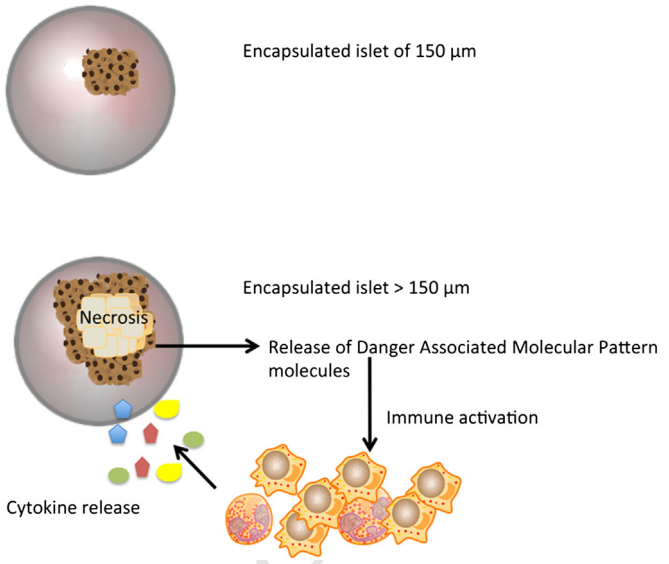

Fig. 2. Size matters. The size of the cell clump is a polymer-independent factor in tissue responses. For pancreatic islets, tissue clumps with a diameter less than 150 μm stay functional and do not develop necrotic zones in the core of the clumps. Above this size, necrosis occurs in the center of the cell clumps due to competition for nutrients. This influences not only the functional metabolic capacity of the graft but also the tissue response in the vicinity of the graft. Necrotic cells release danger-associated molecular pattern molecules, which are potent activators of immune cells found in the transplantation site. After immune activation, cytokines are released that are sufficiently small to pass the capsule membrane and deleterious to islet tissue.

factors involved in the functional survival of grafts. For the last two decades, studies have shown that any polymer that qualifies for the encapsulation of cells should be fully biocompatible. Some groups claim that such materials are available [55,64], but others doubt whether such materials can ever be designed [65–67]. This paradox can be explained by different interpretations of the definition of "biocompatibility" and the specific requirements for encapsulated cells. Biocompatibility is often defined as "the ability of a biomaterial to perform with an appropriate host response in a specific application." Originally, this definition was formulated at a time when the application of fully artificial organs, such as artificial hips and knees, was emerging [68]. These fully artificial organs provoke an innate immune response that results in fibrotic reactions, with integration of the artificial materials in the surrounding tissue. This fibrosis and integration in the surrounding tissue is an "appropriate host response." For bioartificial organs, such as encapsulated cells, defining the appropriate host response is far more difficult because any inflammatory response against the biomaterials is potentially harmful to the cells in the capsules. For these reasons, the field has moved away from the term "biocompatibility." The current leading opinion is that functional encapsulated grafts should have preferably no or at least minimal cellular overgrowth to ensure free diffusion of nutrients and oxygen and the exchange of therapeutic proteins. Rokstad et al. [69] discusses this issue in detail in a different article in this issue and explains that the term "biotolerability" is more appropriate than "biocompatibility" for the encapsulation field. "Biotolerability" is defined as "the ability of a material to reside in the body for long periods of time with only low degrees of inflammatory reactions" [70]. This definition also covers another important requirement for a polymer in cell encapsulation (i.e., the compatibility of the biomaterial with the encapsulated cells). Cells should grow and function in the polymer network as adequately as in their natural environment.

Many biotolerable polymers have been introduced as encapsulation material. In some cases, these matrixes are coated with other polymers to improve biocompatibility [71]. As outlined above, to qualify as an adequate biotolerable polymer for cell encapsulation, the polymer should not interfere with the function and viability of the cells in the capsules [71,72]. Additionally, the polymers should not induce a host

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response that can interfere with the function of the encapsulated cells [73]. In the present review, natural and synthetic polymers that meet the aforementioned prerequisites are discussed from the perspective of their potential and obstacles in the application of encapsulation systems. The limitations of the most commonly applied procedures are discussed, and aspects related to improving the performance of polymers as encapsulation material are reviewed in view of the clinical application of immunoisolating material for mammalian cell encapsulation. Only polymers that have been studied by more than one research group in more than one application over several years are discussed. The origin of the polymers, the way they are processed for capsule formation, and the successful production of immunoprotective capsules based on the polymers are discussed with consideration of the optimal functional survival of the encapsulated cells.

4. Polymers from natural sources

Generally, three main classes of natural polymers can be distinguished (i.e., polysaccharides, polypeptides, and polynucleotides). Polysaccharides are the most commonly used natural polymers in cell encapsulation. The reason for this is probably that polysaccharides allow for the encapsulation of cells under relatively mild conditions and generally do not interfere with the functional survival of the cells [11,74]. Another pertinent reason is that the majority of polysaccharides form hydrogels [75]. Hydrogels have many beneficial properties for cell encapsulation. They are pliable, soft, mechanically stable [76], and reportedly associated with minor host responses [77].

4.1. Alginate

The most commonly applied polymer in encapsulation research is alginate. Alginate was originally introduced for the encapsulation of pancreatic islet cells for the treatment of diabetes [11]. Since then, it has been applied for the encapsulation of not only pancreatic islets [78] but also other endocrine cells and recombinant cells for the delivery of therapeutic gene products [79,80], such as growth hormone and human clotting factor IX.9 [81–84]. It is also applied in bioartificial kidneys [7], for the protection of hepatocytes [85], and for bioartificial parathyroids [86]. Alginate is being applied for both macro- and microencapsulation.

Alginate is a natural anionic polymer and has been isolated from *Azotobacter vinelandii*, several Pseudomonas species, and algae [87]. Alginate is a linear polysaccharide composed of 1,4′-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues in different sequences (Fig. 3). The ratio of G and M blocks depends on the source of algae used for alginate extraction. Alginates with high guluronic acid content are preferred for applications where a more rigid structure is required. Alginates with a higher mannuronic acid content are preferred for applications where pliable gels are desired. This versatile property of alginate is caused by the higher affinity of the guluronic acid residues for divalent ions [13]. The alginate that is most commonly applied for cell encapsulation is obtained from brown algae [71,72].

Sol–gel processes are usually applied to manufacture alginate capsules. This process involves the extrusion of a solution of alginate that contains the therapeutic cells in a crosslinking solution that contains divalent cations, such as Ca^{2+}, Sr^{2+}, or Ba^{2+}. Other divalent cations, such as Pb^{2+}, Cu^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, and Mn^{2+}, will also crosslink alginate gels, but their application is avoided because they are toxic to cells [88]. Alginate's affinity for different divalent ions has been shown to decrease in the following order: $Pb^{2+} > Cu^{2+} > Cd^{2+} > Ba^{2+} > Sr^{2+} > Ca^{2+} > Co^{2+}, Ni^{2+}, Zn^{2+} > Mn^{2+}$ [89]. A higher affinity of the cation for the alginate residues is associated with a stronger gel [90].

Alginate gels are too porous to provide immunoprotection [91]. The pore size of barium-alginate gels have been reported to provide protection for allogeneic tissue but not xenogeneic tissue [92,93]. Therefore, in most applications, researchers choose to coat the alginate gels with cationic polymers of synthetic origin [94–96]. The most intensively studied and characterized cationic polymers for alginate coating are poly-L-lysine [97] and poly-L-ornithine [98]. However, poly(ethylene glycol) (PEG), glutaraldehyde [99], chitosan [99,100], agarose [101], cellulose sulfate with the polycation poly(methylene-co-guanidine) [102], diblock polymers of poly-L-lysine and PEG [103], and poly (allylamine) [104] have also been applied.

A critical issue that always requires confirmatory studies is that the coating of the alginate matrix should not interfere with the diffusion of the therapeutic molecules. The poly-L-lysine coating of alginate has been shown to directly influence the ability of pancreatic islets to respond to a glucose load [37]. The thickness of the poly-L-lysine layer is even more important than the islet diameter and capsule diameter [37]. Typically, the poly-L-lysine membrane should not exceed 4 μm in thickness, and it should not be exposed to poly-L-lysine concentrations higher than 0.1% for 10 min [37]. Pore sizes that are too tight have received only minor attention in the field to date but require considerable consideration when applying coatings to decrease permeability because it may also lead to malnutrition of the tissue or accumulation of toxic waste material in the capsules (Fig. 4). Wikstrom et al. [105] described a model for predicting the permeability of alginate membranes with different crosslinkers. Wikstrom demonstrated that substantial amounts of proteins may accumulate in the microcapsules with permeability less than 0.04 h^{-1} [105]. This will lead to the accumulation of waste materials with toxic effects and necrosis of the cells as a consequence [43].

Other types of coatings are also being applied to decrease the pore size of alginate matrices. In some cases, polymers are being applied to decrease the permeability and simultaneously increase the mechanical stability and durability of the capsules. Polyethylene glycol has often been applied as a coating material for that reason [106]. Chen and colleagues showed that PEG-amines can be stably coated onto the surface of microcapsules to stabilize the capsules and even contribute to the prevention of cell overgrowth on the capsule surface [107]. They used charged derivatives of PEG, methoxypolyoxyethylene amine and polyoxyethylene bis(amine). These derivatives contain charged amine groups (NH_3^+) at one or both ends of the polymers and contain a PEG backbone. The amine groups of the PEG derivatives

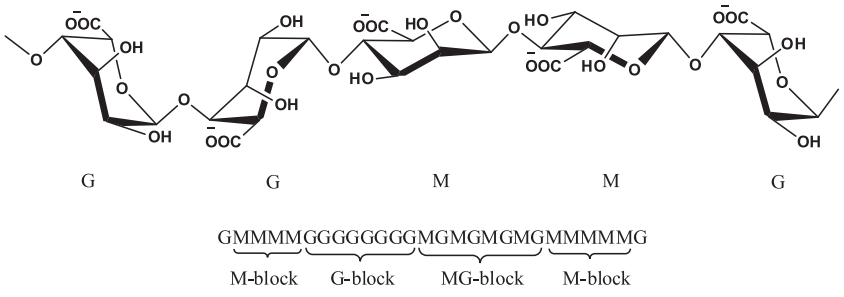

Fig. 3. Alginate. Alginate is a linear polysaccharide composed of 1,4′-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues in different sequences.

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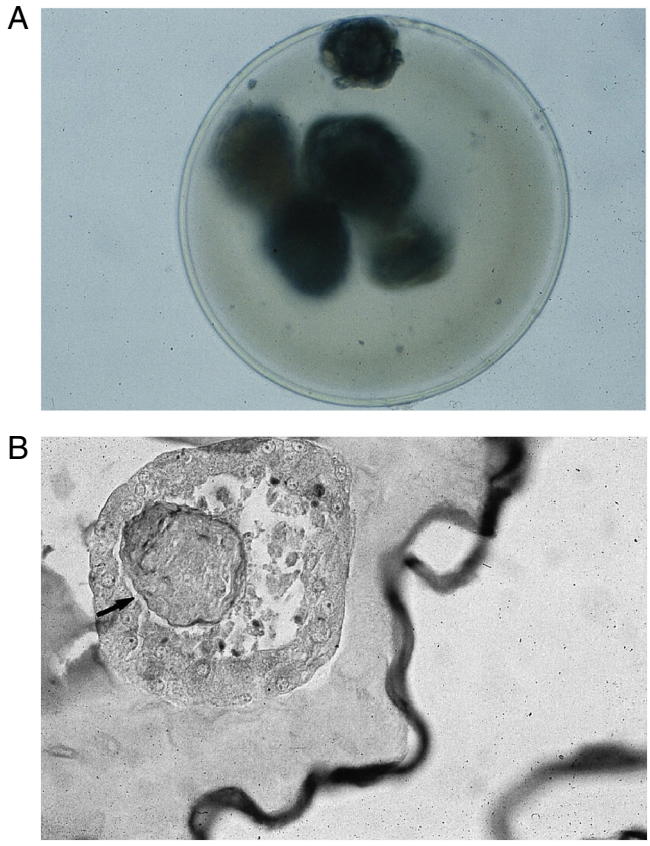

Fig. 4. Retention of metabolic waste material in an alginate–PLL capsule (A). The islets in the capsules are necrotic (B).

can interact with the negatively charged alginate on the microcapsule surface [108]. Another approach for PEG coating has involved the use of glutaraldehyde, which leads to the chemical grafting of PEG on the beads [99]. The incorporation of very low levels of glutaraldehyde during gelation improved not only the stability of the capsules but also the biostability and function of the encapsulated cells [99]. Despite encouraging results, the surface modification of alginate with glutaraldehyde has not been reported since 1999.

Another series of efforts to stabilize alginate gels is the application of covalent crosslinking molecules. The application of photoactive crosslinkers is the most commonly applied method for covalently crosslinking alginate [109–111]. Notably, however, this method does not meet the criterion that an encapsulation procedure should not interfere with the functional survival of the cells. Photoinitiator solutions are associated with free-radical generation following the initiation of bond formation and can lead to cell toxicity [112,113]. Another method for covalently crosslinking alginate molecules is the introduction of aldehyde or hydroxyl groups. These groups can chemically crosslink other polymers that stabilize the capsule and provide adequate semipermeable properties [114,115]. Alginate with phenol moieties (Alg–Ph) were recently applied [114]. This alginate is gelated through the formation of crosslinks by calcium ions or horseradish peroxidase (HRP). Horseradish peroxidase catalyzes the oxidative coupling of phenols with alginate using H_2O_2 dissolved in the aqueous solution or both [114]. However, the synthesis of esters directly onto the alginate carboxyl groups may lead to their consumption and consequently the failure of the capsules.

The biotolerability of alginate-based capsules is probably the best studied of all polymers applied for cell encapsulation. Alginate is the polymer that has shown that purity is an important factor in preventing host responses [38,116]. Many natural polymers, including alginate, contain immunogenic substances, such as proteins, endotoxins, and polyphenols [38]. When these molecules diffuse to the capsule surface, they can provoke strong and deleterious responses [38]. A recent finding is that alginate may contain so-called pathogen-associated molecular pattern molecules (PAMPs), which are highly conserved molecular motifs that are found not only on pathogens but also throughout nature [117]. Similar to DAMPs, they are very strong activators of PRRs and consequently inflammatory responses. The presence of PAMPs is likely not unique for alginate but most likely also present in other polymers. Therefore, we will postpone the discussion about its role in biotolerability until the "Concluding remarks and future considerations" section below.

Other factors that might contribute to enhanced responses are activation of the complement system [118,119]. Rokstad et al. [69] discusses this topic in depth in the present issue, so it will not be discussed here. Complement activation may also be deleterious for islet tissue because it might activate cells in the vicinity to produce large quantities of cytokines that are able to pass the membrane [118]. However, complement activation is not a direct threat for the encapsulated tissue because the complexes are too large to pass the membranes. Thus, the membranes protect against complement activation. In our hands, complement activation was observed with high-G alginates within the first days after implantation and not thereafter.

Additionally, alginate has been the model polymer to demonstrate the importance of the adequate binding of crosslinking molecules with the matrix of the capsules. For poly-L-lysine, adequate amounts of G–M residues should be present in the matrix to allow for the formation of super-helical cores and β-sheets [120]. These conformations mask positive charges on the poly-L-lysine molecules, which are implicated in inflammatory responses [120–122].

A recent study [123], again with alginate, reported that the resistance to changes in the in vivo microenvironment should be considered a prerequisite for the long-term functional survival of encapsulated cells. High-G alginates could be engineered such that they have similar physicochemical surface properties as capsules with a matrix with high amounts of G–M to facilitate poly-L-lysine binding. However, when implanted, the high-G capsule's surface undergoes many changes, including an increase in zeta-potential with protein adsorption and a consequent host response [123]. This was not observed when the capsules were produced with a high G–M content. This illustrates that some compositions cannot withstand the lower pH or osmolarity changes in vivo [124], with inflammatory responses as a consequence (Fig. 5).

Although these facts are well known, they have received minor attention in the area of other natural polymers.

4.2. Agarose

Agarose was first applied for cell encapsulation by Scheirer et al. [125]. It has been applied for macro- and microencapsulation. Agarose macrobeads have been shown to protect islet xenografts from rejection and provide a microenvironment where the islets maintain and support their function in vivo [126,127]. Agarose-encapsulated PC12 cells, a dopaminergic cell-line derived from rat pheochromocytoma, delivered dopamine for at least 5 weeks after transplantation without any signs of immune rejection [128]. Agarose has also been used for the encapsulation of genetically modified fibroblasts to treat brain disorders [129], hybridoma cells for immunological disorders [82], kidney cells [128,130,131], and insulinoma cells for the treatment of diabetes [132,133]. Studies have reported varying degrees of success.

Agarose is a polysaccharide obtained from agar. It is composed of β-D-galactopyranosyl and 3,6-anhydro-L-galactopyranosyl, which are coupled through 1 → 3 binding (Fig. 6). Agarose allows for the encapsulation of cells under mild conditions and reportedly does not interfere with the functional survival of cells [134]. When applied in a pure form, some types of agarose are associated with minimal host responses [135].

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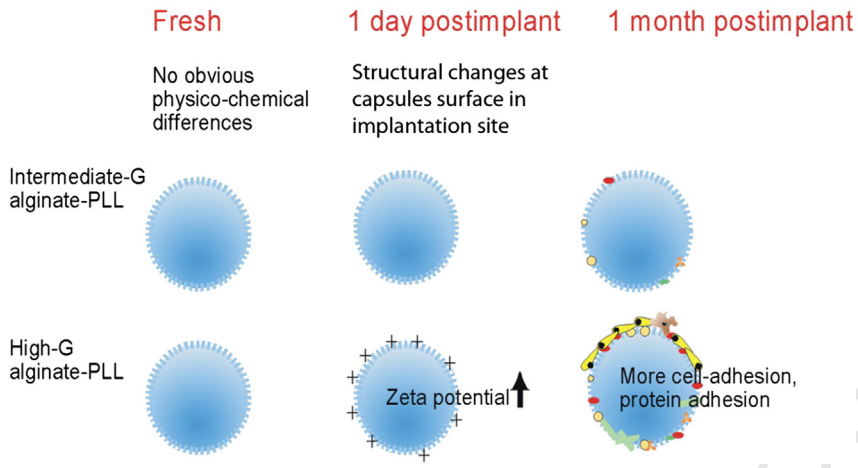

Fig. 5. The physicochemical properties of capsules can change in the implantation environment. With alginate, alginate–poly-L-lysine with a high G-content will undergo a change in surface charge directly after implantation. This is the consequence of a nonspecific immune response that occurs, with a consequent influx of cells and pH changes in the implantation site. This response always occurs independent of the quality of the graft. Some capsule types are insensitive to these changes and do not undergo any change in surface charge. For high-G alginate, an elevation of positive charges on the capsule's surface will occur (zeta-potential elevation) with consequent cell adhesion and inflammatory responses against the high-G microcapsules.
Obtained from reference [121] with permission from the publisher.

Immunoprotective gel formation is based on temperature-induced suspension–gelation methods. The cell/agarose solution is usually pressed though a nozzle at 37 °C. The agarose beads are subsequently collected as droplets at 4 °C to allow the beads to gel [136]. Although the procedure is simple and available in many medical laboratories, it has a major disadvantage. The suspension–gelation method is associated with a broad size distribution of capsules and high shear forces that are deleterious to cells [137]. Therefore, different methods have been proposed and are still under investigation [137].

The immunoprotective properties of agarose gels are controlled by varying the agarose concentration to form the gels. Usually 5% agarose is applied to form immunoprotective capsules [138]. Agarose microcapsules can effectively prolong islet iso- and allografts in mice [139] and canines [140,141]. Xenografts show limited durations of survival [13], which is likely attributable to the fact that the applied agarose gels cannot prevent the penetration of cytotoxic immunoglobulin G (IgG) in xenografts [142,143]. The in vivo graft survival time was improved by increasing the agarose concentration from 5% to 7.5–10% [144] or by providing a coating on the surface with another polymers. To this end, Dupuy et al. [145] coated agarose microcapsules with polyacrylamide. These capsules were shown to be impermeable to antibodies but associated with major host responses that interfered with the functional survival of the islets [146]. Another more successful approach was coating the agarose surface with polybrene and carboxymethyl cellulose (CMC) [147]. To engineer these capsules, microcapsules composed of a mixture of 5% agarose and 5% polystyrene sulfonic acid (PSSa) were formed and incubated with polybrene and CMC. Agarose/PSSa provided immunoprotection and mechanical stability. However, PSSa may provoke host responses. Therefore, the polybrene layer is applied to inhibit PSSa leakage by forming a polyionic complex at the surface of the agarose/PSSa membrane and outer layer. The CMC coating improved the biotolerability of the microcapsules [147].

To facilitate functional survival of cells in agarose gels, agarose has been mixed with polymers with growth-promoting properties.

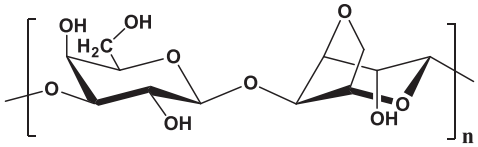

Fig. 6. Agarose is composed of β-D-galactopyranosyl and 3,6-anhydro-L-galactopyranosyl, which are coupled through 1 → 3 binding.

Collagen–agarose macrobeads, for example, showed superior effects on the functionality of rat pancreatic islets compared with agarose alone. These macrobeads were able to maintain normoglycemia in diabetic rats [127,148–150]. Agarose/poly (styrene sulfonic acid)-mixed gels also had positive effects on islet survival. These gels maintained normoglycemia for a period of 38–101 days in mice [151].

Although the principal applicability of agarose for immunoprotective capsules has been demonstrated, some major issues remain unresolved. Tissue reactions against implanted PSS/agarose microcapsules increase when the PSS concentration increases. The 5%/5% agarose/PSS microcapsules were free-floating in the peritoneal cavity, whereas those that contained 10% PSS were surrounded by adipose tissue [152–154]. Another issue is the presence of toxic molecules before, during, and after the encapsulation procedure with agarose [145,155]. Compared with alginate, agarose has less versatile properties with regard to adapting permeability to prevent the entry of deleterious molecules. Complement factors and many cytokines are known to pass through the agarose microcapsules [138,139]. Another major challenge is to find reproducible, pure sources of agarose when widespread application is considered [115,156].

4.3. Chitosan

Chitosan has been applied as a polymer matrix for the encapsulation of PC12 cells for the treatment of Parkinson's disease [157], hepatocytes [158], R208F cells [159,160], fibroblasts [10,16,160,161], human bone marrow stromal cells [162], and cardiomyocytes [163]. It is mostly applied for microencapsulation [164] and is preferred for cells that benefit from a cationic environment [165] or in applications in which biodegradable properties are desired. In addition to cell encapsulation, chitosan has been applied for drug delivery, for dermal substitutions, and as wound healing accelerators [166,167].

Chitosan is a polycation and found in crustacean shells, fungi, insects, annelids, and mollusks. It is commercially produced from chitin [168,169]. Chitosan is a poly β(1 → 4)-2-amino-2-deoxy-β-D-glucan, deacetylated chitin. Chitosan contains reactive amino and hydroxyl groups and has a strong affinity for polyanions. It is soluble in acidic aqueous solution and has versatile mechanical properties [170] (Fig. 7).

Chitosan has not been as intensively tested as alginate or agarose for immunoprotection. The reason for this is that chitosan cannot be easily dissolved in aqueous media at pH > 6, with the exception of low-molecular-weight samples. It is soluble only at non-physiological pH [170]. However, chitosan-alginate matrices have been successfully

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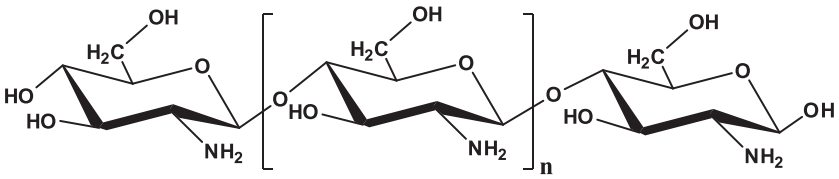

Fig. 7. Chitosan is a poly β(1 → 4)-2-amino-2-deoxy-β-D-glucan.

applied for the implantation of pancreatic islets in streptozotocin (STZ)-induced diabetic mice [171]. The authors, however, did not report how they avoided toxicity at low pH. Chitosan is mechanically not very stable and interferes with the function of cells that do not benefit from a positively charged microenvironment. By combining gelatin with chitosan, both the mechanical and biological properties of the chitosan substrate can improve. Chitosan/gelatin solution with glycerol salt becomes a hydrogel at 37 °C and has been successfully used for the macroencapsulation of insulinoma cells [100,172].

Some groups have studied the applicability of *N*-acetylated chitosan instead of chitosan because of its high solubility in water and aqueous organic solvents [173]. However, the water solubility of *N*-acetylated chitosan decreased as its molar mass increased at the same pH [174,175]. Its mechanical instability also interferes with the stable and reproducible production of microcapsules. Increasing the concentration of *N*-acetylated chitosan has been reported to improve mechanical stability, but this increase in concentration was associated with an undesirable decrease in permeability [175]. Some improvements in mechanical stability without effects on permeability were demonstrated when *N*-acetylated chitosan was combined with alginate as encapsulated HepG2 cells in *N*-acetylated chitosan/alginate matrices. This preserved the viability of the cells over a 1 week culture period [176]. Longer culture periods have not been reported.

Presently, because of its low compatibility with the enveloped cells, chitosan will unlikely be acceptable as a matrix polymer for application in immunoprotective capsules [177]. As a cationic polymer, it is mucoadhesive and exhibits cellular cytotoxicity [94]. It will possibly have more chances for success as a coating material [178]. The application of chitosan instead of poly-L-lysine has been suggested to provide higher mechanical strength and stability because of the stronger bond between chitosan and the alginate gel [164,174,179]. Of course, this depends on the type of alginate applied [180,181] and requires further investigation.

4.4. Cellulose

Cellulose has been applied for the encapsulation of cytotoxic epithelial cells for the treatment of pancreatic cancer [182–184], insulin-producing cell lines (HIT-T15) [185,186], embryonic kidney cells [187], and hybridoma cells [188,189]. Cellulose does not form hydrogels and therefore is mostly applied in inert diffusion chambers that are used as immunoprotective macrocapsules [18,190].

Cellulose is the structural component of the primary cell wall of green plants, many forms of algae, and oomycetes [191]. It is a polysaccharide that consists of a linear chain of β(1 → 4)-linked D-glucose units (Fig. 8). Some species of bacteria also secrete cellulose to form biofilms [192,193]. Cellulose is biodegradable and therefore the subject of debate for application in some forms of tissue repair [183]. However, the degradation of cellulose in animals and humans is considered to be limited [191], if it occurs at all, because of the absence of hydrolase that degrades the β(1,4) linkage in mammals [191]. Physical transformations of higher-order structures of cellulose may even modulate its degradation [191] and make cellulose a versatile and applicable natural polymer.

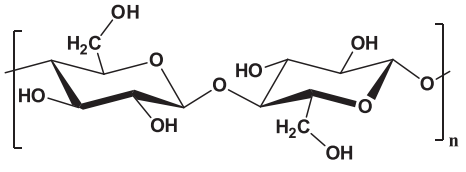

Fig. 8. Cellulose is a polysaccharide that consists of a linear chain of β(1 → 4)-linked D-glucose units.

Cellulose is insoluble in water and most organic solvents, and some groups have explored the application of water-soluble derivatives, such as sodium cellulose sulfate (NaCS) and carboxy methyl cellulose (CMC), for cellular immunoprotection [183,194]. NaCS is the ester derivative of cellulose. It is a product of the reaction of cellulose with sulfuric acid or other sulfuric reagents. By dropping a solution of NaCS into a solution of poly(diallyldimethylammonium chloride [PDADMAC]), very mechanically stable microcapsules may be produced via interfacial polyelectrolyte complexation [183]. The fast coacervation of cellulose sulfate with the polycation results in a mechanically stable membrane around a core of non-reacted cellulose sulfate [195]. Cells can be dissolved in the cellulose sulfate solution under physiological conditions and safely trapped within a liquid core during capsule formation. Sodium cellulose sulfate serves as a polyanion, and PDADMAC serves as a polycation [183]. This procedure reportedly does not interfere with the functional survival of animal and human cells [196]. CS-PDADMAC capsules have been successfully applied with hybridoma cells to deliver monoclonal antibodies into the blood stream of immunocompetent mice [188].

The cellulose derivative CMC contains carboxymethyl groups ($-CH_2-COOH$) bound to some of the hydroxyl groups of glucopyranose monomers on the cellulose backbone. This derivative is mostly applied as a matrix molecule in combination with a coating of the surface to provide mechanical stability and immunoprotection. An evaluation of six polyanion and six polycation combinations revealed that a combination of high-viscosity CMC/chondroitin sulfate A-chitosan has permeability properties and mechanical strength similar to alginate–poly-L-lysine capsules [94,194]. Other approaches that have been explored with CMC include the addition of chitosan molecules. This increases pH and ionic strength and consequently establishes a favorable environment to form a gel structure by reducing electrostatic repulsion and enhancing hydrophobic interactions [197,198]. Thermosensitive chitosan/CMC hydrogels have been tested and applied to encapsulate chondrocytes [194]. Other applications have not yet been published. Although production is technically challenging, these hydrogels are relatively fragile because of the weak molecular interactions and high water content. To improve this situation, Ogshi et al. [199] synthesized CMC with phenol groups and then used HRP-catalyzed oxidation reactions to conjugate phenol groups for the microencapsulation of feline kidney cells. The reaction was performed in the presence of H_2O_2 [199]. The resulting microcapsules were not uniform and in the range of 60–220 μm [200,201]. Many improvements must be made before this procedure can be considered for application in immunoprotection. Considering the harmful effect of H_2O_2, a faster gelation time and lower H_2O_2 content would also be desirable for practical applications. Presently, cellulose only has potential as a polymer for macroencapsulation [18].

The biotolerability of cellulose is the subject of debate [18,202]. However, it is compatible with the functional survival of enveloped cells because it induces not more than minor inhibition of cell

proliferation of the encapsulated cells [203,204]. Some authors have reported strong tissue reactions that result in the infiltration of cellulose-based macrocapsules with immune cells and a fibrous capsular reaction 15 days after implantation in mice [18]. This implies that an inflammatory response can occur against cellulose. Other authors have reported the absence of inflammatory responses, even when cells were present in the cellulose-based capsules [188,205]. Unfortunately, the physicochemical properties of cellulose capsules have never been studied or compared. Differences in these surface properties are likely responsible for the differences in findings. Many issues remain to be resolved for cellulose-based capsules, with minimal optimism for clinical application in the near future.

4.5. Collagen

Collagen matrices are preferred for anchorage-dependent cell types, such as stem cells [64], hepatocytes [206], and fibroblasts [207,208]. Collagen (Fig. 9) is regarded as one of the most versatile polymers for cell encapsulation. Collagen hydrogels can be prepared in a number of different geometries, including strips, sheets, sponges, and beads [209].

Collagen has a high content of glycerin residues (33%) [210]. To date, 29 types of collagens have been identified and described [211]. Collagen can be found throughout the body [209,212], with five dominant types of collagen in the human body. However, over 90% are type I collagen. Of all types, collagen type I is the most commonly applied encapsulation polymer. This is because of its abundance. It also provokes minor humoral responses, and potential allergic reactions can be prescreened [213].

The application of collagen as the major constituent in the capsule matrix is limited because of its weak mechanical properties, short-term stability, and difficulty controlling its permeability [209]. Collagen undergoes very rapid enzymatic degradation [209]. To increase durability, collagen-based microcapsules have been produced with an inner core of collagen and an outer shell of a tetrapolymer of 2-hydroxyethyl methylacrylate (HEMA), methacrylic acid (MAA), and methyl methacrylate (MMA) [206,214]. In this process, the cell suspension is mixed with the collagen at 4 °C to prevent gelation of the collagen solution. The negatively charged tetrapolymer molecules are then added to the outer surface of the microcapsules to form a polyelectrolyte complex. The microcapsules are incubated at 37 °C for 1 h to allow the collagen to gel before the microcapsules are harvested by sedimentation methodologies [158]. This system is applied to enhance cell survival and function [21,215].

Encapsulated allogeneic islets in collagen type I reportedly show no fibrous tissue 3 months after implantation [216]. However, because the stability has a limited duration, collagen capsules require crosslinking with other polymers for long-term biomedical applications [217]. Glutaraldehyde (GA) is the most widely used crosslinker but unfortunately is associated with an inflammatory response and therefore inadequate biotolerability [218]. More research is required to determine whether collagen type I is an adequate, biotolerable matrix for cell encapsulation.

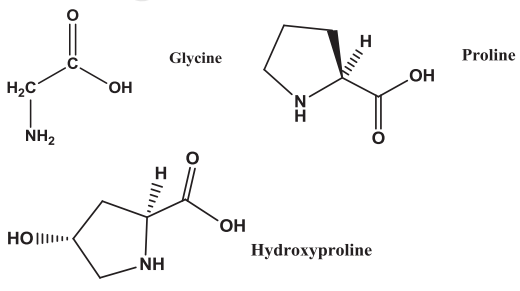

Fig. 9. Collagen is a family of molecules that are available in at least 29 types. A characteristic is that it has a high content of glycine, proline, and hydroxyprolin.

4.6. Xanthan

Xanthan is usually applied for drug delivery applications [219], but it has also recently been introduced for the encapsulation of chondrocytes [220]. Xanthan is a natural polysaccharide derived from the bacterial coating of the bacterium *Xanthomonas campestris*. It is commercially produced by *X. campestris* during the fermentation of glucose or sucrose. Its main chain (Fig. 10) consists of (1 → 4)-β-D-glucose units with a terminal β-D-mannose, β-D-glucuronic acid, and β-D-mannose side chain that has β-D-(1 → 2) and D-(1 → 4) linkages [221,222].

In microencapsulation procedures applied for chondrocytes [220], a cell suspension mixed with aqueous carboxymethyl xanthan (CMX) solution was collected in a crosslinker solution that contained 1.5% $CaCl_2$. To provide immunoprotection and reinforce stability, the beads were coated with poly-L-lysine. After the procedure, the chondrocyte-containing microcapsules were 500 μm in diameter and had a homogenous size distribution [220].

Xanthan has numerous advantages because it is insensitive to a broad range of temperatures, pH, and electrolytes [223]. This might be beneficial for in vivo application because biomaterials should be able to withstand changes in the microenvironment at the implantation site [123,223]. These changes, such as a drop in pH or protein adsorption [124,224], may induce undesirable changes in the surface properties and cause biointolerability [124,224]. However, many more studies that use different cell types should be performed to qualify xanthan as a preferred biomaterial for cell encapsulation and immunoprotection.

5. Synthetic polymers

Synthetic polymers offer several advantages over natural polymers. They can be more readily synthesized in large quantities than most natural polymers. They do not suffer from batch-to-batch variations like natural polymers, and they can be more easily engineered for desired properties. Synthetic polymers can be tailor-made to improve biotolerability or reinforce mechanical properties [225]. However, few synthetic polymers achieve the criteria for optimal compatibility with enveloped cells. Many synthetic polymers are associated with encapsulation procedures that require the application of toxic solvents [226,227]. This implies a loss of viability or loss of cell function. This is especially an obstacle in applications where scarce cadaveric tissue is required, such as in the application of encapsulation of pancreatic islets, hepatocytes, or kidney cells for the treatment of various diseases. In most cases, therefore, synthetic polymers are applied in combination with macrocapsules as macrodevices prepared in the absence of the cells. Just before implantation, the cells are brought into the already manufactured device in the absence of any toxic solvent.

5.1. Poly(ethylene glycol)

Poly(ethylene glycol) (Fig. 11) is a polyether composed of repeating ethylene glycol units. It is an inert biomaterial used for the encapsulation of a broad range of cell types, such as pancreatic islets [228,229], chondrocytes [230], osteoblasts [231], and mesenchymal stem cells [232].

Poly(ethylene glycol) is produced by the interaction between ethylene oxide and water, ethylene glycol, or ethylene glycol oligomers. The reaction is catalyzed by acidic or basic catalysts [233]. When PEG macromeres are terminated with methacrylate or acrylate groups, they undergo rapid crosslinking upon exposure to ultraviolet or visible light in the presence of appropriate photoinitiators. Photoinitiators create free radicals that can initiate polymerization [234,235]. Poly(ethylene glycol) acrylate derivatives and PEG methacrylate derivatives are used to form photopolymerizable hydrogels.

Poly(ethylene glycol) is one of the few synthetic polymers that allow application in both microencapsulation and macroencapsulation because it is not associated with the use of harsh solvents. Many

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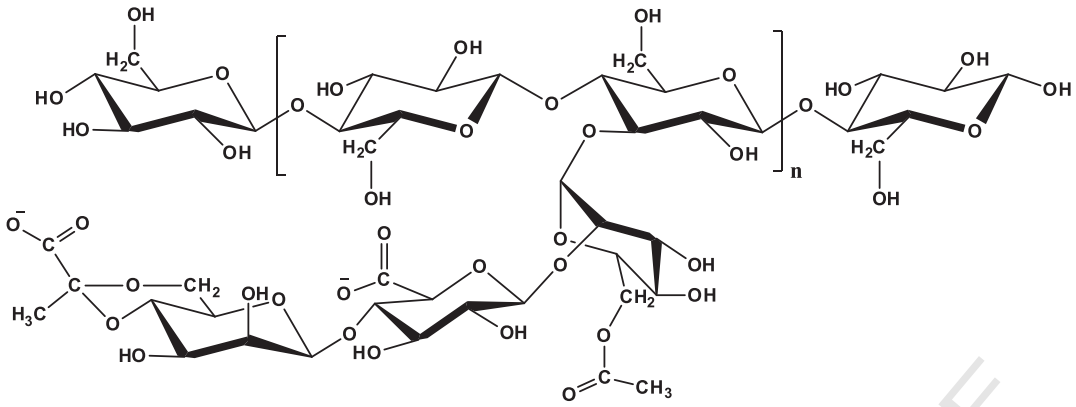

Fig. 10. Xanthan consists of (1 → 4)-β-D-glucose units with a terminal β-D-mannose, β-D-glucuronic acid, and β-D-mannose side chain that has β-D-(1 → 2) and D-(1 → 4) linkages.

different encapsulation procedures have been applied in the past two decades. Cells have been encapsulated in microcapsules by applying the photopolymerization of PEG diacrylate prepolymers. This approach applies PEG macromeres that are terminated with methacrylate or acrylate groups. These groups undergo rapid crosslinking upon exposure to ultraviolet light or in the presence of appropriate photoinitiators [234,235]. Cruise et al. [229] was the first to show that these capsules can provide immunoprotection but suffer from another, unrelated issue. The pores of the capsules were too small to allow adequate nutrition [236]. This problem could partially be solved by decreasing the thickness of the capsule wall [236]. Many successful studies have been published with PEG since then [231,237,238], but one issue has surprisingly gained only minor attention. As outlined above, photopolymerization is associated with the generation of free radicals and consequently cell damage and loss of function [239]. This has been published for other types of polymers [234] but has been the subject of only a few PEG studies [239]. Remaining to be determined is the consequence of this free radical formation for the longevity of encapsulated cells and their function.

Cellesi et al. [240,241] introduced a different concept for the formation of PEG-based capsules. A gelation process was presented, based on a combination of physical and chemical crosslinking. They designed a procedure in which the functional PEG-blpoly(propylene glycol)-bl-PEG (PEGPPG-PEG) was first thermally gelled and subsequently covalently crosslinked by the reaction of polymer end groups [240,241]. The encapsulation process was performed under physiological conditions.

Poly(ethylene glycol) hydrogels have some advantages over other synthetic molecules that form hydrogels. They have a high water content and a short diffusion time scale. Furthermore, PEG molecules can be easily coupled to functional peptides and mimic aspects of the extracellular matrix to support the survival and function of encapsulated cells [242,243]. Another advantage is the low protein adsorption on PEG surfaces. However, this depends on the molecular weight of the applied PEG chains. Protein adsorption is minimal with PEG at a degree of polymerization (DP) above 100 [244]. The decrease in protein adsorption is attributable to the osmotic pressure and elastic restoring forces generated by the PEG chains that are not compatible with interactions with protein molecules [245]. Thus, large PEG molecules are beneficial for diffusion characteristics and biotolerability.

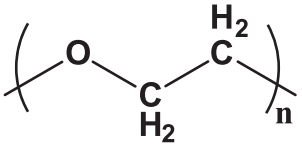

Fig. 11. Poly(ethylene glycol) is a polyether composed of repeating ethylene glycol units.

Despite these beneficial properties, many reports have described deleterious immune responses against PEG-encapsulated cells, suggesting that PEG networks cannot prevent the entry of cytotoxic molecules into the capsules [246]. Applying other strategies may solve this lack of immunoprotection. Some researchers have engineered the capsules by modifying the PEG capsule surfaces with immune cell receptors, such as Fas Ligand (FasL) [247] and tumor necrosis factor receptor 1 (TNFR1) or WP9QY [235].

5.2. Polyvinyl alcohol

Polyvinyl alcohol (PVA) is a water-soluble thermoplastic polymer. It has been applied for the encapsulation of genetically engineered cells that secrete neurotransmitters [157,248] and neurotrophic factors for the treatment of Alzheimer's disease [157,249], Huntington's disease [157,249], and Parkinson's disease [250]. It has also been applied for the macroencapsulation of pancreatic islets for the treatment of diabetes [251] and pituitary disorders [252].

Polyvinyl alcohol is commercially produced from polyvinyl acetate, in which the vinyl acetate groups are hydrolyzed to the vinyl alcohol group (Fig. 12). Polyvinyl alcohol is slightly soluble in ethanol but insoluble in other organic solvents. As a thermoplastic polymer, it can be converted to different structures by freeze-thawing processes. The gelation of PVA is performed through repeated freeze/thaw cycles [253,254]. Some have applied this procedure to a mixture of cells and PVA [254]. The cells were protected during freezing with cryoprotectants, such as glycerol. Obviously, this is associated with a loss of the functional survival of the cells. Its processing into capsules is not compatible with the simultaneous presence of cells. Therefore, it is mainly applied for macrocapsules [255,256].

The most commonly applied co-polymer of PVA for macroencapsulation is polyacrylonitrile and polyvinyl chloride (PAN-PVC). It is typically composed of 40–60% monomer of PAN-PVC with an average molecular weight of 30,000–200,000 g/mol [257]. An XM-50 hollow fiber with a nominal molecular weight of 50,000 g/mol is the most frequently applied type of PAN-PVC. Its application dates back to 1977

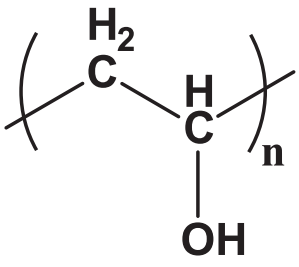

Fig. 12. Polyvinyl alcohol is produced from polyvinyl acetate, in which the vinyl acetate groups are hydrolyzed to the vinyl alcohol group.

when it was applied by Chick et al. [258] for the encapsulation of islets of Langerhans. PAN-PVC macrocapsules have been applied as extravascular [259] and intravascular [260] devices.

An obstacle in the application of PVA is its low hydrophilicity. This makes PVA-based capsules susceptible to cell adhesion in vivo. This cell adhesion interferes with adequate nutrition for the immunoprotected tissue. To solve this issue, Mathews et al. [261] applied chitosan-based composite systems. Although this increased the hydrophilicity of the surface, the composites and gels that formed exhibited stability issues [254]. Therefore, additional crosslinking steps may be required to prolong stability [254].

Polyvinyl alcohol itself is not beneficial for enveloped cells because they cannot easily adhere to the inside part of the capsules [262]. Therefore, a natural polysaccharide (e.g., alginate or chitosan) is used as a supportive matrix for the enveloped cells [160]. As mentioned above, the surface of PVA-based capsules can provoke a chronic inflammatory response [263], with the consequent death of immunoprotected cells. Many efforts have been made to increase biotolerability by coating the surface with alginate or PEG [264] or modifying the number of PAN units in the device [265]. Although this has brought some improvement [265], it has not avoided another pertinent issue that occurs in vivo. The permeability of PAN-PVC decreases after long-term in vivo application [266]. This interferes with the functional survival of the cells. Shoichet modified PAN-PVC by grafting poly(ethylene oxide) (PEO) to the surface, which resulted in a 40% decrease in protein adsorption to the membrane [267] but unfortunately could not avoid strong fibrotic responses against the grafts [268]. Some have applied incubation in 70% ethanol to increase permeability and facilitate solute diffusion. Although promising [268,269], the number of reports on successful application in the past decade is limited.

5.3. Polyurethane

Polyurethane (PU) is an elastomer polymer (Fig. 13) with widespread biomedical applications. It is commonly applied in vascular grafts and artificial hearts. It is applied in macrocapsules in the geometry of hollow fibers and used for the encapsulation of pancreatic islets [270], pituitary tissue [271], and PC12 cells [272]. Polyurethane is mainly produced by a covalent reaction between polyol, typically a polypropylene glycol or polyester polyol, and diisocyanate in the presence of catalysts [273].

To facilitate cell growth in PU hollow fibers, the cell suspension is usually embedded in a matrix of collagen or alginate and subsequently injected into the hollow fibers [76]. The advantage of using polyurethane membranes instead of PAN-PVC is the thin wall thickness, which improves oxygen and nutrient transport [270]. A pitfall of using PU, however, is its biodegradability [76]. After implantation, this may lead to inadequacies at the capsule surface with consequently complete degradation of the membrane and failure of the graft. To overcome this problem, PU has been mixed with hydrophilic or hydrophobic polymers, such as polydimethyl siloxane (PDMS) [274].

Although PU membranes show beneficial blood and tissue compatibility in vascular prostheses, blood filters, catheters, pacemaker insulators, heart valves, and artificial organs, its biocompatibility or biotolerability as an immunoisolation barrier is still a subject of debate [275,276]. Because of its hydrophobic nature, PU macrocapsules can trigger a host response [277]. An approach to overcoming this problem is treating the surface of the PU membrane with hydrophilic

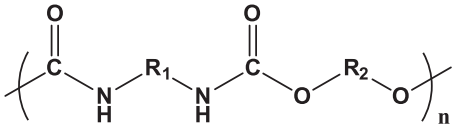

Fig. 13. Polyurethane is formed by a covalent reaction between polyol, typically a polypropylene glycol or polyester polyol, and diisocyanate in the presence of catalysts.

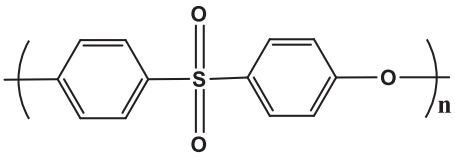

Fig. 14. Poly(ether-sulfone) fibers are formed by the polymerization of dichlorodiphenyl sulfone with dihydroxydiphenyl sulfone in the presence of sodium carbonate.

reagents, such as Tween 80 [278]. This method increases the hydrophilicity of the PU membranes and decreases its surface energy. This is associated with a reduction of the severity of the host response, but it is still associated with failure of the enveloped tissue [276].

5.4. Poly(ether sulfone)

Poly(ether-sulfone) (PES; Fig. 14) is a thermoplastic polymer that is predominately applied for cell macroencapsulation in the form of hollow fibers. Poly(ether-sulfone) hollow fibers have been used for pancreatic islets [279], myoblasts [280], and fibroblasts [281]. The fibers are formed by the polymerization of dichlorodiphenyl sulfone with dihydroxydiphenyl sulfone in the presence of sodium carbonate [282]. The cells are mixed with a matrix of collagen or alginate to facilitate functional survival, after which it is injected in PES hollow fibers. The fiber is usually sealed at both ends by photopolymerized acrylic glue.

The rough, open porous outer surface of the polysulfone capillary has been shown to provide a suitable area for vascular tissue formation, which may be beneficial for the function of cells after transplantation [283]. The hydroxy methylation (CH_2OH) of polysulfone capillaries has also been reported to support vascular ingrowth and consequently enhance the secretory behavior of macroencapsulated cells [284,285]. The main disadvantage of PES hollow fibers, however, is the limited viability of the encapsulated cells because of an insufficient nutrient supply, especially in the center of the macrocapsules [286].

Poly(ether-sulfone) as a membrane in dialysis therapy shows acceptable biotolerability with blood [282]. However, as an extravascular immunoprotection device, it must meet other biotolerability requirements. It should be more hydrophilic because its current hydrophobicity is associated with a high risk of protein adsorption after prolonged periods of implantation [287]. Blending hydrophilizing additives, such as polyvinylpyrrolidone (PVP), or coating with silane is a conceivable approach for increasing PES membrane biotolerability [287]. These methods have not yet been used for cell encapsulation.

5.5. Polypropylene

Polypropylene (PP; Fig. 15) is a thermoplastic polymer. It has been applied for the macroencapsulation of hepatocytes [288,289], OKT3 cells for secreting monoclonal antibodies [290], human parathyroid cells [23], and WEHI-3B mouse cell lines that produce IL-3 [290]. Polypropylene is synthesized through the polymerization of propylene in the presence of a Ziegler–Natta catalyst [291]. Also with PP, the adherence of cells to the polymeric membrane is an issue, and the

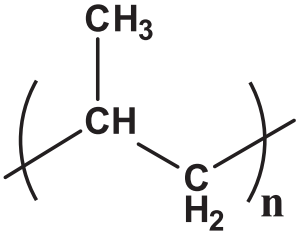

Fig. 15. Polypropylene is synthesized through the polymerization of propylene in the presence of a Ziegler–Natta catalyst.

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cells, therefore, are embedded in collagen or alginate before they are brought into the macrocapsule [290].

Because of the strong host responses against PP, the application of PP for immunoisolation is not without problems [292]. The presence of macrophages, fibroblasts, and lymphocytes was observed on the surface of empty PP hollow fibers 4 months after implantation under the skin in mice [292]. Like other synthetic membranes, minimizing surface free energy by coating PP membranes with hydrophilic agents may increase its biotolerability [287]. Siliconization has been reported to improve the in vivo biotolerability of empty PP membranes [293]. However, the long-term survival of allo- and xenografts in PP hollow fibers has not been reported to date.

5.6. Sodium polystyrene sulfate

Sodium polystyrene sulfate (PSS) is the sodium salt of polystyrene sulfonic acid. The polymer is a polystyrene, a thermoplastic polymer [294]. Sodium polystyrene sulfate has the advantage that it is readily soluble in water (Fig. 16). It has been used for the encapsulation of pancreatic islets [153,154] and red blood cells [295,296].

Sodium polystyrene sulfate has been used in combination with the natural polymer agarose. As an anionic polymer, it is also applied in a layer-by-layer technique in combination with neutralizing cationic polymers, such as poly(allylamine hydrochloride) (PAH) or poly (diallyldimethylammonium chloride) (PDADMAC) [297]. In this approach, immunoprotective and biocompatible layers are formed by alternating the adsorption of oppositely charged polymers onto a charged surface [298] (Fig. 17). Although comprehensive, the technology must overcome one large obstacle before application can be considered: it suffers from mechanical instability issues. Sodium polystyrene sulfate/PAH layers cannot withstand the shear forces during and after transplantation [299].

Biotolerability is also an issue. Sodium polystyrene sulfate evokes an undesired complement-activating effect [300]. Therefore, it can unlikely compete with other polymers applied for encapsulation.

5.7. Polyacrylate

Polyacrylate is a large family of thermoplastic polymers. The most commonly applied polyacrylates for cell encapsulation are poly(hydroxyethyl methacrylate) (PHEMA) (Fig. 14) and hydroxyethyl methylacrylate–methyl methacrylate (HEMA–MMA) (Fig. 18) [301,302]. Water-insoluble polyacrylates have been applied for the microencapsulation of hepatocytes [303], fibroblasts [304], PC12 cells [305], human hepatoma cells [8], hybridoma cells [306], and pancreatic islets [307]. In macroencapsulation approaches, PHEMA has been applied for the encapsulation of insulin-producing pancreatic islet cells [308], but it has not yet entered in vivo applications.

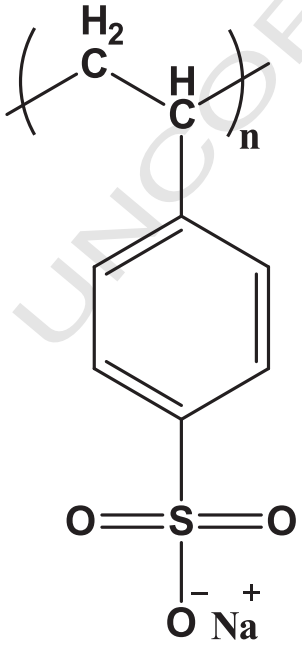

Fig. 16. Sodium polystyrene sulfate is the sodium salt of polystyrene sulfonic acid.

Poly(hydroxyethyl methacrylate) is synthesized by crosslinking HEMA using ultraviolet radiation [264,309]. In this process, polyethylene glycol dimethacrylate is applied as the crosslinking agent, and benzoin isobutyl ether (BIE) is applied as the ultraviolet-sensitive initiator [264,309]. A copolymer of HEMA–MMA is usually prepared by solution copolymerization using azobisisobutyronitrile as the initiator and applying polyethylene glycol as a solvent [303].

A copolymer of HEMA and MMA was synthesized to obtain a polyacrylate that combines optimal biocompatibility and adequate permeability [310]. Capsules made from these polyacrylates can be tailor-made for desired geometries and physicochemical properties using different acrylate monomers. Despite this potential advantage, most capsule types prepared from polyacrylates have shown low membrane permeability for water-soluble nutrients [302]. The permeability of polyacrylate capsules can also vary significantly from capsule to capsule, despite application of the same acrylates [311]. The reasons for this are still largely unknown, but the heterogeneity of polymer distribution in the capsule is probably involved. Another issue associated with HEMA-based capsules is that HEMA does not allow for the adherence of cells in the intracapsular core. For some cell types, this implies interference with the normal capacity to proliferate [302]. This is usually solved by co-encapsulation of a matrix in the core of the capsule. Agarose [302] and chitosan [160] matrices have been applied for this purpose. In addition to this intracapsular adhesion issue, maintaining cell viability in the presence of the mandatory organic solvents during the microencapsulation process also threatens the long-term functional survival of the cells [312].

Poly(hydroxyethyl methacrylate) membranes have some advantages over other polyacrylates. It does not suffer from protein adsorption and consequently cell adhesion [313]. However, it suffers from low mechanical stability. To overcome this issue, mixing PHEMA with natural polymers, such as collagen [313] and synthetic polymers [314], has been proposed. Although these studies showed some degrees of success, for unknown reasons, PHEMA has not received much attention from the scientific community in the last 5 years.

Although a wide variety of mammalian cells can be encapsulated in HEMA–MMA or other polyacrylates, a considerable gap exists between their performance in vitro and in vivo. This is probably attributable to biotolerability issues. On the surface of implanted HEMA–MMA capsules, deposits of fibrinogen, IgG, fibronectin, and components of the complement system were found [312,315,316]. Allo- and xenotransplantation of microencapsulated hepatoma cells in HEMA–MMA cause severe host responses that lead to failure of the graft within 7 days of implantation in rats [316]. The presence of ethylene glycol dimethacrylate (EGDMA) has been suggested because contamination in HEMA monomer solutions can be the cause of this biotolerability issue [317]. No reports have suggested a solution for this issue.

5.8. AN69

AN69 has wide applications in medical devices, such as hemofilters and hemodialysis membranes [318]. It has also been used for the encapsulation of pancreatic islets [319] and hepatocytes [320]. AN69 or poly(acrylonitrile-sodium methallylsulfonate) (Fig. 19) is produced by the co-polymerization of acrylonitrile and methallylsulfonate. AN69 is applied for the production of macrocapsules.

The AN69 hollow fiber is formed in a coagulation step at room temperature, followed by a solvent/non-solvent/polymer exchange phase.

Please cite this article as: P. de Vos, et al., Polymers in cell encapsulation from an enveloped cell perspective, Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.11.005

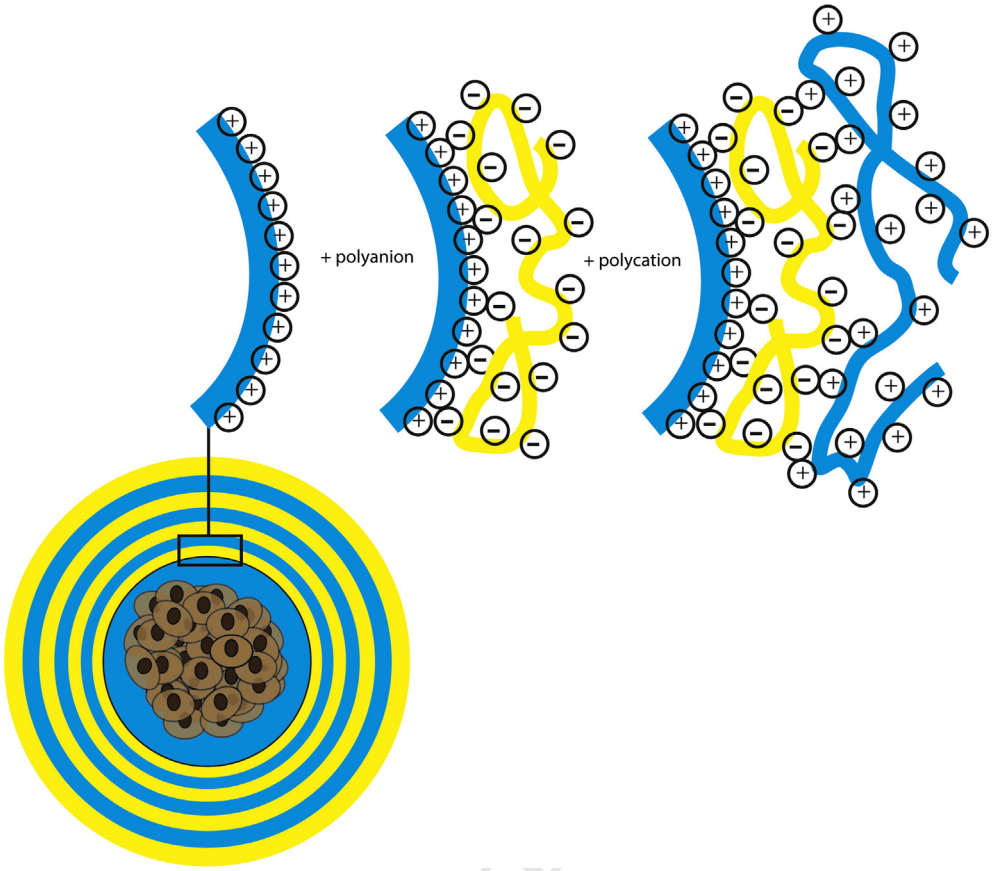

Fig. 17. The principle of the layer-by-layer technique for forming capsules. The alternate adsorption of oppositely charged polymers onto a charged surface can result in capsules with multiple layers.

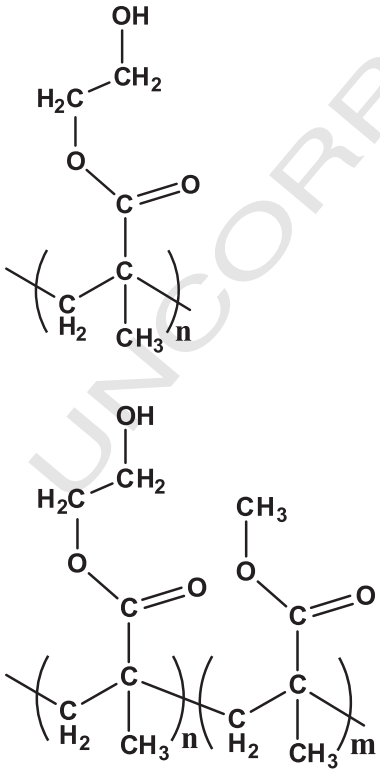

Fig. 18. The polyacrylates applied in cell immunoprotection are poly(hydroxyethyl methacrylate) (top) and hydroxyethyl methylacrylate–methyl methacrylate (bottom).

The solvent is dimethylsulfoxide, the non-solvent is saline solution, and the polymer is AN69 [321].

Because of its favorable characteristics for immunoisolation, some researchers prefer the application of AN69. The membranes have a defined molecular cutoff of 65 kDa, adequate hydraulic permeability, and some beneficial hemocompatibility features [322]. The initial success of AN69, however, was limited by extreme protein adsorption in vivo with consequences for its permeability properties after implantation [323]. Applying vascular endothelial growth factor as a supplement for cell survival and the promotion of vascularization of the surface of the device increased the in vivo viability and functionality of encapsulated cells [324].

Prevost et al. evaluated the biotolerability of an AN69 hydrogel by transplanting and comparing the efficacy of encapsulated islets in curing diabetes in rats [321]. The biotolerability of AN69 was reportedly adequate because host reactions to syngeneic implants of pancreatic islets were minor and composed of a thin layer of fibroblasts [325]. Surprisingly, however, neither glycemia nor diuresis completely returned

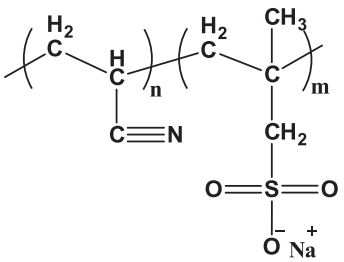

Fig. 19. Poly(acrylonitrile-sodium methallylsulfonate) or AN69 is a co-polymer of acrylonitrile and methallylsulfonate.

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to normal levels, suggesting that the macrocapsules were incompatible with long-term survival [321]. Subsequent studies showed that the assumed minimal response could not be neglected because macrophages from the surface of the device produced IL-1β that passed the membrane and decreased cell functionality [326]. This problem was solved by incorporating physicochemical modifications of the membrane. The surface of AN69 macrocapsules was made more hydrophobic by corona discharge [319,327]. This increased biotolerability and promoted the diffusion of insulin through the membrane [319,327]. Despite these technical advances, no follow-up studies have been performed in the past decade.

6. Concluding remarks and future considerations

Many new polymers have been introduced for cell encapsulation in the past decades. All of these polymers have been introduced to overcome the obstacle of other polymers, such as a lack of sufficient biotolerability in the host [328,325], undesired loss of the enveloped cells, an inability to achieve appropriate mechanical stability in vivo, and too low permeability that interferes with cell survival [329]. A major pitfall has been that none of these new polymers have been well characterized in the application of cell transplantation and that investigations of applicability have mostly resulted in descriptions of new challenges that must be overcome to apply the polymer for cell encapsulation. Alginate is the only polymer for which large numbers of researchers have chosen to identify the factors that determine the success or failure of encapsulated cellular grafts [329].

Alginate as a polymer has been well-characterized. Its composition and sequential characteristics have been studied in depth [330,331]. Its composition and sequential structure have been shown to vary and have a pertinent effect on the properties of capsules. A seemingly minor elevation of 10% in guluronic acid content results in capsules that are far stronger, are more mechanically stable [123], and exhibit a reduction of cell protrusion [332] because of a profound decrease in swelling of the gels during capsule formation. This illustrates the relationship between the chemical structure of the polymer and its functional importance in capsule formation. This has not yet been addressed for other polymers.

Studies with alginate have demonstrated that numerous characteristics should be documented to make sound interpretations of the results and compare immunoprotecting systems. The first is the molecular weight of the polymer. The polymer's molecular weight determines the viscosity and rheological properties of the polymer solution. These parameters are not documented in the vast majority of the reviewed papers but determine the quality and mechanical strength of the final capsule [333]. Another issue is contamination in the polymer solution. Endotoxins are devastating to biotolerability [44,334,335]. Only studies of alginate have reported the purity of the polymer solution [72]. This interferes with interpretations of the data and immune responses to the polymers, in which the results may be confused with responses to contamination in the polymers. Much attention has also been focused on the influence of lipopolysaccharide (LPS) as the principal endotoxin responsible for inflammatory responses [336]. A recent study from our own group revealed that alginate applied for encapsulation research does not contain LPS. We found that other PAMPs in alginate can be classified as endotoxins. We found various PAMPs, including peptidoglycan, lipoteichoic acid, and flagellin, which are all highly potent inflammatory molecules. Special steps are required to remove these molecules. Currently unknown are whether other polymers proposed for encapsulation contain similar contaminants and whether this contributes to the observed biotolerability. Based on experience with alginate, we feel that the presence and identity of contaminants in the polymers is a pertinent parameter that should be documented in every report of encapsulation research. As long as these parameters are not reported, it is difficult if not impossible to select adequate polymers for cellular immunoprotection.

Moreover, the permeability of the devices is only rarely reported [72]. This is rather surprising because the devices are being applied as a barrier for the immune system and should at least not allow for the entry of cytotoxic molecules above 160 kDa [72]. Based on our review of the literature, we conclude that the best documented and studied polymer is alginate and thus presently has the highest chance of success in clinical application [72]. Nonetheless, this conclusion does not indicate that alginate is the most adequate polymer. The field needs a more systematic approach to characterizing the properties of the applied polymers to allow for sound interpretations of the results and further innovation.

Acknowledgments

PdV is grateful for financial support from the Dutch Diabetes Foundation and Juvenile Diabetes Research Foundation.

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Please cite this article as: P. de Vos, et al., Polymers in cell encapsulation from an enveloped cell perspective, Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.11.005

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Please cite this article as: P. de Vos, et al., Polymers in cell encapsulation from an enveloped cell perspective, Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.11.005

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Please cite this article as: P. de Vos, et al., Polymers in cell encapsulation from an enveloped cell perspective, Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.11.005

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Please cite this article as: P. de Vos, et al., Polymers in cell encapsulation from an enveloped cell perspective, Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.11.005

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Please cite this article as: P. de Vos, et al., Polymers in cell encapsulation from an enveloped cell perspective, Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.11.005

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Please cite this article as: P. de Vos, et al., Polymers in cell encapsulation from an enveloped cell perspective, Adv. Drug Deliv. Rev. (2013), http://dx.doi.org/10.1016/j.addr.2013.11.005