Types of microencapsulation pdf

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Spherical microparticles containing an antineoplastic agent to avoid its systemic toxicity. Coating of powdery solid products or liquids with a film of polymeric or fatty material giving rise to free-flow particles of micron size. The substances to be encapsulated may be in the solid or liquid state. As a coating material different types of polymers can be used: natural (as alginate and chitosan), semisynthetic (as cellulose derivatives) or synthetic (aliphatic polyesters, polyorthoesters, polyalkylcyanoacrylates ...). These polymeric materials may be biodegradable (by the action of environmental agents or by enzymes or body fluids) or non-biodegradable (which may lead to systems with high persistence). Fatty substances with different melting points can also be used. Two types of structures can be obtained: reservoir type, in which the encapsulated substance, in the form of micrometric particles or liquid droplets is surrounded by the coating material forming an insulating cover from the outside; Or matrix type, wherein the encapsulated substance is dispersed, in the form of micrometric particles or at the molecular state, in a matrix of the coating material. The encapsulated substance may be released from the microparticles by degradation or melting of the coating, by mechanical rupture of the system or by slow diffusion through the structure. By suitable selection of the type of coating material and the structure of the microcapsules the rate of release of the encapsulated substance or the conditions under which it is produced can be modulated. The micrometric size of the systems together with their versatility in terms of the release conditions of the encapsulated substance make microencapsulation a technology with numerous applications in different areas, such as drug development, cosmetics, food technology, plant protection area, biocides... Application on skin of a microencapsulated cosmetic product. There are different microencapsulation methods. The selection depends on: The characteristics of the material to be encapsulated: if it is a solid or a liquid; its stability in different solvents; its stability against high temperatures, its chemical compatibility with the coating material. The coating material used: its selection directly depends on the objective of the microencapsulation (see section “advantages”). Not all the coating materials can be applied by using any microencapsulation method. The equipment available: the methods based on the formation of emulsions only need thermostatic containers provided of an agitation system, whereas the mechanical methods need more specific equipment (special centrifuges, extrusion nozzles, spray driers, fluid beds). Essentially, the microencapsulation is based on the deposit of the coating material, in liquid state (due to its fusion or dissolution in a solvent), on the material to be encapsulated, which is dispersed as small particles (in case of a solid) o droplets (in case of a liquid) in an appropriated medium (liquid or gas). In a later step, the solidification of the coating is produced and microparticles are obtained. These microparticles will be collected, washed and conditioned in a different way depending on their application. Among the works carried out with this technology are: Microencapsulation of sodium butyrate by a variant of the solvent evaporation technique based on the formation of non-aqueous emulsions and using polymers of pH-dependent solubility in order to achieve a delayed release of the active substance at the intestine level after its oral administration. Microencapsulation of perfumes, using the complex coacervation technique with gelatin and gum arabic as polymers; for their application in adhesive strips which release the perfume after breaking the microcapsules. Microencapsulation of oils, using the complex coacervation technique with gelatin-gum arabic as polymers; and by the spray drying technique using different coating materials. The purpose of microencapsulation is to protect the active against oxidation, to avoid its unpleasant smell and taste and to transform it into a free-flowing powder product, easy to incorporate into different processed products. Microencapsulation of insecticides by means of the interfacial polymerization technique, obtaining a non-biodegradable polyurea coating that prevents the toxicity of the insecticide on mammals, birds and fish in an accidental ingestion or contact, by which the insects break with their jaws and ingest the insecticide. Microencapsulation of naloxone, by the technique of evaporation-solvent extraction using biodegradable polymers of the group of aliphatic polyesters. Matrix-type systems are available for subcutaneous administration, and release the active substance over time, resulting in an alternative to improve compliance in patients undergoing opiate withdrawal. Microencapsulation of dexamethasone, by means of the evaporation-solvent extraction technique using biodegradable polymers of the group of aliphatic polyesters; and by the spray drying technique using lipid coatings. Different types of parenteral administration systems are obtained in which the effect of glucocorticoid is prolonged and potentiated because of the increase of their interaction and internalization into cells. Microencapsulation of proteins by means of the evaporation-solvent extraction technique based on the formation of multiple emulsions and using biodegradable polymers of the group of aliphatic polyesters. When the systems are administered parenterally, a prolonged release of the active is achieved, avoiding its exposure to the tissue proteases that cause its degradation. Microencapsulation of cannabinoids by means of the evaporation-solvent extraction technique and using biodegradable polymers of the group of aliphatic polyesters. A free flow product is obtained, which solves the manipulation and dosing problems associated with the high lipophilicity of these compounds; providing prolonged release of the active substances for 2-4 weeks after subcutaneous administration, with a bioavailability significantly higher than those present orally or sublingually. Microcapsules with an insecticide inside. There are numerous reasons why it may be interesting to microencapsulate a drug. Some of them are: To avoid loss of volatile compounds (flavors in feeding, perfumes in cosmetic, drugs in pharmacy..), to mix incompatible compounds, to avoid degradation of the products due to environmental agents (in agriculture, pharmacy, cosmetic...), to prevent the irritant effect of certain drug substances when they are administered, to increase the duration of the effect of the drug substances due to a slow release after their administration. Where has it been developed This technique has been developed in the University Institute of Industrial Pharmacy, located in the Faculty of Pharmacy. The Institute has all the necessary equipment to apply most of the microencapsulation techniques: reacting tanks, blade stirrers, propellers and turbines, homogenizers of different type, atomizer (Spray drier). Additional equipment for collection and conditioning of the resulting product (filtration equipment, centrifuges, drying cabinets, freeze drier), and for analysis and control thereof (HPLC, DSC, laser particle size analyzer, equipment for release studies, etc.) Microencapsulation of any type of materials. Advice on the advantages, technique and variables of the process Resolution of formulation problems. Analysis and control of microcapsules, including content release studies and stability studies Training of personnel: theoretical and practical teaching of the different techniques of microencapsulation. Microencapsulation has been the most frequently used technique for several different disciplines such as cell-based therapies and/or transplantation. Technology is based on the idea of combining and coating a material or isolating from an external source. Microencapsulation may be performed with different materials and, among natural biocompatible materials, alginate-based microencapsulation technique is the most appropriate material for microencapsulation. The structural components of alginate materials are the derivatives of alginic acid, which is found in brown algae as an intercellular gel matrix. This alginate is preferred for clinical applications due to its safety in human studies. Therefore, the choice and the combined system need to be carefully optimized to achieve biocompatible application through cell microencapsulation especially for long term. Specifications of alginate such as primary source, isolation process, viscosity, and purity contribute to improve its biocompatibility. Clinically, cell microencapsulation is the major contribution to the field of transplantation by its technique and additionally provides local immune isolation. This chapter discusses the potential benefits of clinically suitable alginates and their applications. This promising technology may highlight its considerable potential for patients that require transplantation and/or replacement therapy in the future.microencaspulationalginatecell therapydrug deliverytransplantationCell encapsulation is a process that involves immune protection of the living cell by using different polymers. The polymers can be distinguished into two main groups: natural origin (i.e., polysaccharides, polynucleotides, polypeptides) [1] and synthetic polymers (i.e., polyethylene glycol, polyvinyl alcohol, polyurethane, etc.). Several attempts have been made by scientists to use natural, synthetic, and semi-synthetic polymers in the field of encapsulation. The first approach was made in 1933 by Bisceglie et al. and used enveloped membrane to demonstrate tumor cell survival in the abdominal cavity of guinea pigs [2]. In his report, the cells survived for 12 days by diffusion of the nutrients. However, at that time immunoisolation technology was not known or understood [3]. Later, in 1943 Algire et al. reported a transparent chamber for atherapeutic approach in vivo[4]. Since this report, therapeutic demands enhanced this encapsulation technology in a way that combines the polymer source (produced synthetically or isolated from natural sources) and their functionality by using its characterization.Several advantages and disadvantages have been reported about synthetic polymers [5]. Mechanical specifications can be more easily engineered or modified with the desired characteristics and particularly can be produced with larger amounts [6, 7, 8]. The main deficit of synthetic polymers is that they require toxic substances during the capsulation process; therefore, cell viability is a true obstacle after encapsulation [8, 9]. In this regard, synthetic polymers are frequently used in combination with different devices such as macrocapsules. Before accommodation of the encapsules, first, synthetic polymers are manufactured in the absence of living tissue/cells, and second, tissue/cells are combined with the device to preserve direct contact of the toxic solvents [1]. The most common synthetic polymers are poly(ethylene glycol) [10], polyvinyl alcohol [11], polyurethane [12], poly(ether sulfone) [13], polypropylene [14], sodium polystyrene sulfate [15], polyacrylate [16], polyphosphazene [17], AN69 [18], and lastly polytetrafluoroethylene [19].Natural polymers have been proposed for immunoisolation based on two distinct features. First, there is no interference with the functionality of cells/tissues and second, the stability of the structure they provide during encapsulation [1, 20]. Conventionally, the most frequently used polymers from natural sources are cellulose [21], chitosan [22], collagen [23], agarose [24], and alginate [25]. The experimental success mainly depends on the application and mimicry potential of the natural polymers. Among these, in this chapter, we mainly focused on the alginate-based encapsulation and its clinical application.AdvertisementThe most versatile biomaterials among natural polymers are alginates, which are used in a wide range of applications including diffusion systems, drug delivery, as a wound dressing, and for encapsulation when the transplantation has to be a substitute [25, 26, 27]. Alginates are hydrophilic compounds that are naturally found in the cell wall, extracellular matrix of brown algae and some species of bacteria, for example, Pseudomonas aeruginosaand Azotobacter vinelandii[26, 27]. The most common algae source is brown seaweed. During alginate extraction, alginic acid is generally obtained and converted to a form of salt [26]. Several forms of alginates are currently approved by the Food and Drug Administration (FDA) for use, particularly in the replacement of missing/nonfunctioning endocrine-related diseases [28].Alginates are linear copolymers that include two hexuronic acid residues that become dimeric blocks, which are composed of -D-mannuronic (M) and -L-guluronic (G) acids for building the entire molecule [29]. These blocks are known as the building blocks of alginates. Mainly, the ratio of G and M blocks depends on the source of the algae type [9]. The important feature of these building blocks is the sensitivity to binding of multivalent cations. This is the starting point of this water-soluble polysaccharide, which allows alginate to form as hydrogels. This characteristic of the hydrogel equilibrates between the environment and the relatively physiologic internal environment [29]. The divalent cations and hydrogel feature depends on the divalent ion’s affinity to alginate. Several studies reported high-rate ion affinity results in a stronger gel structure. In order to decrease the ion binding strength, divalent cations should be chosen from the following order: Pb2+>Cu2+>Cd2+>Ba2+>Sr2+>Ca2+>Co2+>Ni2+>Zn2+>Mn2+ [1, 29, 30] (Figure 1). Controlling cation addition to maintain a porous alginate structure is a critical step.Representative image for the formation of egg-box ionic cross-links between guluronic acid-rich monomer units (box) and the divalent cations (eggs). Reprinted from Baumberger and Ronsin (2009) [31], an open access article distributed under the terms of the creative commons by attribution 4.0 (CC-BY 4.0).Successful formation of alginate spheres for delivery purposes requires suitable and selective methods. In 2006, Darrabie et al. identified gelling-cation stability by determining swelling, which contributes to colloid osmotic pressure. They suggested that Ca2+ is more hygroscopic and less prominent swelling occurs when compared with Ba2+ [32]. Protecting the conformational polymer blocks during preparation of the alginate gels for microencapsulation has been reported using different methods including conjugation of long alkyl chains [33] or dodecylamine [34], temperature (up to 60°C ± 1°C) [35, 36], emulsification by cationic agent [37], and ionotropic gelation of alginate layers [38], etc. Slow gelation utilizes the alginate solution in a more uniform structure in a gradual manner [35].In the latter case, Lee et al. reported a degree of cross-linking of the alginate can influence a low dose of drug entrapment and unsuitable pore sizes for transplantation. In addition, the efficiency of the microcapsule size or content was found irrelevant, although the preparation step of the water-soluble alginate itself appears to be responsible for the arrangement of the polymer blocks [37]. Cross-linking capacity of the alginates can be modifiable and flexible (Figure 2). There are more than 200 types of biocompatible alginates manufactured so far [25, 26]. Moreover, due to the different cross-linking degree of various alginate types, switch in homogenous distribution of the graft/drug during the encapsulation process may occur [36].Representative image of alginate gelation process by continued calcium cations. Reprinted from Dumitru et al. [39], an open access article distributed under the terms of the creative commons by attribution 4.0 (CC-BY 4.0).Both features of alginates promote several advantages over other polymers such as the stability of the building blocks (-G and/or/both -M repetitively); elasticity of the alginate hydrogel; surface roughness, which is related to elasticity as well, approximately 1% of the alginate can entrap a hundred times more water than its weight; and lastly permitting the ability of oxygen and nutrient permeation inside the spheres.Source-dependent impurities may have detrimental effects. Safe and effective delivery of the therapeutic graft/drug with the alginate carrier is frequently mentioned as biocompatible. This naturally derived product provides immunoprotection and most of the studies reported purity of its building block structure preventing a host response when transplanted. Therefore, this makes alginate the most common material for microencapsulation. Higher water-carrying capability of alginates has been shown to directly maintain diffusion and this shows immune-safe characteristics [3]. A decade ago, Kendall et al. focused on the various components of alginate blocks and compared their purity and sphere sizes depending on the cationic agent. They reported that higher purification of alginate prevents imperfections and size/shape properties would affect immunogenicity [40]. Several other reports also demonstrated that -G and -M blocks of the alginate gel need a balance whereas the distribution of these proportions indicates the biocompatibility of the purified alginate is influenced by its viscosity [41, 42, 43]. One of the most obvious results from the studies that explains the difference between the building block’s balance in alginate gels is higher -M blocks mainly stimulate and induce an immune response [41, 44, 45, 46].There are many immunogenic substances such as endotoxins, proteins, and polyphenols in natural polymers including alginates. Those molecules may diffuse the outer surface from the capsules and then induce an unwanted immune response against the capsules [3]. There are highly conserved molecular motifs that are present in nature and pathogens known as pathogen-associated molecular patterns (PAMPs). PAMPs provoke pattern recognition receptors (PRRs) to enhance inflammatory response [47]. The presence of PAMPs in natural products and alginate as well is not a direct threat; however, complement activation has been reported for encapsulated islets [48]. Therefore, complement activation has a more destructive effect than the inflammatory response; it may activate and produce large quantities of cytokines to induce a stronger response.Immunoprotective properties still require the exact characterization and preparation of the material to be used as a delivery agent. Despite giving most of the efforts to optimize the encapsulation process, the applicability of this technology has still resulted in an insufficient investigation of graft/drug delivery. In 2014, Rokstad et al. described the duration and the type of host responses and divided the whole process into three categories: acute inflammation, chronic inflammation, and the long-lasting granulation tissue phase [48]. Based on the publications from islet transplantation studies, it was reported that the granulation phase mainly refers to the “vascularized fibrous tissue containing a moderate epithelial histiocytic response” [49, 50, 51, 52]. Solely, it is important to observe these responses and that leads to the question: Why do alginate microencapsules contribute to these chain of events even when their purity, stability, and biocompatibility are comparable to most other polymers? Immunocompatibility of the alginate microencapsules should not be determined only by the features of alginate and its preparation process, but should also be evaluated for its protein absorption capability as well.A profound impact might be introduced with the biotolerability term. Biotolerability is a term for a strategy of making biocompatible encapsulations to induce none/minimal host response. A seemingly minimal cellular overgrowth for graft provides the free diffusion of nutrients, oxygen, and some therapeutic proteins, and controlled drug release from the microcapsules. We should emphasize that the alginate microspheres are not meant to prevent an immune response yet to protect the carrier against an immune response. Therefore, the biocompatibility term not clear enough to explain the biotolerability of the carrier system.The vascularization process of the microencapsules is another requirement to increase the survival of the transplanted graft. Sufficient vascularization may be achieved by improving the physical features of the spheres such as the size of the spheres or micropores and the amount/density of the graft/cells. The main argument against vascularization is hypoxia and oxidative stress whereby it develops inside the microspheres [53]. Insufficient oxygenation and nutrition occur particularly in the absence of ideal vascularization. A prerequisite is that the functional performance of the microencapsules often depends on the surface-to-volume ratio. This implies that free diffusion of nutrients and oxygen is necessary and this directly interferes with vascularization.The majority of researchers developed different strategies to allow a fast exchange of nutrition and demonstrated several boundaries to ensure a low or no inflammatory response while supplying oxygen-nutrients inside [29, 53]. Currently, the accepted limitations of the islet transplantation are defined with three main strategies: first, the cell-to-volume ratio should not exceed 10% even if a large number of cells are required to reach curative treatment. Second, microencapsules should be kept

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