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Review

Cell microcarriers and microcapsules of stimuli-responsive polymers

Amanda K. Andriola Silva Brun-Graeppi [a,b], Cyrille Richard [c,d,e,f], Michel Bessodes [c,d,e,f], Daniel Scherman [c,d,e,f], Otto-Wilhelm Merten [b,*]

[a] Université d'Évry Val d'Essonne, École doctorale des Génomes Aux Organismes, Boulevard François Mitterrand, F–91025 Evry cedex, France
[b] Genethon, 1 bis rue de l'Internationale, BP 60, F–91002 Evry cedex, France
[c] Unité de Pharmacologie Chimique et Génétique; CNRS, UMR 8151, F–75270 Paris cedex, France
[d] Inserm, U1022, F–75270 Paris cedex, France
[e] Université Paris Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, F–75270 Paris cedex, France
[f] ENSCP Chimie Paristech, F–75231 Paris cedex, France

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ABSTRACT

Cell microcarriers and microcapsules have presented a wide range of potential applications. This article overviews their role in biotechnology with focus on the progress accomplished using stimuli-responsive polymers. Key properties of cell microcarriers and microcapsules are identified, followed by a description of the chemistry and gel formation mechanism of some of the stimuli-responsive polymers used to design them. Production methods are introduced and characterization techniques for evaluating such microsystems are equally presented.

Contents

* Corresponding author. Tel.: +33 1 69 47 25 90; fax: +33 1 60 77 86 98.
E-mail address: omerten@genethon.fr (O.-W. Merten).
URL: http://www.genethon.fr (O.-W. Merten).

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1. Introduction

Most cells cannot grow in suspension and need to adhere to a solid extracellular matrix. Biomaterials can be used as scaffolds to provide three-dimensional templates and synthetic extracellular environments to mimic certain advantageous characteristics of the extracellular matrix (ECM) [1]. The ECM is the natural scaffold for cells, tissue and organ growth. Native ECM does far more than just provide a physical support for cells. It also represents a substrate with specific ligands for cell adhesion and migration, and regulates cellular proliferation and function by means of various growth factors. It is reasonable to expect that biomaterials should have a similar role. However, there is still a design challenge to fabricate biomaterials that mimic ECM structure with defined shape and complex porous architecture [2].

Polymeric particles are a promising attempt to achieve this goal. Such systems are small in size, typically less than 500 μm in diameter, and their surface area of up to 500 cm^2/g can enable the culture of a large amount of cells in small volumes [3]. Polymeric particles may be constituted from hydrogels in which the cells are kept in an aqueous medium, in contact with soft material similar to the ECM. Some of these hydrogels may respond to changes on their external environment, such as temperature and ion concentration [4,5]. These structural changes may be used to free the cell from their carrier for subsequent collect and/or replating. Examples of microparticles composed of such materials, also known as stimuli-responsive, will be outlined herein.

In fact, cells may grow as monolayers on the surface of the microparticles [6], these systems are considered as microcarriers. Alternatively, cells may be entrapped in the inner compartment, and such structures are regarded as microcapsules. For the latter, the encapsulation process physically isolates the cell mass from the outside environment and aims to maintain normal cellular physiology within a barrier of desired permeability [7]. A schematic representation of microcarriers and microcapsules is indicated in Fig. 1. Both approaches are discussed in this review.

The use of microparticles to culture mammalian cells has been practiced since the early 1950s [7]. Since then, it has been extensively used to expand anchorage-dependent cells in culture. Cytodex 1 is an example of a frequently used microbead system. Microparticles have made possible the practical high-yielding culture of such cells for the study of animal cell structure, function and differentiation and for the production of many important biological materials, such as vaccines, enzymes, hormones, antibodies, interferons and nucleic acids [6].

This principle was extrapolated to cell therapy research and tissue engineering. The increasing incidence of age-related diseases and the current shortage of donor organs raised the interest of using this technique as a therapeutic tool [8]. Some examples comprise the treatment of kidney failure [9], cardiovascular diseases [10,11], liver failure (by the delivery of encapasulated hepatocytes [12] or umbilical cord blood cells [13]) and diabetes mellitus (by the microencapsulation of islets of Langerhans [14–22]). Concerning microcapsule-type particles, the main goal of this approach is not only to develop a confined barrier to entrap living xenogeneic or allogeneic cells to be transplanted, but also to prohibit the entrance of the hosts' antibodies and immune cells. Encapsulated cells are expected to be capable of restricted interactions and remain physically segregated from the host. By this physical barrier, the implanted tissue can be masked from the immune surveillance at a local level [23]. Even though, short-term immunosuppression is a suitable approach to reduce inflammatory response after xenotransplantation [24].

Alternatively, the physical barrier of microcapsules may be intended, for instance, to protect cells from the harsh conditions of the stomach and to deliver them into the intestinal tract [25].

The encapsulation of cells may also be very promising for the sustained release of bioactive molecules. The microencapsulation of cells instead of therapeutic products allows the delivery of molecules for a longer period of time as cells release them continuously. Moreover, with classical approaches, when the encapsulation device is broken, the toxicity caused by a quick delivery of high concentrations of the drug could be avoided. In addition, genetically modified cells can express any desired protein *in vivo* without the modification of the host's genome [26]. These artificial cells can be transplanted into a variety of tissues and organs, making this technology suitable for local, regional, oral or systemic delivery of therapeutics [8]. The applicability of this approach has been tested for the treatment of a wide variety of diseases, including (i) anemia by means of erythropoietin-secreting cells immobilized in microcapsules [27], (ii) dwarfism using encapsulated cells producing the human growth hormone [28], (iii) hemophilia B by the encapsulation of cells secreting human factor IX [29,30], (iv) Parkinson's disease by the transplantation of microencapsulated retinal pigmented epithelial cells that are able to produce both dopamine and neurotrophic support to the basal ganglia [31,32], (v) neurodegenerative disorders using VEGF-secreting microencapsulated fibroblast cells [33] etc.

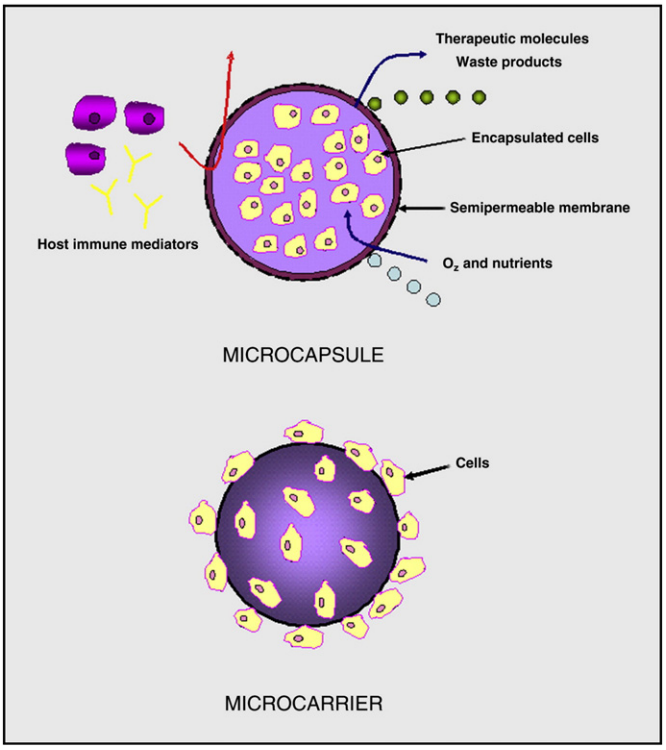

Fig. 1. Schematic representation of microcapsules and microcarriers. Reprinted from Advanced Drug Delivery Reviews, Vol 62, RM Hernández, G Orive, A Murua, JL Pedraz, Microcapsules and microcarriers for *in situ* cell delivery, 711–730, Copyright (2010), with permission from Elsevier. License number 2476450633373.

Independently of the biomedical application considered (cell expansion, cell therapy or sustained release of bioactive molecules), the properties of the microparticles and the choice of suitable methodologies to produce and characterize them are key issues. These concepts, together with examples of microparticles constituted of stimuli-responsive polymers are the subject of the following sections.

2. Microparticle properties

According to the biotechnological application, the requirements for micropaticle materials may include: biocompatibility, ease of processing into particles, sterilizability, long-term biostability, and mild gelling or crosslinking conditions. Considering microcapsules, this last point is essential since they are in some cases formulated in