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Materials in particulate form for tissue engineering. 1. Basic concepts

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Abstract
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Keywords
microparticles, nanoparticles, drug delivery, tissue engineering, polymers, ceramics, natural origin

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Materials in particulate form for tissue engineering. 1. Basic concepts

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Abstract

For biomedical applications, materials small in size are growing in importance. In an era where 'nano' is the new trend, micro- and nano-materials are in the forefront of developments. Materials in the particulate form aim to designate systems with a reduced size, such as micro- and nanoparticles. These systems can be produced starting from a diversity of materials, of which polymers are the most used. Similarly, a multitude of methods are to produce particulate systems, and both materials and methods are critically reviewed here. Among the varied applications that materials in the particulate form can have, drug delivery systems are probably the most prominent, as these have been in the forefront of interest for biomedical applications. The basic concepts pertaining to drug delivery are summarized, and the role of polymers as drug delivery systems conclude this review.
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Keywords **microparticles; nanoparticles; drug delivery; tissue engineering; polymers; ceramics; natural origin**

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1. Definition

The key feature of particulate materials systems being their reduced size, the question regarding the threshold size for considering a system to be a particulate one is of value. Across the literature, many authors differ regarding this question. Herein, micron (μm)-sized systems in the range 1–1000 μm will be considered first. Nano-sized particle systems, within this context, are those for which the sizes are below 1 μm (Kreuter, 1991), and they will be described next.

2. Classification of materials in particulate form

2.1. Microparticles

Microparticles consist of particles in a size range 1–1000 μm (Couvreur and Puisieux, 1993). These include microcapsules, vesicular systems in which a cavity is surrounded by a unique polymeric membrane, and microspheres, which are matrix-filled systems (Couvreur and Puisieux, 1993). Polymer microspheres have attracted attention as carrier matrices in a wide variety of medical and biological applications, such as affinity chromatography, immobilization, immunoassay, nuclear imaging and cell culture (Tuncel *et al*., 1996; Kamyshny and Magdassi, 2000; Shinkai, 2002). Additionally, the incorporation of bioactive agents into small polymeric

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particles was recognized years ago by the pharmaceutical industry as a viable means of improving drug delivery (Bissery *et al*., 1984; Bezemer *et al*., 2000a, 2000b; Pillai *et al*., 2001). This use arose because conventional dosage forms, such as oral delivery and injection, were not able to control the rate of delivery or the target area of the bioactive agent and were often associated with an immediate or rapid release (Tao and Desai, 2003).

The main advantages of microparticles is that they may be administered by injection or intranasally as a dry powder, so that a surgical procedure is not required (Baldwin and Saltzman, 1998; Eliaz and Kost, 2000; Tinsley-Brown *et al*., 2000), and that they may contain a greater amount of biologically active molecules per unit volume (Langer, 1991; Grassi *et al*., 2001; Janes *et al*., 2001a). Various parameters, including particle size and distribution, porosity, pore structure and surface area, are considered to describe the overall performance of polymer microparticles in biomedical applications (Tuncel *et al*., 1996; Allemann *et al*., 1998; Yang and Alexandridis, 2000). Additionally, the use of microparticles composed of biodegradable polymers eliminates the need for device removal after release of the agent (Baldwin and Saltzman, 1998). Based on these features, microparticles have been the subject of numerous studies with the intent to overcome a number of issues related to the therapeutics of biologically active molecules.

In summary, microparticles have the following properties that render them attractive:

- *Size:* small size allows them to be inserted in the target area in a non-invasive manner, thus increasing effectiveness.
- *Size distribution:* microparticles ranging from a few to a few hundred μm can be selected according to a specific application.
- *Porosity and pore structure:* the presence of pores allows the tailoring of the release profile.
- *Surface area:* large surface area and a capacity for loading the bioactive agent at a high fraction of the total weight of the particle.

However, for some applications, particles with an even smaller size – nanoparticles – can be preferable to microparticles.

2.2. Nanoparticles

Nanoparticles, being submicron systems, have the advantage of an even larger surface area compared with microparticles, because the total surface area is inversely proportional to the third power of the diameter (Berton *et al*., 1999; Kawaguchi, 2000). In these systems the bioactive agent can be dissolved, entrapped, encapsulated, adsorbed, immobilized or attached to the matrix (Orive *et al*., 2004) and, depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained (Couvreur and Puisieux, 1993; Soppimath *et al*., 2001). Nanocapsules are vesicular systems in which the bioactive agent is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the bioactive agent is physically and uniformly dispersed (Soppimath *et al*., 2001). Nanospheres and nanocapsules are the morphological equivalents of microspheres and microcapsules, respectively (Allemann *et al*., 1998).

Nanoparticles can be injected and, as a result, can circulate in the blood stream (Madan *et al*., 1997). However, in some cases, nanoparticles are phagocytosed by macrophages (Lee *et al*., 2001), and this can lead to an adverse immunological response. However, such reaction may be desirable in applications such as vaccination therapies, and when enhanced uptake of exogenous compounds, such as anti-human immunodeficiency virus (HIV) drugs (Lee *et al*., 2001), is sought. Nanoparticle polymeric carriers, when their size is less than 100 nm, have a high potential for being accumulated in tumour sites, according to the enhanced permeation and retention (EPR) effect (Nishikawa *et al*., 1996; Yasugi *et al*., 1999). Hydrophilic modification, particularly by introducing poly(ethylene)glycol (PEG) by physical coating or covalent linking – a process known as pegylation – to the surface, prolongs the half-life of the carriers (Kumar, 2000; Seal *et al*., 2001; Diwan and Park, 2003) during circulation in blood by reducing opsonization and thus minimizing carrier clearance in organs such as liver, spleen, lung and bone marrow (Gref *et al*., 1994; Peracchia *et al*., 1997). This long-circulating stealth characteristic of the carrier produces the EPR effect, which is valuable in passive cancer targeting (Berthold *et al*., 1998; Maeda *et al*., 2000).

Nanoparticles hold great potential for the treatment of tumours. An example is related to the ability of those materials to include within their matrix magnetic particles and by directing nanoparticles to the target (e.g. tumour cells) through magnetic fields created around the tumour. This brings great advantages, such as a reduction of the dosage and side-effects, as well as a rise in the therapeutic effect, together with controlled and, most importantly, direct targeting of the tumour site (Brigger *et al*., 2002).

Nanoparticles offer other specific advantages over liposomes, because they increase the stability of bioactive agents/proteins and possess a better set of controlled release properties (Jain, 1994; Hrkach *et al*., 1997; Gaspar *et al*., 1998; Berton *et al*., 1999; Kumar, 2000; Soppimath *et al*., 2001).

To summarize, nanoparticles possess the following advantages:

- *Stability:* increased stability over liposomes and promotion of increased stability of entrapped bioactive molecules.
- *Surface area:* higher surface area, even when compared with microparticles.
- *Size:* depending on their size, they can be phagocytosed or can circulate in the blood long enough to promote the therapeutic effect.

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- *Stealth effect:* controlled by size and modification by coating with polymers such as PEG.
- *Delivery to target site:* easily delivered by injection, without the need of invasive procedures.

3. Overview of synthesis methods

There are several methods for the production of micro- and nanoparticles, but the most widely used techniques are methods based in emulsions, such as suspension polymerization, solvent evaporation and, to a smaller extent, organic phase separation (coacervation) and spray-drying methods, as reviewed/described in detail in the literature (Kreuter, 1991; Gref *et al*., 1994; Tuncel *et al*., 1996; Madan *et al*., 1997; O'Donnel and McGinity, 1997; Lin and Yu, 2001; Soppimath *et al*., 2001).

In suspension polymerization, the monomer phase is broken into droplets (a few μm in diameter) within a dispersion medium (usually an aqueous phase) and stabilized by a surfactant dissolved in the medium (Piskin *et al*., 1993). These monomer droplets containing a monomer phase soluble initiator are then individually polymerized by applying a temperature/agitation programme (Piskin *et al*., 1993). In the emulsion/solvent evaporation method, the polymer is solubilized/dispersed in an organic solvent (e.g. methylene chloride, chloroform) and the resultant solution is then emulsified with an aqueous phase (Soppimath *et al*., 2001; Perez *et al*., 2002). The formation of the particles is achieved by hardening resulting from the evaporation of the organic solvent. Stirring speed is usually the parameter controlling the size of the particles. This method is easy to implement and yields very good results with a variety of raw materials.

Most of the methods for the production of particle-based systems are actually based on the creation of emulsions between organic and aqueous phases, and suffer one common drawback – the need for organic solvents (e.g. methylene chloride, chloroform, acetonitrile, tetrahydrofuran) in at least one of the production steps (Ghaderi *et al*., 1999; Kim and Park, 1999; Sendil *et al*., 1999; Birnbaum *et al*., 2000). The residual content of the organic solvent in the microparticles after preparation has to be removed in time-consuming drying steps (Nykamp *et al*., 2002), and in many cases the presence of an organic solvent can lead to loss of the activity of the agent to be loaded into the system. Currently, methods that obviate the use of organic solvents are in demand, and this aspect is particularly critical when there is a risk of hindering the activity of the biological agent. An interesting new approach in efforts to address this particular issue is that described by Nykamp *et al*. (2002), who used a jet-milling technique to produce polylactic acid (PLA) and polylactic/glycolic acid (PLGA) microparticles with different ratios of the two polymers. Conceivably, this method could also be used for other polymers. However, the first step of this process involves melting the starting material, which obviously has to be taken into account when aiming to use the developed systems for delivery of bioactive agents. Similarly, Lin *et al*. (1999) have used a solvent-free method to produce polycaprolactone (PCL) microparticles, by dispersing polyethylene glycol (PEG) in the PCL phase. Although the melting temperature of PCL is low (close to 60 °C), this temperature might still be deleterious for the activity of bioactive molecules.

One has to be cautious in choosing the method of production, and weigh carefully between the risks of using an organic solvent or using high-temperature conditions, two major parameters influencing the biological activity of an agent.

Although micro- and nanoparticles can be produced using a vast array of possible techniques, a number of variables that affect the product obtained have to be taken into account when choosing a material and method. These include (Bissery *et al*., 1984; Ronneberger *et al*., 1997; Bezemer *et al*., 2000a):

- Type and amount of material used.
- Degradation rate of the polymer.
- Type and payload of bioactive agent being incorporated (in case of drug delivery applications).
- Organic solvent being volatilized.
- Type and amount of surfactant dissolved in the aqueous phase.
- Temperature.
- Pressure during solvent evaporation.
- Ratio of the volume of organic solvent : volume of aqueous phase.

By 'playing' with these parameters, researchers have been able to use a wide array of materials and methods for a number of applications.

4. Materials used in the synthesis of materials in particulate form

The polymeric class of materials has been regarded as the primary choice for applications in which small-sized particles are needed, since many polymers can be formed into microparticles and nanoparticles for delivery and other applications. These may be non-degradable or degradable polymers, from synthetic or natural origin, or even blends (synthetic–synthetic, synthetic–natural or natural–natural). Nevertheless, polymers are not the only materials used for producing materials in particulate form; across the literature there is a wide array of materials used for the synthesis of particle-based materials, including ceramics and metals. This review deals primarily with polymers and to some extent ceramics. Some examples of polymer–ceramic composites will also be described.

Table 1 summarizes the most frequently used materials for the synthesis of materials in particulate form, and also includes the methods for production of these systems and intended applications, with a brief description of the most widely used groups following the table.

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Table 1. Overview of the materials and methods used for the production of materials in particulate form and envisioned applications (information compiled in the scope of this review)

Material	Type	Method	Application	Description	Ref.
Synthetic polymers and blends					
Polylactic acid (PLA)	Microspheres	o/w solvent evaporation Solvent evaporation Double emulsion technique	Incorporation and release	Release of epidermal growth factor (EGF) Release of somatostatin Release of cisplatin Delivery of antisense oligonucleotides Release of the antiischaemic drug N6-cyclopentyladenosine Entrapment of tetanus toxoid for immunization	(Herrmann and Bodmeier, 1995, 1998; Delie *et al.*, 2001; Han *et al.*, 2001; Dalpiaz *et al.*, 2002; Tamura *et al.*, 2002; Katare *et al.*, 2005)
Polylactic acid/polyethylene glycol (PLA/PEG)	Micro and nanoparticles	Emulsion–solvent evaporation	Incorporation and release	Release of cyclosporine A	(Gref *et al.*, 2001)
Polylactic (PLGA)	Microspheres	Water-in-oil-in-water o/w emulsion solvent evaporation Double emulsion (w/o/w) solvent evaporation ProLease® and spray freeze-drying	Incorporation and release	Release of active lysozyme Release of dexamethasone (DEX) and vascular endothelial growth factor (VEGF) Release of ipriflavone (for osteopenia treatment) Release of enoxacin Release of somatostatin Release of human IgG Release of recombinant human GDNF Release of rIGFI Release of oligonucleotide for antisense therapy Release of baclofen for spinal spasticity	(Herrmann and Bodmeier, 1998; Cruaud *et al.*, 1999; Abazinge *et al.*, 2000; Lam *et al.*, 2000; Perez *et al.*, 2002; De Rosa *et al.*, 2003; Perugini *et al.*, 2003; Jollivet *et al.*, 2004; Wang *et al.*, 2004; Norton *et al.*, 2005)
	Microparticles Microspheres	w/o/w–double emulsion–solvent evaporation	Incorporation and release	Release of insulin-like growth factor-I (IGF-I)	(Meinel *et al.*, 2001; Singh *et al.*, 2001b; Carrascosa *et al.*, 2004)
	Microparticles	Water-in-oil-in-water emulsion–extraction–evaporation Multiple emulsion solvent evaporation	Incorporation and release Carrier for cells Carrier for antigen	Release of parathyroid hormone (PTH) Release of gentamicin Release of bFGF Microcarriers for cells Release of nerve growth factor (NGF) Gene transfer via adenovirus Release of 5-fluorouracil Adjuvant in for immune response Release of acyclovir (for Herpes simplex I) Encapsulation of *Brucella ovis* antigens for immunization Encapsulation of *Helicobacter pylori* lysates for immunization Release of bone morphogenetic protein (BMP) Release of VEGF	(Isobe *et al.*, 1996; Yamazaki *et al.*, 1996; Isobe *et al.*, 1999; Walter *et al.*, 1999; King and Patrick, 2000; Kim and Park, 2001; Ain *et al.*, 2002; Hedberg *et al.*, 2002; Murillo *et al.*, 2002; Zhu *et al.*, 2002; Diwan and Park, 2003; Jalón *et al.*, 2003; Perets *et al.*, 2003; Sanchez *et al.*, 2003; Schlapp and Friess, 2003; Gárcia Del Barrio *et al.*, 2004; Matzelle and Babensee, 2004; Siepmann *et al.*, 2004; Wei *et al.*, 2004; Tatard *et al.*, 2005)

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				Release of TP508 from particles as components of composite scaffolds. TP508 (Chrysalin)-23-amino acid synthetic peptide representing the non-proteolytic receptor-binding domain of thrombin Release of NFκB decoy oligonucleotides for inhibition of tumour cell proliferation Release of interferon-α (treatment of hepatitis C) Delivery of antitubercular drugs Release of human growth hormone	
	Microcapsules	Solvent evaporation	Encapsulation and release	Release of human growth hormone Release of TAK-778	(Hoshino *et al*., 2000; Takada *et al*., 2003)
	Nanospheres	Water-in-oil-in-water emulsion solvent evaporation	Incorporation and release	Release of plasmid DNA (gene transfection)	(Labhasetwar *et al*., 1999)
	Nanoparticles	Double emulsion solvent evaporation	Incorporation and release	Release of antiproliferative 2-aminochromone U-86983 on neointimal hyperplasia Release of paclitaxel (Taxol)	(Humphrey *et al*., 1997; Song *et al*., 1997; Gaspar *et al*., 1998; Mu and Feng, 2002)
		Emulsification/solvent evaporation		Release of U-86983, U-61431F, U-74389G, dexamethasone for prevention of post-angioplasty restenosis Release of L-asparaginase	
PLGA/poly-acryloyl hydroxyethyl starch	Microspheres	Adsorption and encapsulation by solvent extraction evaporation	Incorporation and release	Release of insulin	(Jiang *et al*., 2003)
PLGA/ε PCL	Microparticles	Water-in-oil-in-water emulsification and evaporation	Incorporation and release	Release of heparin	(Jiao *et al*., 2002)
	Microspheres	Precipitation from solution under reduced pressure	Incorporation and release	Release of progesterone and estradiol	(Buntner *et al*., 1998)
Polyorthoester (POE)-PLGA	Microparticles	Water-in-oil-in-water (w/o/w) double emulsion	Incorporation and release	Potential for release of water-soluble and -insoluble drugs	(Yang *et al*., 2003)
Poly(L-lactic-co-glycolic acid) and polyethylenoxide (PLGA-PEO-PLGA)	Microspheres	Double emulsion (w/o/w)	Incorporation and release	Release of human recombinant erythropoietin	(Morlock *et al*., 1997; Morlock *et al*., 1998)
Poly(γ-benzyl L-glutamate)-poly(ethylene oxide) (PBLG-PEO)	Nanoparticles	Diafiltration	Incorporation and release	Release of clonazepam (anticonvulsant)	(Jeong *et al*., 1998)
Poly(acrylic acid) (PAA)	Microparticles Nanoparticles	Inverse (w/o) emulsion polymerization	Incorporation and release	Release of peptides and other hydrophilic drugs	(Kriwet *et al*., 1998)
Polyacrylic acid-co-methyl methacrylate	Microparticles	Free radical emulsion polymerization	Incorporation and release	Release of cisplatin	(Yan and Gemeinhart, 2005)
Poly-(isobutyl-cyanoacrylate) (PIBCA)	Nanoparticles	Anionic polymerization in the presence of series of cyclodextrins and derivatives	Encapsulation	Encapsulation of steroid-loaded cyclodextrins	(Duchêne *et al*., 1999)
		Emulsion polymerization	Adsorption and release Incorporation and release	Ciproflexin (antibiotic) Release of haematoporphyrin for tumour targeting	(Brasseur *et al*., 1991; Fawaz *et al*., 1997)
Polyisohexylcyanoacrylate (PIHCA)	Nanoparticles	Emulsion polymerization	Adsorption and release	Endocytosis of ampicillin and gentamicin nanoparticles for intracellular delivery	(Henry-Michelland *et al*., 1987)
Poly(MePEGcyanoacrylate-co-hexadecylcyanoacrylate)	Nanoparticles	Nanoprecipitation	Incorporation and release	Release of tamoxifen	(Brigger *et al*., 2001)

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Table 1. (*Continued*)

Material	Type	Method	Application	Description	Ref.
Polymethyl methacrylate (PMMA)	Microparticles	o/w solvent evaporation Dispersion polymerization Suspension radical co-polymerization	Entrapment and release	Release of verapamil Delivery of HIV-1 Tat protein for vaccination applications Buformin tosylate – a classical hypoglycaemic drug	(Streubel *et al*., 2002) (Fundueanu *et al*., 2001; Caputo *et al*., 2004)
Poly(methacrylic acid-*g*-ethylene glycol) P(MAA-*g*-EG)	Microparticles	Free-radical solution polymerization	Entrapment and release	Release of insulin	(Morishita *et al*., 2002)
Poly (trimethylene carbonate)-poly(ethylene glycol)-poly (trimethylene carbonate) (PTC-PEG-PTC)	Nanoparticles	Dialysis	Incorporation and release	Release of methotrexate (anticancer drug)	(Zhang and Zhuo, 2005)
Polyvinylpyrrolidone (PVP)	Nanoparticles	Polymerization	Carrier for antigen	Delivery of the antigen of *Aspergillus fumigatus* for immune system response	(Madan *et al*., 1997)
Polyvinyl alcohol (PVA/P(Vpi/Vac)	Microparticles Nanoparticles	Suspension polymerization	Embolic materials	Introduced through catheters in the management of gastrointestinal bleeders, traumatic rupture of blood vessels	(Lyoo *et al*., 2002)
Poly(diethylaminoethyl-g-ethylene glycol)	Microparticles	Suspension polymerization	Incorporation	Incorporation of glucose oxidase for treatment of diabetes	(Podual *et al*., 2000)
ε-Polycaprolactone (ε-PCL)	Microparticles	Reverse micelle solvent evaporation Simple and double emulsion–solvent evaporation	Incorporation and release	Release of superoxide dismutase Release of nitrofurantoin (antibacterial agent) Release of vancomycin Release of fludrocortisone acetate for hormonal therapy Release of diclofenac	(Dubertnet *et al*., 1987; Pérez *et al*., 2000; Gibaud *et al*., 2002a, 2002b; Le Ray *et al*., 2003; Schaffazick *et al*., 2003; Youan, 2003; Gibaud *et al*., 2004)
	Nanoparticles	Nanoprecipitation		Nifedipine (calcium antagonist) and propranolol HCl (β-blocker), for treatment of hypertension Melarsoprol for the treatment of human trypanosomiasis Release of 3,4-diaminopyridine (3,4-DAP) for multiple sclerosis and Lambert–Eaton myasthenia syndrome	
Poly-ε-caprolactone/poly(methyl methacrylate)	Microparticles	Suspension polymerization	N.A.	N.A.	(Abraham *et al*., 2002)
Poly-ε-caprolactone/ poly(ethylene glycol)	Nanoparticles	Polymerization and precipitation	Encapsulation and release	Release of all-*trans*-retinoic acid	(Jeong *et al*., 2004)
D-α-tocopheryl polyethylene glycol 1000 succinate/ poly-ε-caprolactone	Microparticles	Double emulsion followed by spray drying	Incorporation and release	Nasal immunization with diphtheria toxoid	(Somavarapu *et al*., 2005)
Polystyrene	Microparticles	Emulsion solvent evaporation	Incorporation and release Carrier of antigen	Release of ibuprofen Release of indomethacin Adjuvant for immune response	(Tamilvanan and Sa, 2000a, 2000b) (Matzelle and Babensee, 2004)
Cytoline 2® (polyethylene and silica)	Microparticles	N.A.	Carrier for cell culture	Culture of hybridomas (anti-neuroblastoma monoclonal antibodies)	(Voigt and Zintl, 1999)
Natural polymers and blends					

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Alginate	Beads	Physical crosslinking of calcium ions to sodium alginate polymer (gelation) by needle extrusion	Incorporation and release	Release of bFGF Release of glucocorticosteroids Release of VEGF	(Berthold *et al*., 1998; Chinen *et al*., 2003; Gu *et al*., 2004)
	Microparticles	Atomization and gelation using Ca^{2+} Microemulsion Gelation using micro-nozzle array Spray drying Spray–coagulation method	Carrier for cells Purification Incorporation and release	Encapsulation of cells for angiogenic factors release Magnetic affinity adsorbents for purification of enzymes Cell encapsulation of human kidney 293 cells Release of L-lactate dehydrogenase enzyme Release of model compounds Incorporation of *Aeromonas hydrophila* for fish oral vaccination	(Coppi *et al*., 2002; Safarikova *et al*., 2003; Keshaw *et al*., 2005; Rodrigues *et al*., 2005; Sugiura *et al*., 2005; Tu *et al*., 2005)
	Microspherical hydrogels (microspheres)	Gelation using Ca^{2+} Emulsion crosslinking	Carrier for vaccines Incorporation and release	Delivery of several vaccines Incorporation of glucose oxidase for biosensors Delivery of ibuprofen	(Bowersock *et al*., 1996; Kidane *et al*., 2001; Arica *et al*., 2005; Brown *et al*., 2005)
Alginate–heparin	Microparticles	N.A.	Incorporation and release	Release of bFGF	(Chinen *et al*., 2003)
Alginate–poly-L-lysine	Microparticles	N.A. Air atomization Gelation with Ca^{2+} and crosslink	Incorporation and release	Release of NGF Encapsulation of bifidobacteria for food applications Release of antisense oligonucleotides	(Maysinger, Jalsenjak *et al*., 1992; Cui *et al*., 2000; Ferreiro *et al*., 2002)
Alginate–poly-L-ornithine	Capsules	Gelation with Ca^{2+}	Incorporation and release Carrier for cells	Simultaneous incorporation of ketoprofen-loaded microspheres and rat pancreatic islets	(Ricci *et al*., 2005)
Alginate–carboxymethyl chitin	Beads	Dropping the solution into an iron solution	Incorporation and release	Release of model compound (albumin)	(Shi *et al*., 2005)
Alginate–protamine	Microcapsules	Layer-by-layer adsorption of Na alginate and protamine to surface of melamine formaldehyde microparticles	Incorporation and release	Release of α-chymotrypsin, a proteolytic enzyme	(Tiourina and Sukhorukov, 2002)
Alginate–agarose	Microcapsules	Thermal gelation	Carrier of cells	Cell encapsulation (BHK fibroblast and C_2C_{12} myoblast)	(Orive *et al*., 2003)
Alginate–chitosan Chitosan-coated alginate	Microparticles	Spraying–ionic crosslinking	Incorporation and release	Release of BDNF Incorporation of mytomycin-C for chemoembolization	(Mittal *et al*., 1994; Misirli *et al*., 2005)
Amphiphilic cyclodextrins	Nanoparticles	N.A.	Encapsulation and release	Release of steroids	(Duchêne *et al*., 1999)
Chitosan	Microspheres Microparticles	Emulsion–ionic cross-linking Spray drying Emulsion–solvent evaporation Precipitation with sodium sulphate Crosslinking with TPP	Incorporation and release	Release of teicoplanin Release of metoclopramide for emesis prevention Release of gentamicin Release of model agent ovalbumin Release of model drug felodipine	(Ganza-Gonzalez *et al*., 1999; Lim *et al*., 2000; van der Lubben *et al*., 2001; Ko *et al*., 2002; Yenice *et al*., 2002)
	Nanoparticles	Ionotropic gelation with polyanion incorporation	Incorporation and release	Release of insulin for intestinal absorption Release of doxorubicin (anticancer agent) DNA carriers	(Janes *et al*., 2001b; Mao *et al*., 2001; Pan *et al*., 2002)
Chitosan–poly(acrylic acid)	Nanoparticles	Template polymerization	Incorporation and release	Release of silk peptide	(Hu *et al*., 2002)
Chitosan-poly(methyl vinyl ether-co-maleic anhydride) (CH-PVM/MA)	Microparticles	Spray drying	Incorporation and release	Propranolol hydrochloride (β-blocker)	(Cerchiara *et al*., 2005)

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Table 1. (*Continued*)

Material	Type	Method	Application	Description	Ref.
HSA (human serum albumin)	Nanoparticles	Coarcevation Desolvation	Incorporation and release Incorporation and release	Release of TGFβ1 Release of betamethasone Release of antisense oligonucleotides	(Huang *et al*., 2003; Lee *et al*., 2004; Wartlick *et al*., 2004)
	Particles	N.A.	Incorporation/adsorption and release	Release of antisense oligonucleotides	(Arnedo *et al*., 2002; Wartlick *et al*., 2004)
HSA–magnetite	Microspheres	N.A.	Incorporation and release	Release of dexamethasone	(Ghassabian *et al*., 1996)
Hyaluronan and derivatives	Microparticles Microspheres	Solvent evaporation Spray drying Coacervation/phase separation	Incorporation and release	Release of pilocarpine Delivery of inactivated influenza vaccines	(Zimmer *et al*., 1994; Singh *et al*., 2001a)
Gelatin	Microparticles	Crosslinking Emulsification and crosslinking	Incorporation and release Encapsulation and release Carrier for cell culture	Release of model drugs (metrodinazole, prednisolone, cromolyn) Encapsulation of bone stromal cells Release of TGFβ1 Microcarrier for the culture of human nasal chondrocytes	(Payne *et al*., 2002a, 2002b; Holland *et al*., 2003; Malda *et al*., 2003a; Esposito *et al*., 2005)
	Microspheres	N.A. Chemical crosslinking in a water-in-oil emulsion Liophilization with PEG	Pore-forming role Incorporation and release	Porogen for the formation of foams Release of TGFβ2	(Thomson *et al*., 1998; Morita *et al*., 2001; Kojima *et al*., 2004)
	Beads	N.A.	Encapsulation and release	Release of methotrexate (cancer drug)	(Narayani and Rao, 1994)
Collagen	Microparticles	Emulsion crosslinking	Incorporation	Incorporation of an antigen for immunization Carriers for glucocorticoids Delivery of all-*trans*-retinol	(Berthold *et al*., 1998; Suckow *et al*., 2002; Swatschek *et al*., 2002)
Collagen–PLGA	Microparticles (PLGA)	Dispersion polymerization	Incorporation and release	Release of gentamicin	(Schlapp and Friess, 2003)
Zein (corn protein)	Microparticles	Phase separation	Incorporation and release	Release of ivermectin	(Liu *et al*.,)
Casein	Microparticles	Coacervation	Incorporation and release	Potential for release of agents of interest	(Santinho *et al*., 1999)
Gliadins	Nanoparticles	Desolvation (drowning-out precipitation)	Incorporation and release	Vitamin E, benzalkonium chloride	(Duclairoir *et al*., 2003)
Amylopectin	Nanoparticles	Conjugation followed by diafiltation (dialysis, filtration and precipitation)	Encapsulation	Encapsulation of cells	(Rabanel and Hildgen, 2004)
Pullulan acetate–sulphonamide	Microspheres	N.A.	Dialysis	Loading of adriamycin for tumour targeting	(Na *et al*., 2003)
Cellulose	Microspheres	o/w solvent evaporation	Cell carriers	Microcarrier with cell adhesive peptides for bioartificial liver technology	(Kobayashi *et al*., 2002)
Ethylcellulose	Microparticles	Water-in-oil-in-water (w/o/w) double-emulsion Emulsion solvent evaporation	Incorporation and release	Release of verapamil Release of herbicide 2,4-D	(Streubel *et al*., 2002; Elbahri and Taverdet, 2005)
Dextran (Cytodex®)	Microspheres	N.A.	Entrapment and release Carriers for cell culture	Release of liposomes Transplantation of rat adrenal chromaffin cells seeded at the surface of the carrier Culture of cells producing inactivated influenza virus Culture of rabies-virus producing cells for vaccination purposes	(Stenekes *et al*., 2001) (Borlongan *et al*., 1998) (Genzel *et al*., 2004) (Frazzati-Gallina *et al*., 2001)
Starch–acetate	Microspheres	N.A.	Incorporation and release	Release of peptides and proteins	(Touvinen *et al*., 2004)
Poly(acryl starch)	Microparticles	Solvent extraction Polymerization in water-in-oil emulsion Water-in oil-emulsion with stabilizing hydrocarbon chains	Incorporation and release Carrier for antigen	Release of a vaccine for a rotavirus Immunization against diphtheria Adjuvant for oral immunization	(Sturesson and Wikingsson, 2000; Wikingsson and Sjoholm, 2002; Rydell and Sjoholm, 2004)

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Starch–PLA	Microparticles	Solvent extraction	Incorporation and release	Release of corticosteroids (DEX and methylprednisolone) Release of PDGF	(Silva *et al*., 2005; Silva *et al*., submitted)
Curdlan (carboxymethylated)	Nanoparticles	Self assembly	Incorporation and release	Release of all-*trans*-retinoic acid AQ1	(Na *et al*., 2000)
Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)	Microparticles	w/o/w double emulsion	Incorporation and release	Release of tetracycline Encapsulation of catalase and asparaginase	(Baran and •Hasirci, • • ••; Sendil *et al*., 1999)
Poly(γ-methyl-L-glutamate)	Microspheres	Suspension–evaporation	Carrier for cell culture	Cell culture	(Kato *et al*., 2003)
Ceramics					
Hydroxyapatite (HA)	Spherical granules	N.A.	Adsorption and release	Potential for release of bone bioactive agents (cytochrome *c* as model)	(Komlev *et al*., 2002; Matsumoto *et al*., 2004)
		Wet method	Coating	Plasma sprayed to coat scaffolds for bioactivity induction	(Weng *et al*., 2002)
	Granules	N.A.	Adsorption and release	Potential for release of bone bioactive agents (cytochrome *c* as model)	(Komlev *et al*., 2002; Matsumoto *et al*., 2004)
	Particles	N.A.	Adsorption and release	Release of growth hormone Tetracyclin	(Guicheux *et al*., 1997; Domingues *et al*., 2004)
	Nanocrystals	*In situ* and *ex situ* processes	Adsorption and release	Release of BSA (as a model)	
Bioactive glass	Particles	N.A.	Reconstruction	Dental and periodontal reconstruction Augmentation of the alveolar ridge Elevation of the sinus floor	(Schepers *et al*., 1991, 1993; Schepers and Ducheyne, 1997; Schepers *et al*., 1998; Huygh *et al*., 2002; Gosain, 2004)
			Coating	Coating of polymer fibres for enhancement of cell adhesion	(Day *et al*., 2004)
Coral (exoskeleton from madreporic corals)	Particles	N.A.	Adsorption and release	Release of TGFβ1	(Demers *et al*., 2002)
β-Tricalcium phosphate (β-TCP)	Particles	N.A.	Filling	Maxillary sinus floor augmentation	(Zerbo *et al*., 2005)
Silica aerogel	Microparticles	Sol–gel process using supercritical fluids	N.A.	N.A.	(Moner-Girona *et al*., 2003)
Si–Ca–P xerogels	Granules	Sol–gel process	Incorporation and release	Release of BPM-2 Release of vancomycin	(Santos *et al*., 1998; Falaize *et al*., 1999)
Hollow ceramic (58–72% SiO_2, 28–42% Al_2O_3 wt%)	Microspheres	[N.A.] Coated with synthesized calcium hydroxyapatite (HA) particulate sol	Microcarriers	Microcarriers for bone tissue formation in rotating bioreactors	(Qiu *et al*., 1999)
Composites					
Biphasic calcium phosphate (BCP)/ε-PCL particles	Microparticles	Solvent evaporation/extraction	Incorporation and release	Injectable bone substitute with release of vancomycin	(Iooss *et al*., 2001)
HA (coralline)–alginate	Microspheres	Dispersion polymerization	Encapsulation and release	Gentamicin	(Sivakumar and Panduranga Rao, 2003)
Polylactic acid–bioactive glass (PLA/BG)	Microspheres	Solvent evaporation	Microcarriers	Microcarriers for bone tissue formation in rotating bioreactors	(Qiu *et al*., 1998, 2001)
Starch–polylactic acid–bioactive glass (SPLA/BG 45S5)	Microparticles	Solvent evaporation/extraction	Incorporation and release	Potential for release of bioactive agents and for scaffold materials	(Silva *et al*., 2004)

N.A., information not available; o, oil; w, water.

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The use of synthetic polymers as carriers has predominantly focused on polyhydroxyalkanoates (Ueda and Tabata, 2003), in particular poly(α-hydroxy esters), because the material has long been used in sutures (Hollinger *et al.*, 1996; Hollinger and Leong, 1996). The most widely used poly(α-hydroxy ester) polymers for particle-based strategies are polylactide (PLA), polyglycolide (PGA) and their co-polymers (poly-DL-lactide-co-glycolide) (PLGA) (Brekke, 1996; Hollinger and Leong, 1996; Whang *et al.*, 1998). Their widespread use stems from the ability of these materials to serve a multitude of purposes and applications.

PLA nanoparticles, in general, have the advantage to be able to pass through the capillary bed and to be mainly concentrated in the liver (60–90%), spleen and lungs (2–10%) and, to a lesser degree, blood marrow (Kreuter, 1983; Brannon-Peppas, 1995). For PLA nanoparticles injected subcutaneously or intramuscularly, they are able to reside at the injection site until biodegradation yields a certain critical molecular weight that enables removal of the degradation products (Kreuter *et al.*, 1983). These particular traits render these systems very interesting for drug delivery applications. Furthermore, tuning of the biodegradability can be performed by blending PLA and PGA in a co-polymer (PLGA), and by changing the proportion of each of these materials in the co-polymer (Miller *et al.*, 1977; Pillai and Panchagnula, 2001; Grayson *et al.*, 2004), as PLA degrades much slower than PGA. Degradation of PLA and PLGA is known to proceed by hydrolytic scission of the polymer chain and depolymerization is influenced by molecular weight (MW), polydispersity and crystallinity (Weinhold *et al.*, 1998; Li and Wozney, 2001).

Although PLGA represents the 'gold standard' (exemplified by more than 500 patents) of biodegradable polymers, increased local acidity because of breakdown products of these polymers can lead to irritation at the target site and may also be detrimental to the stability of protein bioactive agents (Pillai and Panchagnula, 2001). Additional potential problems with these synthetic materials include poor clearance – particularly for high MW polymers – and chronic inflammatory response (Kirker-Head, 2000; Li and Wozney, 2001). For this reason, research has been focusing on other synthetic materials, such as poly(ε-caprolactone) (ε-PCL), which was, for instance, found to meet the requirements of a biodegradable reservoir or monolithic device for controlled drug delivery, especially in the contraceptive field (Pitt *et al.*, 1979; Dubertnet *et al.*, 1987).

Polyorthoesters (POE) have been under development since the 1970s, and they are unique among all biodegradable polymers, as choosing appropriate diols or mixture of diols in their synthesis can readily vary many of their properties. A number of applications have been found for this class of polymers, such as delivery of 5-fluorouracil, periodontal delivery systems of tetracycline and pH-sensitive polymer systems for insulin delivery (Zignani *et al.*, 2000; Pillai and Panchagnula, 2001).

Polyanhydrides have been considered to be useful biomaterials as carriers of bioactive agents to various organs of the human body, such as bone tissue, blood vessels, brain and eyes (Kumar *et al.*, 2002). They can be prepared easily from readily available, low-cost resources, can be manipulated to meet desirable characteristics, are biocompatible and degrade *in vivo* into non-toxic diacid counterparts that are eliminated from the body as metabolites (Kumar *et al.*, 2002).

However, synthetic materials do not completely fulfil current needs in terms of biomedical applications, and in recent years many researchers have been turning their research focus to materials of natural origin, as these might obviate several of the drawbacks of synthetic materials.

Polyaminoacids, such as poly(γ-methyl-L-glutamate), that have already shown good biocompatibility, have been investigated for the delivery of low MW compounds (Nathan and Kohn, 1994; Pillai and Panchagnula, 2001). However, their widespread use is limited by their antigenic potentials and some difficulties in the control of release that might arise from the dependence on enzymes for biodegradation.

Collagen, viz. type I collagen, is the most widely used natural polymer and is typically derived from bovine or porcine bone, skin or tendon (Winn *et al.*, 1998). The fact that collagen is of animal origin raises concerns, such as the possibility of transmitting diseases. This is particularly critical for materials from bovine sources, due to malignancies such as bovine spongiform encephalopathy (BSE) and the human variant, Creutzfeldt–Jakob disease (CJD). For this reason, other sources of collagen, such as recombinant forms, are seen as an alternative. Collagen exhibits biodegradability, weak antigenicity and superior biocompatibility (Maeda *et al.*, 1999; Lee *et al.*, 2001). This material is regarded as very promising for the delivery of growth factors, as it was found that an electrostatic interaction was the main driving force for the complexation between acidic gelatin and basic fibroblast growth factor (bFGF) (Lee *et al.*, 2001). Biodegradable collagen-based nanoparticles or nanospheres are thermally stable and readily sterilizable (Rossler *et al.*, 1994; Lee *et al.*, 2001). Moreover, nanoparticles can be taken up by the reticuloendothelial system (Marty *et al.*, 1978) and enable an enhanced uptake of exogenous compounds, such as anti-HIV biologically active agents, by a number of cells, especially macrophages (Bender *et al.*, 1996), which may be an additional advantage of collagen-based nanoparticles as a systemic delivery carrier (Lee *et al.*, 2001). Coupled to a small size and a large surface area, high adsorptive capacity and ability to disperse in water to form a clear colloidal solution, the potential of collagen-based nanoparticles has been demonstrated in their use as a sustained release formulation for anti-microbial agents or steroids (Lee *et al.*, 2001). However, some disadvantages of collagen-based systems include the difficulty of assuring adequate supplies, poor mechanical strength (Friess, 1998) and problems related to the use

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of animal origin (especially bovine) collagen due to the possibility of disease transmission. Alternatives to animal origin collagens – those produced by recombinant technologies – still present a high cost.

Hyaluronan (hyaluronic acid), typically derived from rooster combs, is a minor component of bone extracellular matrix (ECM) (Li and Wozney, 2001). It has been used as a carrier for bone morphogenetic proteins (BMPs) and sodium hyaluronate gel was used as the delivery system for bFGF (Li and Wozney, 2001). One advantage of hyaluronic acid is that it is negatively charged and can form ionic bonds with positively charged BMPs to increase affinity. Disadvantages of hyaluronic acid include its rapid resorption unless it is crosslinked or chemically modified to decrease its intrinsic hydrophilicity (Li and Wozney, 2001).

However, the fear that some of these materials might additionally be carriers for diseases has led researchers to find other sources of natural products, mostly originating from plants and produced by microorganisms. These might present additional advantages, such as ready supply, low cost, ability to be processed by several methodologies and ability to tailor their properties.

In this field of polymers from nature, poly(glucoses), such as starch and dextrans, have long been used for encapsulating materials for pharmaceutical, cosmetic or food applications (Shahidi and Han, 1993; Pereswetoff-Morath, 1998; Zeller *et al.*, 1999; Engelmann *et al.*, 2004). *Dextrans* are being actively investigated for sustained delivery of therapeutic and imaging agents, particularly for injectables and colon-specific DDSs. *Starch*-based polymers have been proposed by Reis and Cunha (1995) as materials with potential for biomedical applications, particularly as scaffolds for bone tissue engineering applications (Gomes *et al.*, 2001, 2002), bone cements (Espigares *et al.*, 2002; Boesel *et al.*, 2003) and recently as drug delivery systems (Elvira *et al.*, 2002; Silva *et al.*, 2005). These materials have been shown to be biocompatible *in vitro* (Mendes *et al.*, 2001; Marques *et al.*, 2002), and to possess a good *in vivo* performance (Mendes *et al.*, 2003; Salgado *et al.*, 2005). A very important feature of most natural-origin materials, besides the ones described above, is the reaction of the host to degradation products (in the case of starch, the degradation products are oligosaccharides, which can be readily metabolized to produce energy). Regarding their biodegradability, enzymes typically catalyse the hydrolysis of natural biodegradable polymers, e.g. α-amylase catalyses the hydrolysis of starch, which may constitute a strategy to tailor the biodegradability of the material (Azevedo *et al.*, 2003; Araújo *et al.*, 2004; Touvinen *et al.*, 2004).

Chitosans are promising natural polymers that show biocompatibility, good absorption-enhancing, controlled release (Janes *et al.*, 2001a; Mao *et al.*, 2001; Pillai and Panchagnula, 2001), bioadhesive properties (Pillai and Panchagnula, 2001), as well as cell culture, enzymatic immobilization and chromatograph support (Kumar, 2000). Chitosan is a product of the deacetylation of chitin, produced with varied degrees of deacetylation, and its use is only limited by the poor solubility or insolubility of chitosan in water (Wang *et al.*, 2002). However, growing attention given to this material for several applications, not only for drug delivery, makes us believe that chitosan holds promise to become a very successful material for biomedical applications.

Another widely used polymer of natural origin is *alginate*, a natural polysaccharide extracted from brown algae and composed of various proportions of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. This naturally occurring biopolymer has many applications in various areas of biosciences and biotechnology (e.g. as a matrix for the entrapment and/or delivery of a variety of proteins and cells) and in the food and beverage industry (as a thickening or gelling agent and a colloidal stabilizer) (Smidsrød and Skjåk-Bræk, 1990; Safarikova *et al.*, 2003; Gu *et al.*, 2004). Besides the best-known method to prepare alginate beads – which is a gelation method in which a sodium alginate solution is single-dropped into a calcium solution, forming particles several μm in diameter – several other well-known methods (atomization, spraying and water-in-oil emulsification methods) can also be used to prepare alginate microparticles that are less than 200 μm in diameter (Gombotz and Wee, 1998; Safarikova *et al.*, 2003). Gelation occurs by an ionic interaction between the calcium ions and the carboxylate anions of G–G blocks as calcium ions diffuse from the external source into the droplet (Gu *et al.*, 2004). The main advantage of using alginate is that the alginate gelation process occurs under very mild conditions without using high temperatures or chemical crosslinking agents (Gu *et al.*, 2004), thus allowing the preservation of the viability and biological activity of the entrapped cells and other agents, respectively. However, the application of this system has been limited by poor mechanical stability. Combining alginate with other polymers and ceramic materials has been shown to obviate this feature (Sivakumar and Panduranga Rao, 2003). Recent studies have described a dual function of alginate microparticles as carriers for both cells and drugs, for application in diabetes (Ricci *et al.*, 2005), an idea that we also propose for bone tissue engineering applications using starch-based microparticles (Silva *et al.*, submitted).

Polyhydroxybutyrate is a polyester produced as granules by microorganisms (Fidler and Dennis, 1992; Saito and Doi, 1994; Jung *et al.*, 2005) and has been widely studied for tissue engineering applications (Chen and Wu, 2005), mainly for scaffold materials in combination with ceramic materials (Doyle *et al.*, 1991; Knowles *et al.*, 1992, 1993; Li and Chang, 2004; Li *et al.*, 2005) and also as a vehicle for drug delivery (Koosha and Muller, 1987; Koosha *et al.*, 1989).

Although polymers are seen as the most versatile class of materials, other classes have been widely studied for biomedical applications. Among these are ceramic materials, which are refractory, polycrystalline compounds, composed of ionically bonded compounds (de Groot,

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1983; Bajpai and Billote, 1995). Ceramic materials, such as *tricalcium phosphate* (TCP), *hydroxyapatite* (HA) and *bioactive glasses* (BG) have been widely investigated for hard tissue applications (Balla *et al*., 1991; Schepers *et al*., 1991, 1993, 1998; Meenen *et al*., 1992; Gatti *et al*., 1994; Schepers and Ducheyne, 1997; Chu *et al*., 2002; Huygh *et al*., 2002; Artzi *et al*., 2005; Kim *et al*., 2005; Chu *et al*., 2006), for filling, support and promotion of regeneration. Their role as drug delivery devices derives from their compatibility and physical characteristics, such as non-immunogenicity and degradability. Ceramics as drug delivery systems were basically in the form of porous materials and using the well-known ceramics mentioned above. As proposed by Ducheyne and co-workers (Nicoll *et al*., 1997; Santos *et al*., 1998, 1999), sol–gel technology for the formation of silica-based xerogels, which allows the introduction of functional proteins into glass-like materials, is a very interesting strategy that couples the bioactive behaviour of these systems with drug delivery capability and the additional ability to tailor other properties. Another major advantages relate to room temperature processing without the need for solvents.

Further details on ceramic materials in bone tissue engineering can be found in the second part of this review (Silva *et al*., •2006).

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5. Applications

Although some applications of materials in particulate form have been mentioned so far, Table 2 lists the major applications of such materials in the biomedical field. By far the greatest field of application for these materials, as found in the literature, is as drug delivery systems (DDS) and a few important principles regarding this field follow.

5.1. Basic concepts in drug delivery

Drug delivery routes are normally four (Langer, 1991; Nitsch and Banakar, 1994): (a) oral, for pills and syrups; (b) rectal; (c) intramuscular or intravenous, for solutions; and (d) topic, as for eye drops. These conventional systems of drug delivery have a major disadvantage, which is that with time the concentration of the bioactive agent decreases to a minimum, leading to the need for a new dose of bioactive agent within a short time interval. Another problem is that the bioactive agent will be distributed systemically throughout the body of the patient (Langer, 1991; Williams, 1998). In general, for oral drug delivery systems, the major problem is the rapid loss of activity of the therapeutic agent in the hostile environment of the stomach (Ponchel and Irache, 1998; Chellat *et al*., 2000; Grassi *et al*., 2001). It has also been observed that chemically attaching a bioactive agent to a polymer (bioactive agent–macromolecule conjugate) may alter such properties as its distribution in the body, rate of appearance in certain tissues, solubility or antigenicity (Langer, 1991; Kumar, 2000).

Since oral drug administration remains the easiest and the most comfortable method (Ponchel and Irache, 1998; Chellat *et al*., 2000; Pillai *et al*., 2001; Keegan *et al*., 2003), the microencapsulation of bioactive agents seemed to be an alternative to overcome the problem, allowing their slow release and protection against the acidic and enzymatic gastric environment (Berthold *et al*., 1998; Chellat *et al*., 2000). All these were reasons that led to the development of delivery systems, whose aim is to facilitate the dosage and duration of effect of the bioactive agent, causing minimal harm and improving patient compliance (Langer, 1991; Pillai *et al*., 2001), since they would allow a reduction of the dosage frequency (Kumar, 2000; Pillai and Panchagnula, 2001).

For drug delivery applications, the development of intravenously administrated carriers with blood circulation times long enough to continuously deliver bioactive compounds (Gref *et al*., 1994; Hrkach *et al*., 1997; Berton *et al*., 1999; Kumar, 2000), imaging agents or other entities to specific sites of action (Gref *et al*., 1994) has been a major challenge, since these carriers must possess a set of features compatible with the task they are required to perform. The desired features of such a carrier include (Gref *et al*., 1994; Soppimath *et al*., 2001):

Table 2. Major applications of materials in particulate form in the biomedical field (information compiled in the scope of this review)

Applications in the biomedical field	References
Chromatography	(Attebery, 1975; Rocca and Rouchouse, 1976; Fahlvik *et al*., 1990; Zhang and El Rassi, 1999; Spegel *et al*., 2001)
Imaging	(Cuthbertson *et al*., 2003; Cavalieri *et al*., 2005; Huang *et al*., 2006; Klibanov, 2006)
Filling of defects	(Schepers *et al*., 1991; Guicheux *et al*., 1997; Santos *et al*., 1998; Schepers *et al*., 1998; Falaize *et al*., 1999; Huygh *et al*., 2002; Day *et al*., 2004; Domingues *et al*., 2004; Gosain, 2004)
Adjuvants in vaccines	(Ohagan *et al*., 1993; Moore *et al*., 1995; Nakaoka *et al*., 1995; Ertl *et al*., 1996; Heritage *et al*., 1996; Ohagan *et al*., 1997; Stertman *et al*., 2006)
Cell culture	(Malda *et al*., 2003b; Xu *et al*., 2003; Zhang *et al*., 2003; Liu and Wu, 2004; Yokomizo *et al*., 2004; Hong *et al*., 2005; Melero-Martin *et al*., 2006)
Drug delivery	(Herrmann and Bodmeier, 1995; Guicheux *et al*., 1997; Berthold *et al*., 1998; Herrmann and Bodmeier, 1998; Jeong *et al*., 1998; Cruaud *et al*., 1999; Ganza-Gonzalez *et al*., 1999; Lam *et al*., 2000; Lim *et al*., 2000; Brigger *et al*., 2001; Delie *et al*., 2001; Han *et al*., 2001; Singh *et al*., 2001a, 2001b; van der Lubben *et al*., 2001; Dalpiaz *et al*., 2002; Demers *et al*., 2002; Ko *et al*., 2002; Morishita *et al*., 2002; Perez *et al*., 2002; Tamura *et al*., 2002; Yenice *et al*., 2002; Chinen *et al*., 2003; De Rosa *et al*., 2003; Perugini *et al*., 2003; Gu *et al*., 2004; Jeong *et al*., 2004; Jollivet *et al*., 2004; Wang *et al*., 2004; Norton *et al*., 2005; Silva *et al*., 2005)

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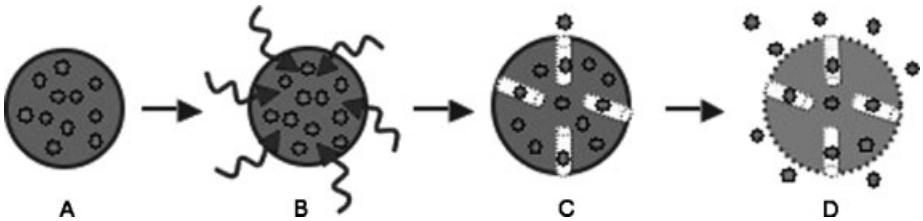

Figure 1. Schematic of the release● of entrapped bioactive agents from biodegradable polymeric particles. When the polymer device incorporating the active agent (A) is inserted into the environment, the fluid from the surrounding medium enters the matrix (B), causing swelling of the device (C). The fluid creates diffusion channels (C) and the incorporated active agent is released to the external environment (D). In the case of biodegradable polymers, device removal will occur by degradation of the material

1. That the agent to be encapsulated comprises a reasonably high weight fraction (loading) of the total carrier system (e.g. >30%).
2. The amount of agent used in the first step of the encapsulation process is incorporated into the final carrier (entrapment efficiency) at a reasonably high level (e.g. >80%).
3. The ability to be freeze-dried and reconstituted in solution without aggregation.
4. Biodegradability.
5. Small size.
6. Characteristics to prevent rapid clearance of the particles from the bloodstream.

Also, within drug delivery systems, it is essential to distinguish between sustained and controlled delivery systems, as these two types denote very different applications. *Sustained* systems imply that the bioactive agent is delivered over a prolonged period of time to overcome the highly periodic nature of tissue levels associated with conventional (enteral or parenteral) administration of single doses by tablets or fluids (Langer, 1991; Silvio *et al*., 1994; Williams, 1998). The term '*controlled*' is used generically to indicate any device in which some control is exerted over the way in which the bioactive agent is delivered to the tissues once it has been administrated to the patient (Langer, 1991; Silvio *et al*., 1994; Williams, 1998). This is best exemplified in the concept of thermally and pH-responsive materials, where variation in the temperature/pH discontinuously or sharply changes properties such as volume (De Jaeghere *et al*., 2000; Kawaguchi, 2000; Morishita *et al*., 2002). This concept is extremely important, as it can be used as a means to trigger the release of the entrapped bioactive agent, and thus allow control to be exerted over the system.

If other ways of controlling the system can be developed, besides temperature and pH, e.g. the presence of a certain agent would trigger the release of the incorporated agent, this could be used for other applications. One such application has been described by Cavanaugh *et al*. (2001), in which the microparticles released their load of adenovirus only upon cell contact, thus preventing inactivation of the viral load.

5.2. Polymers as the primary choice for DDS

The class of materials that has been most widely studied for drug delivery applications is the polymeric one. Polymeric delivery systems generally release bioactive agents by the following mechanisms (Langer, 1991; Chellat *et al*., 2000): diffusion, chemical reaction or solvent activation. The release of a bioactive agent from a matrix is primarily controlled by diffusion of the bioactive agent through the polymer, erosion of the polymer being an additional but important factor (Grassi *et al*., 2001). For biodegradable polymers, degradation is a chemical process, whereas erosion is a physical phenomenon dependent on dissolution and diffusion processes. As soon as the bioactive agent-containing polymer (A) comes into contact with the external liquid environment, it enters the polymer matrix (B), resulting in a swelling process (C), which allows the diffusion of the bioactive agent into the external environment (Grassi *et al*., 2001) (D), as illustrated in Figure 1. Factors influencing the release rate include the molecular size of the bioactive agent and loading percentage into the polymer, as well as polymer composition, molecular weight and the dimensions and shape of the matrix (Langer, 1991).

There are usually three distinct phases of release for biodegradable polymers (as shown in Figure 2):

1. A burst or initial period of rapid diffusion of active agent located close to the surface of the polymer.
2. A period of minimal release, during which the polymer is gradually hydrolysed in bulk but has not yet decreased sufficiently in molecular weight to allow an increased diffusional release of the active agent.

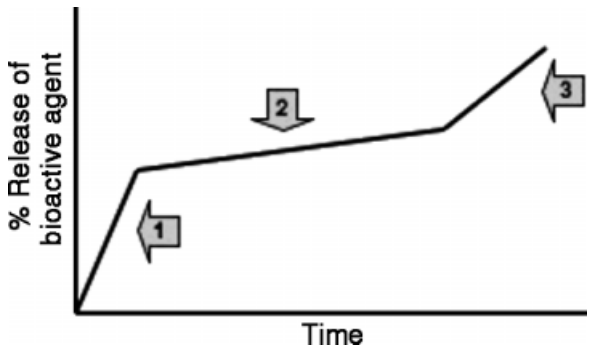

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Figure 2. Release profile for biodegradable polymers. The first stage (1) is a burst release, caused by diffusion of the bioactive agent located closer to the surface. The second stage (2) is caused by gradual degradation of the polymer, and the third stage (3) is characterized by massive degradation (solubilization) of the material

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3. The molecular weight of the polymer is sufficiently low as to allow its solubilization in the aqueous environment, and the release of the remaining active agent occurs as the polymer is eroded (Weinhold *et al.*, 1998; Berkland *et al.*, 2002).

This release profile is generally regarded as a problem common to many biodegradable systems, where the release is dependent upon degradation of the system with time (Silvio *et al.*, 1994), thus there is no possibilty of achieving any kind of control. This type of device is therefore more suitable for sustained rather than controlled release.

In short, and for drug delivery systems in general, the bulk properties of the polymer that need to be considered include (Langer, 1991; Pillai and Panchagnula, 2001):

- Molecular weight.
- Physical properties (bioadhesiveness, mechanical stability).
- Solubility based on the release mechanism (diffusion or dissolution-controlled).
- Site of action.

Bioadhesiveness needs to be taken into account when drug delivery systems are targeted to mucosal tissues, whereas polymers for ocular devices have to be water- or lipid-soluble in addition to having good film-forming ability and mechanical stability for good retention. The structural properties of the matrix, its micromorphology and pore size, are important with respect to mass transport (of water) into and (of bioactive agent) out of the polymer (Pillai and Panchagnula, 2001).

Of great importance, however, is the assurance that the biological activity of the incorporated agent is preserved throughout manufacturing, storage, delivery and release (King and Patrick, 2000). This, together with the release profile, is of particular importance when designing a delivery system, because much as the release profile may be adequate, there is no point in having it if the biological activity of the agent to be delivered is lost during processing. This idea is mostly coupled with the use of solvents in the production of the delivery system because, as mentioned before, organic solvents might cause inactivation of the agent to be loaded into the system. For growth factors, BSA has been shown to be protective when used as an adjuvant during the loading process (Kim and Valentini, 1997; Morlock *et al.*, 1998), but methods that obviate this step are needed.

Regarding the release profile, strategies to control or render it more adequate for a particular application, by means of modifying parameters such as the surface (by coating, chemical modification) or creating dual-release systems (layers of materials that can incorporate different molecules) (Kim and Valentini, 1997; Vaz *et al.*, 2004), can greatly improve the properties of several materials, and should be actively pursued.

6. Conclusions

Materials in the particulate form have been employed in a diversity of biomedical applications. This derives from their properties, such as size, surface area, and physicochemical properties, which stem from the diverse materials and methods combined for their production. Within the range of applications, drug delivery has had a highlighted role, because of its promise as a means of overcoming limitations inherent to conventional delivery methods. Currently, the use of these systems in innovative strategies, where they can play a multitude of roles – delivery of bioactive agents, structural support and carriers of cells – makes it mandatory for researchers to become even more creative in developing such a system. Within this perspective, an area of tissue engineering that can obviously benefit from the specific properties of materials in particulate form is bone tissue engineering.

Part B of this review (this issue) deals with the roles – played and potential – of particle-based systems in this specific subset of tissue engineering applications, bone tissue engineering.

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