Review Article

Therapeutic Strategies Based on Polymeric Microparticles

C. Vilos\(^{1,2}\) and L. A. Velasquez\(^{1,2}\)

\(^{1}\) Center for Integrative Medicine and Innovative Science (CIMIS), Facultad de Medicina, Universidad Andrés Bello, Santiago, Echaurren 183, 8370071 Santiago, Chile

\(^{2}\) Center for the Development of Nanoscience and Nanotechnology (CEDENNA), Avenida Ecuador 3493, 9170124 Santiago, Chile

Correspondence should be addressed to L. A. Velasquez, luis.velasquez@unab.cl

Received 14 December 2011; Revised 28 February 2012; Accepted 13 March 2012

Academic Editor: Soldano Ferrone

Copyright © 2012 C. Vilos and L. A. Velasquez. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The development of the field of materials science, the ability to perform multidisciplinary scientific work, and the need for novel administration technologies that maximize therapeutic effects and minimize adverse reactions to readily available drugs have led to the development of delivery systems based on microencapsulation, which has taken one step closer to the target of personalized medicine. Drug delivery systems based on polymeric microparticles are generating a strong impact on preclinical and clinical drug development and have reached a broad development in different fields supporting a critical role in the near future of medical practice. This paper presents the foundations of polymeric microparticles based on their formulation, mechanisms of drug release and some of their innovative therapeutic strategies to board multiple diseases.

1. Introduction

The discovery and development of new drugs for the treatment of diseases is a lengthy and costly process \([1]\). The drug development typically requires about 14 years, and studies demonstrated that by the year 2013 the cost to reach phase III of clinical trials will be around $1.9 billion \([2]\). Moreover, the number of drug approvals is minimal, reaching less than 32 new molecular entities per year last decade (NME) \([3]\). The long time required to develop a new drug application and its high costs illustrate the need to develop new therapeutic strategies, which improve the effectiveness of available drugs. Figure 1 shows a scheme of the different stages of drug development required by the Food and Drug Administration (FDA) from discovery of an NME until its marketing.

The conventional administration of drugs (i.e., tablets, capsules, and injections), and the limited solubility of the drugs often require high doses in order to reach enough concentrations of drug at its site of action to achieve an appropriate therapeutic effect \([4]\). In other cases, the application of some therapeutic protocols requires the administration of repeated doses to maintain an adequate concentration of drug in the bloodstream and provide therapeutic action for long periods of time \([5]\). The high blood concentrations of drugs and the administration of multiple doses can generate significative fluctuations of the drug in the bloodstream, which can reach the toxicological parameters, and generate adverse reactions for the patients. All this drawbacks have lead to develop new therapeutic strategies more effective and with fewer side effects for patients.

The advancement of materials science and pharmaceutical technology has allowed the creation of several strategies for drug delivery such as osmotic pumps \([6, 7]\), liposomes \([8, 9]\), hydrogels \([10–12]\), and polymeric microparticles \([13, 14]\). The main goals of those drug delivery devices are the generation of a sustained release of drug over time, a reduced number of doses required to the treatment of diseases, and the protection of the drugs from inactivation before reaching the target tissue.

The polymeric microparticles (p-MPs) as a drug delivery strategy have advantages over other systems since they do not require surgical procedures for their application or removal from the body like the osmotic pumps. Furthermore, the p-MPs have exhibited a better stability in the biological environment than liposomes, and their highly reproducible formulation methods provide support to encapsulate hydrophilic and hydrophobic drugs, which gives them a wide range of therapeutic applications.
On the other hand, the release of drugs from p-MPs shows several benefits compared with the conventional drug administration methods, which include their ability to modulate the rate of drugs release for a long time periods and their capacity to reduce the drug toxicity.

The extensive benefits of administration of encapsulated drugs into p-MPs serve as the foundation for many future medical endeavors. This paper provides an overview of the basics of polymeric microparticles based on their formulation, their mechanisms of drug delivery, and their applications in the treatment of diseases.

2. Polymers

The use of biodegradable and biocompatible polymers has generated significant advances in modern medicine because it has impacted different fields of biomedicine, which include tissue engineering and diagnostic and therapeutic strategies [15, 16].

The p-MPs, as drug delivery systems, have been developed using different natural and synthetic polymers [17]. The natural polymers include chitosan [18], alginate [19], dextran [20], gelatin [21], and albumin [22], and the synthetic polymers comprise to poly(lactide-co-glycolide) (PLGA) [23], (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) [24], poly(sebacic anhydride) [25], poly(ε-caprolactone), among others [26].

During the last years, the advances in materials sciences have generated different polymers tailored for drug-conjugated, which include smart response that supported the development of novel drug delivery systems [27]. Recently, the use of thermoresponsive (i.e., NIPAAm and CMCTS-g-PDEA) [28, 29] and pH-responsive (i.e., Eudragit L100, Eudragit S and AQQAT AS-MG) [30, 31] polymers in the formulation of p-MPs was described, which promises improved approaches to the delivery of drugs.

3. Microencapsulation Methods

Understanding the physicochemical properties of drugs is essential before determining the appropriate method for the synthesis of the p-MPs because the wide range of pharmaceutical agents such as peptide, proteins, nucleic acids, antibiotics, and chemotherapeutics, have distinctive solubility and stability at different conditions (i.e., temperature, pH, and organic solvents) [32, 33]. On the other hand, the fundamental properties of the polymers for the development of p-MPs involve their solubility and stability, their biodegradability and biocompatibility [34], and their physical (i.e., crystallinity and glass transition temperature) and mechanical properties (i.e., strength, elongation, and Young’s modulus) [35].

The microemulsion methods provided a highly reproducible platform to formulate p-MPs with a uniform size and predictable inner structure, which can be determined by the use of single- or double-emulsion process. The single-emulsion method consists in an oil/water (O/W) or water/oil (W/O) emulsion that generates solid spherical microparticles, with a polymeric inner core, which is favorable to encapsulate hydrophobic drugs [36]. On the other hand, the proteins and other hydrophilic drugs are usually encapsulated using the water/oil/water (W/O/W) double-emulsion method, because it generates core-shell microparticles characterized by hydrophilic pockets [37]. Figure 2 presents a scheme of the morphology of p-MPs, formulated by the single- and double-emulsion-evaporation method. Studies about the conditions of preparation of p-MPs have shown that high concentrations of polymers generate an increase of the particles size and a decrease-loading yield. This phenomenon may be attributed to the increment in the viscosity of the polymeric phase that emulsified to drug [38]. In addition, other studies have described that the intensity with which it generates the emulsion affects its internal conformation of microparticles. Mao et al. (2007) showed by transmission electron microscopy that a high intensity of emulsion reduced significantly the internal porosity of p-MPs [39].

Despite the high loading efficiency that supports the conventional emulsion methods, recently, innovative procedures based on double-emulsion method such as the solid/oil/water (S/O/W), the solid/oil/oil (S/O/O), and the water/oil/oil (W/O/O) methods have been described, which allows to maintain their complete structural and functional integrity of proteins after the microencapsulation process [40].

Another method to synthesize polymeric micro- and nanoparticles is through microfluidic technology [41–43]. This technique generates droplets or particles in a device (T-junction) supplied with the polymers and drugs dissolved in immiscible solutions, followed by the solidification of the droplets by means of polymerization or solvent evaporation [44]. The main advantage of microfluidics is to obtain large volumes of particles, which have a highly uniform and
predictable size, which determines their potential use in the synthesis of multiple polymeric colloids loaded with drugs and pharmaceutical application [45].

Spray-drying is a method widely used in the pharmaceutical and biotechnology industry for the synthesis of p-MPs because it allows to produce large quantities of particles with spherical and amorphous morphology and it can display roughness or porosity in their surface [46]. In the last years, spray-freeze-drying methods were able to formulate p-MPs loaded with poor water-soluble drugs and temperature-sensitive molecules. In addition, these methods produce microparticles with controlled size and porosity, making them particularly attractive to load a wide range of drugs with biomedical interest [47, 48].

Figure 3 illustrates images of p-MPs prepared in our laboratory from PLGA and PHBV and characterized using a confocal laser scanning microscopy, a transmission electron microscopy, and a scanning electron microscopy.

4. Mechanisms of Drug Release

The release of drugs from p-MPs arises as a consequence of the degradation and/or erosion of the polymeric device [49]. Therefore, the knowledge about the chemical nature of polymers is essential to understand the mechanism of release. In the cases when degradation of polymeric matrix occurs, the drug diffuses through the channels generated by the breaking of the polymer chains without loss of volume in the particle. In contrast, when the polymeric carrier undergoes erosion, together with the polymer mass loss the drug is released. In this case, there is a decrease in volume of polymeric matrix according to the drug release [50–52].

Studies have demonstrated that the rate of degradation of polyesters such as PLGA or PHBV is inversely proportional to the molecular weight of the polymers. Furthermore, the degradation time of PLGA (copolymer) depends on the ratio of its monomers, poly(lactic acid) and poly(glycolic acid), such that polymers containing a higher concentration of poly(lactic acid) exhibited a slower degradation [49]. Others studies have showed that high temperatures and low pH condition increase the degradation of polymers with a subsequent increment of the release rate of drug encapsulated into polymeric microparticles [53, 54].

5. Therapeutic Strategies Based on Polymeric Microparticles

The p-MPs formulations have unique properties in terms of particle size, shape, inner structure, porosity, drug loading, encapsulation efficiency, and profile of release [55, 56]. Therefore, the selection of an appropriate route of administration of p-MPs (i.e., intramuscular, intraperitoneal, intra-articular, and intrapulmonary) is a critical element to achieve an expected pharmacological action.

5.1. Oncologic Disease. Cancer is one of the most significant causes of death worldwide, and the gliomas are the leading brain tumors of the nervous system in adults. It has been described that gliomas have an exceptional ability to infiltrate to healthy tissue, which makes them extremely difficult to be treated [57]. Chemotherapy is one of the most widely used strategies to treat cancer. However, its low specificity and high toxicity generate negative effects for patients that may cause serious complications, affecting in some cases other healthy physiological systems [58–60]. Therefore, the administration of chemotherapeutic agents loaded in polymeric microparticles provides a secure platform to achieve a sustained release in the cancerous tissue, decreasing the use of high doses of drugs and their potential harmful effects [61, 62].

Recently, Y. H. Zhang et al. (2010) described a study using orthotopic implantation of C6 glial cells in a rat brain to evaluate the activity of polymeric microparticles loaded with
temozolomide (tm-MPs) injected into the tumor area. The results showed a better survival to the group that received tm-MPs (46 days) than the control group treated orally with nonencapsulated temozolomide (27 days). Moreover, through magnetic resonance imaging (MRI), they found that the group treated with tm-MPs showed the greatest reduction of the tumor size and decrease of the proliferative activity of cells. Furthermore, the cells also presented an increased rate of apoptosis, suggesting that the encapsulation of temozolomide in p-MPs enhanced its chemotherapeutic effect [63]. Other in vitro studies, using similar strategies for the localized release of paclitaxel and cisplatin from polymeric microparticles, also exhibited greater efficacy than the administration of nonencapsulated drug [64, 65].

In the last few decades, the use of intraperitoneal chemotherapy has showed high efficacy in the treatment of peritoneal and ovarian cancer, which has allowed enhancing the survival of many patients [66–68]. However, the use of intraperitoneal therapy also has presented some limitations that increase the risk of infection due to the use of catheters for the administration of drugs [69]. Other drawbacks have been associated with the use of chemotherapeutic agents that present hematologic and hepatic toxicity such as cisplatin, melphalan, and etoposide [70–73] and the slow absorption of less toxic drugs, such as paclitaxel, mitoxantrone, and doxorubicin, which do not have a deep tumor penetration [74–77]. Studies have shown that intraperitoneal treatment of ovarian cancer in mice model with paclitaxel-loaded p-MPs has overcome the limitations of free paclitaxel therapy. The administration of paclitaxel-loaded polymeric microparticles exhibited biphasic release kinetics, characterized by a rapid initial release that was sufficient to prevent tumor proliferation and a second phase of sustained release that allowed for the gradual eradication of the tumor [78]. Furthermore,
intraperitoneal chemotherapy based on microparticles has reduced the removal of the drug from the peritoneal cavity, leading to slow systemic absorption and maintaining the therapeutic concentrations for longer periods of time (10 to 45 times) in the intraperitoneal region, which generated a significant increase of survival groups treated with p-MPs [79].

5.2. Cardiac Disease. Cardiac dysfunction followed by acute myocardial infarction is one of the leading causes of death worldwide [80, 81]. The excessive inflammatory response after the ischemic heart disease generates a chronic elevation of inflammatory cytokines and reactive oxygen species, which may lead to cardiac dysfunction [82–84]. Recently, the release of anti-inflammatory drugs from polymeric microparticles administrated via intracardiac injection has shown promising results to treat the myocardial infarction and other inflammatory diseases, due to blocking the activation of macrophages and thereby reducing the apoptosis or necrosis of cardiomyocytes [85, 86].

Recent therapeutic approaches to prevent the development of cardiac failure after myocardial infarct include the direct administration of proangiogenic growth factors [87] and stem cell therapy [88, 89]. However, despite the promising results obtained in animal models and clinical trials [90, 91], some studies have shown limited effectiveness with the administration of growth factors because the native and recombinant proteins exhibited a short half-life and instability [92, 93]. In order to improve those drawbacks, Formiga et al. (2010) have described the synthesis of PLGA microparticles loaded with the cytokine VEGF165, a proangiogenic growth factor, and evaluated their vasculogenic effect in a rat model of myocardial infarction. The results obtained showed an excellent angiogenic and arteriogenic effect induced by the sustained release of the cytokine VEGF165 from the polymeric microparticles [94].

5.3. Immunological Response. Studies under preclinical drug development based on p-MPs have been focusing on the development of strategies that reduce organ rejection and prevent autoimmune diseases. Wu and Horuzsko (2009) proposed a method for improving immune tolerance by dendritic cell receptor stimulation with ILTs (immunoglobulin-like transcripts). Dual coating the surface of p-MPs with the HLA-G1-peptide, an ILTs receptor ligand, and a monoclonal antibody against the CD11c marker improved the modulation of dendritic cells. This system could provide a method to regulate specific immune responses that occur during transplantation, autoimmunity, and allergy [95].

New approaches in the vaccine field include polymeric microparticles loaded with antigens against bacterial pathogens such as Vibrio cholerae [96], Pseudomonas aeruginosa [97], and Bordetella pertussis [98], providing a potent and long-time immune response.

On the other hand, the gene delivery from p-MPs provides a highly attractive strategy because it can generate the in situ expression of target antigens and preserve the native structure of proteins [99]. In addition, the p-MPs can codeliver DNA and adjuvants generating an improved immune response [100, 101]. The current strategies have used polymers with cationic charge such polyethyleneimine to increase the loading and encapsulation efficiency of DNA inside particles [102]. Despite great advances in the development of DNA vaccines and their potential against several diseases, the biggest challenge is to establish the safety of using DNA vaccines in human medicine [103].

5.4. Diabetes. In the last decade, there was a notable increase of diabetes around the world [104]. The islet transplantation to patients with severe diabetes has improved their quality of life [105, 106]. However, these transplanted cells are highly susceptible to oxidative stress, which may decrease their proliferative capacity and lead to cellular death [107, 108]. The antioxidant effect of vitamin D3-loaded polymeric microparticles was evaluated in cultured islets isolated from adult rat. The results exhibited a significantly increased insulin production compared to the untreated control groups [109].

Other studies have described novel strategies for the oral and parenteral administration of insulin-loaded PLGA and poly(N-vinylcaprolactam-co-methacrylic acid) microparticles [110]. The particles were synthesized using flow focusing, double-emulsion-solvent evaporation method, and the free radical polymerization procedure [111, 112].

Recently, Technosphere/Insulin, an inhalable formulation under development by MannKind Corporation (Valencia, CA), have initiated the Phase III in both Europe and the US. The Technosphere technology allows to administer insulin via pulmonary and offers several competitive advantages over other pulmonary drug delivery systems. Recent studies have been conducted to analyze the lung deposition and clearance after administration. Their findings showed a uniform distribution throughout the lungs and absorption of insulin into the systemic circulation. Based on the results of clinical trials and on published reports, Technosphere is better than other inhaled insulin platforms [113].

6. Prospects

Multidisciplinary work in the 21st century of physicians, biomaterials and chemical engineers, and researchers in biotechnology has allowed creating new frontiers to the landscape of pharmaceuticals.

The incorporation of polymeric microparticles as carriers of drugs in medical practice improves the disadvantages generated by elevated plasma levels short-term and adverse reactions caused by the traditional pharmaceutical formulation. It also creates novel strategies for localized and sustained release sites with low vascular permeability. Moreover, the wide range of biomaterials with different physicochemical properties allow the creation of smart systems for drug delivery, which promote an optimal response and long-term efficacy in the treatments of different diseases.

The development of polymeric microparticles, as drug delivery systems, has set the foundation for the emerging and significant role of nanomedicine based on polymeric
nanoparticles as carriers of drugs [114–116]. We are optimistic about the marketing in the near future of innovative technology based on polymeric microparticles because it may generate a new era in modern medicine.

**Acknowledgments**

Support by FONDECYT Grant 1090589, by BASAL Grant FB0807, and by CONICYT under “Proyecto Tesis en la Industria TPI06” is gratefully acknowledged.

**References**

[1] J. M. Reichert, “Trends in development and approval times for new therapeutics in the United States,” *Nature Reviews Drug Discovery*, vol. 2, no. 9, pp. 695–702, 2003.

[2] J. A. DiMasi, R. W. Hansen, and H. G. Grabowski, “The price of innovation: new estimates of drug development costs,” *Journal of Health Economics*, vol. 22, no. 2, pp. 151–185, 2003.

[3] A. Mullard, “2011 FDA drug approvals,” *Nature Reviews Drug Discovery*, vol. 11, pp. 91–94, 2012.

[4] R. Ottenbrite, “Controlled release technology,” in *Encyclopedia of Polymer Science and Engineering*, J. I. Kroschwitz, Ed., Wiley, New York, NY, USA, 1990.

[5] A. D. Bendrea, L. Cianga, and I. Cianga, “Review paper: progress in the field of conducting polymers for tissue engineering applications,” *Journal of Biomedical Materials Research A*, vol. 96, no. 3, pp. 580–598, 2011.

[6] A. Mullard, “2011 FDA drug approvals,” *Nature Reviews Drug Discovery*, vol. 2, no. 9, pp. 695–702, 2003.

[7] A. Jesorka and O. Orwar, “Liposomes: technologies and analytical applications,” *Annual Review of Analytical Chemistry*, vol. 1, no. 1, pp. 801–832, 2008.

[8] W. T. Al-Jamal and K. Kostarelos, “Liposomes: from a clinically established drug delivery system to a nanoparticle platform for theranostic nanomedicine,” *Accounts of Chemical Research*, vol. 44, no. 10, pp. 1094–1104, 2011.

[9] A. Desoky and O. Orwar, “Liposomes: technologies and analytical applications,” *Annual Review of Analytical Chemistry*, vol. 1, no. 1, pp. 801–832, 2008.

[10] A. S. Hoffmann, “Hydrogels for biomedical applications,” *Advanced Drug Delivery Reviews*, vol. 54, no. 1, pp. 3–12, 2002.

[11] J. Cabral and S. C. Moratti, “Hydrogels for biomedical applications,” *Future Medicinal Chemistry*, vol. 3, pp. 1877–1888, 2011.

[12] N. A. Peppas, Y. Huang, M. Torres-Lugo, J. H. Ward, and J. Zhang, “Physicochemical foundations and structural design of hydrogels in medicine and biology,” *Annual Review of Biomedical Engineering*, vol. 2, no. 2000, pp. 9–29, 2000.

[13] W. Jiang, R. K. Gupta, M. C. Deshpande, and S. P. Schwendeman, “Biodegradable poly(lactic-co-glycolic acid) microparticles for injectable delivery of vaccine antigens,” *Advanced Drug Delivery Reviews*, vol. 57, no. 3, pp. 391–410, 2005.

[14] E. Mathiowitz, J. S. Jacob, Y. S. Jong et al., “Biologically erodible microspheres as potential oral drug delivery systems,” *Nature*, vol. 386, no. 6623, pp. 410–414, 1997.

[15] B. D. Ulery, L. S. Nair, and C. T. Laurencin, “Biomedical applications of biodegradable polymers,” *Journal of Polymer Science B*, vol. 49, no. 12, pp. 832–864, 2011.
[30] K. Rizi, R. J. Green, O. Khutoryanskaya, M. Donaldson, and A. C. Williams, “Mechanisms of burst release from pH-responsive polymeric microparticles,” *Journal of Pharmacy and Pharmacology*, vol. 63, no. 9, pp. 1141–1155, 2011.

[31] M. A. Alhnan, E. Kidia, and A. W. Basit, “Spray-drying enteric polymers from aqueous solutions: a novel, economic, and environmentally friendly approach to produce pH-responsive microparticles,” *European Journal of Pharmacuetics and Biopharmaceutics*, 2011.

[32] M. N. Aamir and M. Ahmad, “Production and stability evaluation of modified-release microparticles for the delivery of drug combinations,” *AAPS PharmSciTech*, vol. 11, no. 1, pp. 351–355, 2010.

[33] A. Wieber, T. Selzer, and J. Kreuter, “Characterisation and stability studies of a hydrophilic decapeptide in different adjuvant drug delivery systems: a comparative study of PLGA nanoparticles versus chitosan-dextran sulphate microparticles versus DOTAP-liposomes,” *International Journal of Pharmaceutics*, vol. 421, no. 1, pp. 151–159, 2011.

[34] G. Winzenburg, C. Schmidt, S. Fuchs, and T. Kissel, “Biodegradable polymers and their potential use in perarterial veterinary drug delivery systems,” *Advanced Drug Delivery Reviews*, vol. 56, no. 10, pp. 1453–1466, 2004.

[35] I. Engelberg and J. Kohn, “Physico-mechanical properties of degradable polymers used in medical applications: a comparative study,” *Biomaterials*, vol. 12, no. 3, pp. 292–304, 1991.

[36] C. Yang, D. Plackett, D. Needham, and H. M. Burt, “PLGA and PHBV microsphere formulations and solid-state characterization: possible implications for local delivery of fusidic acid for the treatment and prevention of orthopaedic infections,” *Pharmaceutical Research*, vol. 26, no. 7, pp. 164–1656, 2009.

[37] X. Jia, D. Chen, X. Jiao, and S. Zhai, “Environmentally-friendly preparation of water-dispersible magnetite nanoparticles,” *Chemical Communications*, no. 8, pp. 968–970, 2009.

[38] H. Zhao, J. Gagnon, and U. O. Hafeli, “Process and formulation variables in the preparation of injectable and biodegradable magnetic microspheres,” *Biomagnetic Research and Technology*, vol. 5, p. 2, 2007.

[39] S. Mao, J. Xu, C. Cai, O. Germershaus, A. Schaper, and T. Kissel, “Effect of WOW process parameters on morphology and burst release of FITC-dextran loaded PLGA microspheres,” *International Journal of Pharmaceutics*, vol. 334, no. 1-2, pp. 137–148, 2007.

[40] D. Yejian and V. Budd, “Novobiocin: activity in vitro and in experimental tuberculosis,” *American Review of Tuberculosis*, vol. 76, no. 2, pp. 272–278, 1957.

[41] Z. T. Cygan, J. T. Cabral, K. L. Beers, and E. J. Amis, “Microfluidic platform for the generation of organic-phase microreactors,” *Langmuir*, vol. 21, no. 8, pp. 3629–3634, 2005.

[42] R. Karnik, F. Gu, P. Basto et al., “Microfluidic platform for controlled synthesis of polymeric nanoparticels,” *Nano Letters*, vol. 8, no. 9, pp. 2906–2912, 2008.

[43] P. M. Valencia, P. A. Basto, L. Zhang et al., “Single-step assembly of homogenous lipid-polymeric and lipid-quantum dot nanoparticles enabled by microfluidic rapid mixing,” *ACS Nano*, vol. 4, no. 3, pp. 1671–1679, 2010.

[44] G. E. Christopher, N. N. Noharuddin, J. A. Taylor, and S. L. Anna, “Experimental observations of the squeezing-to-dripping transition in T-shaped microfluidic junctions,” *Physical Review E*, vol. 78, no. 3, Article ID 036317, 2008.

[45] Q. Xu, M. Hashimoto, T. T. Dang et al., “Preparation of monodisperse biodegradable polymer microparticles using a microfluidic flow-focusing device for controlled drug delivery,” *Small*, vol. 5, no. 13, pp. 1575–1581, 2009.

[46] R. Vehring, “Pharmaceutical particle engineering via spray drying,” *Pharmaceutical Research*, vol. 25, no. 5, pp. 999–1022, 2008.

[47] T. Niwa, H. Shimabara, M. Kondo, and K. Danjo, “Design of porous microparticles with single-micron size by novel spray freeze-drying technique using four-fluid nozzle,” *International Journal of Pharmaceutics*, vol. 382, no. 1-2, pp. 88–97, 2009.

[48] S. M. D’Addio, J. G. Chan, P. C. Kwok, R. K. Prud’homme, and H. K. Chan, “Constant size, variable density aerosol particles by ultrasonic spray freeze drying,” *International Journal of Pharmaceutics*, vol. 427, no. 2, pp. 185–191, 2012.

[49] A. Göpferich, “Mechanisms of polymer degradation and erosion,” *Biomaterials*, vol. 17, no. 2, pp. 103–114, 1996.

[50] A. Göpferich and J. Tessmar, “Polyanhydrodegradation and erosion,” *Advanced Drug Delivery Reviews*, vol. 54, no. 7, pp. 911–931, 2002.

[51] F. V. Burkersroda, L. Schell, and A. Göpferich, “Why degradable polymers undergo surface erosion or bulk erosion,” *Biomaterials*, vol. 23, no. 21, pp. 4221–4231, 2002.

[52] X. Xu and P. I. Lee, “Programmable drug delivery from an erodible association polymer system,” *Pharmaceutical Research*, vol. 10, no. 8, pp. 1144–1152, 1993.

[53] N. Faisant, J. Siepmann, and J. P. Benoit, “PLGA-based microparticles: elucidation of mechanisms and a new, simple mathematical model quantifying drug release,” *European Journal of Pharmaceutical Sciences*, vol. 15, no. 4, pp. 355–366, 2002.

[54] B. S. Zohnik and D. J. Burgess, “Effect of acidic pH on PLGA microsphere degradation and release,” *Journal of Controlled Release*, vol. 122, no. 3, pp. 338–344, 2007.

[55] H. T. Wang, H. Palmer, R. J. Linhardt, D. R. Flanagan, and E. Schmitt, “Degradation of poly(ester) microspheres,” *Biomaterials*, vol. 11, no. 9, pp. 679–685, 1990.

[56] R. van Dijkhuizen-Radersma, S. C. Hesseling, P. E. Kaim, K. De Groot, and J. M. Bezemer, “Biomaterials and E. Schmitt, “Degradation of poly(ester) microspheres: in vitro and in vivo evaluation,” *Biomaterials*, vol. 23, no. 24, pp. 4719–4729, 2002.

[57] T. Demuth and M. E. Berens, “Molecular mechanisms of glioma cell migration and invasion,” *Journal of Neuro-Oncology*, vol. 70, no. 2, pp. 217–228, 2004.

[58] C. H. Chang, J. Horton, D. Schoenfeld et al., “Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. A joint radiation therapy oncology group and Eastern cooperative oncology group study,” *Cancer*, vol. 52, no. 6, pp. 997–1007, 1983.

[59] V. R. Recinos, B. M. Tyler, K. Bekelis et al., “Combination of intracranial temozolomide with intracranial carmustine improves survival when compared with either treatment alone in a rodent glioma model,” *Neurosurgery*, vol. 66, no. 3, pp. 530–537, 2010.

[60] T. Walbert, M. R. Gilbert, M. D. Groves et al., “Combination of 6-thioguanine, capecitabine, and celecoxib with temozoloamide or lonstatine for recurrent high-grade glioma,” *Journal of Neuro-Oncology*, vol. 102, no. 2, pp. 273–280, 2011.

[61] P. Menei and J. P. Benoit, “Implantable drug-releasing biodegradable microspheres for local treatment of brain
ischemia-reperfusion model,” *Journal of Controlled Release*, vol. 147, no. 1, pp. 30–37, 2010.

[95] J. Wu and A. Horuzsko, “Expression and function of immunoglobulin-like transcripts on tolerogenic dendritic cells,” *Human Immunology*, vol. 70, no. 5, pp. 353–356, 2009.

[96] G. Ano, A. Esquisabel, M. Pastor et al., “A new oral vaccine candidate based on the microencapsulation by spray-drying of inactivated *Vibrio cholerae*,” *Vaccine*, vol. 29, no. 34, pp. 5758–5764, 2011.

[97] S. Taranejoo, M. Janmaleki, M. Rafienia, M. Kamali, and M. Mansouri, “Chitosan microparticles loaded with exotoxin A subunit antigen for intranasal vaccination against *Pseudomonas aeruginosa*: an in vitro study,” *Carbohydrate Polymers*, vol. 83, no. 4, pp. 1854–1861, 2011.

[98] S. Garlapati, N. F. Eng, T. G. Kiros et al., “Immunization with PCEP microparticles containing pertussis toxoid, CpG ODN and a synthetic innate defense regulator peptide induces protective immunity against pertussis,” *Vaccine*, 2011.

[99] D. T. O’Hagan, M. Singh, and J. B. Ulmer, “Microparticles for the delivery of DNA vaccines,” *Immunological Reviews*, vol. 199, pp. 191–200, 2004.

[100] R. K. Evans, D. M. Zhu, D. R. Casimiro et al., “Characterization and biological evaluation of a microparticle adjuvant formulation for plasmid DNA vaccines,” *Journal of Pharmaceutical Sciences*, vol. 93, no. 7, pp. 1924–1939, 2004.

[101] A. Caputo, K. Sparnacci, B. Ensolì, and L. Tondelli, “Functional polymeric nano/microparticles for surface adsorption and delivery of protein and DNA vaccines,” *Current Drug Delivery*, vol. 5, no. 4, pp. 230–242, 2008.

[102] S. P. Kasturi, K. Sachaphibulkij, and K. Roy, “Covalent conjugation of polyethyleneimine on biodegradable microparticles for delivery of plasmid DNA vaccines,” *Biomaterials*, vol. 26, no. 32, pp. 6375–6385, 2005.

[103] D. N. Nguyen, J. J. Green, J. M. Chan, R. Langer, and D. G. Anderson, “Polymeric materials for gene delivery and DNA vaccination,” *Advanced Materials*, vol. 21, no. 8, pp. 847–867, 2009.

[104] I. G. de Quevedo, L. Siminerio, R. L’Heveder, and K. M. Narayan, “Challenges in real-life diabetes translation research: early lessons from BRIDGES projects,” *Diabetes Research and Clinical Practice*, vol. 95, no. 3, pp. 317–325, 2012.

[105] S. Matsumoto, H. Noguchi, Y. Yonekawa et al., “Pancreatic islet transplantation for treating diabetes,” *Expert Opinion on Biological Therapy*, vol. 6, no. 1, pp. 23–37, 2006.

[106] N. Onaka, G. B. Klintmalm, and M. F. Levy, “Pancreatic islet cell transplantation: a treatment strategy for type 1 diabetes mellitus,” *Nutrition in Clinical Practice*, vol. 19, no. 2, pp. 154–164, 2004.

[107] R. P. Robertson and J. S. Harmon, "Pancreatic islet β-cell and oxidative stress: the importance of glutathione peroxidase," *FEBS Letters*, vol. 581, no. 19, pp. 3743–3748, 2007.

[108] H. Kaneto, Y. Kaijimo, Y. Fujitani et al., “Oxidative stress induces p21 expression in pancreatic islet cells: possible implication in beta-cell dysfunction,” *Diabetologia*, vol. 42, no. 9, pp. 1093–1097, 1999.

[109] G. Luca, G. Basta, R. Calafiore et al., “Multifunctional microcapsules for pancreatic islet cell entrapment: design, preparation and in vitro characterization,” *Biomaterials*, vol. 24, no. 18, pp. 3101–3114, 2003.

[110] J. Emami, H. Hamishehkar, A. R. Najafabadi et al., “A novel approach to prepare insulin-loaded poly (lactic-co-glycolic acid) microcapsules and the protein stability study,” *Journal of Pharmaceutical Sciences*, vol. 98, no. 5, pp. 1712–1731, 2009.

[111] R. C. Mundargi, V. Rangaswamy, and T. M. Aminabhavi, “Poly(N-vinylcaprolactam-co-methacrylic acid) hydrogel microparticles for oral insulin delivery,” *Journal of Microencapsulation*, vol. 28, no. 5, pp. 384–394, 2011.

[112] M. J. Cozar-Bernal, M. A. Holgado, J. L. Arias et al., “Insulin-loaded PLGA microparticles: flow focusing versus double emulsion/solvent evaporation,” *Journal of Microencapsulation*, vol. 28, no. 5, pp. 430–441, 2011.

[113] S. S. Iyer, W. H. Barr, and H. T. Karnes, “A ‘biorelevant’ approach to accelerated in vitro drug release testing of a biodegradable, naltrexone implant,” *International Journal of Pharmaceutics*, vol. 340, no. 1–2, pp. 119–125, 2007.

[114] J. M. Chan, P. M. Valencia, L. Zhang, R. Langer, and O. C. Farokhzad, “Polymeric nanoparticles for drug delivery,” *Methods in Molecular Biology*, vol. 624, pp. 163–175, 2010.

[115] J. Shi, Z. Xiao, N. Kamaly, and O. C. Farokhzad, “Self-assembled targeted nanoparticles: evolution of technologies and bench to bedside translation,” *Accounts of Chemical Research*, vol. 44, no. 10, pp. 1123–1134, 2011.

[116] J. Shi, Z. Xiao, A. R. Votruba, C. Vilos, and O. C. Farokhzad, “Differentially charged hollow core/shell lipid-polymer-lipid hybrid nanoparticles for small interfering RNA delivery,” *Angewandte Chemie*, vol. 50, no. 31, pp. 7027–7031, 2011.