Mini Review **Open Access**

Rocha-García Denisse, Guerra-Contreras Antonio, Rosales-Mendoza Sergio, and Palestino Gabriela*

Role of porous silicon/hydrogel composites on drug delivery

DOI 10.1515/mesbi-2016-0011
Received October 6, 2016; revised November 4, 2016; accepted November 15, 2016

Abstract: Nanomaterials are applied with great success in biomedical applications as templates for the development of new generation devices, which can be used to solve current health problems. These new nanoscale systems are designed with multifunctions to perform specific and selective tasks. One of the most important applications of this new nanotechnology; focuses on developing new systems for the controlled release of drugs, mainly due to their capability to improve the temporal and spatial presentation of drugs in the body and their ability to protect them from physiological degradation or elimination. Hydrogels, porous silicon (PSi), and PSi-composites have been widely adopted in this field due to their biological, morphological, and physicochemical properties; which can be tuned to obtain sensitive responses to physiological stimuli. Despite the fact that some recent academic papers have shown the benefits of these nanomaterials in a wide range of biological applications, more in vivo studies are needed to take these hybrid systems towards clinical trials. In this mini-review some of the hydrogels, PSi, and PSi-composites latest applications and prospects in this field of science are presented.

Keywords: Hydrogels, porous silicon, composites, drug carriers, biomaterials

***Corresponding Author: Palestino Gabriela:** Laboratorio de Biopolímeros y Nanoestructuras, Universidad Autónoma de San Luis Potosí, Manuel Nava No. 6, C.P. 78210, San Luis Potosí, México, E-mail: palestinogabriela@fcq.uaslp.mx and gpalestino.uaslp@gmail.com
Rocha-Garcıa Denisse, Guerra-Contreras Antonio: Laboratorio de Biopolímeros y Nanoestructuras, Universidad Autónoma de San Luis Potosí, Manuel Nava No. 6, C.P. 78210, San Luis Potosí, México
Rosales-Mendoza Sergio: Laboratorio de Biofarmacéuticos Recombinantes, Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, Manuel Nava No. 6, C.P. 78210, San Luis Potosí, México

1 Introduction

Research dealing with controlled release system has grown rapidly in the last years since these systems offer advantageous properties such as improved efficiency, minimal toxicity, and friendly administration when compared to the traditional drug administration procedures. Most of these systems have been synthetized using biocompatible and biodegradable biopolymers. But over the last years the development of particle based polymers for drug delivery has increased due to the growing advance in manufacturing nanostructured particles with biocompatible, nontoxic and biodegradable properties [1–3]. The main goal in the development of this controlled delivery technology has been focused on improving the dosage of the drug for large periods, ensuring drug usage maintaining the concentrations within the therapeutic window. This could increase the patient compliance by reducing the administration frequency, which in turn reduces drug dependence and minimizes secondary effects. Moreover the controlled delivery systems have an important benefit for drugs that are rapidly metabolized; they allow maintaining the drug for larger periods in the body, thus increasing the therapeutic effects [4, 5]. The design of smart controlled delivery systems requires the preparation of a nanostructure (or microstructure) that can be loaded with the desirable drug. In these systems the drug vehicle can protect the cargo from degradation enzymes in the body, extend the circulation half-life, and enhance the penetration and accumulation at the target site. Importantly is to consider that the smart vehicles should be also designed to be responsive to specific stimulus such, that the therapeutic agent is only released or activated when desired [6, 7].

The most common ways to administer drugs into the body are oral (pills) and parenteral (injections). This has the disadvantage that the drug at the beginning stays a long period in the toxic dosage region, while staying only for a short period in the therapeutic region. Controlled release systems have the main advantages of not reach the toxic dosage, and maintain the drug concentration for longer periods of time within the therapeutic window [8].

Research in drug delivery systems has been focused not only on improving oral and injectable systems but also on opening new administration routes. Figure 1 is a search on the clinicaltrials.gov page (updated to October, 2016) and modified from reference [9], showing different the types of drug controlled release systems that are under clinical studies. The high number of clinical trials that are active and currently ongoing confirms the interest in the field for developing new controlled release formulations.

Microparticle-based depots are usually produced by mixing inorganic or organic microparticles with biopolymers [9], in this formulation, the microparticles are used as cargo vehicle and the biopolymers allow for the protection of the drug cargo; helping at the same time to control drug release [10, 11]. Hydrogels, derived from biopolymers, are often used for these applications; however they are limited because of their poor mechanical properties and a difficulty controlling their degradation times and microstructure. A partial solution is to combine them with synthetic hydrogels (rendering structural and mechanical flexibility) but with the disadvantage of presenting low biocompatibility [12]. An option to solve this problem is to produce biopolymer composites by using emerging nanomaterials [13], such as clays [14, 15], silica nanoparticles [16, 17], graphene [18, 19], carbon nanotubes [20], and porous silicon (PSi) [21, 22]. These composites consisting of a dispersion of nanostructured materials (having different geometric forms) in organic polymers play a dominant role in modern technologies for coating, reinforcing, and in the construction of barrier materials. The intermolecular interactions and energy dissipation between the nanostructured materials and the macromolecules in a close proximity on a molecular scale led to a qualitatively new macroscopic properties of the composite compared with those of the individual components [12]. The better control of properties that can be achieved with these hybrid systems, has generated a great scientific interest to design materials with tunable morphologies and controlled pore size for to be used in the development of a new generation of smart drug delivery systems [23–25]. In this context, the current pharmaceutical technology focuses on making new controlled release systems; primarily using biopolymers, micro- and nanoparticles, and composites [1]. Thus in this mini-review, an overview of the current controlled release systems based on hydrogels, porous silicon microparticles, and porous silicon composites is presented and discussed.

2 Hydrogels in controlled release

Hydrogels have attracted considerable attention as excellent candidates for the development of controlled release devices of therapeutic agents mainly due to their biological and physical properties. Hydrogels are polymeric networks with three-dimensional configuration capable of absorbing considerable amounts of water or biological fluids. They show a swelling behavior as a consequence of the type of crosslink present in the hydrogel structure, which can be classified as: physical (intermolecular forces) and chemical (chemical bonds). These materials may exhibit swelling behavior dependent on the external environment (pH, temperature, ionic strength, nature and composition of the swelling agent, enzymatic or chemical reactions, and electrical or magnetic stimuli [26–28]). A further feature of hydrogels is their ability to protect drug molecules from the aqueous environment during preprogrammed periods. This protection involves controlling the dosage, solubility and diffusion of drug molecules [8]. In general, the main objective of the hydrogels is to reduce the rate at which the drug molecules are exposed to the aqueous environment surrounding the delivery system. A variety of formulations based on hydrogels have been proposed in recent years, aiming at developing controlled drug delivery systems. In this approach the hydrogels have been commonly administered by oral, rectal, ocular, epidermal, and subcutaneous routes [26–30].

The most used systems based on hydrogels are sensitive to the environmental stimuli, but they still have certain drawbacks due to their soft nature [31, 32]. For example they may be slow to respond to stimuli or conversely, also having, poor mechanical properties. These behaviors are undesirable for delivery systems [26, 33]. In drug delivery systems it is important to have control over the synthesis parameters to manipulate the degradation rate of hydrogels. Once these delivery systems are in the human body, it is of the utmost importance that the hydrogels have good biocompatibility and that the degradation products formed have a low toxicity. This means that the compounds formed can be metabolized into harmless products. In this regard, it is advisable to synthesize compounds with a hydrophilic surface since the adhesion of proteins and cells to the surface of this kind of materials is minimized. In the same context, for hydrogel-drug conjugation it is desirable to promote physical interactions since the use of toxic solvents is minimized. However, these have certain disadvantages because using hydrophilic and physically bioconjugated hydrogels produce faster kinet-

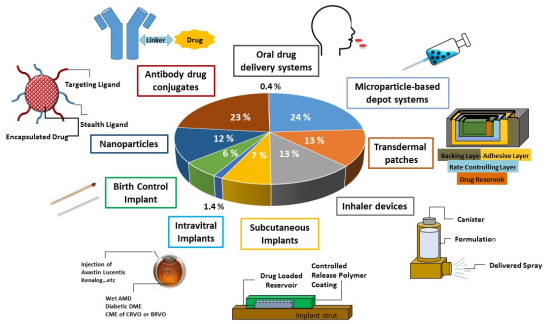

Figure 1: Normalized pie chart for clinical trial search. Search on clinicaltrials.gov that counted the hits for clinical trials that are active and currently ongoing (but not recruiting). This data presents trials that are actually in process. Data has been normalized to the total hits (283) for the following search keywords: (a)"Depot" (68), (b)"Transdermal" (37), (c)"Inhaler" (36), (d)"Subcutaneous implant" (21), (e)"Intravitreal implant" (4), (f)"Birth control implant" (16), (g)"Nanoparticle and cancer" (35), (h)"Antobody drug conjugates" (65) and (i) Oral drug delivery systems (1). (Search conducted in October 2016). It can be observed that the microparticle-based depots (24 %) and antibody conjugates (23 %) are the most active systems; followed by inhaler devices (13 %), transdermal patches (13 %), nanoparticles (12 %), subcutaneous (7 %), birth control (6 %), intravitral implants (1.4 %) and oral drug delivery pills (1 %).

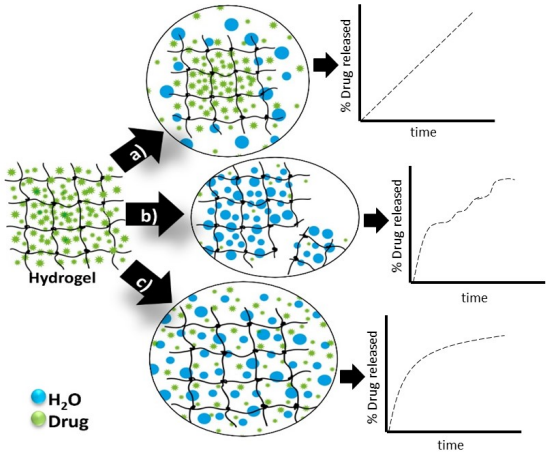

Figure 2: Hydrogels drug release mechanisms and their respective kinetic profiles. Fig. 2a illustrates the case when the governing mechanism is given by the drug diffusion; Fig. 2b when is imposed by the degradation of the polymeric matrix and Fig. 2c when the hydrogel swelling governs the process

ics of drug release and in the case of hydrophobic drugs a lower loading efficiency.

Hydrogels are classified on the basis of the drug release mechanism as: i) diffusion controlled systems, ii) swelling controlled systems, iii) chemically controlled systems, and iv) environmental responsive systems [34]. Diffusion is the most common mechanism for controlling the release in drug delivery systems; however this mechanism promotes a fast release when the drug is highly soluble, which is undesirable. Thus to control drug delivery, an important parameter to consider during hydrogel synthesis is the type of crosslinking and the desirable density of the 3D network; in this regard it is well known that a more reticulated mesh allows for a better drug dosing. The release mechanism in these 3D hydrogels networks is produced by the relaxation of the chains during the swelling process, causing a water barrier that allows for better control of dosing [31, 35, 36]. Figure 2 shows the most known drug release mechanisms of hydrogels together with their characteristic kinetic profiles (% drug released vs t). Despite the efforts to control drug release, most of the hydrogels follow an anomalous release kinetics, which is determined by the combination of mechanisms: relaxation of the polymeric chains and drug diffusion.

With this framework, it is clear that the design of hydrogels and the desirable release mechanism must be carefully established according to its intended application. For example, conventional hydrogel-based contact lenses exhibited relatively low drug loading capacity and often showed a burst release mechanism upon ocular administration [37]. Venkatesh et al. [38] had overcome this problem by developing 'biomimetic hydrogels', their devices showed high potential to load significant amount of ocular medication (H1-antihistamine) with, a controlled release of a drug therapeutic dosage in vitro for 5 days. Another case is the vaginal insert (cervical ripening), which has been used to bring on labor in patients who are at or near the time of delivery. In this system the drug release was triggered by the hydrogel swelling when it was placed in a moist vaginal environment [39]. For oral applications, Park et al. [40, 41] proposed the use of superporous hydrogel composites as gastric retentive devices for long-term oral drug delivery. This biomaterial was able to remain in the stomach up to 24 h allowing the slow release of the loaded drug. In this area, many patents and academic papers on possible applications of hydrogels in drug delivery have been published; however, only a few have resulted in commercial products (e.g. contact lenses and skin tissues) [42–44]. The development of hydrogel-based products for biomedical applications is increasing and is expected to soon represent an alternative as drug delivery system for everyday use. However, it is noteworthy that there are some important aspects that must be improved in these materials before reaching clinical trials; some of them are related with achieving the optimal control in the rate of drug release and increasing their mechanical stabil-

ity. These improvements can be obtained by manipulating the synthesis parameters and adding reinforcing additives (the major example nowadays are nanomaterials such as carbon nanotubes, graphene, metallic and porous particles). In this regard, the addition of inert materials such as porous silicon (PSi) to the polymeric matrices is a topic of current interest; mainly due to the excellent biological and physicochemical properties of PSi, which will be discussed with more details in the next sections.

3 Porous Silicon Particles in Controlled Release

Nowadays PSi microparticles have gained attention for applications in the biomedical and pharmaceutical fields, mainly due to their biocompatible and bioresorbable properties [45]. These advantages together with the fabrication simplicity and surface modification methods have positioned these nanostructures at the forefront of implantable drug delivery systems. In addition, the optical properties of PSi microparticles have been used in developing high-resolution imaging techniques; in this regard detailed images of cancerous cells and lesions have been obtained [46] demonstrating the incredible synergetic capabilities of these materials to perform simultaneously therapeutic and diagnosis applications.

To develop PSi-based drug delivery systems, PSi microparticles should be loaded with a drug to be released into the body after PSi dissolution or following a pore diffusion mechanism [47]. The loading of molecules onto PSi particles is a big challenge at the present and it is carried out via a number of methods. Those include mechanisms of physical adsorption, solvent evaporation, covalent attachment, or drug entrapment by oxidation [46]. The most commonly used method is by simple immersion of the PSi particles or layers into the loading solution, in which the desired drug is dissolved in a suitable solvent. In this strategy the volume of the loading solution should be higher than the volume of the loaded material (PSi). Another method is impregnation. In this case, a controlled amount of drug solution is added to the particles or layers for drug infusion under capillary action into the pores. The first method is controlled more easily while, the latter is more applicable in the case of expensive drug molecules, small amounts of sample, or when the nanostructured PSi layer is still attached to the silicon wafer [26].

Another important aspect that should be taken into account during developing PSi-based drug delivery systems is the surface chemistry of PSi nanostructured material, because it plays an important role during the in vivo, ex vivo and in vitro degradation of PSi-hybrid systems. In as-anodized PSi, the hydrogen-terminated surface (Si_3SiH, Si_2SiH_2 and $SiSiH_3$) is hydrophobic and oxidizes easily even at room temperature, leading to continuous changes in its structure and properties [45]. Hence, stabilization and surface modification can be used to add functionalities to the PSi surface to enable use it in specific applications. Surface modification of PSi can be divided into two broad categories: oxidation and chemical functionalization. Oxidation occurs via the controlled exposure of PSi to various oxidizing agents to induce the formation of oxide species (OySiH, OySiOH and O\Si\O) on the surface. Functionalization is generally regarded as the attachment of carbon chains to the surface via various mechanisms, where both the Si\H and Si\Si bonds are reactive [45, 47].

Nowadays the major focuses of PSi particles with respect to drug delivery have been on controlled drug release and increasing the oral biodistribution of poorly soluble drugs (hydrophobic), mainly due to the hydrophilic nature of PSi. Thus, in the next section some examples for these applications will be described [26, 48–63].

The loading of five model drugs (antipyrine, ibuprofen, griseofulvin, ranitidine, and furosemide) onto the PSi microparticles, produced by thermal carbonization (TCPSi), and their subsequent release behavior was investigated [50]. Loading of drugs into TCPSi showed that in addition to the effects concerning the stability of the particles in the presence of aqueous or organic solvents, the surface properties played an important effect on the drug affinity towards the particle. In addition to the surface properties, the chemical nature of the drug and the loading solution seemed to be critical during the loading process. This was reflected in the obtained loading efficiencies, which varied from 9 to 45%. The release rate of the loaded drugs from TCPSi microparticles was found to be dependent on the characteristic dissolution behavior of the drug. When the dissolution rate of the unloaded drug was high, the TCPSi microparticles produced slightly delayed release. Antipyrine was the drug with which was obtained the highest loading efficiency, this result was attributed to the highest solubility of the drug and to its pH-independent dissolution behavior, which was derived from its weak basic character. In the case of drugs with poor solubility, it was found that drug loading into the functionalized mesoporous microparticles highly improved its dissolution.

Thermally hydrocarbonized porous silicon (THCPSi) microparticles and thermally oxidized porous silicon (TOPSi) micro and nanoparticles have also been investigated as potential biomaterials for drug delivery in biological models (e.g. heart tissue) and for the treatment of my-

ocardial infarction (MI) [64]. Although both particle types were non-cytotoxic [65] and showed good in vivo biocompatibility, they differed in the in vivo inflammation and fibrosis promoting responses. These results are attributed to the particles size and shape, the authors of this study claimed that morphological parameters might have influence in the route of particle internalization by the cell, as well as in the particle interaction with the cell wall. Local injection of THCPSi microparticles into the myocardium led to significantly greater activation of inflammatory cytokine and fibrosis promoting genes compared to TOPSi micro and nanoparticles. Neither PSi particle altered the cardiac function or the hematological parameters. These data suggested that THCPSi and TOPSi microparticles and TOPSi nanoparticles could effectively improve the cardiac delivery of therapeutic agents, thus, in this framework, the PSi biomaterials might serve as a promising platform for the treatment of heart diseases. For biomedical applications, PSi nanoparticles have shown to be less toxic than PSi microparticles. In general, nanoparticles have a very high surface area to volume ratio compared with the microparticles, providing a very large interfacial surface area. A very low content of nanoparticles (generally <2-3 wt %) provides an exceptional increase in mechanical strength [66].

Native and thermally oxidized PSi based carriers have been developed for the loading and release of antiviral drug Acyclovir (ACV) [67]. The results obtained by SEM and FTIR characterization suggested that ACV was present within the PSi carriers in amorphous form. The surface chemistry of PSi played a vital role in both drug loading and drug release behaviors. The amphiphilic surface of the native PSi showed high loading and slower release (up to 8 h). In contrast to this, thermally oxidized PSi showed low loading and burst release within 3 h. This was attributed to the shrinkage of pore diameters and the decrease in open porosity after thermal oxidation. Release kinetics studies using Higuchi and Korsmeyer–Peppas models suggested that drug diffusion as well as silicon erosion mechanisms were involved in drug release from the PSi carriers.

PSi may be used in various forms for biomedical applications including: chip-attached films, free-standing films, particles and micro-needles. For in vivo use, PSi behavior may be tuned from bioinert, bioactive, to biodegradable by varying the pore morphology (porosity and pore size) and surface chemistry [68]. These parameters also affect the loading and release behavior of payloads (e.g., drugs and nanoparticles) from PSi hosts.

4 Porous silicon-polymer-composites

Hybrid materials, in which the payload consists of an organic polymer or a biopolymer, are an additional class of host/payload systems. Composite materials are attractive candidates for drug delivery devices since they can display a combination of advantageous chemical and physical characteristics not exhibited by the individual constituents [23, 69–71]. The combination of a flexible and soft polymeric material with a hard inorganic porous material with high drug loading capacity may generate improved control over degradation and drug release profiles and be beneficial for the preparation of advanced drug delivery devices and biodegradable implants or scaffolds [26, 72].

There are academic reviews about novel properties and biomedical applications of silicon–polymer hybrid materials with particular emphasis on drug delivery [26, 73]. The biocompatible and bioresorptive properties of mesoporous silica and porous silicon make them attractive candidates for biomedical applications. The combination of polymers with silicon-based materials has generated a large range of novel hybrid materials tailored to applications in localized and systemic drug delivery [74]. The most common structures are: PSi infiltrated with a polymer, polymer-coated PSi, polymer-trapped PSi, and PSi particles mixed with polymer [75–77]. Each of these structures possesses different properties, which can be further refined by a proper choice of the polymer constituent and the PSi nanostructure. The most used biopolymers in these applications are natural polymers such as chitosan, collagen, gelatin, dextran, polylysine, pectin, hyaluronic acid, carboxymethyl chitin, agarose; synthetic polymers such as poly(lactic acid) (PLA), poly(ethylene glycol) (PEG), polycaprolactone (PCL), poly(hydroxy butyrate) (PHB), cyclodextrin (CD), polyacrylamide (PAAm), poly(vinyl alcohol) (PVA) , poly (N-vinyl pyrrolidone) (PNVP), poly(acrylic acid) (PAA), poly(ethylene oxide) (PEO), poly(propylene oxide) (PPO), poly(methyl methacrylate) (PMMA); and combinations of natural and synthetic polymers such as: P(PEG-co-peptides), alginate-g-(PEO–PPO–PEO), P(PLGA-co-serine), collagen-acrylate, alginate-acrylate [1, 27, 28].

There are many synthetic approaches for integrating polymers with PSi but, the most common used techniques are: incorporating a preformed polymer with the Si scaffold, in situ polymerization of monomers within/on the PSi and, mixing of PSi with the polymer matrix (Fig. 3a) [75]. These ways to synthesized composites produce various formulations such as: interpenetrating composite, entrapping composite and supported composite

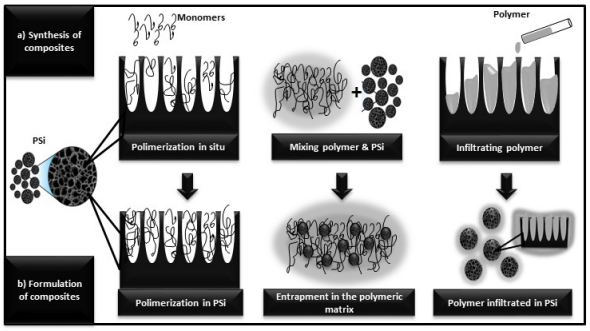

Figure 3: a) Synthesis and b) formulation of PSi-composites.

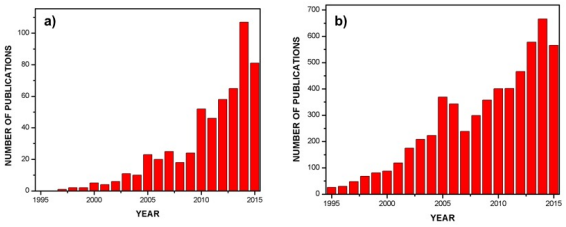

Figure 4: Distribution of number of publications per year related to a) porous silicon and b) composites, both used on controlled drug release. Search from www.scifinder.cas.org using the following keywords: PSi/drug delivery and composites (drug delivery).

(Fig. 3b). Because each formulation has specific properties, we can choose the appropriate synthesis for the necessary application.

Some papers show examples of composites such as PSi and poly(L-lactide) (PLLA), both display good biocompatibility and tunable degradation behavior; which suggests that composites of these materials are suitable candidates as biomaterials for localized drug delivery into the human body [70]. Taking advantage of the large pore volume of porous silicon, atorvastatin was first loaded into the PSi matrix, and then encapsulated into the pH-responsive polymer microparticles containing celecoxib by microfluidics in order to obtain multi-drug loaded polymer/PSi microcomposites [78]. Other composites based on a combination of bioactive mesoporous silicon and bioresorbable polymers such as poly-caprolactone (PCL) were synthetized. The cytotoxicity and cellular proliferation through fibroblast cell culture assays were explicitly evaluated [72]. The polimerization was carried out within the pores by radical polymerization to graft thermosensitive poly(N-isopropylacrylamide) (PNIPAM) of controlled thickness from porous silicon films to produce a stimulus-responsive inorganic-organic composite material [79].

It should be emphasized that in situ polymerization within nanostructures is a complex process in which nanoconfinement conditions may affect the polymerization kinetics and the resulting properties of the polymer. Recent studies have shown that the imprisonment of hydrogels in PSi nanoscale pores induces significant changes in the confined polymer properties, e.g., volume phase transition (VPT) kinetics; compared to that observed for the bulk "free" polymers [80–82]. These findings indicate that in situ polymerization and polymer confinement conditions have a profound effect on the nanostructure and resulting behavior of the polymeric phase. Since PSi-polymer composites exhibit unique properties that are culminated by the characteristics of each building block, they can be rationally designed to display highly tunable mechanical, chemical, optical, and electrical properties. Over the past decade, these attractive nanocomposites have been studied as platforms for designing different devices [77, 83].

In order to see the true impact of PSi and composites in the ongoing research we made a search in the scifinder page (www.scifinder.cas.org) (September 2016) using the following key words: PSi/drug delivery and composites/drug delivery. Figure 4a shows the number of publications per year dealing with PSi substrates and Figure 4b those related with composites (including PSi-composites). From these figures it can be seen that the research on both systems reached a maximum in 2014; slightly decreasing in 2015. It is also noticed that the investigation conducted using PSi particles is rather small compared with that carried out in composites. Therefore, in order to generate the knowledge that allows in the near future demonstrate the benefits of PSi based drug delivery technology, more research and clinical trials are necessary to truly understand the mechanism of releasing and the interaction between the host biological system and the guest hybrid vehicle.

5 Conclusions

Nanomaterials have been constantly evolving over the last few years for manifold applications in electronic, optical and biomedical fields. Promising applications of these materials in medicine and/or biology is the creation of nanoscale devices for improved therapy and diagnostics. The combination of flexible materials such as biopolymers with PSi microparticles has generated emergent devices with excellent mechanical properties and high drug loading capacity improving the control over degradation and drug release profiles. That is how the versatility of the poly-

mers in combination with the unique properties of PSi offers a wealth of opportunities for the design of new functional materials for a range of biomedical applications. This mini-review has shown that the main emphasis during the development of PSi-drug delivery system is focused on: 1) improving the loading of drugs into the PSi carriers, 2) understand the mechanisms of drug release and 3) to have a clear comprehension of the interactions between the host biological system and the guest hybrid vehicle. It should be noticed that most of these devices have been studied with in-vitro assays, therefore, in order to reach real applications, more efforts by using in vivo trials and studies of clinical translation have to be conducted to ensure their real application in the near future.

Acknowledgement: This work was supported by CONACYT grants: Bilateral M-H No.193555, and Infrastructure No. 225843. DRG and AGC thank CONACYT fellowships No.329106 and No. 291018 respectively and Doctorado Institucional en Ingeniería y Ciencias de los Materiales (DICIM/UASLP) for the support provided to obtain the post-doctoral fellowship.

References

[1] Hamidi, M., Azadi, A., Rafiei, P., Hydrogel nanoparticles in drug delivery. Adv. Drug Deliv. Rev., 2008. 60 (15): p. 1638–1649.

[2] Joye, I. J., McClements, D. J. Biopolymer-based nanoparticles and microparticles: fabrication, characterization, and application. Curr. Opin. Colloid Interface Sci., 2014. 19(5): p. 417-427.

[3] Wu, B. C., McClements, D. J. Functional hydrogel microspheres: Parameters affecting electrostatic assembly of biopolymer particles fabricated from gelatin and pectin. Food Res Int., 2015. 72: p. 231-240.

[4] Bae, K. H., Wang, L. S., & Kurisawa, M. Injectable biodegradable hydrogels: progress and challenges. J. Mater. Chem. B., 2013. 1(40): p. 5371-5388.

[5] Steichen, S. D., Caldorera-Moore, M., Peppas, N. A. A review of current nanoparticle and targeting moieties for the delivery of cancer therapeutics. ur. J. Pharm. Sci., 2013. 48(3): p. 416-427.

[6] Mura, S., Nicolas, J., Couvreur, P. Stimuli-responsive nanocarriers for drug delivery. Nat. Mater., 2013. 12(11): p. 991-1003.

[7] Fleige, E., Quadir, M. A., Haag, R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: concepts and applications. Adv. Drug Deliv. Rev., 2012. 64(9): p. 866-884.

[8] Uhrich, K. E., Cannizzaro, S. M., Langer, R. S., Shakesheff, K. M., Polymeric systems for controlled drug release. Chemical reviews, 1999. 99(11): p. 3181-3198.

[9] Anselmo, A. C., Mitragotri, S., An overview of clinical and commercial impact of drug delivery systems. J. Control. Release. 2014. 190: p. 15-28.

[10] Perez, R. A., Kim, H. W. Core–shell designed scaffolds for drug delivery and tissue engineering. Acta Biomater., 2015. 21: p. 2-19.

[11] Dowling, M. B., Bagal, A. S., Raghavan, S. R. Self-destructing "mothership" capsules for timed release of encapsulated contents. Langmuir, 2013. 29(25): p. 7993-7998.

[12] Gaharwar, A.K., Peppas, N.A., Khademhosseini, A., Nanocomposite hydrogels for biomedical applications. Biotechnol. Bioeng., 2014. 111 (3): p. 441–453.

[13] Kumar, D. S., Banji, D., Madhavi, B., Bodanapu, V., Dondapati, S., Sri, A. P., Nanostructured porous silicon—a novel biomaterial for drug delivery. Int J Pharm Pharm Sci, 2009. 1(2): p. 8-16.

[14] Viseras, C., Aguzzi, C., Cerezo, P., Bedmar, M. C. Biopolymer–clay nanocomposites for controlled drug delivery. Mater. Sci. Tech., 2008. 24(9): p. 1020-1026.

[15] Viseras, C., Cerezo, P., Sanchez, R., Salcedo, I., Aguzzi, C. Current challenges in clay minerals for drug delivery. Appl Clay Sci., 2010. 48(3): p. 291-295.

[16] Slowing, I. I., Vivero-Escoto, J. L., Wu, C. W., Lin, V. S. Y. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Adv. Drug Deliv. Rev., 2008. 60(11): p. 1278-1288.

[17] Song, B., Wu, C., Chang, J. Dual drug release from electrospun poly (lactic-co-glycolic acid)/mesoporous silica nanoparticles composite mats with distinct release profiles. Acta Biomater., 2012. 8(5): p. 1901-1907.

[18] Goenka, S., Sant, V., Sant, S. Graphene-based nanomaterials for drug delivery and tissue engineering. J. Control. Release, 2014. 173: p. 75-88.

[19] Das, T. K., Prusty, S. Graphene-based polymer composites and their applications. Polym Plast Technol Eng., 2013. 52(4): p. 319-331.

[20] Cirillo, G., Hampel, S., Spizzirri, U. G., Parisi, O. I., Picci, N., Iemma, F. Carbon nanotubes hybrid hydrogels in drug delivery: a perspective review. Biomed Res Int., 2014.

[21] Low, S.P., Williams, K.A., Canham, L.T., Voelcker, N.H., Evaluation of mammalian cell adhesion on surface-modified porous silicon. Biomaterials, 2006. 27 (26): p. 4538–4546.

[22] DeLouise, L.A., Fauchet, P.M., Miller, B.L., Pentland, A.A., Hydrogel-Supported Optical-Microcavity Sensors. Adv. Mater., 2005. 17 (18): p. 2199–2203.

[23] Hernandez-Montelongo, J., Naveas, N., Degoutin, S., Tabary, N., Chai, F., Spampinato, V., Martel, B., Porous silicon-cyclodextrin based polymer composites for drug delivery applications. Carbohydr. Polym., 2014. 110: p. 238–52.

[24] Anirudhan, T., Parvathy, J., Nair, A., A novel composite matrix based on polymeric micelle and hydrogel as a drug carrier for the controlled release of dual drugs. Carbohydr. Polym., 2016. 136: p. 1118-1127.

[25] Jia, X., Kiick, K.L., Hybrid multicomponent hydrogels for tissue engineering. Macromol. Biosci., 2009. 9 (2): p. 140–156.

[26] Anglin, E.J., Cheng, L., Freeman, W.R., Sailor, M.J., Porous silicon in drug delivery devices and materials. Adv. Drug Deliv. Rev., 2008. 60 (11): p. 1266–1277.

[27] Peppas, N., Hydrogels in pharmaceutical formulations. Eur. J. Pharm. Biopharm., 2000. 50 (1): p. 27–46.

[28] Hoffman, A.S., Hydrogels for biomedical applications. Adv. Drug Deliv. Rev., 2012. 64: p. 18–23.

[29] Patil, J. S., Hydrogel System: An Approach for Drug Delivery Modulation. Adv. Pharmacoepidemiol. Drug Saf., 2015. 4 (5).

[30] Dwivedi, S., Hydrogel-A conceptual overview. Int. J. Pharm. Biol. Sci. Arch., 2011. 2(6).
[31] Qiu, Y., and Park, K., Environment-sensitive hydrogels for drug delivery. Adv. Drug Deliv. Rev., 2012. 64: p. 49–60.
[32] Koetting, M. C., Peters, J. T., Steichen, S. D., Peppas, N. A., Stimulus-responsive hydrogels: Theory, modern advances, and applications. Mater. Sci., 2015. 93: p. 1-49.
[33] Peppas, N.A., Huang, Y., Torres-Lugo, M., Ward, J. H., Zhang, J., Physicochemical Foundations and Structural Design of Hydrogels in Medicine and Biology. Annu. Rev. Biomed. Eng., 2000. 2: p. 9–29.
[34] Acharya, G., Park, K. Mechanisms of controlled drug release from drug-eluting stents. Adv. Drug Deliv. Rev, 2006. 58(3): p. 387-401.
[35] Canal, T., Peppas, N.A., Correlation between mesh size and equilibrium degree of swelling of polymeric networks. J. Biomed. Mater. Res., 1989. 23 (10): p. 1183–1193.
[36] Drury, J.L., Mooney, D.J., Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials, 2003. 24: p. 4337–4351.
[37] Hu, X., Hao, L., Wang, H., Yang, X., Zhang, G., Wang, G., Zhang, X. Hydrogel contact lens for extended delivery of ophthalmic drugs. Int J Polym Sci., 2011. 2011: p. 1-9.
[38] Venkatesh, S., Sizemore, S. P., Byrne, M. E. Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. Biomaterials, 2007. 28(4): p. 717-724.
[39] Cervidil website. www.cervidil.com [accessed October 2016].
[40] Park, K., Enzyme-digestible swelling hydrogels as platforms for long-term oral drug delivery: synthesis and characterization. Biomaterials, 1988. 9 (5): p. 435–441.
[41] Chen, J., Park, K., Synthesis and characterization of superporous hydrogel composites. J. Control. Release, 2000. 65 (1): p. 73–82.
[42] Caló, E., Khutoryanskiy, V. V., Biomedical applications of hydrogels: A review of patents and commercial products. Eur. Polym. J., 2015. 65: p. 252–267.
[43] Vashist, A., Vashist, A., Gupta, Y.K., Ahmad, S., Recent advances in hydrogel based drug delivery systems for the human body. J. Mater. Chem. B, 2014. 2 (2): p. 147.
[44] Elvira, C., Mano, J.F., San Román, J., Reis, R.L., Starch-based biodegradable hydrogels with potential biomedical applications as drug delivery systems. Biomaterials, 2002. 23 (9): p. 1955–1966.
[45] Palestino, G., Agarwal, V., Aulombard, R., Perez, E., Gergely, C., Biosensing and protein fluorescence enhancement by functionalized porous silicon devices. Langmuir., 2008. 24(23): p. 13765-13771.
[46] Donnorso, M. P., Miele, E., De Angelis, F., La Rocca, R., Limongi, T., Zanacchi, F. C., Di Fabrizio, E., Nanoporous silicon nanoparticles for drug delivery applications. Microelectron. Eng., 2012. 98: p. 626–629.
[47] Anglin, E. J., Schwartz, M. P., Ng, V. P., Perelman, L. A., Sailor, M. J., Engineering the chemistry and nanostructure of porous silicon Fabry-Pérot films for loading and release of a steroid. Langmuir, 2004. 20 (25): p. 11264–9.
[48] Martin-Palma, R.J., Biomedical applications of nanostructured porous silicon: a review. J. Nanophotonics, 2010. 4 (1): p. 42502.
[49] Jarvis, K.L., Barnes, T.J., Prestidge, C.A., Surface chemistry of porous silicon and implications for drug encapsulation and delivery applications. Adv. Colloid Interface Sci., 2012. 175: p. 25–38.
[50] Salonen, J., Laitinen, L., Kaukonen, A. M., Tuura, J., Björkqvist, M., Heikkilä, T., Lehto, V. P., Mesoporous silicon microparticles for oral drug delivery: loading and release of five model drugs. J. Control. Release, 2005. 108 (2): p. 362–374.
[51] Salonen, J., Lehto, V.P., Fabrication and chemical surface modification of mesoporous silicon for biomedical applications. Chem. Eng. J., 2008.137 (1): p. 162–172.
[52] Sarparanta, M., Mäkilä, E., Heikkila¨, T., Salonen, J., Kukk, E., Lehto, V. P., Airaksinen, A. J., 18F-labeled modified porous silicon particles for investigation of drug delivery carrier distribution in vivo with positron emission tomography. Mol. Pharm., 2011. 8 (5): p. 1799–1806.
[53] Bimbo, L. M., Sarparanta, M., Santos, H. A., Airaksinen, A. J., Mäkilä, E., Laaksonen, T., Salonen, J., Biocompatibility of thermally hydrocarbonized porous silicon nanoparticles and their biodistribution in rats. ACS Nano, 2010. 4 (6): p. 3023–3032.
[54] Kilpeläinen, M., Mönkäre, J., Vlasova, M. A., Riikonen, J., Lehto, V. P., Salonen, J., Herzig, K. H., Nanostructured porous silicon microparticles enable sustained peptide (Melanotan II) delivery. Eur. J. Pharm. Biopharm., 2011. 77 (1): p. 20–25.
[55] Sarparanta, M. P., Bimbo, L. M., Mäkilä, E. M., Salonen, J. J., Laaksonen, P. H., Helariutta, A. K., Airaksinen, A. J., The mucoadhesive and gastroretentive properties of hydrophobin-coated porous silicon nanoparticle oral drug delivery systems. Biomaterials, 2012. 33 (11): p. 3353–3362.
[56] Vaccari, L., Canton, D., Zaffaroni, N., Villa, R., Tormen, M., di Fabrizio, E., Porous silicon as drug carrier for controlled delivery of doxorubicin anticancer agent. Microelectron. Eng., 2006. 83 (4): p. 1598–1601.
[57] Haidary, S. M., Córcoles, E. P., Ali, N. K., Nanoporous silicon as drug delivery systems for cancer therapies. J. Nanomater., 2012. p. 18.
[58] Santos, H. A., Mäkilä, E., Airaksinen, A. J., Bimbo, L. M., Hirvonen, J., Porous silicon nanoparticles for nanomedicine: preparation and biomedical applications. Nanomedicine, 2014. 9 (4): p. 535–554.
[59] Hou, H., Nieto, A., Ma, F., Freeman, W. R., Sailor, M. J., Cheng, L., Tunable sustained intravitreal drug delivery system for daunorubicin using oxidized porous silicon. J. Control. Release, 2014. 178: p. 46–54.
[60] Maniya, N.H., Patel, S.R., Murthy, Z.V.P., Fabrication and application of porous silicon multilayered microparticles in sustained drug delivery. Superlattices Microstruct., 2015. 85: p. 34–42.
[61] Wang, C. F., Mäkilä, E. M., Kaasalainen, M. H., Hagström, M. V., Salonen, J. J., Hirvonen, J. T., Santos, H. A., Dual-drug delivery by porous silicon nanoparticles for improved cellular uptake, sustained release, and combination therapy. Acta Biomater., 2015. 16 (1): p. 206–214.
[62] Korhonen, E., Rönkkö, S., Hillebrand, S., Riikonen, J., Xu, W., Järvinen, K., Kauppinen, A., Cytotoxicity assessment of porous silicon microparticles for ocular drug delivery. Eur. J. Pharm. Biopharm., 2016. 100: 1–8.
[63] Wang, M., Hartman, P. S., Loni, A., Canham, L. T., Coffer, J. L., Stain Etched Nanostructured Porous Silicon: The Role of Morphology on Antibacterial Drug Loading and Release. Silicon. 2016. p. 1-7.
[64] Tölli, M. A., Ferreira, M. P., Kinnunen, S. M., Rysä, J., Mäkilä, E. M., Szabó, Z., Salonen, J. J., In vivo biocompatibility of porous

silicon biomaterials for drug delivery to the heart. Biomaterials, 2014. 35 (29): p. 8394–8405.
[65] Liu, D., Mäkilä, E., Zhang, H., Herranz, B., Kaasalainen, M., Kinnari, P., Santos, H. A., Nanostructured porous silicon-solid lipid nanocomposite: Towards enhanced cytocompatibility and stability, reduced cellular association, and prolonged drug release. Adv. Funct. Mater., 2013. 23 (15): p. 1893–1902.
[66] Fu, S. Y., Feng, X. Q. Lauke, B., Mai, Y. W. Effect of particle size, particle/matrix interface adhesion and particle loading on mechanical properties of particulate-polymer composites, Compos. Part B, 2008. 39: p. 933–961.
[67] Maniya, N.H., Patel, S.R., Murthy, Z.V.P., Development and in vitro evaluation of acyclovir delivery system using nanostructured porous silicon carriers. Chem. Eng. Res. Des., 2015. 104: p. 551–557.
[68] Bonanno, L. M., Segal, E. Nanostructured porous silicon–polymer-based hybrids: from biosensing to drug delivery. Nanomedicine, 2011. 6(10): p. 1755-1770.
[69] Liu, D., Zhang, H., Herranz-Blanco, B., Mäkilä, E., Lehto, V. P., Salonen, J., Santos, H. A. Microfluidic Assembly of Monodisperse Multistage pH-Responsive Polymer/Porous Silicon Composites for Precisely Controlled Multi-Drug Delivery. Small, 2014. 10(10): p. 2029-2038.
[70] McInnes, S. J., Irani, Y., Williams, K. A., Voelcker, N. H. Controlled drug delivery from composites of nanostructured porous silicon and poly (L-lactide). Nanomedicine, 2012. 7(7): p. 995-1016.
[71] Nan, K., Ma, F., Hou, H., Freeman, W. R., Sailor, M. J., Cheng, L. Porous silicon oxide–PLGA composite microspheres for sustained ocular delivery of daunorubicin. Acta Biomater., 2014. 10(8): p. 3505-3512.
[72] Coffer, J. L., Whitehead, M. A., Nagesha, D. K., Mukherjee, P., Akkaraju, G., Totolici, M., Canham, L. T. Porous silicon-based scaffolds for tissue engineering and other biomedical applications Phys. Status Solidi (a), 2005. 202(8): p. 1451-1455.
[73] Bonanno, L. M., Segal, E. Nanostructured porous silicon–polymer-based hybrids: from biosensing to drug delivery. Nanomedicine ,2011. 6(10): p. 1755-1770.
[74] McInnes, S., Voelcker, N., Silicon-polymer hybrid materials for drug delivery. Future Med. Chem.2009. 1(6): p. 1051-1074.
[75] Segal, E., Krepker, M., Polymer-porous silicon composites. Handb. Porous Silicon. 2014. p. 187-198.
[76] Yoon, M., Ahn, K., Cheung, R., Sohn, H., Covalent crosslinking of 1-D photonic crystals of microporous Si by hydrosilylation and ring-opening metathesis polymerization. Chemical. 2003. 6: p. 680-681.
[77] Li, Y. Y., Cunin, F., Link, J. R., Gao, T., Betts, R. E., Reiver, S. H., Sailor, M. J., Polymer replicas of photonic porous silicon for sensing and drug delivery applications. Science, 2003. 299(5615): p. 2045-2047.
[78] Liu, D., Zhang, H., Herranz-Blanco, B., Mäkilä, E., Lehto, V. P., Salonen, J., Santos, H. A., Microfluidic Assembly of Monodisperse Multistage pH-Responsive Polymer/Porous Silicon Composites for Precisely Controlled Multi-Drug Delivery. Small, 2014. 10 (10): p. 2029–2038.
[79] Vasani, R. B., McInnes, S. J., Cole, M. A., Jani, A. M. M., Ellis, A. V., Voelcker, N. H., Stimulus-responsiveness and drug release from porous silicon films ATRP-grafted with poly (N-isopropylacrylamide). Langmuir. 2011. 27(12): p. 7843-7853
[80] Wang, J., Gan, D., Lyon, L. A., El-Sayed, M. A., Temperature-jump investigations of the kinetics of hydrogel nanoparticle volume phase transitions. J. Am. Chem. Soc., 2011. 123(45): p. 11284-11289.
[81] Jones, C. D., & Lyon, L. A., Shell-Restricted Swelling and Core Compression in Poly(N-isopropylacrylamide) Core–Shell Microgels. Macromolecules, 2003. 36(6): p. 1988-1993.
[82] Wiedemair, J., Serpe, M. J., Kim, J., Masson, J. F., Lyon, L. A., Mizaikoff, B., Kranz, C., In-Situ AFM Studies of the Phase-Transition Behavior of Single Thermoresponsive Hydrogel Particles. Langmuir, 2007. 23(1): p. 130-137.
[83] Shawgo, R. S., Grayson, A. C. R., Li, Y., Cima, M. J. BioMEMS for drug delivery. Curr Opin Solid State Mater Sci., 2002. 6(4): p. 329-334.

Dr. Gabriela Palestino received a B.S. and Master degree in Chemical Engineering from San Luis Potosí University. She obtained her PhD in Biomolecular Engineering at the Montpellier II University, France (2008). Currently she holds a position as full time Professor at the Faculty of Chemical Sciences in the University of San Luis Potosi, Mexico. She is member of the Mexican National Research System since 2009 and recently joined the Mexican Academy of Sciences. Her research expertise connects fundamental principles of nanostructured materials processing with specific engineering and biomedical needs, with special emphasis on biopolymers and multifunctional materials for sensors, biosensor, technological, biological and environmental applications. Her work is supported by grants from the Mexican Council of Science and Technology (CONACYT), and a variety of industrial partners. She is head of the biopolymers and nanostructures group, and has published over 30 papers and book chapters. Her scientific work has been published in journals as Langmuir, Sensors and actuators, Biomedical Materials Research B: Applied Biomaterials, Biomacromolecules, Chemical Engineering , Electrochimica acta, Catalysis, Nanoscale Research Letters, Applied physics letters among others, and have been presented in over 60 invited, contributed, and poster presentations at local, national, and international meetings.