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Review

Nanocarriers for the Oral Delivery of Drugs With Special Focus on Porous Silicon: A Review

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Abstract. The focus concerning controlled drug release requires the growth of appropriate drug carriers that could move adequate amount of the drug to injured area with controlled and sustained manner. A variety of nanoparticles including magnetic nanoparticles, the staes, liposomes, polymers dendrimers, solid lipid nanoparticles (SLN) and porous silicon have been investigated as drug carriers in drug delivery cases. Nanocarriers have achieved significant importance in the stabilization of proteins and peptides, anti-cancer drug camptothecin (CPT) and bone tissue engineering offering improved buccal access and protection according to the desired function. Moreover, tailored formulation along with functionalization and bio-compatibility has importance in fabrication of nanoparticles for proteins or peptides *via* oral delivery systems, which has advantage over parenteric delivery systems because of their comfort running and observance to treatment. The review summarizes interesting approaches on existing publications for drugs such as proteins or peptides carrier nanoparticles with special focus on porous silicon for delivery systems. Fabricatioan of nanoparticles e.g. porous silicon nanocarriers for oral delivery, advantages and disadvantages, prospective use of porous silicon in drug delivery systems will be addressed.

Keywords: drug carriers, functionalization, porous silicon, electrochemical etch method, applications of porous silicon

Introduction

An extensive class of drugs such as proteins or peptides is considered as curative drugs for the healing and administration of numerous diseases. The history of biological drugs is early known when Food and Drug Administration (FDA) of USA had accepted first re-combinant human insulin in 1982 (Schiffter *et al*., 2011).

Currently, several bioactive drugs are under clinical examination and more or less than 35 have been licensed for commercialization by FDA. Parenteral administration route is still significantly in use due to size obstacle, stability and low bioavailability issues in gastrointestinal region in spite of having several functional protein or peptide bio-technological drugs. Parenteral route is hurting, having possibility of contamination for the patients plus requires presence of medical personnel for its delivery (Prantera *et al*., 1997). Moreover, parenteral route is costly and requires method of preparation under hygienic condition, while oral route is preferable due to friendly falling in line to treatment (Harloff-Helleberg *et al*., 2017). The achievements of nano technological materials opened several ways of drug conjugation with different nanoparticles. Due to easy size modification and surface enhancement properties of nanomaterials, they are considered as smart drug nanocarriers. The objective of smart drug nanocarriers is that drug pursuing target tissues or organs release with slow rate or proper rate of action and will not move freely during blood circulation. Premeditated drug nanocarriers or stimuli-responsive drugs mechanism towards exogenous or endogenous stimulus is illustrated in Fig. 1. Endogenous parameters (disease pathological) such as small biomolecules, redox gradient, pH- value, glucose, hormone level, enzyme concentration and exogenous parameters like magnetic field, temperature, electric or high energy pulse, light and ultrasound can be in use for controlled release of drugs over the target (Kelley *et al*., 2013; Mura *et al*., 2013). Oral route types comprise sublingual, gastrointestinal, gingival and buccal routes. Drug release methods can be modified to definite function and unclear target for absorption according to the prescriptions of pharmaco-kinetics of specific drug. Buccal delivery is suitable when unstable

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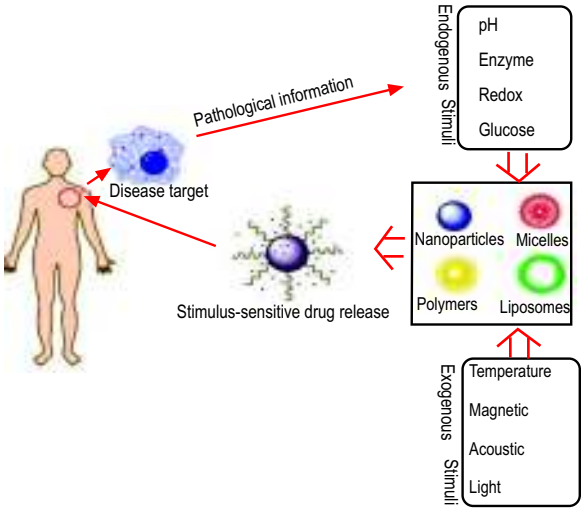

Fig. 1. Schematic illustration for stimulus drug delivery mechanism (Nagal *et al*., 2013).

carried drugs at severe pH-value subject to undergo enzymatic absorption or metabolization of inactive products.

Gastrointestinal route is used when drug nanocarriers are stable with higher bio-availability. Numerous methods have been used to shield therapeutic drugs with nanocarriers in order to increase immovability and diffusion across absorption in gastrointestinal route. Encapsulation of therapeutic drugs within nanocarriers has revealed improved bio-compatibility. Size of the nanoparticles is identified to be 10 to 100 nm and can be ordered as alone or incorporated with a variety of nanomaterials such as synthetic polymers, metals, lipids, proteins and polysaccharides (Maruthi *et al*., 2011). The designing of nanoparticles for drug delivery systems requires controlled size, toxicity and surface properties against release of active drugs at therapeutically optimal rate. Nanostructures reveal excellent biological and physico-chemical properties with an improved ability to cross tissue barrier and reliable with cell environment (Nagal *et al*., 2013). Mesoporous silica nanocarriers have been rigorously recommended for stable drug delivery systems, biomarking, gene transport, biosignal probing and several other biomedical applications due to its excellent properties such as bio-compatibility, bio-degradability, high surface area, increased pore volume, tunable pore structure and physico-chemical stability (Patel *et al*., 2014). However, 10 to 100 nm size of nanoparticles is not acknowledged by the Royal Society and Royal Academy of Engineering (RSRE) 2004. According to RSRE, the biological properties do not depend on size variation (Jong *et al*., 2008). Modern delivery systems (frequently used proteins or peptides *via* oral route) for therapeutic purposes have shown a greater impact economically and are allocated a budget of US$ 479,752 million for year 2024 (Global Biologics Market *et al*., 2017). Function of nanoparticles in drug delivery tasks have major advantages like mucoadhesion, increased permeability round epithelia absorption, increased surface area, good functionalization, accuracy over target delivery, affinity to intestinal cells will be further discussion topics in this article. Several upto date examples of drug nanocarrier's e.g. porous silicon nano or meso particles for protein or peptide drugs and main results that were obtained will be addressed in this review article critically.

Characterization methods and characteristics for encapsulation of nanocarriers and drug interaction. Polymer nanoparticles have a collection of properties with controlled and tuned circumstances which are assigned to respond drug targeting. Nanoparticles as drug carriers must be in possession of good physical characteristics such as drug loading efficiency, polydispersity indicator and size, surface carrier behaviour with controlled and favourable conditions (Global Biologics Market *et al*., 2017).

Scanning electron microscopy (SEM), atomic force microscopy (AFM), transmission electron microscopy (TEM), dynamic light scattering (DLS), Fourier-transform infrared (FTIR), Raman spectroscopy, X-ray photoelectron spectroscopy (XPS) and energy dispersive spectroscopy (EDS) are commonly used techniques for the measurement of nanoparticles size, presence of agglomerates, rate of action and surface morphology. Zeta-potential, a central task for the idea of *in vivo* performance of nanocarriers when set on with cellular arrangement is measured by electrophoretic light scattering (ELS). Synthesis of nanoparticles is an essential requirement for specific tasks and remains a problem for researchers worldwide (Lin *et al*., 2014). Specific physico-chemical properties such as morphology, aggregation, mean size, polydispersity index (size distribution), surface properties, drug content, conformational effects, concentration and drug discharge, are commonly examined during characterization (Crucho *et al*., 2017).

Formulation of a certain nanoparticle have strong dependence on the targeting application, therefore quite

difficult to recognize nanoparticle as a standard tool but it must be proven to predict *in vivo* conditions, toxicity and guarantee effectiveness. Researchers have proven that shape and size of nanoparticles have a strong role in loading and interaction with biological interfaces (Banerjee *et al*., 2016). Usually, it is the supposition that nanoparticles with spherical shape are taken as the most appropriate drug carriers is not a true fact in all situations. In order to modify size, shape and surface properties of nanoparticles for oral drug carrier, researchers manufactured polystyrene nanoparticles of various shapes like rod- shaped, sphere, flakes and disc-shaped of sizes 500, 200, and 50 nm respectively. Researchers tested the rate of action, cellular transport or immovability and uptake capacities across certain drugs such as Caco-2 Caco-2/HT29 and Caco-2/HT29/Raji-B triple culture. Confocal microscopy confirmed that drugs Caco-2 and Caco-2/HT-29 cells have increased capacity to load when particle size was small (Lynch *et al*., 2008). Knowledge about drug and nanocarries interaction e.g. formulation and association of the drug meso/nano carriers and drug release time of the nanoparticle has much importance during drug delivery administration. Drugs like proteins with increased association rate constants and increased concentration are initially exist at the nanocarrier surface, but after a short time nanocarrier structure may act as proteins of higher affinity, slower exchange rate and lower concentration (Lynch *et al*., 2008). Interactions such as hydrophobic, chemical and electrostatic (regarding protein adsorption) play important roles. According to various studies, some proteins show strong adsorption and release rate to the nanocarriers while others have weak residence times and weak affinities (Lynch *et al*., 2008). Polymers due to their outstanding biocompatibility and biodegradability, such as polylactic acid (PLA), amphiphilic copolymer polyethylene glycol (PEG), chitosan, polylactide co-glycolide (PLGA), gelatin, starch polycaprolactone (PCL) and alginate are generally used for manufacturing nanoparticles (Patel *et al*., 2014; Giovino *et al*., 2012; Lynch *et al*., 2008; Mundargi *et al*., 2008; Rawat *et al*., 2006). Solvents such as acetone, dichloromethane, ethyl acetate, acidic solutions, diffusing agents like cyclo-dextrins and phospho- lipids along with surfactants such as polyvinyle alcohol and polyssorbate are commonly preferred for the synthesis of nanocarriers (Lai *et al*., 2014). The preparation of nanoparticles must be done according to the fulfillment of certain properties such as drug loading and drug release time, association efficiency, zeta potential, size of nanoparticles, surface properties i.e. charge and shape, the degree of bio-compatibility, bio-degradability, toxicity, and the antigenicity of the host (Maruthi *et al*., 2011; Mohanraj *et al*., 2006).

Functionalization of nanoparticles as drug carriers. For drugs such as protein or peptide delivery, solid lipid nanoparticles (SLN), porous silicon and polymeric nanocarriers have been most frequently explored (Patel *et al*., 2014). Solid lipid nanoparticles (SLN) have achieved commercial as well as scientific interest as therapeutic drug delivery carriers recently. SLN have shown proved advantages over controlled drug release and functionalization to target (diseased organs or tissues) accurately. Functionalization of the surface chemistry helps the nanopartile to achieve the specific targeted organ. For instance, with the help of chitosan as a coating agent e.g. non-covalent approach, Solid lipid nanoparticles (SLN), porous silicon nanoparticles and polylactide-coglycolide (PLGA) can be modified and functionalized to have intestinal cells as target (Araujo *et al*., 2014; Mura *et al*., 2013). Solid lipid nanoparticles (SLN) were functionalized by coating chitosan on the surface of solid lipid nanoparticles for oral delivery of insulin (Mura *et al*., 2014). Under comparison with uncoated solid lipid nanoparticles (SLN), chitosan coated- SLN have successfully showed improved insulin across drugs such as Caco-2 and Caco-2/HT29. Under vitro assay, relative pharmacological conditions such as relative pharmacological bio-availabilities were of 8% for insulin carried by uncoated-SLN and 17% for insulin carried by chitosan coated SLN when hypoglycemic effect in diabetic mice was tested. It was found that high effectiveness of insulin loaded with chitosan- coated solid lipid nanoparticles was linked due to positively increased zeta potential and rigid junction i.e.(disorderly reaction of chitosan) (Kelley *et al*., 2013; Cano-Cebrian *et al*., 2005). Fluorescent marker was used to label insulin in order to verify increased adsorption by intestinal cells inside the intestinal wall. It is important to note that increased positive zeta potential increases both mucoadhesion and contact with the help of non-covalent functionalization of nanocarriers with chitosan, while covalent functionalization is stable and extra valuable with distinct biological properties as compared to non-covalent functionalization (Araújo *et al*., 2017; Hermanson *et al*., 2009). Functionalization of nanocarriers is an important tool to achieve targeting

delivery and increased permeability. Without functionalization of nanocarriers, it is difficult to investigate functionalization rate of individual carrier which is covalently bonded. Moreover, it is noted that non-covalent functionalization as well as the gastrointestinal tract may perhaps lose appearance as it is usually weaker than covalent functionalization (Araújo *et al*., 2009). Functionalization of nanocarriers take part in increasing residence time of loaded drug and drug released amount from nanocarriers according to redox reaction or specified pH-value (Huo *et al*., 2014; Colombo *et al*., 2009). Therefore, functionalization methods as well as functionalizing agents are important factors for the functionalization of nanocarriers. Solid lipid nanoparticles (SLN) can be synthesized with the help of biocompatible lipids that have physiological body melting temperature round about 37 °C. Cetyl palmitate, beeswax and carnauba wax lipids utilized for the synthesis of solid lipid nanoparticles are digested by intestinal juices and have higher melting temperature as compared to physiological body temperature (Madureira *et al*., 2016; Mundargi *et al*., 2011). Studies have shown that solid lipid nanoparticles are proved more protective and sensitive due to chemical, thermal and oxidative degradation behavior (Righeschi *et al*., 2016). Moreover, solid lipid nanoparticles are low cost with excellent properties such as conjugation of hydrophilic and lipophilic compounds, avoidance of using organic solvents, better functionalization for targeted delivery than biodegradable polymers and phosphor lipids. Hence, solid lipid nanoparticles have been suggested as an excellent drug carrier designed for several drug delivery systems (Aditya *et al*., 2015). While polymeric nanocarriers with the help of different production methods can be designed as nanocapsules or nanospheres according to uniform distribution of bioactive drugs within a matrix or membrane (Khalid *et al*., 2017).

Synthesis of nanoparticles. Chemical and physico-chemical methods are major categories of nanocarriers fabrication intending the encapsulation and release of bioactive drugs such as protein or peptides (Iqbal *et al*., 2015) Polymerization techniques like emulsion polymerization, interfacial polymerization and mixed-emulsion polymerization fall in chemical methods category, while numerous emulsion techniques such as spray drying, solvent diffusion emulsion and bilayer emulsion fall in physico-chemical methods (Kumari *et al*., 2010; Soppimath *et al*., 2001).

Emulsion polymerization technique is further subdivided into single and double emulsion techniques which are trouble-free and reliable techniques for the synthesis of nanoparticles (Danhier *et al*., 2012). Ionic solvent diffusion and spontaneous emulsification processes contains miscible solvent and an immiscible water organic solvent in the form of grease phase and create an interfacial instability in phases due to which production of small particles takes place. Size of particles is dependent on the concentration of water solvent. Hydrophobic and hydrophilic drugs can be treated by both solvent evaporation and diffusion processes (Mohanraj *et al*., 2006). Simple emulsion processes (water/oil) are valuable carrier routes for the trap of lipophilic molecules. It was noted that polymer concentration, type, stabilizer concentration and homogenizer speed affect particle size. Nanoparticles produced by this technique are not considered suitable for majority of drugs as carriers due to their low association or binding efficiency with hydrophilic molecules (Chung *et al*., 2011; Mohanraj *et al*., 2006; Kwon *et al*., 2001). Interfacial emulsion techniques are more multifarious as compared to uncomplicated emulsions because of existence of nanocacrriers having extra carriers within the medium. Interfacial emulsions (Water/oil/water) are valuable for the amalgamation of lipophilic as well as hydrophilic molecules collectively and are selected for the trap of bioactive drugs such as proteins or peptides (Iqbal *et al*., 2015). Interfacial emulsion technique has certain drawbacks such as high polydispersity index, leakage of bioactive molecules and is a two step production technique. Particle reproduction in non-wetting profile has also been utilized for production of nanoparticles (Mohanraj *et al*., 2006).

In the absence of organic solvents, Interfacial emulsion (solid/ oil/ water) is a reasonable approach (Bilati *et al*., 2005). Nano-precipitation is an ideal method to produce small sized nanoparticles for drugs to suffer hydrolytic degradation due to avoidance of water. Also, nano-precipitation method has drawbacks like high shear stress and poor encapsulation (Bilati *et al*., 2005). Protein ion coupling is an appropriate stable technique used for nano entrapping drugs at pH values lying below isoelectric position. Ion coupling involves the existence of a surfactant and excites an increased hydrophobicity which causes excellent encapsulation efficiency (Meyer *et al*., 1998; Quintanar-Guerrero *et al*., 1997). Finally, buccal delivery of drugs offer stability as well as protection against enzymatic degradation and have

general utility and encapsulation strength into mucoadhesive films, strips, hydrogels, scaffolds. Mucoadhesive films are usually prepared by solvent casting method (Castro *et al*., 2015).

Electrochemical etching method. Formation of porous silicon by electrochemical etching method is illustrated in Fig. 2.

Porous Si is an artifact of an electrochemical anodization of Si wafers in single crystalline form in a hydrofluoric acid electrolyte solution. The factors such as current density, the electrolyte concentration, the type and concentration of dopant and the crystalline orientation of the wafer help in variation of size (macro, meso and micropores) and pore morphology. Pore sizes from 1 nm to a few microns range can be prepared (Canham *et al*., 1994). The mechanism of pore formation is generally a combination of electronic and chemical factors (Zhang *et al*., 2004). The type of dopant establishes the availability of valence band holes in the original silicon wafer which are the key oxidizing agents in the reaction shown in Fig. 2. Configuration of dopants to morphology of host on the basis of type and concentration can be classified into four groups namely p-type, n-type, highly doped p- type and highly doped n-type. "Highly doped," corresponds to dopant levels, where conductivity performance of the material is more metallic as compared to semiconducting. "Moderate doping" corresponds to n-type silicon wafers where barring of valence band holes from the space charge region determines the pore diameter. Quantum well effects are considered to handle pore size moderately in p-doped materials. Reaction for both dopant types is crystal face selective which allows pores to propagate primarily in the <100> direction of the single crystal. An electrolyte containing hydrofluoric acid is the base

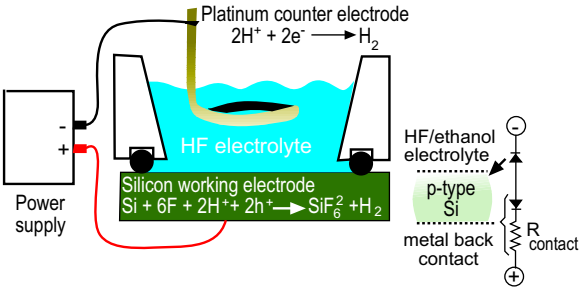

Fig. 2. Schematic illustration of the etch cell for the synthesis of porous silicon (Canham *et al*., 1994).

of electrochemical reaction. Anode current oxidizes a surface silicon atom which is further reacted by fluoride. The whole process involves four electrons of oxidation from which two are supplied from current source and other two electrons come from reduction reaction of proton in SiF_2 species. Pores are formed when Si atoms are removed in the form of Sif_4 in reaction with two corresponding F-atoms in solution to from SiF_6^{-2}. The process of growing porous Si layer i.e. porosity is found to be proportional to applied current density and has range between 40 to 80%. During etching process, morphology of pores remains constant and form only at the Si and porous Si interface. However, the applied current density can change the porosity of a growing layer e.g. In photonic crystals having a stack of layers with discontinuous refractive index can be fabricated by periodically adjusting the current density during an etch (Berger *et al*., 1997; Vincent *et al*., 1994). Porous Si has unique property to tune pore sizes and volumes during electrochemical etching process which is a positive impact of porous Si in drug delivery applications. Porous materials other than Si require complicated design to maintain pore size and volume and still have drawback of spanning pore sizes. Larger pores can be formed with larger current density and larger pores are required to form when sizable molecules or drugs are encapsulated within pores. Porosity and pore size are important factors for determining degradation rates of porous Si host matrix and are basis for loading drugs (Anderson *et al*., 2003). Smaller pores with large surface area have more capacity for attack of aqueous media and yield greater dissolution rates with controlled degradation rates of host matrix. Porous Si *in vivo* applications is desired to prepare in the form of particles where porous layer can be removed from Si substrate with the help of a procedure called electropolishing or lift-off. The etching electrolyte is substituted with lower concentration of hydrofluoric acid and a current pulse is applied for short time. Other conventional methods such as lithography and micro droplet patterning can be formulated if particles require more uniform shapes (Meade *et al*., 2007).

Chemistry of porous silicon. Silicon is considered as connective and bone tissue trace element and health of tissue strongly depends on silicon. Chemical species like silane (SiH_4) and oxides of silicon represent toxicity of porous silicon. Si-H, SiH_2 and SiH_3 are surface species of porous silicon that like to convert into silane (Meade *et al*., 2004; Jay *et al*., 2000). Silane is toxic

and chemically reactive when inhaled, while other species such as silicon hydrides of porous silicon have oxidizing ability in aqueous solution. Thermodynamically, silicon itself has unstable oxidation behaviour and water provides sufficient oxidizing potential to precede a spontaneous reaction. The following three equations represent oxidized chemical species of porous silicon.

$$SiH_4 + 2H_2O \rightarrow SiO_2 + 4H_2 \quad \text{.....1}$$

$$Si + O_2 + \rightarrow SiO_2 \quad \text{.....2}$$

$$SiO_2 + 2H_2O \rightarrow Si(OH)_4 \quad \text{.....3}$$

The act of SiO_2 as well as Si-H when absorbed in hydrofluoric acid solutions causes suspension of silicon momentarily slow due to its extremely porous structure. Reasonably large quantity of silicon having species from oxidized porous silicon can be obtained from spontaneous aqueous solution shortly. Soluble silicon dioxide contains different silicic acidic SiO_4^{-4} ions as the fundamental constituent and these oxides are found to be toxic in doses (Lai *et al.,* 2005; Kawanabe *et al.,* 1992). The problem with silica based drug carriers is the increased rate of degradation and desorption. The contribution of Bayliss, Canham and other researchers determined relatively low toxic behavior of porous silicon in various cellular and live animal cases (Chin *et al*., 2001; Bayliss *et al*., 1997). The by products of porous silicon showing easy degradation and low toxicity have opened new doors in controlled drug delivery systems for researchers.

Porous silicon with controlled release of drugs. Controlled as well as confined release of peptides or proteins is thought to be key functions for the elimination of potential side effects and tends to increase the efficacy (Wise *et al*., 2000). Due to certain excellent properties such as increased porosity, low toxicity and favourable surface chemistry of porous silicon and porous SiO_2 have grown them as potential candidate or fundamental craft for diagnostics, therapeutics and several other types of drugs as carriers. Numerous methodologies of loading proteins or peptides into porous silicon host have been experimented and can be characterized into covalent binding, adsorption and physical traping. Covalent binding method is useful to link bimolecular capture directly into inner pore walls of porous silicon for biosensing applications as well as for drug carrier encapsulation (Schwartz *et al*., 2005). It was found that bimolecular attachment *via* silicon-carbon bonds is more stable than silicon-oxygen bonds because of susceptibility of silicon- oxygen species against nucleophilic beat. The flexibility of the hydrosilylation response was early famous in the history of surface chemistry of silicon to prepare functional porous silicon (Buriak *et al*., 2002). The most common step was graphitization of an organic molecule like carboxylic species on terminal alkene (Dorvee *et al*., 2008; Boukherroub *et al*., 2002). If the physical trapping of drugs is relatively robust then locking or encapsulation can be occurred due to oxidation of porous silicon host matrix. Trapping or locking is an excellent property of porous silicon when porous silicon is oxidized to SiO_2 due to which volume expansion contain additional oxygen atoms and shrink the pores and locked or trapped the drugs in pores. Similarly, iron oxide (Fe_3O_4) nanocarriers have been overloaded and accumulated with the porous silicon nanostructure using aqueous ammonia to stimulate oxidation (Dorvee *et al*., 2004).

Composites of porous silicon. Composites have gained strong attention of researchers for drug delivery devices due to advantageous physical and chemical characteristics as individual constituents are deficient of these properties. Composite design preference of nanostructure composites have greatly expanded in the last few years (Gurny *et al*., 2006). The nanostructure template has proven as a versatile method to create periodic nanostructures during synthesis of materials. Templates such as zeolites, crystalline colloidal arrays and micro or mesoporous membranes have been used and numerous mechanical, electronic and optical structures have been created or formed. Porous silicon is a potential candidate for applying as a medium due to good tuneability of the porosity and regular pore size. Moreover, one, two and three dimensional photonic crystals are being manufactured from porous silicon. Porous silicon composites are proving better with improved mechanical stability and excellent control rate over drug release mechanism for an oral delivery case. Polymers such as polystyrene, polycaprolactone, poly (N-isotropyl acrylamide), polydimethyl siloxane, zein (a kind of biopolymer obtained from maize) and polylactide have been encapsulated or incorporated into porous silicon matrix. Oxidation of porous silicon from a polymer or biopolymer can be completed *via* chemical dissolution method with the help of aqueous potassium hydroxide [KOH] and hydrofluoric acid solutions respectively from which an isolated porous composite

structure with excellent optical properties can be obtained. The concept of porous silicon and polymer composite was primarily known in 1990 (Koshida *et al*., 1993). Two techniques have been demonstrated, first the polymer is fabricated inside the porous silicon matrix and secondly melts or solution casting processes are used to inculcate polymer into the porous silicon matrix (Li *et al*., 2006). Porous silicon formed an excellent matrix of nanocrystalline domains but one drawback is its mechanical stability in applications where porous silicon is subjected to mechanical stress or thermally in use. Chemical encapsulation of porous silicon need correct choice of polymerization conditions.

Importance of optical properties of porous silicon *in vivo* monitoring. Some drug carriers provide information regarding drug loading and its release time on self based report and for others, it is important to investigate a new time for next dose. The engineered optical characteristics of porous silicon have ability to detect such investigations *in vivo* conditions. The production of porous silicon with modified refractive index has measured drug loading capacity from reflection spectrum of the nanostructure. From optical spectrum of molecular functionalized encapsulation with porous silicon, drug content as well as drug degradation can be measured (Chan *et al*., 2000; Lin *et al*., 1997). Characterization and quantification of drug loading or release time can be assessed under *ex vivo* case accordingly. Description and interpretation of optical interference spectra can be studied elsewhere, a brief overview will be presented here. It is evident from studies that refractive index can be linked to the mass as well as composition of a nanostructure (thin film or sensor). The reflectivity spectra of a thin film (air-porous silicon or porous silicon-crystalline) shown in Fig. 3 displays Fabry-Perot interference fringes.

The refractive index and thickness of the film can be find out using Fast Fourier Transform (FFT) from constructive and destructive interference of reflected light at the borders of interface. Shifts and refractive index in the reflectivity spectra present relationship with composition and mass loading of film according to Bruggeman effective medium model (Janshoff *et al*., 1998; Bohren *et al*., 1983). A shift in the reflectivity spectra also provides information about oxidation mechanism of porous silicon. Porous silicon and oxidized porous silicon have refractive index approximately 2.1 and 1.6 (Ouyang *et al*., 2005). Optical structures such as Bragg stack, micro activity, rugate and Fabry-Perot

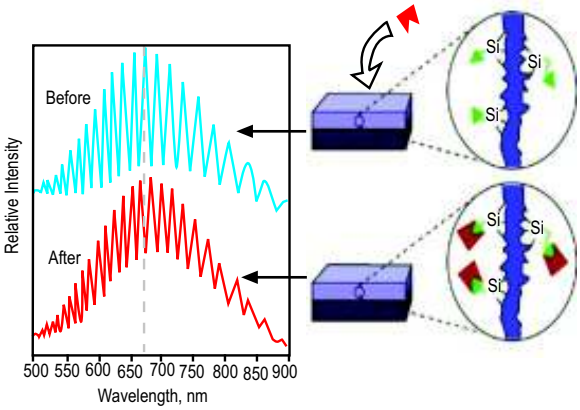

Fig. 3. Schematic illustration of reflectivity spectrum of single layered porous silicon upon encapsulation of bioactive molecular species into the host porous silicon matrix (Li *et al*., 2003).

have shown similar trends of sensitivity when analyzed in provisions of substrate concentration verses spectral shift at the pores of optical structure (Ouyang *et al*., 2005).

Monitoring a porous silicon fixture *in vivo*. Optical interference spectrum obtained from a diode laser interferometer or a CCD (charge coupled device) spectrometer can be used to measure drug loading capacity of porous silicon nanoparticles (Gao *et al*., 2002; Gao *et al*., 2000), e.g., monitoring of porous silicon carriers for ocular drug delivery in the vitreous of rabbit eyes shown in Fig. 4 (Li *et al*., 2003).

Drug release or dissolution of the particles causes deviation into the refractive index of the porous silicon film that is analyzed as a wavelength shift in the reflectivity spectra. Clinically, this colour shift change can be analyzed by spectroscopy or fundus camera in the living eye. Deoxi carboxylic nucleic acid (DNA), dexamethasone (Anglin *et al*., 2004), caffeine, bovine serum albumin (Collins *et al*., 2002) and several other molecules has been found using this technique. Detection of optical interferometric test and high surface area results high sensitivities as compared to surface plasmon resonance method for several systems. The optical spectrum of porous silicon for human tissue having thickness up to 1 mm can be easily detected and have shown the feasibility as *in vivo* self reporting medium (Li *et al*., 2003). The optical technique is significantly important for controlling intraocular drug release activity

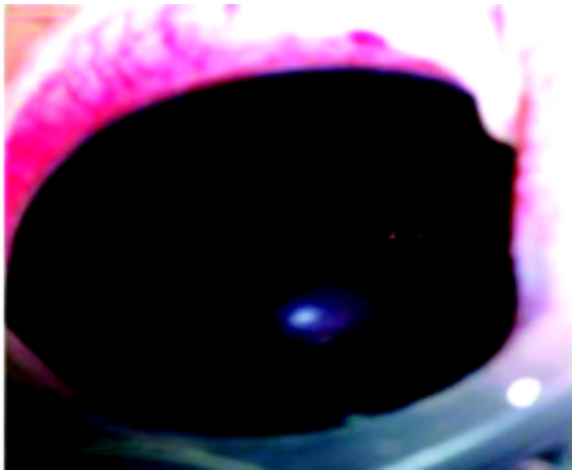

Fig. 4. Photograph showing presence of porous silicon micro carriers in the eye of a rabbit (Li *et al*., 2013).

in composite films or by using porous silicon carriers as illustrated in Fig. 5.

The microparticles of porous silicon shown in Figure 5 have been reported as self-reporting drug carriers for certain diseases like age related macular collapse where long durability is the initial requirement in intraocular drug delivery case (Park *et al*., 2006).

Applications of porous silicon in medical science. The efficacy and bio-compatibility of different types of porous silicon have been investigated for medical purposes and clinical trials are ongoing. The encapsulation of anti-cancer therapeutics (Vaccari *et al*., 2006; Coffer *et al*., 2003) anti-inflamatory agents (Salonen *et al*., 2005; Li *et al*., 2003) analgesics and corresponding medicinally drugs has been demonstrated. Porous silicon as an oral drug carrier has been investigated for a dietary supplement of silicon (Canham *et al*., 2007). Porous silicon drug carriers have opted different forms in order to take drug according to specific function such as particles, films, microneedls and flakes in the form of composite materials (Segal *et al*., 2007; Canham *et al*., 1994). Due to its easy encapsulation and bio-compatibility microns as well as nanoparticles of porous silicon have been utilized in biomedical applications. Oxides of porous silicon as well as porous silicon as a brachytherapy device have been used by porous Si media,Inc for diagnosing cancer. They have taken porous silicon particles of approximated size 20ìm as implants containing radioactive 32p to diagnose tumor. Elemental transmutation method was used to load radioactive isotope in the porous silicon and induced *via* high energy neutrons exposure from a nuclear reactor. Silicon implants hydrolysis to silicic acid and absorbs in body after the radiation dose delivery. Physiological conditions were maintained according to level of toxicity of silicic acid (Lai *et al*., 2005; Kawanabe *et al*., 1992). Anticancer drugs have been successfully encapsulated into porous silicon, for example, calcium phosphate and porous silicon have been taken as carriers for eis-platin in simulated body fluid (Li *et al*., 1998). Porous silicon films loaded with doxorubicin have shown toxic behavior towards adenocarcinoma cell lines of human colon. Singlet oxygen can be formed when photoexcitation of quantum confined silicon nanostructures encapsulated with aqueous aerated medium has been categorized. The harmless toxicity of silicic acid has achieved priority over molecular (porphrin-based) sensitizers for photodynamic therapy (Fujii *et al*., 2006; Fujii *et al*., 2004). Particles as drug carriers have dependence on their size, for example, quantity of drug encapsulated with porous silicon microparticle is increased because of its high pore volume. Singlet porous silicon cubic carrier with approximated size 10 ìm and porosity of 80 % stored a maximum 0.8 pL (picoliter) of free volume (Thomas *et al*., 2006). The incorporation of porous silicon with super paramagnetic iron oxide structures has been reported for magnetic resonance imaging (MRI) and remote radio frequency (RF) heating (Park *et al*., 2006). Salonen along with his coworkers have explored drug

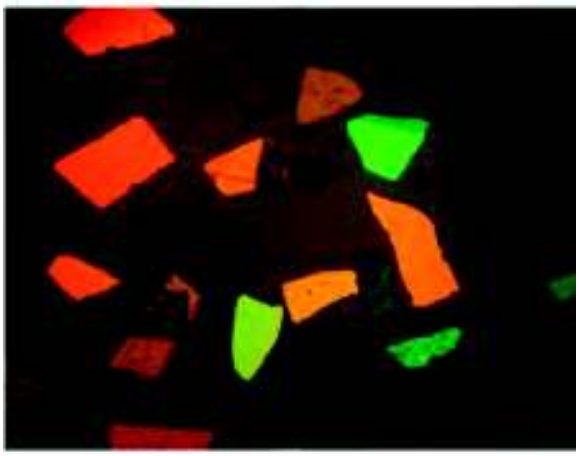

Fig. 5. Porous silicon microcarriers image taken with the help of light microscope (Li *et al*., 2003).

release mechanism of porous silicon microparticles for oral delivery application.

Future prospects and conclusion.

Natural molecules such as proteins have potential applications in biomedicine and may considered as inherent protein biorecognition, target agent and utilized in therapies (Pelegri- O'Day *et al*., 2014). Proteins have been used for the fabrication of nanocarriers due to their ease of surface adaptation, biodegradability and metabolization. Excellent challenges need to be modified in order to prepare protein or peptide therapeutic solutions, an effective delivery carrier and suitable techniques to overcome the formulation. Unconventional delivery systems and formulation techniques will be implemented in oral drug delivery systems in future as predicted by researchers. For example, three dimensional printing and layering precision (nanometer) of oral delivery of drugs as a dozage agent to picoliter (Goyanes *et al*., 2015). Three dimensional printings have not only provided more convenient predictable delivery schemes but also in research of approximately 100% efficient homogeneous nanocarriers.

Therapeutic categorization may realize as a short term reality due to fast and easy 3D printing production methods. Most favorable usage of 3D printing production does not involve use of organic solvents in fabrication of drugs with nanocarriers which will be more convenient and cost effective. The trend of creation of bilayer delivery systems opened many doors for multiphasic delivery (Goyanes *et al*., 2015). Buccal and mucoadhesive delivery routes with encapsulated nanocarriers could be recognized as superior delivery systems for therapies entailing drug absorption while others used to decrease allergies, pain relief, relaxing, sleep, nervous system defects and antihypertensive reactions. Surface modifications and drug carrier encapsulation may improve stability, toxicity to tissue cells, their kinetic release, *in vivo* sensing and circulation rate. Conjugation of drug carriers may improve durability of drug release and provide protection against enzymatic degradation. Oral delivery systems focusing buccal delivery show promising business trend in biomedical and pharmaceutical industries.

Porous silicon micro as well as nano particles have interesting properties for controlled drug delivery. Because of low toxicity of silicon nanoparticles, they have promising pharmaceutical applications. However, their biostability presents little challenges for chronic use due to metabolization after encapsulation. Secondly, pore size, surface area and free volume matter during fabrication. Generation of pores from nanometer to a number of hundreds in diameter is also possible. Surface chemistry of silicon can be modified according to engineering of drug release profile. Amazing optical features of porous silicon have been provided dimensions for *in vivo* sensing or therapeutics. Fluorescence can be obtained from porous silicon having application in silica quantum dots. Porous silicon can be produced with desired optical reflection spectrum. These promising features of porous silicon have opened new doors for the growth of advanced purposeful structures that are in use with sensors, chips for control as well as for diagnostic and therapeutic functions (Prasad *et al*., 2016) Porous silicon can be integrated into well circuited silicon microelectronic fabrication processes which could be converted into active devices for storage as well as for medical applications (Mayne *et al*., 2000; Stewart *et al*., 1998; Nassiopoulos *et al*., 1995). In the last decade, drug nanocarriers have achieved greater importance for therapeutic applications. This review highlighted major advancements in drug carrier systems and biological improvements in drug carrier administration. The growth of oral formulations for drugs encapsulation with biodegradable and biocompatible porous silicon, its composites with polymers like nanostructures have been proven best for oral drug delivery systems.

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