Chapter 12
Diatoms in Biomedicines and Nanomedicines

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Abstract Diatoms are unicellular photosynthetic microalga typically found in an aquatic environment, featuring a 3D nanopatterned silica enclosure called 'frustules'. The deposition of silica by diatoms allows the formation of a porous micro- or nanoscale 3D structure shells with several significant properties like thermal stability, high chemical and mechanical resistance, high specific surface area, tailorable surface chemistry with simple chemical functionalisation/modification procedure, optical/photonic characteristics, biocompatibility and eco-friendly. These characteristics are advantageous in fulfilling a wide range of environmental, agricultural, industrial, biotechnological and biomedical applications. Moreover, high renewability, ease of cultivation through an artificially induced environment, abundant availability and mineable fossilised mineral deposits (diatomaceous earth or diatomite) are economically favourable. This chapter will cover the recent advancements in the application of diatoms in the biomedical field like nanoparticle synthesis, drug delivery, bioimaging/biosensing and tissue engineering.

Keywords Diatoms · Drug delivery · Diatom nanoparticles · Tissue engineering · Biosensors/bioimaging

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12.1 Introduction

Diatoms are photosynthetic unicellular microalgaes commonly found in soil and water (Dugdale and Wilkerson 1998). There are more than 110,000 known species across 200 genera recognised with silica-based shells, and these shells have a wide range of diverse shapes and structures containing pores with a diameter ranging from nano to micrometres (Parkinson and Gordon 1999). Through CO_2 fixation, it plays a vital role for photosynthetic producers within the food chain, globally contributing significantly to carbon stabilisation and immobilising a large percentage of the ocean's CO_2 (Kurkuri et al. 2011). The diatom cell wall is known as frustules which are well-organised porous silica micro shells (silicon dioxide hydrate, $SiO_2 \cdot nH_2O$) (Gordon et al. 2009). The frustule, on the other hand, is bilaterally symmetrical and consists of two valves known as thecae, one of which is slightly larger (epitheca) and overlaps the other (hypotheca) (Lopez et al. 2005). The frustules are organised through stacks of several inner layers known as areolae, cribrum and cribellum. Areolae are a honeycomb-like porous chamber roofed with cribrum having tiny and highly ordered pore patterns; cribellum is the thin siliceous membranes with several tiny pores, as shown in Fig. 12.1. The synthesis of frustules occurs with the help of a specialised compartment known as silica by intracellular polymerisation of silicic acid monomers (Chao et al. 2014). Silaffins transport proteins that appear to facilitate the formation of silica deposition in diatom frustules. The frustules can vary in size, morphology and function depending on the environment for their growth and species of diatom (Bradbury 2004).

In recent years, drug delivery application of mesoporous material of silica has been extensively studied to address the traditional challenges related to drug

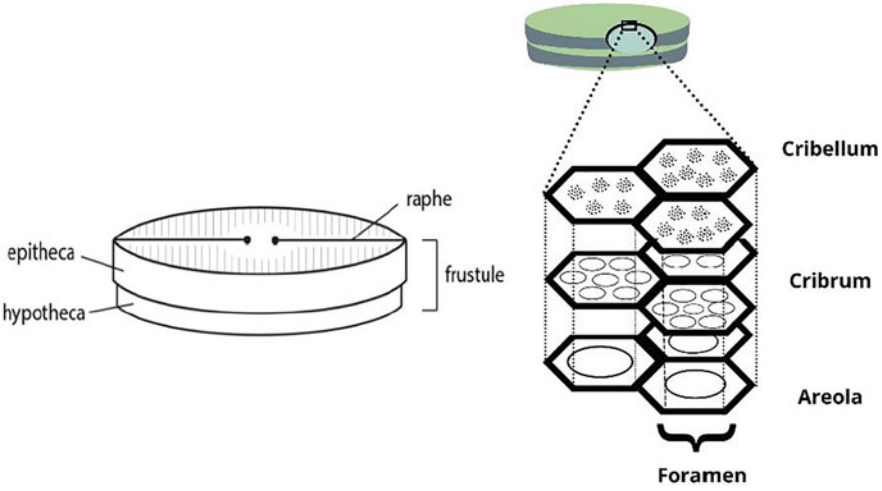

Fig. 12.1 Schematic structure of centric diatom frustule

delivery, such as low solubility and bioavailability, unappaling properties of pharmacokinetics and short activity (Vallet-Regí et al. 2007). They provide numerous benefits in the drug development process when utilised as a drug carrier in a drug delivery system because of their unique qualities, such as large surface area, adjustable structure, chemical resistivity, mechanical rigidity, increased drug loading capability, etc. (Bariana et al. 2013). Apart from their massive success in the drug delivery system, mesoporous material also has drawbacks, such as complicated synthesis processes, time-intensive, costly, high energy, unsafe and generating waste. MCM-41 and SBA-15, being the most popular series, also couldn't escape such drawbacks (Slowing et al. 2007; Vallet-Regí et al. 2007). As a consequence, there was a need for an alternative that could fit in place of mesoporous silica, yet again nature has offered an alternative that has the potential to replace the mesoporous silica. Diatoms are closely similar to mesoporous silica and are renewable, abundantly present, cost-effective, non-toxic and compatible with the drug delivery system (Bariana et al. 2013; Rabiee et al. 2021). Diatoms have been extensively studied for their potential application in a variety, and several researchers have independently proven them, such as molecular separation, drug delivery, immunoprecipitation, photonics, biosensing, nanofabrication, etc. (Fuhrmann et al. 2004; Lopez et al. 2005; Gordon et al. 2009; Aw et al. 2013; Bariana et al. 2013; Rea et al. 2016). The diatom's surface can be easily modified with simple chemical processes. The silicon dioxide building blocks provide scope for tailoring the surface properties in various engineered biomaterials for fulfilling desired biomedical applications. The hydroxyl groups on the diatomaceous earth (DE) surface are exploited for modification through well-established chemical processes. The surface functionalisation processes resemble previously discovered processes for modifying synthetic silica particles, including various applications such as organic monolayers and inorganic layers of oxide, proteins, polymers and coating with metal (Howarter and Youngblood 2006). Most of the processes include the modification through silanol (SiOH) groups present on the DE surfaces, which are reactive moieties. Several other reactive species, e.g. -NH_2, -COOH, -SH and -CHO, are employed for the surface modification exploiting silanol groups, which provide coupling points for several chemical and biological particles like drugs, DNA, proteins, antibodies, sensing probes, etc., hence, helping in the immobilisation of these particles (De Stefano et al. 2013; Terracciano et al. 2013). It is worth mentioning that the silanisation process occurs through the covalent bond of Si-O-Si, which provide a stable attachment for various active moieties on the surface of the diatom (Losic et al. 2010). Figure 12.2 illustrates the distinctive surface functionalisation of diatom microcapsules using organosilanes through the self-assembled layer (Rea et al. 2016).

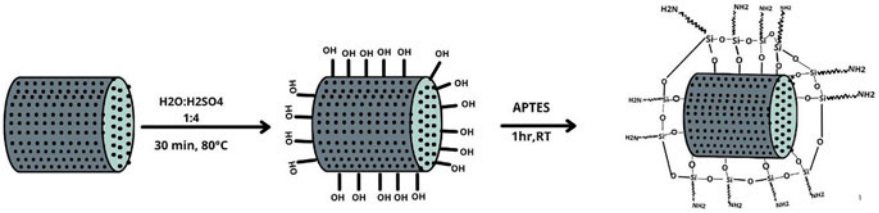

Fig. 12.2 Schematic represention of surface functionalisation of diatoms

12.2 Application of Diatoms

12.2.1 Diatoms for the Biosynthesis of Nanoparticles (NPs)

The characteristics of gold nanoparticles were widely anticipated for a catalytic property, photonic bandgap behaviour, localised surface plasmon resonance (LSPR) response and surface-enhanced Raman spectroscopy (SERS) (Link and El-Sayed 2003; Meldrum and Cölfen 2008). When reducing 4-nitrophenol to 4-aminophenol ($NaBH_4$) in the presence of reductants, the catalytic characteristics were significantly verified (Yu et al. 2010). Similarly, gold nanoparticles were fabricated by depositing gold onto the silica of diatomaceous earth (DE) via photo deposition. The molecules in the solution get captured in the pore structure, and the formed gold nanoparticle amplifies spectroscopy signals by many folds through the SERS effect (Onesto et al. 2018).

The photosynthetic pigments released by the diatoms (*Amphora* sp.) were noticed to have a reducing property implicated successfully in the synthesis of polycrystalline spherical silver nanoparticles via bioreduction of the silver ions into silver nanoparticles. The formulated silver NPs displayed high antimicrobial effects, especially gram-positive or gram-negative microorganisms (Jena et al. 2015). Similarly, another silver nanoparticle was synthesised on the diatom's surface by exploiting fucoxanthin. Reducing silver ions by the current carotenoid with a hydroxyl group and proteins averted the possible future aggregation and/or sedimentation of NPs with a carboxyl group (Chetia et al. 2017). Remarkably, under a given physiological setting, diatom frustules derived from peptides demonstrate excellent conditions for synthesising silver NPs. The kinetic reaction of silver NP formation was a highly sensitive photoreduction process—the reaction rate was hugely dependent on the peptide-diatom interaction (Gupta et al. 2018). Therefore, silver NPs are a highly antimicrobial compound and are effective against problematic pathogens such as *Streptococcus pneumonia*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Aeromonas* sp., etc. Hence, it resulted in the increased popularity of silver NPs.

Consequently, several attempts were made with different diatom species to prepare silver NPs (Mishra et al. 2020). Similarly, several attempts have been undertaken using various techniques to create NPs, such as *Nitzschia* diatoms for

the biosynthesis of silicon-germanium oxide nanocomposite (Mansuy-Aubert et al. 2013). Another study has indicated the plausible preparation for gold-silica nanocomposites with the feasible structural organisation (spherical, hexagonal and triangular) using *Amphora copulate* diatoms (Roychoudhury et al. 2016). The mechanism for the biosynthesis of silver NPs via bioreduction of silver ions into NPs within the diatoms were implicated with the role of photosynthetic pigments, although silanol (with hydroxyl group) was identified with a crucial role in forming silver NPs (Mishra et al. 2020). The synthesised NPs were tested for a few other properties, and in a study, it was undoubtedly noticeable that the affinity of biosynthesised NPs bond with DNA without any further modification requisites—which was confirmed using agarose gel electrophoresis—"Y"-shaped chainlike and coiled structures were observed for the interacted particles and DNA molecules. Such properties could be highly beneficial in the field of biomedical applications. However, the biosynthesis of nanocomposites is possible only on the surface of the live diatoms, whereas dead diatoms remain unaffected (Roychoudhury et al. 2016).

12.2.2 Diatoms in Drug Delivery

The ideal drug delivery system should target only specific diseased cells with an adequate concentration of drug discharge and minimum adverse effect on healthy tissues (Wagner et al. 2006; Maher et al. 2018). Furthermore, most of the new drug targets and currently popular drug molecules are contained in the Biopharmaceutics Classification System, which shows inadequate physicochemical properties such as class II or class IV, poor solubility, poor uptake into cells, restricted biodistribution, efficacy, etc. Therefore, over the past, scientists have focused on developing new enhanced techniques for drug delivery, which led to the concept of drug carrier systems. These carriers are designed to protect drugs from degradation/rapid clearance, lift physiochemical properties and elevate cellular uptake. As a result, scientists have practically developed several drug carrier systems with enhanced drug distribution and efficient immobilisation of drugs in the tissues of interest with few negative consequences (El-Aneed 2004; Taylor and Triggle 2007; Van der Meel et al. 2013). Evidently, the physicochemical properties of synthetic silica are much fruitful for this purpose. However, the major drawbacks were the high cost of manufacturing, time-consuming and high cost of manufacturing. In addition, the usage of harmful solvents for the manufacturing process also poses a threat to the final product due to trace residue (Tran et al. 2009; Maher et al. 2018). Although these drawbacks could be overcome through biosilica exploitation with the propensity towards diatoms as bioresource—diatoms have high regeneration capacity, and a huge amount of DE silica already exists. Therefore, biosilica has huge potential for producing futuristic drug carriers with minimal negative impact all-embracing (Anderson et al. 2000; Dolatabadi and de la Guardia 2011).

In 1999, The first-ever idea of exploiting diatoms to construct productive material was mentioned by Morse. He showed the current incapability of humans to produce

a synthetic replica of the architectural construct of silica as produced by diatoms (Morse 1999). The release of gold nanoparticles from DNA-functionalised diatom surfaces has been successfully controlled and scalable in medication delivery (Rosi et al. 2004). However, few studies also demonstrated (in vitro) the practical application of DE silica as a drug carrier through the encapsulation of therapeutic drugs (Aw et al. 2011, 2012). Indomethacin was loaded onto the DE silica with a drug loading capacity of 22 wt% drug loading capacity and a 2-week continuous release of the drug, which depicts the efficacy of the DE silica for the application as a drug carrier. The drug release ensued in two phases, and the first phase exhibited a rapid release for incessant 6 h due to surface detachment of the adsorbed drug. The other phase lasted 2 weeks and had zero-order kinetics due to the slow release of drugs from diatoms' interior pores. Likewise, prednisone and mesalamine were also put onto DE silica for oral administration. The results validated the drug's prolonged release, and toxicity testing revealed that diatom frustules had no deleterious effects even at 1000 g/mL when tested in various cells (Caco-2, HT-29 and HCT-116) individually and Caco-2/HT-29-cocultured cells (Zhang et al. 2013).

The hydroxyl-enriched DE silica surface provides huge scope for the modification to enhance the surface properties to achieve improved drug loading and release profile (Aw et al. 2013). Several strategies have been developed in recent years to modify silica surfaces with metal and inorganic oxide layer coating, polymer, proteins and organic monolayer; these strategies are frequently used for developing synthetic silica (Rabiee et al. 2021). The most popular method is the application of the silanol group to functionalised it with several reactive species (e.g. -NH_2, -COOH, SH and CHO), generating a vigorous coupling point for biological and chemical moieties such as drugs, proteins, antibodies, aptamers, DNA, sensing probes, etc. (De Stefano et al. 2013; Terracciano et al. 2013). Mesoporous silica-based NPs are the finest, with a pore size of ~2–50 nm for the drug delivery aptitudes (Terracciano et al. 2018). Remarkable characteristics of diatoms such as thermal stability, modification thru the simple chemical procedure, enormous surface area (up to 200 m^2/g), biocompatibility, mechanical resistance, eco-friendly, optical/photonic characteristics and ease of genetic manipulation make it an excellent choice for drug/gene delivery (Rabiee et al. 2021). Some of the examples of drug delivery employing diatoms are mentioned in Table 12.1. Fabrication of DE silica for the drug delivery system via the silanisation process is quite a popular procedure due to its chemical stability due to Si-O-Si covalent bonds (Mohammadinejad et al. 2015; Schröfel et al. 2011). Figure 12.2 provides a pictorial representation of the chemically induced modification of the surface of diatom microcapsules via the formation of a self-assembled layer using organosilanes (Pytlik et al. 2017). In a study, various modifications were tested by imparting hydrophilic (2-carboxyethyl-phosphonic acid), APTES (3-aminopropyl triethoxysilane), and AEAPTMS (3-aminopropyl trimethoxysilane) and hydrophobic (16-phosphono-hexadecanoic acid) properties to microcapsule (Fig. 12.3). Observation shows contrasting behaviour; the hydrophilic modification showed enhanced drug loading having 15–24 wt% and prolonged drug release (6–15 days), whereas hydrophobic modification showed lower drug loading and rapid drug release (Maher et al. 2018). A thorough analysis

Table 12.1 Some examples of drug delivery systems employing diatoms

Drugs	Surface functionalisation	Loading process/loading capacity	Release duration	Remarks	References
Mesalamine	–	Immersion; 9.9–11.5%		• Functions as permeation enhancer for oral ingestion.	Zhang et al. (2013)
Prednisone				• Minimises toxicity of diatoms	
Indomethacin	–	Wetted and sonicated; 22%	14 days (6 h—burst release)	• For implant and oral ingestion	Aw et al. (2012)
Indomethacin	Graphene oxide-APTES	Immersion; 30%		• Controlled drug delivery	Kumeria et al. (2013)
Indomethacin	mPEG-silane	Simple incipient wetness; 14–24%	13–26 days	• Improving drug loading and release profile	Bariana et al. (2013)
Gentamicin	7-OTS				
	3-GPTMS				
	2-CEPA				
	16-PHA				
	APTES				
Indomethacin	Dopamine (DOPA) functionalised iron oxide NPs	Immersion; 28%	8 h	• Enhanced targeted drug delivery	Medarević et al. (2016)
Gentamicin					
Sorafenib	APTES	Silanisation; 10.4 ± 1.1%	4–24 h	• Dual biofunctionalisation	Terracciano et al. (2015)
	APTES-PEG (polyethyline glycol)	DNPs-PEGylation; 22 ± 2%		• Enhanced stability, biocompatibility, cellular uptake for anti-cancer drug	
	APTES-PEG-CPP (cell-penetrating peptide)	DNPs-PEGylation and peptide bioconjugation; 17 ± 2%		• Increased solubility	

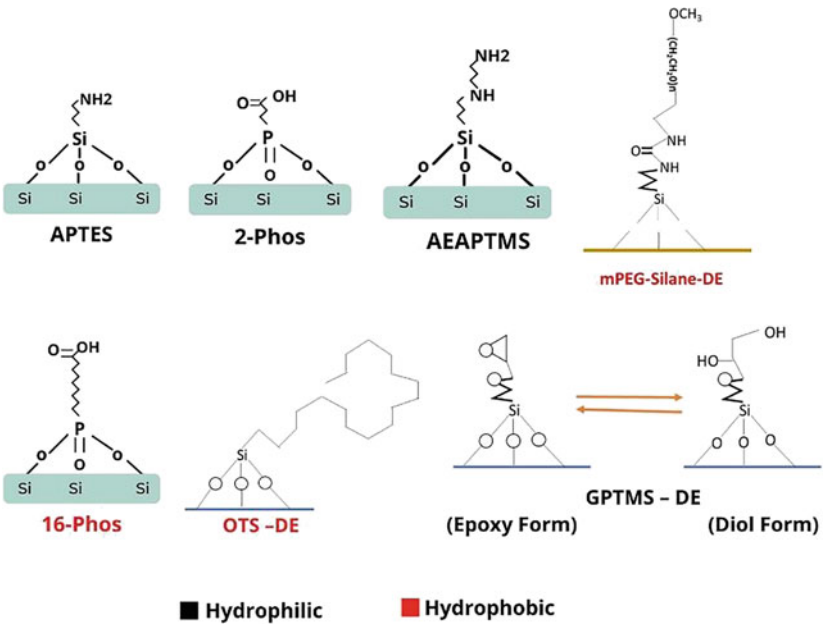

Fig. 12.3 Structure of DE microparticle structure as well as surface functionalisation with organosilanes (APTES, GPTMS, OTS and mPEG-Silane) and phosphonic acid (2-CEPA and 16-PHA) to make DE surfaces hydrophilic or hydrophobic

of the different hydrophobic and hydrophilic DE surface modifications for the hydrophobic indomethacin and the hydrophilic gentamicin (hydrophilic). Similarly, Bariana et al. (2013) have successfully analysed the grafting of several functional groups, and their interfacial properties were confirmed through Fourier transform infrared (FTIR) analysis. Their findings are shown in Table 12.2; water-soluble drugs (gentamicin) and water-insoluble drugs (indomethacin) were tested against hydrophilic and hydrophobic modifications. Because of a polar carboxyl, amine or hydrolyzed epoxy group in hydrophilic changes, indomethacin release was prolonged, but hydrophobic modifications with a long-chain hydrocarbon resulted in gentamicin release being prolonged (Kim et al. 2009; Bariana et al. 2013).

12.2.3 Diatoms in Biosensing and Bioimaging

Biosilica can be improved by incorporating antibodies, enzymes, drugs and DNA aptamers as detection components to obtain a series of promising biosensors. In one study, in order to detect breast cancer cells from normal cells using iron oxide NPs, researchers chemically modified biosilica structures from *Chaetoceros* sp. diatoms to create a new functionalised system containing trastuzumab antibodies. In vitro investigations using these nanosystems in applying a magnetic field show that

Table 12.2 Comparative overview of loading capacity for the hydrophobic and hydrophilic modification with hydrophobic and hydrophilic drug. 3-Aminopropyltriethoxysilane (APTES); 7-octadecyltrichlorosilane (OTS); 3-(glycidyloxypropyl) trimethoxysilane (GPTMS); 2-carboxyethylphosphonic acid (2 CEPA); 16-phosphono-hexadecanoic acid (16 PHA); methoxy-poly-(ethylene-glycol)-silane (mPEG-silane)

	Indoemthacin (water-insoluble drug)	Gentamicin (water-soluble drug)
Hydrophobic functionalisation	**(Wt.% loading)**	**(Wt.% loading)**
OTS-DE	14 ± 5	–
16-PHA-DE	14 ± 5	22 ± 5
mPEG-silane-DE	17 ± 5	–
Hydrophilic functionalisation	**(Wt.% loading)**	**(Wt.% loading)**
APTES-DE	22 ± 5	15 ± 5
GPTMS-DE	19 ± 5	–
2-CEPA-DE	24 ± 5	16 ± 5

SKBR3 cells may be selectively trapped and separated (Esfandyari et al. 2020). APTES was employed to detect bovine serum albumin, and frustules from *Amphora* sp. diatoms were functionalised. A significant reduction in photoluminescence intensity of bovine serum albumin was obtained at 445 nm as a result of interaction with the amine-functionalised diatom bovine serum albumin protein complex, with a detection limit (LOD) of 3105 M (Viji et al. 2014). Subsequently, cardiovascular protein biomarkers (myeloperoxidase and C-reactive proteins) use nanoporous biosilica materials such as silicon chips with an array of gold electrodes and instantaneous label-free electrochemical properties. It can be determined from human serum samples. For devices with the potential for point-of-care protein biomarker detection, they can be used as a biosensor platform with significant sensitivity (1 pg/mL) and selectivity (Lin et al. 2010).

It has been discovered that the biosilica frusta from the diatom *Coscinodiscus concinnus* can be used as an optical biosensor with high sensitivity and low-level detection (LOD) of 100 nM. These new systems could be beneficial for laboratory particle applications. Gold nanoparticles were integrated into a biosilica-based ultrasensitive surface-enhanced Raman spectroscopy (SERS) immunoassay to detect interleukin 8 (IL8) in the human blood (De Stefano et al. 2009; Kamińska et al. 2017). Diatom biosilica was used to make ultrasensitive immunoassay biosensors with increased fluorescence spectroscopy and imaging, which are valuable attributes for biosensing applications with advantages (Squire et al. 2018). In another study, diatomaceous earth biosilica was used to fabricate nanoplasmonic sensors using in situ growth of silver NPs (based on SERS). These sensors can be used for various purposes, including medical and biomedical research (biomolecule identification), food detection and quality monitoring of air and water (Kong et al. 2016). Optical imaging and magnetic resonance imaging can benefit from porous silica-based NPs (Calfon et al. 2011). Herr et al. examined fluorescence intensities of dye-doped

silica-based NPs and diaptamers only and found that aptamers manipulated with dye-doped silica-based NPs exhibited superior brightness and stability compared to diaptamers alone (Herr et al. 2006). The main advantage of these nanoparticles was that the silica matrix prevented dye fading, enabled long-term imaging of tumour cells and was suitable as a highly sensitive biosensor (Santra et al. 2001). It has been demonstrated that diatomite NPs paired with a nontargeting siRNA may be localised in H1355 lung malignant cells for more than 72 h using Raman imaging (Managò et al. 2018). Due to their low systemic toxicity, chemical/thermal stability and cost-effectiveness, these NPs can be used as potential anti-cancer therapeutics and nanovectors. Aptamer-bound NPs were prepared for tumour cell extraction and fluorescence imaging (Medley et al. 2011). Researchers used fluorophore-doped silica-coated magnetic and silicon-based NPs to detect and isolate malignant cells (Wu et al. 2015). The hormone N-terminal pro-B-type natriuretic peptide (NT-proBNP), a well-known cardiovascular disease biomarker, was detected using diatom frustules as fluorescent imaging immunoassay platforms. The glass slides inhabited by diatoms were aminated with glutaraldehyde (GA) for surface functionalisation and APTES for amination. The reaction of aldehyde functional groups with amine groups occurred with anti-NTproBNP, antibodies and bovine serum albumin (BSA). BSA inhibited the remaining active aldehydes and restricted non-specific binding. The antibody binds to the antigen and creates a sandwich structure for the antiNT-ProBNP (FITC) fluorescent tag. You can then evaluate the fluorescence and report the detected event (Squire et al. 2019).

12.2.4 Diatoms in Tissue Engineering

Biosilica materials are used for in vivo and on bone healing (Saos-2 cells) because it is highly stable and biocompatible because of their unique properties, such as being morphogenetically active and assisting in the mineralisation of osteoblast-like cells (Granito et al. 2017; Venkatesan et al. 2015; Wang et al. 2012). The procedure for preparing microcapsules of β-tricalcium phosphate (β-TCP) encapsulated in a polymer (D, lactide coglycolide) alone or combined with silicate-in or silica is depicted in the image (Wang et al. 2014a, b). In comparison to those containing simply β-TCP, silica-containing microspheres increased Saos-2 cell adhesion. Following that, as a source of biosilica, biocomposite and chitosan were created for bone tissue engineering utilising the lyophilisation approach resulting in chitosan-biosilica composite scaffolds which were highly porous (Tamburaci and Tihminlioglu 2018). The wet chitosan-diatomite composite scaffolds' compression moduli were comparable to that of chitosan alone. Biosilica and polyphosphate have previously been used because they affect osteoblasts in morphogenesis. Their effects have been assessed in differentiating mesenchymal stem cells and human pluripotent stromal cells (hMSCs) encapsulated in biocompatible plant polymer alginate beads (Wang et al. 2014a, b). Induction of both biosilica and polyphosphate into osteogenic cells resulted in increased mineralisation, morphogenetic protein 2 expressions of bone

(BMP-2) and increased expression of alkaline phosphatase. The type I and type II expression of collagen differed depending on whether they were exposed to polyphosphate or biosilica. Osteogenic cells express a lot of collagen type I. In chondrogenic cells, the level of collagen II transcript was found to be higher than the osteogenic cells. When combined with morphogenetically active inert alginate polymers, polyphosphate and biosilica can be used to transfer in 3D printing of human mesenchymal stem cells and fractures (Wang et al. 2014a, b). As we know, Chitosan-coated diatoms are biocompatible and can absorb fluid and hemostasis influence, which help prevent bleeding (Feng et al. 2016). Chitosan/dopamine/diatom biosilica composite beads have desirable biocompatible hemostasis potential. Dopamine was used as a bioglue to combine chitosan and diatom biosilica. The system is built on a porous structure that can quickly absorb large amounts of water and stop the bleeding immediately (Wang et al. 2018). A unique and ecologically friendly calcium-doped biosilica system for water absorption has been established to integrate calcium into the diatom frustules of *Coscinodiscus* sp. with excellent competence and biocompatibility. In vivo, it can also consolidate blood clotting pathways, accelerate blood clotting and manage haemorrhages more quickly (Li et al. 2018).

12.3 Conclusion

In recent years, diatoms have emerged and become popular for various applications in several fields such as drug delivery, nanotechnology, biosensors, bioimaging, photodynamic therapy, biophotonics and molecular filtrations. Diatoms have 3D nanostructures with unique hierarchical porous structures with large surface area, tailorable surface modification, excellent biocompatibility, chemical stability and distinctive optical and photoluminescence capabilities that are difficult to obtain with synthetic silica. Besides, the generation of diatoms took place in genetically controlled cellular processes, hence, providing scope for synthesising various new-fangled biomaterials via biotechnological aids. Porous and mesoporous silica-based nanoparticles are most famous for drug/gene delivery due to their advantageous properties such as high biocompatibility, adjustable surface chemistry, rate of drug loading, solubility and release profile and, foremost, their cost-effectiveness. However, future studies should target their renewability, enhancing bioavailability, biodegradability analysis and occurrence of plausible toxicity.

Furthermore, they have been highlighted for their probable application in biotechnology, ecological monitoring, phytoremediation of heavy metals and hazardous pollutants, biofuel production and CO_2 fixation. With such broad applicability, it has a high chance of industrial level cultivation. However, for the industrial level requirement, it should be studied meticulously to improve and eliminate any undesired characteristics.

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