Biosurfaces : A Materials Science and Engineering Perspective

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APPLICATIONS OF BIOMATERIALS

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The previous chapter discussed about the four broad classes of biomaterials being used in the health sector. Each biomaterial type has its own set of properties that makes it suitable for a particular application, which varies from surgical suture for sewing up wounds to tissue scaffold for artificial tissue generation. This chapter deals with the various applications of biomaterials and their specific properties required for those applications. Firstly, we understand the basic structure of natural bone, which is a most important part toward implanted materials into a host.

10.1 MULTI-SCALE HIERARCHY IN NATURAL BONE

Bone is a metabolically active tissue and constantly remodeled, as with time, cells break down old tissue and other cells make new tissue. Bone is composed of organic (∼20–30 wt.%) collagen fibers, elastic protein, inorganic calcium phosphate mineral

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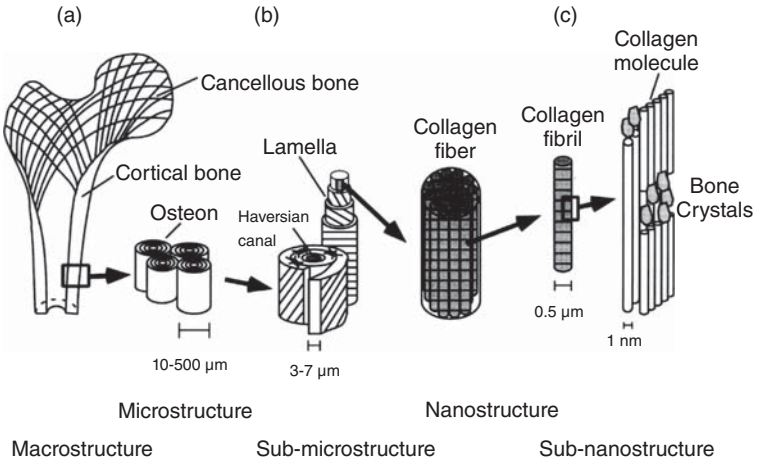

Figure 10.1. Multi-length scale hierarchy in natural bone: from left to right (a) bone types cancellous as well as cortical (b) haversian and osteons systems (c) collagen fibres, lamellae and hydroxyapatie crystals. (Reproduced with permission from Elsevier, [1].)

(∼60–70 wt.%) and water (∼10 wt.%). For the order of complexity an engineer must understand in order to mimic the architecture that nature has created, it becomes essential to understand the fundamental components at different length scales. In human bone, proteins, cells and tissues naturally occur in nano-length, as represented in Fig. 10.1. For example, the dimension of hydroxyapatite (HAp) crystals comes in the range of approximately 50 nm in length and 5 nm in diameter. The fibrils with the dimensions of 300 nm length and 0.5 nm width were typically found in Type I collagen with the periodicity in the order of 67 nm [2]. The nano-porous composite material, which forms natural bone is 30% matrix and 70% nano-sized rigid materials [3, 4]. Thus, it is predicted that if the bone implant should be made up of nano-structured materials, then all its properties must be improved as compare to the present bone implants.

10.1.1 Hydroxyapatite

The structure of HAp (Fig. 10.2) consists of hexagonal unit cells with space group $P6_3/m$ and values of $a = 9.880$ Å and $c = 6.418$ Å. It consists of the crystallite dimension of HAp in the range of $2 \times 20 \times 40$ nm with two units of $Ca_5(PO_4)_3OH$. XRD analysis shows line broadening of bone, which is responsible for complicating the process involved in identification of additional phases. The crystallinity of this mineral component is responsible for rendering strength to the structure and making it load bearing. Thus, its synergistic control of structure and synergy with collagen can create a tough load-bearing system of natural bone (Table 10.1).

10.1.2 Collagen Triple Helix

Different types of collagen proteins exist and are most abundant in animals. Collagen is a fibrous protein that plays an essential and major role of structural support in connective

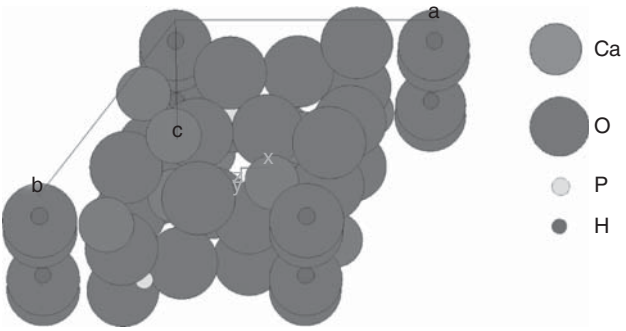

Figure 10.2. Crystal structure of hydroxyapatite ($a = b = 9.435$Å, $c = 6.865$Å, $\alpha = 90°$, $\gamma = 120°$, JCPDS# 86-1201). (Reproduced with permission from Elsevier, [5].)

TABLE 10.1. Fractions (with Site Occupancy) and Equivalent Isotropic Displacement and Positional Parameters of HAp

Atom	Site	Oxidation state	X	Y	Z	Occupancy
Ca1	4f	2	0.3333	0.6667	0.0015 (7)	0.98 (2)
Ca2	6h	2	0.2454 (5)	0.9928 (5)	0.250	0.96 (2)
P1	6h	5	0.3991 (5)	0.3688 (4)	0.250	1
O1	6h	−2	0.3272 (4)	0.4825 (4)	0.250	1
O2	6h	−2	0.5883 (4)	0.4657 (4)	0.250	1
O3	12i	−2	0.3435 (3)	0.2584 (3)	0.0705 (3)	1
O4	4e	−2	0	0	0.206 (2)	0.30 (1)
D1	4e	1	0	0	0.168 (3)	0.30 (1)

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tissue, extracellular matrix (ECM) with organs and bone. Collagen holds tissues together. Collagens are composed of a triple helix of three polypeptide α-chains. About 20 types of collagen have been reported, and type I, II and III are the most abundant in the animal kingdom. The rod-shaped structure formed by triple helix plays significant function in the formation of fibril and structural integrity. This rod-shaped structure comes in contact with molecules, which regulate the organization and functions of ECM. There are certain proteins with collagen triple helix, which play host defence functions [6]. Collagen contains 19 amino acids with two specific proteins, namely, hydroxyproline and hydroylsine. It has a characteristic amino acid sequence: GLY-X-Y (where, X and Y represent proline and hydroxyproline, respectively) with exclusive features: (i) glycine, which generates a selectively repeating (Gly-X-Y) pattern (as shown Fig. 10.3a), and (ii) a higher content of residues (∼20%) is the amino acids hydroxyproline and proline (Fig. 10.3b, inset). The NHC−O hydrogen bonds, which are present in peptide, represent the NH of glycine, H-bonded via C=O in proline. This pattern is intermittent in the Gly ∼Ala exchange regions shown in Fig. 10.3b [6]. Three alpha chains coil to form tropocollagen, in the dimensions of approximately 300 nm in length and 1.5 nm

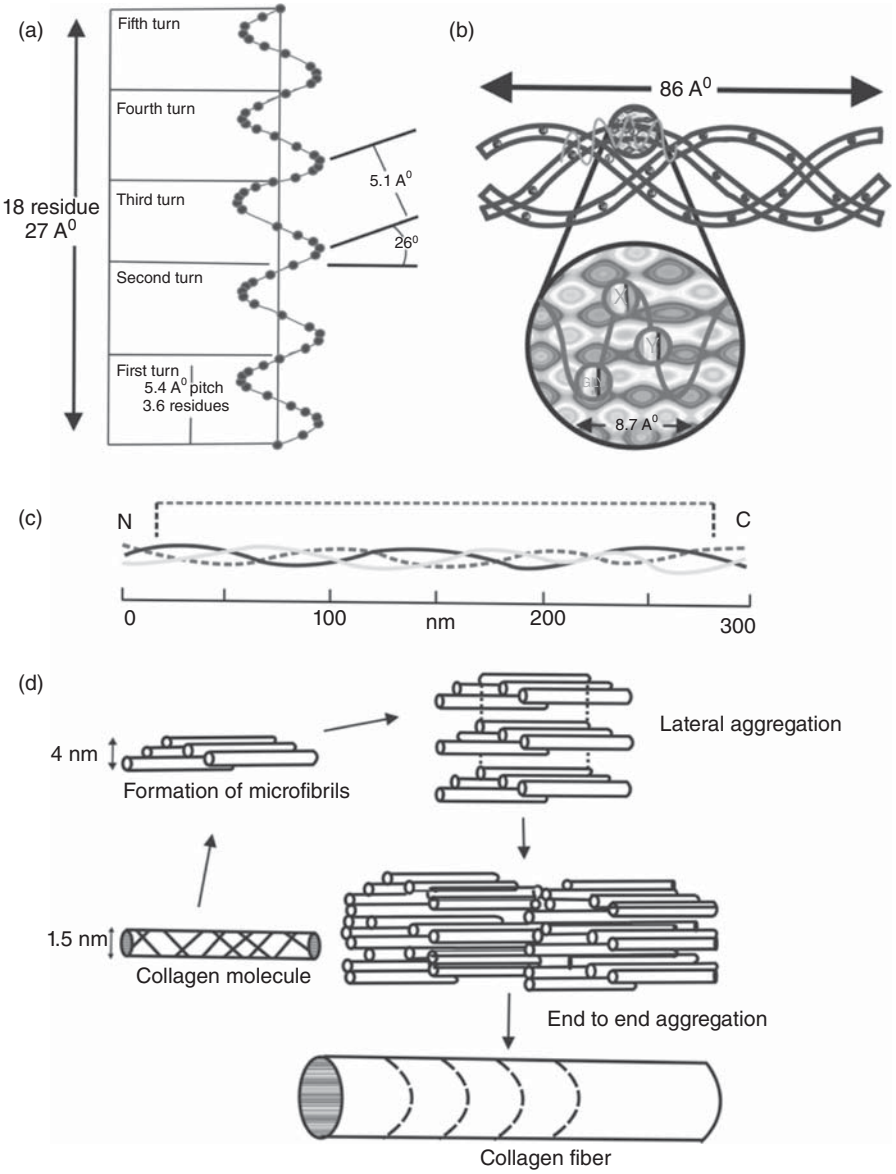

Figure 10.3. Schematic showing (a) single strand or repeating pattern of Gly-X-Y showing its pitch and residue, and (b) collagen triple helix structure with turn, residues and H-bond between glycine and X, Y, respectively (where, X/Y may be proline or hydroproline, see inset), and (c) hierarchical structure of collagen with triple helix. (*See insert for color representation of this figure*.)

in diameter termed as *fibrils*. The fibrils made by three polypeptide strands (a peptide) of a left-handed helix form protofibril (an elongated unit appearing in the formation of fibre), and its hierarchical structure is shown in Fig. 10.3c.

10.1.3 HAp Collagen Organization

The bone is a natural nano-biocomposite of organic and inorganic compounds composed of nanocrystals of HAp ($Ca_{10}(PO_4)_6(OH)_2$). The size of crystals may vary from 20 nm to approximately 300 nm with collagen molecules. The analysis of micro-level of bone reveals that the collagen molecules are covered with HAp crystals. In such a way, nanocomposite fibers are formed, which contain HAp crystals along with collagen molecules, aligned in c-axes. In biological condition, HAp is formed especially in nanocrystalline order. Collagen is formed in growing process as a structural organic molecule and organic component of endoskeleton. HAp accumulated in the endoskeleton forms well-aligned nanostructure-nanocomposites of HAp and collagen. Due to this, organic (collagen fibres) as well as inorganic (HAp nanocrystals) ingredients give rise to a hard and elastically touch composite, and also the collagen structure changes during formation, resulting in inferior physical properties of bone (confirmed via bone pathology), where HAp is observed both intra- and inter-fibrillary with collagen. The elastic properties can be modeled by playing weighed/volume ratio of HAp or collagen reinforcements. Thus, it may conclude that an artificial HAp/collagen nanocomposite is a potential material due to its excellent biological properties such as biocompatibility, cytocompatibility and bioactivity. Furthermore, this composite is also beneficial as a scaffold material with controlled pore size.

10.1.4 Lamellae Structure

The most abundant bone in mammals is the lamellar bone, which is made up of five sub-layers and mineralized collagen fibrils. The orientations of these arrays of mineralized collagen fibrils are different in two ways: crystal layers and collagen fibril axes. Fig. 10.4 presents the lamellar cross-section of bone. Since elastic modulus (E) for cortical bone in the longitudinal direction (axial) is ~1.5 times than that of transverse direction, mechanical properties of lamellar bone follow direction-dependent anisotropic pr. In brief, the lamellar structure of bone describes as follows:

- Fibrillar composites form fiber and fiber bundles
- Lamellar type units
  - Circular lamellar units forming secondary osteons or Haversian systems (in mature human bone)
  - Plexiform bone formed by straight lamellar units (source: young quadruped animals)
  - Composite analysis to evaluate the elastic properties of tissue can render macroscopic properties of bone.

10.1.5 Multi-Functionality of Bone

There are several important properties of bone, which enable it to perform different tasks. The presence of composite structure of mineral microcrystal and protein leads to stiffness of bone. Slow creep results between osteons at cement lines, and the toughness of bone is mainly due to the presence of cement lines as weak interfaces. The bone provides space in the form of ellipsoidal pores (lacunae) for living cells, that is osteocytes. These bone cells permit remodeling the bone tissue structure in response to existing stresses. Blood vessels present in Haversian canals (cylindrical pores) help in nourishing these tissues. Due to the physical activity, bone experiences mechanical stress, which is found to be important in pumping nutrients by fine channels known as canaliculi radiating from the lacunae. The most important feature of natural bone (Fig. 10.4) is to adapt to mechanical stress and maintain its viability, which is possible because of its pore structure.

Elizabeth A. Zimmermann et al. studied the fracture of human cortical bone under mixed mode and characterize the crack-initiation fracture toughness under combined mode I (tensile) and mode II (shear). These tests were carried out under loading in asymmetric as well as symmetric four-point bending test. It was observed that with increasing mode mixity, the fracture toughness was significantly decreased. Mode mixity is an important parameter to explain the interfacial fracture properties. The mode mixity (termed as fracture phase angle) is the relative proportions of tractions in front of the crack tip in opening mode (mode I) and sliding mode (mode II) in the facture. Three samples of cadaveric femurs of frozen human in the age group of men from 48 to 80 years were chosen for study. A notched asymmetric four-point bending test was

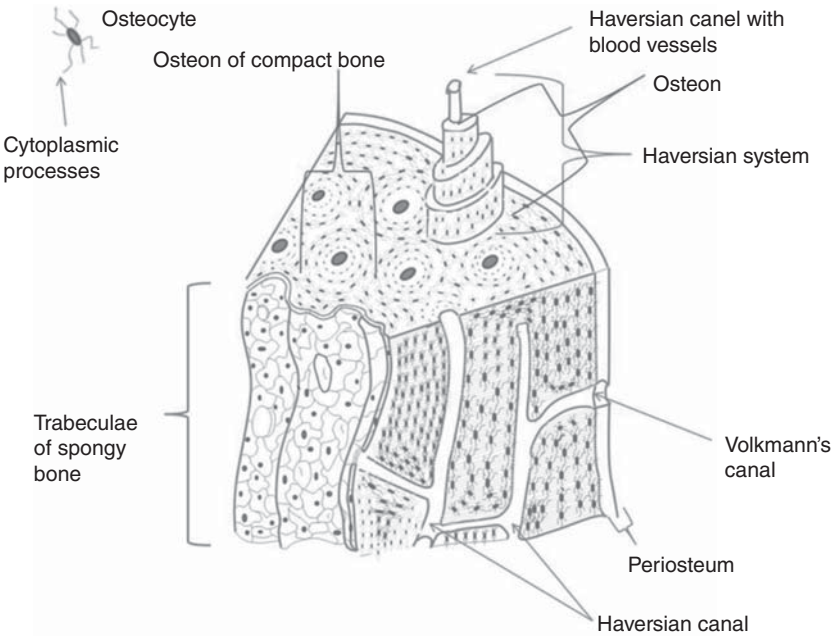

Figure 10.4. Cross-section of lamellar-type natural bone. Courtesy Mr. Dhruv Mehta, IIT Kanpur.

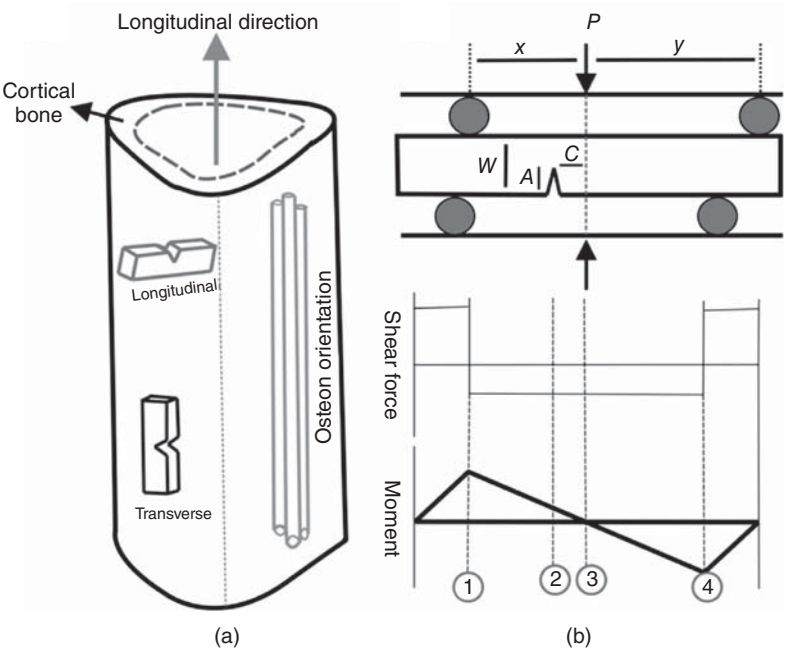

Figure 10.5. Schematic representation of fracture toughness of human bone (a) structure of human bone with two orientations (longitudinal and transverse) (b) The single-edge notched specimen tested sample (top) with an asymmetric four-point bend arrangement (bottom).

used to determine the mixed-mode fracture toughness with a total 25 test samples (seven from the 48-year-old, 11 from the 52-year-old and seven from the 79-year-old donor). The notch was made with the help of a low speed saw in the transverse direction and oriented to crack growth direction and perpendicular to the osteons (out-of-plane transverse), as shown in Fig. 10.5a [7].

Fig. 10.6(a) explains the variation of fracture toughness with loading from mode II to mode I in transverse orientation of human cortical bone. It was found that the value of fracture toughness of cortical bone in transverse direction is the highest with mode I test and decreases continuously by a factor of four or more with increasing values of phase angle. However, in the longitudinal orientation (shown in Fig. 10.6b), the toughness increases with increasing values of phase angle. It was observed that in the transverse direction, human cortical bone is less defiant to fracture in shear stress with a mode II compared to mode I (~25% less fracture resistant than mode I) [9]. In this case, longitudinal data show the expected values of lower bound and compared to the data of Norman et al. [10].

Hard tissue damage is one of the most common problems of the present century due to the significantly changing life style of human beings. It can happen due to several reasons such as accidents, disease, ageing and so on. Generally, the treatment preferred by doctors for bone healing consists of pushing the dislocated bone back to the original position and fixing it with the use of a plaster from outside. But then, there is long waiting time (4–6 weeks) for the bone's natural healing process to occur. Another treatment is

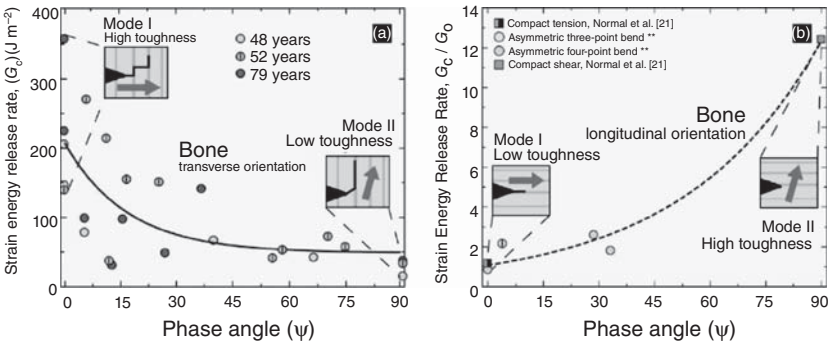

Figure 10.6. Schematic representation of release rate (G_c) of critical strain energy with phase angle (J) of human cortical bone in (a) transverse and (b) longitudinal orientation. (Reproduced with permission from Elsevier, [8].)

bone grafting, which involves removal of bone either from the patient's body (*autografts*) or from the donor (*xenografts*) and directly using it to fill up the defected bone. However, this treatment involves (i) healing of the newly damaged bone in case of autografts and (ii) high risk of infection due to incompatibility of grafted bone, in xenografts, at the site of defect. This brings the need of synthetic bone grafts/bone implant, which can help quick bone regeneration and can reduce the risk of infection at the site of defect. A large number of synthetic biomaterials are used for such applications, which have unique physical and chemical properties and that resemble natural tissue, and thus, they can be safely implanted in the biological system.

The three main categories of materials used in the fabrication of bone implants are ceramics, polymers and composites [11]. Ceramics are one of the oldest and most used materials as bone substitute due to their important properties such as biocompatibility, bioactivity and osteoconductivity. However, some limitations associated with ceramics are slow degradation and poor mechanical properties. Thus, polymer-based materials are used to fabricate biodegradable implants, because their properties can be easily tailored as per our requirements. Nowadays, composites of polymer and ceramic are used to merge the advantageous properties of both in a single composite material to fabricate bone implants. Figure 10.7 shows the important properties of biomaterials that are required for serving as potential bone implant.

Some examples of materials used to prepare bone implants are Ti and its alloys (Ti-6Al-4V, β-Ti etc.), CoCr alloys, stainless steel, Ta, polyethylene, aluminum and zirconium oxide, silicone and so on. Hydroxyapatite (HA, $Ca_{10}(OH)_2(PO_4)_6$) is the most common material used to prepare bone substitute because of its similar chemical composition to that of bone. Thus, HA-coated implant results in fast healing and strong integration of implant with natural bone [12]. Figure 10.8 shows the image of implants made up of pure titanium and HA-coated one.

HAp has the ability of reconstruction and growth of the new bone tissues (proliferation) at the implant surface into the host, making them biocompatible with natural bone. It is because of similar composition to natural bone with Ca/P ratio = 1.67. When HAp-coated biomaterials are implanted into the host, the interaction between

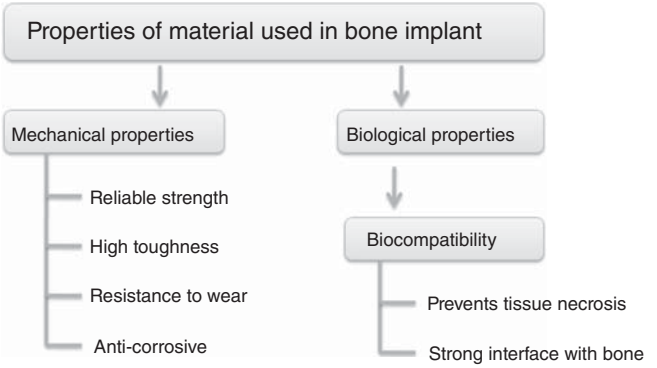

Figure 10.7. List of important properties of materials used in bone implants.

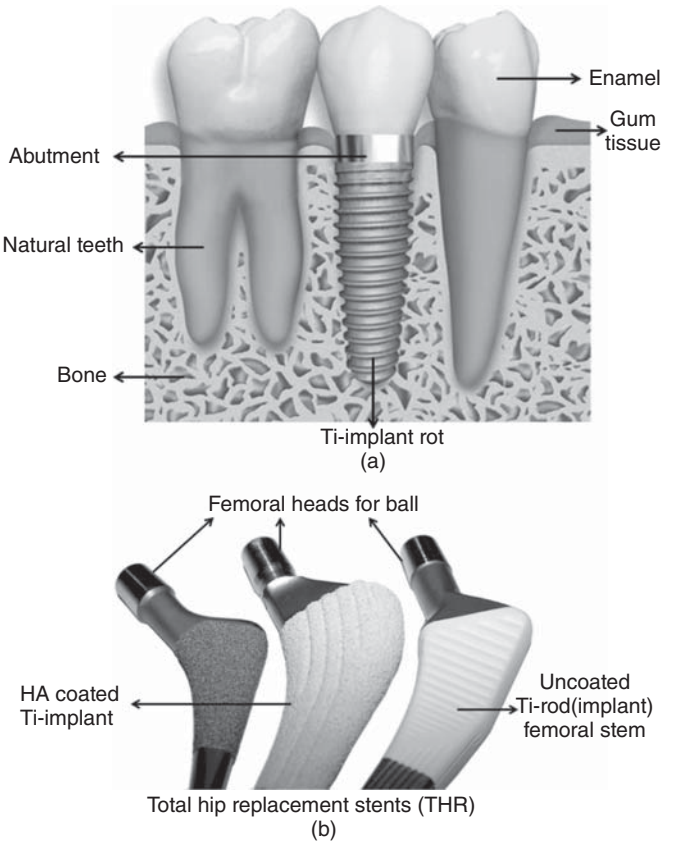

Figure 10.8. (a) Pure titanium implant; (b) HA-coated titanium implant. (Courtesy: https://www.healthtap.com/user_questions/341219-what-are-dental-implants-made-from and http://www.ceramed.pt/servicos.)

the implanted materials and the host tissues leads to the creation of new bone tissues around the implanted surface. It was observed that porous HAp coatings at the implant surfaces support the growth of new bone tissues formation through pores, which give rise to good biocompatibility, mechanical stability and osseointegration.

On the basis of the properties of biomaterials used in the fabrication of bone implant, their evolution can be divided into three generations with significant improvement in one after the other (shown in Fig. 10.9). Dental and bone implants are the best ways to replace a damaged or fractured part of teeth or bone. An implant consists of an artificial biocompatible material; for example, for teeth, Ti-rod-coated or non-coated with HAp is used, which is placed directly into the jaw bone. The implant allows new bone cells to grow around to integrate with the newly formed bone that locks it, via "osseointegration." In the first generation, tolerant and inert types of implants were prepared so that they have high resistance to wear and are almost non-reactive with the surrounding atmosphere. While in the second generation, responsive type of bone implants were prepared, which are capable of showing biological responses (consist of bioactive molecules) at the site of defect and thus facilitate the healing. Biodegradable materials were also used to prepare bone implant in this generation, which helps to replace the bone substitute materials with natural bone tissue. Later, the third generation implants have the unique ability to provide instructions for the biological healing process at the site of defect and thus help the implant to form a strong and firm interface with the bone.

The development of bone–implant interface is the important phenomenon through which one can evaluate the performance of an implant. If the interface is strong, mechanical stability and service life of an implant are increased, while if it forms a thick fibrous layer, mechanical stability is decreased, which results in premature loosening of the implant. Branemark et al. reported direct contact between Ti implants and bone without a fibrous layer and named the phenomenon as *osseointegration* [13]. Osseointegration was originally defined as a direct structural and functional connection between the surface of a load-carrying implant and ordered living bone by Branemark in 1985 [13, 14]. In 1990, he gave a modified definition of his own "a continuing structural and functional

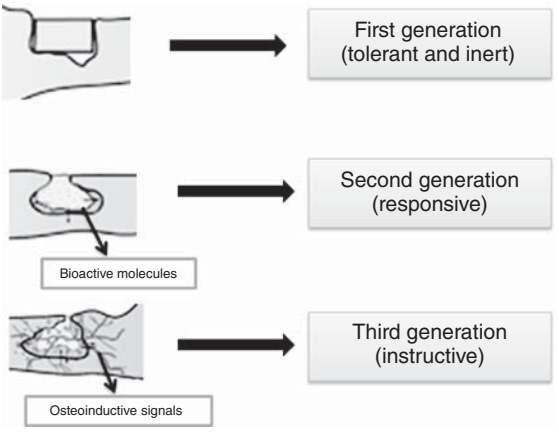

Figure 10.9. Different generations of bone implants.

coexistence, possibly in a symbolic manner, between differentiated, adequately remodeling, biologic tissues and strictly defined and controlled synthetic components providing lasting specific clinical functions without initiating rejection mechanism" [15].

The osseointegration is highly dependent on the surface finishing. H.E. Gotza et al. reported the pore size effect on the osseointegration. A laser-textured titanium alloy (Ti6Al4 V) implant material with varying pore sizes of 100, 200, and 300 μm was used for this study. It was observed that using a 200-μm pore size implanted material resulted in an intense enhancement in osseointegration, after 12 weeks into the host implant. Figure 10.10 explains the effect of pore size on the osseointergration. The bone remoulding has pronounced time lag for a smaller pore (100 μm) than a larger one, and 300-μm pores show the delayed osseointegration and vice versa [16].

When these implants are placed in the human body, they undergo bone healing, which consists of a series of complex process. Thus, it is important to study the process in detail. As soon as the implant is placed at the site of the defect, it is immediately surrounded by a layer of water molecules [17, 18]. This layer facilitates protein and other molecules to adsorb on the implant surface [18, 19]. In the second stage, within 30 s to hours after implantation, the surface of the implant is covered by a layer of ECM proteins. These proteins come from tissue fluids and blood at the wound site [20]. In the third stage, interaction of cells occurs on the surface of the implant through adsorbed protein, which initiates cellular adhesion, migration and differentiation [21]. This whole process required few hours to several days for its completion.

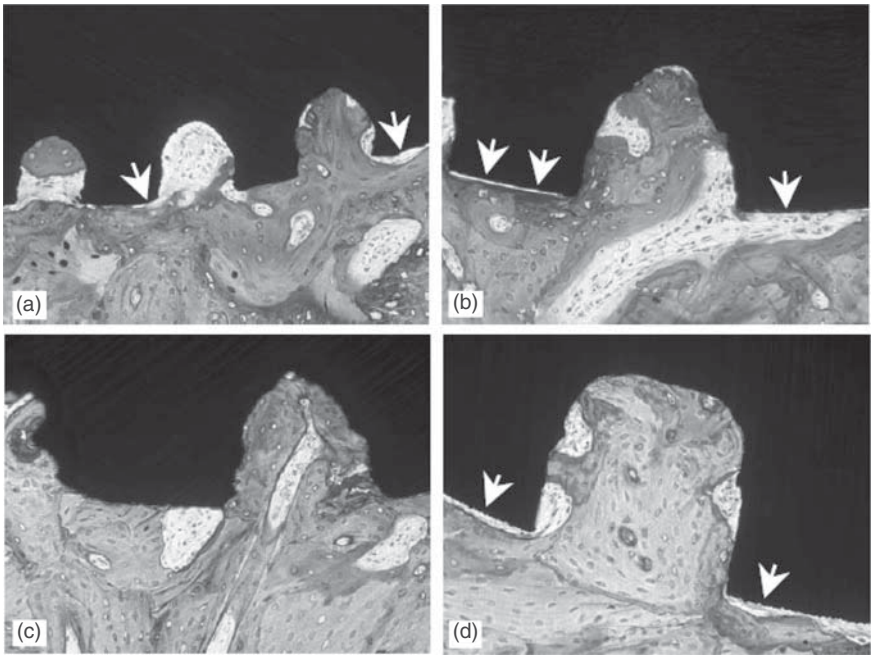

Figure 10.10. Micrographs of laser-textured TiAlV implants with varying pore size (a) 100 (b) 200 surface-blasted (c) 200 and (d) 300-μm pores 12 weeks after implantation. (Reproduced with permission from Elsevier, [16].)

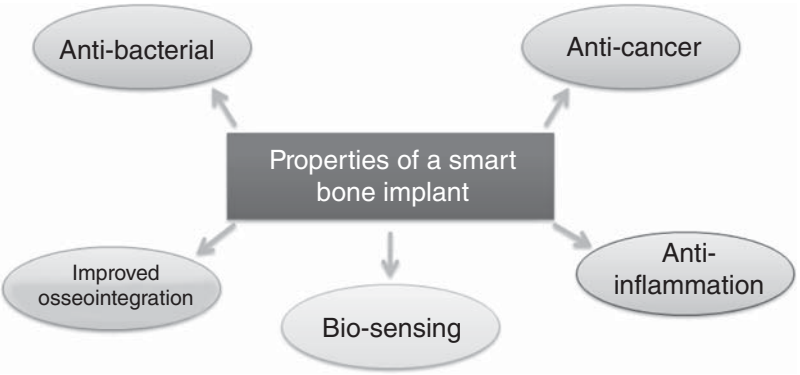

Figure 10.11. Properties of a smart bone implant.

According to several studies conducted, it is suggested that the function of bone-forming cells over nano-structured materials is more as compare to that of current implant surfaces. This leads to the formation of "smart bone implant" possessing all the essential properties (shown in Fig. 10.11) required for long service life of an implant because of inherent structural nano features analogous to natural bone.

In the radiography, the high energy X-ray radiations are used to create diagnostic images of the body. These X-rays are used in the form of light, which can pass very easily though the materials and image our bodies. Thus, in medical X-ray imaging, these high energy X-rays very easily pass through the soft tissues of the body parts but absorbed by denser tissues, for example, teeth and bones [22]. Figures 10.12–10.14 show the X-ray images of bones from different parts of the body [23–25].

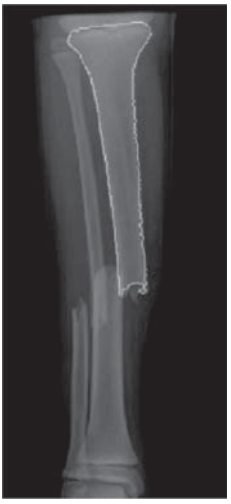

Figure 10.12. X-ray image of fractured human bone. (Reproduced with permission from Elsevier, [23].)

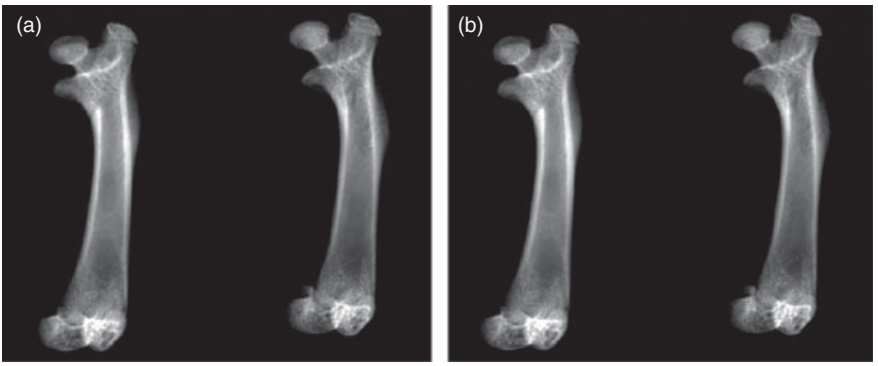

Figure 10.13. X-ray radiography images of (a) calcified bones and (b) natural bones. (Reproduced with permission from Elsevier, [24].)

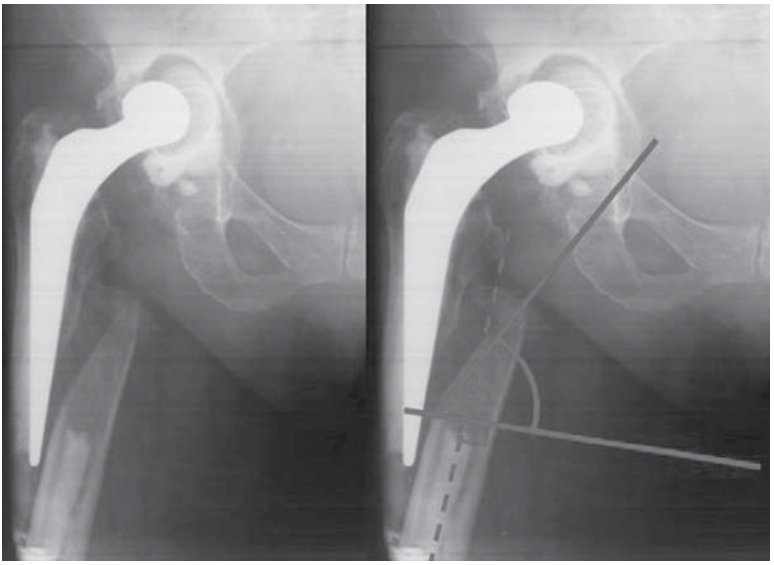

Figure 10.14. X-ray images of total hip showing the methodology of fracture angle measurement. The fracture angle is calculated on the basis of an initial line drawn perpendicular to the long axis of the bone. (Reproduced with permission from Elsevier, [25].)

Now, we move on to coronary stents, which, in brief, are the car-jack-like structures, which keep the blood vessels expanded.

10.2 CORONARY STENTS

Unhealthy lifestyle including lack of physical activity, improper diet, stress, smoking and alcohol all contribute to coronary artery disease (CAD). Today, it is one of the most

common diseases amongst adult population worldwide with a high rate of mortality. What is even more worrying is the rate at which it is moving down the age groups to affect the youth. Plaque is a waxy substance made of low density lipoproteins (LDLs), fats, unabsorbed calcium, cell debris and fibrin (responsible for clotting of blood). Atherosclerosis is the medical term for the condition in which the arteries in the body witness a build up of (arterial) plaque. In CAD, plaque accumulates and blocks the arteries and with no medical intervention, will ultimately stiffen and may clog the artery completely. Furthermore, this plaque may dislocate/break up due to blood pressure. Such a case may lead to lesions in the vessel wall and once ruptured, blood clots as a repair mechanism. This further narrows down the vessel in a very short span. This is called stenosis, and when this happens, especially in the arteries that carry oxygen and other essential nutrients to the heart tissue itself, one may experience angina as an initial symptom and if untreated will lead to a heart attack, which may further lead to heart failure.

Angina is a discomfort in the chest, which shows up as recurring pain. This pain is a sign of atherosclerosis tending to coronary complications.

Heart attack, medically known as myocardial infarction, occurs when oxygen-rich blood does not reach the heart, resulting in the damage or death of the cells making up the heart muscle.

Heart failure is a condition in which the heart is unable to supply enough oxygenated blood to the body, leaving the body cells oxygen-starved and ultimately leading to their death and the tissues/organs they make up, proving fatal to the patient.

The atherosclerotic clogs in the arteries must be treated before complete blockage occurs else they become unstable and rupture. The treatment could be via medication, usually employed during early stages, or through surgical intervention when complications arise at advanced stages. Medications prescribed for treating or preventing CAD include blood thinners, statins: cholesterol-lowering drugs and beta-blockers to dilate the blood vessels and decrease the heart rate, calcium channel blockers and vasodilators to dilate or widen blood vessels, amongst many. One of the two kinds of surgical procedures, CABS (coronary artery bypass surgery) or PTCA (percutaneous transluminal coronary angioplasty, shown in Fig. 10.15, also known as PCI, percutaneous coronary intervention), may be adopted when medication cannot be employed or fails to treat the patient. Common with both the techniques is the means of identifying the sites of stenosis. This is conventionally performed via X-ray fluoroscopy; a radio-opaque dye is introduced into the blood stream to achieve satisfactory contrast and pinpoint the site of stenosis. In the bypass surgery, the blood flow to the given location, which has otherwise been interrupted due to atherosclerosis or clots, is resumed via a bypass route. This route is created by grafting an autologous vessel from a different part of the body so that it connects the sites before and after the block, thereby avoiding the clogged region. This surgery is not as common as PTCA, because it is an open-heart procedure and is performed only in dire situations such as the presence of multiple narrow vessels. PTCA, however, is a procedure that involves guiding a balloon to the stenosis site using a thin wire and enlarging the vessel by inflating the balloon. The wire guide is inserted through

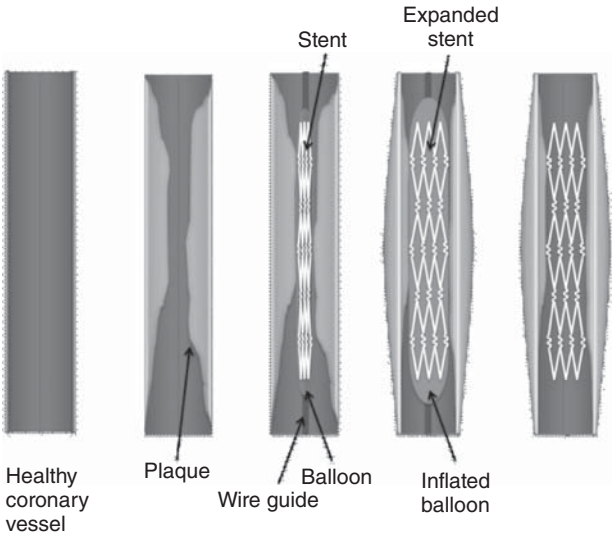

Figure 10.15. Schematic of the PTCA technique.

the vessels in the arms or legs and hence is percutaneous (through the skin), and the whole procedure is rather less invasive. This original procedure was then supplemented with a metallic structure called a stent to support the invaded site. Today, the state of the art in stents technology is the drug-eluting stents (DESs) and the bioresorbable stents, with most stent manufacturers trying to incorporate both of these characteristics into one design.

The period between the early 1960s and the late 1970s saw the interventional technique of angioplasty being envisaged and undergo a plethora of improvements. It is considered as a giant leap in terms of medical science and technology. However, it came with a set of disadvantages mainly comprising uncontrolled plaque disruption, early failure (1 week) due to elastic recoil of the weakened vessel, acute thrombosis at the site of stenosis and so on, and long-term failure (4–6 months) due to restenosis, which is the recurrence of stenosis. Restenosis, observed in a large percentage of the patients who underwent PTCA, occurs in response to the injury presented by the angioplasty technique. This led to the advent of stents in the 1980s. A stent is a scaffold with a tube-like structure (usually) made of metallic mesh and introduced into the artery in order to allow a consistent and large lumen profile. It serves a twofold purpose as a conduit for blood flow in the inside and as a support to the weakened vessel on the outside. The *Benestent* [26] and the *Stress* [27] trials proved that PTCA was far more beneficial when stenting was carried out. As such, an ideal stent should have satisfactory mechanical properties and possess excellent corrosion resistance. On the biocompatibility side, it is expected that the material should allow endothelialization but resist excessive inflammatory response and proliferation. Flexibility, ease of deployment, MRI compliance (low magnetic susceptibility) and radio-opacity are also necessary requirements.

Most coronary stents are fabricated with expanded diameters of a few millimeters, lengths of the order of centimeters and strut (wire) thickness in the range of 70–200 μm. During PTCA involving stents, the stents are inserted in a collapsed form and take their shape only at the required site. Two mechanisms are used to expand the stents to the shape of the vessel. On the one hand, balloon-expandable stents are fabricated with a narrow diameter so that the inflating balloon can cause a plastic deformation in the stent, allowing it to take the expanded shape. On the other hand, self-expanding stents are fabricated in their actual shapes and then compressed. They are guided to the site where the delivery system holding the constrained stent releases it, allowing the stent to self-expand. Thus, as one may realize, low yield stress and high elastic modulus are desirable for balloon-expanded stents, while a low elastic modulus and a high yield stress are required for self-expanding stents. Stainless steels, tantalum alloys, martensitic nitinol, platinum–iridium, certain polymers, niobium alloys and certain cobalt alloys are used to make balloon-expandable stents, while superelastic nitinol and nickel–titanium alloys, hard stainless steels and cobalt–chromium alloys are used to make self-expanding stents. In addition to these two models are the smart nitinol stents that may use their thermal shape memory effect to change the shape at the requisite location. Coatings are discussed separately. These stent-expanding mechanisms and the material composition are two ways of classifying stents. Other classifications (in addition are certain hybrid configurations) are based on the following:

Form	wire, tube, sheet and ribbon.
Fabrication	braiding, knitting, welding, laser cutting, photochemical etching, vapor deposition and water jet cutting.
Overall geometry	coil, woven, sequential rings (divided into open cell and closed cell configurations) and helical spiral.

Commendable progress has been made in both materials science and design of stents, however, we still face problems related to biocompatibility and late thrombogenesis. In-stent restenosis (ISR), reduction of the diameter in an already stented area by 50% or more, is common. In addition, metallic stents can interfere with the production of action potentials *in vivo,* especially in case of those exhibiting ferromagnetism. To deal with the above-mentioned issues, research is being carried out in the direction of the use of polymer stents as against bare metal stents or the latter's coating with polymers and ceramics. Apart from these, issues related to diagnosis emanate from the low radio-opacity of the stent materials. Markers in the form of tabs, sleeves, weldments, and coatings are used; gold, tantalum, platinum, and so on are common examples of materials used for these purposes.

Non-biodegradable permanent synthetic polymers include poly(organo) phosphazene, polyurethane, poly(dimethyl)siloxane, polyethylene terephtalate, phosphoryl chloride, polyvinylidene fluoride, polytertafluoroethylene and its expanded variant, and so on. Short-term synthetic polymers can be degraded/eroded or absorbed and include polyglycolic/polylactic acid copolymer, polycaprolactone, polyhydroxy-butyrate/valerate copolymer, polyorthoester, polyethylene oxide/polybutylene terephtalate copolymer and so on. Depending on their respective properties, while some have been used to make stents, the others have been used as coatings.

While non-degradable stents offer improved biocompatibility, the rationale behind the use of biodegrable/resorbable materials is to offer a temporary support only, until the recovery of the vessel. Both these classes of materials offer their own advantages with drug release and gene therapy.

The other category of coatings to achieve a barrier between the base material and the physiological environment is the ceramic (inorganic) coatings. Implants can be coated with just sub-micron levels of ceramics and achieve necessary properties required for stenting applications. Let us consider the following three well-researched ceramics. While silicon carbide coatings have shown no evidence of advantage over bare metal stents [28], the iridium oxide stents have demonstrated encouraging initial results [29]. On the other hand, the performance of titanium nitride oxide coatings has been highly satisfactory both in animal [30] and clinical [31] studies and is available in the market (TITANOX^{TM} from Hexacath, Rueil-Malmaison, France). Carbon coatings have been proposed and used to offer a neutral coating on metallic stents, as they reduce the reactivity of the base towards toward the hemo-environment. Carbon coatings can come in the form of pyrolytic carbon (Sorin Sirius Carbostent) or diamond-like carbon coatings (Diamond Flex AS and Phytis^{TM} DLC-coated stent from Phytis Medical Devices). Ion implantation (ARTHOS^{Inert} from amg International GmbH, Raesfeld-Erle) is another path to attain carbon-based surfaces.

An important addition to the coatings domain is the incorporation of drugs into these polymer coatings aimed at highly effective solution to issues such as late thrombosis and restenosis. Stent-assisted PTCA using DESs has steadily taken the center stage today. These stents are prepared either by introducing the immunosuppressant or anti-proliferation drugs into the polymer coatings of bare metal stents or as an exclusive layer themselves on metal stents or their polymer coatings thereof. Some stents use reservoirs fabricated in the struts. Key drugs that have been used include immunosuppressive drugs such as rapamycin (everolimus, sirolimus and zotarolimus) and anti-proliferatives such as paclitaxel. Examples are the Xience V everolimus-eluting stent from Abott Vascular and the Taxus Express paclitaxel-eluting stent from Boston Scientific. Similarly, another concept relates to the introduction of low doses of β and γ emitters into stents so as to reduce the rate of restenosis [32, 33] and may also thwart any tumerogenic progress. Some common radioisotopes are ^{90}Sr, ^{90}Y, ^{32}P for β emission and ^{192}Ir for γ emission. DESs are related to issues such as slow and sometimes incomplete endothelialization, fibrin presence and so on. Biomimetics is transforming into another facet of materials research. In this direction, *in vitro* and *in vivo* endothelialization of stents [34] are being studied. Similar are the advantages that drive studies with the bone-mimicking hydroxypatite coatings [35]. In fact, sewing the patient's own vessels to a bare metal stent before implantation has shown interestingly low levels of immune response [36, 37].

10.3 MEDICAL DEVICES

10.3.1 Surgical Devices

As per the US Food and Drug Administration (FDA), medical devices are the tools or reagents that are intended to diagnose, treat, cure or mitigate any physiological condition or affect the structure or function of body; in addition, their primary function

should not be dependent on metabolism or through chemical reactions. They range from simple tongue depressors to the complex programmable pacemakers. The materials used to make these surgical devices are biocompatible and have various other properties as per their application. In this chapter, we would be reading in brief about sutures.

Sutures are the surgical devices that are used to close a wound or tie up tissues. Sutures consist of three parts, namely strand, needle and packaging. The strand can be absorbable, that is can be metabolized by the body, or non-absorbable, that is, they are not metabolized by the body and are removed manually. On the basis of the desired toughness, the strand can be monofilament or multi-filament. Monofilament strands exhibited lesser tissue drag compared to multi-filament strands but are weaker. The materials generally used to make strands vary from bovine collagen to stainless steel.

The needle used should be inert, stable, sharp, rigid, ductile, sterile and corrosion resistant and hence is made up of high quality stainless steel. It generally comes pre-attached to the suture strand and can be straight, curved or compound curved. One end of the needle is drilled to make a hole that would hold the suture, while the other end is shaped and polished to give the desired geometry. At times, these needles are also lubricated with silicone oil to allow easy passing through the tissue.

Next comes the packaging, which not only keeps the suture sterile, but also in absorbable sutures, it keeps the suture moisture free, which would otherwise lead to strand degradation. Apart from these three parts, there are two more crucial elements for suture design: dyes and suture coatings. When a suture is put in the tissue, it becomes difficult to differentiate between the tissue and the suture, especially in the presence of blood. Therefore, the sutures used are either naturally colored or are colored using dyes that are biocompatible. The suture is coated with lubricating agents, which reduce not only tissue drag, but also void spaces, tendency to wick and carry antimicrobial agents. These coatings, again, can be natural such as beewax or synthetic such as silicone derivatives. Coating thickness is an important parameter for coated sutures. A poor coating would not sufficiently reduce the tissue drag and would also lead to problems in knot tying, whereas a very thick coating would compromise the knot strength and loosen the strand.

The next application is *scafflods*. These are the structures that form the moulds for growing the body organs artificially.

10.3.2 Scaffolds

Tissue engineering is a growing area of interest for biomaterial scientists because of the growing need of tissues and organs required for implants. According to a news report in 2013, in India, the average number of kidney transplants being performed is about 3500–4000/year, whereas the requirement is approximately 100 000/year [38]. This huge gap in the supply and demand, due to the limited number of donors, motivates researchers to explore alternate options for getting the organs. Tissue engineering is an approach that can bridge this gap by supplying artificially produced organs. It involves using a scaffold and seeding it, either *in vitro* or *in vivo*, with the target cells, various molecular and mechanical signals to induce them to grow into the required functional tissue.

The scaffolds used for tissue engineering are the three-dimensional constructs made up of porous biomaterials and shaped according to the need. On interaction with the target cells and when induced with the specific cues, scaffolds allow adherence and proliferation of the cells until they grow into the whole tissue. The scaffolds can be used in either of the two ways on the basis of their location of seeding with the target cells as follows [39]:

a. *In vitro* approach – this approach involves seeding the scaffolds *in vitro* and inducing the cell growth and proliferation in a sterile environment. Cells proliferate and cover the surface of the scaffold while still outside the host body. This process is controlled by various signaling molecules and mechanical cues. Once the tissue is ready, it is then implanted into the host system where it integrates and takes over the function of the desired tissue.
b. *In vivo* approach – in this approach, the scaffold is not seeded *in vitro* but is pre-conditioned with various signaling molecules and growth factors and implanted into the host system. The host cells surrounding the scaffold adhere to the scaffold and proliferate. After a period, the cells completely cover the scaffold and degrade it, leaving a newly formed tissue.

Scaffolds, analogous to other implants, must be biocompatible besides meeting the following specifications:

1. Biodegradability – the whole purpose of scaffold is to allow the body to regenerate the tissue, so it becomes essential that with the advent of time, the scaffold is completely replaced by the body's own cells. Hence, it becomes mandatory that the scaffold material should be degradable by the host system and should neither produce toxic nor immunogenic by-products. Moreover, it should not have an unwanted interaction with other organs of the body. On the basis of how a polymer gets disintegrated within a host system, there are three classes of such polymers as follows:
   I. Bioerodible – these polymers are degraded by the addition of water.
   II. Bioresorbable – these polymers require cellular activity for degradation.
   III. Biodegradable – these polymers require enzymatic activity for degradation.
   Throughout the book, we refer to these three as biodegradable polymers.
2. Scaffold architecture – as mentioned earlier, scaffolds need to be highly porous. Their porosity plays an important role not only in cell penetration, but also in the diffusion of nutrients and wastes in and out of the scaffold, respectively. The pore size of the scaffold varies from tissue to tissue and may range from about 0.8 μm for capillaries to about 250 μm for bone and cartilage. Scaffold architecture also plays an important role in binding of ligands to it so as to facilitate the adhesion of cells.
3. Mechanical properties – usually, all implants need to have enough mechanical strength so as to fit the anatomical site of implantation, but it becomes a major

concern in case of scaffolds, as they need to be highly porous for the cells to infiltrate as well as maintain the desired mechanical strength.

4. Manufacturing technology – it should be possible to scale up the scaffold from laboratory to a larger scale, with maintaining its cost effectiveness. Moreover, the storage and the delivery conditions also play a role in deciding the scaffold material.

On the basis of the above-mentioned specifications, there can be two broad classes of scaffold biomaterials as follows:

1. Biologic materials – these consist of allografts or xenografts and other purified natural polymers such as proteins and polysaccharides. Allografts or xenografts are made acellular to reduce their immunogenicity, but the process may alter the proteins, which in turn become more foreign. Amongst proteins and polysaccharides, collagen and gelatin are the most widely used because of their low immunogenicity.
2. Synthetic polymers – these are the long chain molecules made up of repeating monomeric units. A wide range of their properties can be tailored by varying the polymer chain length and the interaction between chains.

   Polymers can be either homopolymers, made up of same monomers, for example poly(methyl methacrylate) [PMMA] for intraocular lens, or copolymers, made up of different monomers in different arrangements, for example poly(lactic-co-glycolic acid) [PLGA].

   Hydrogels are a kind of polymers that are finding wide applications in tissue engineering. These are made by cross-linking of water-soluble polymers to form an insoluble, water-swollen structure.

10.3.3 Prosthesis

Prosthesis is an artificial device used to replace or supplement a missing or damaged part of the body. These devices are made from biocompatible biomaterials unless their site of implant does not let them come in contact with the fluid connective tissue, that is, blood. They vary from the pacemakers to limb prosthesis. Bone and dental implants have already been discussed in the previous sections, so we will discuss about the contact lenses in the following section.

Contact lenses are the lenses that are put over the cornea of the eye to improve the vision and also for cosmetic reasons. These lenses, analogous to all other lenses, must have good transmittance of visible light. Apart from high transmittance, these lenses should also be chemically stable, permeable to oxygen, wetable and should not allow accumulation of any sort of film or dust over their surface.

Cornea is an avascular tissue, which means that it is not in a direct contact with blood, and so takes its supply of oxygen directly from air. Hence, the contact lenses to be designed must have enough permeability to oxygen such that the amount of oxygen required by the corneal metabolism is not compromised. A wide variety of contact lenses are being made using hydrogels, either homogenous or heterogenous. Both of these hydrogel-based lenses have a comfort fit over the cornea. Homogenous hydrogels

are made up of water-rich hydrophilic phases and thus have a high water of hydration, which helps in oxygen permeability. Oxygen permeability was also a factor of lens thickness and so the lenses were fabricated as thin as possible. Earlier, these lenses were made out of poly(2-hydroxyethylmethaacrylate) (PHEMA), but their fabrication into thin lenses was an issue. The property of high water of hydration also carried its own disadvantage of quick dehydration, which further increased in the case of thin lenses.

To overcome these shortcomings, newer lens materials were made called *heterogenous hydrogels*. These were the copolymers of hydrophilic polymers such as PHEA and hydrophobic siloxane derivatives. The maximum amount of oxygen transport took place through the siloxane-rich phase, but to make this phase to gel in with the hydrophilic phase, it has to be treated with RF plasma to render the surface hydrophilic.

Apart from hydrogels, flexible non-hydrated perfluoropolyether lenses and rigid contact lenses were also fabricated. Flexible perfluoropolyether lenses had very high oxygen permeability and very low adherence of proteins because of their high fluorine content. Rigid contact lenses, which had a loose fit over the cornea and slid over the thin tear film between the cornea and the lens, were modified and copolymerized with siloxane derivatives to improve oxygen permeability [39]. Fluorinated rigid contact lenses have also been fabricated to improve the oxygen permeability and to reduce the surface protein adhesion. Apart from the above-mentioned technical considerations, ease of manufacturing, cost, cleaning and disinfection also govern the choice of material for contact lens fabrication.

Biomaterials are also being used for the developing area of drug delivery, which is involved with the development of novel methods and materials so as to ensure the delivery of the drug within the body while maintaining its specificity, efficacy, controllability and effective concentration.

10.4 DRUG DELIVERY

Drug delivery deals with the proper treatment of diseases using various forms of therapeutics, depending on their administration route. Although the discovery of drug for a specific disease is important, administering the drug effectively is a major concern. Problems related with drug toxicity as well as poor penetration through the membrane will decrease the drug efficiency. The route of drug administration is adopted depending on the physiochemical properties of the drug such as size, stability, solubility and so on and its biological interaction (sensitivity to first pass metabolism and side effects) and bioavailability. Bioavailability is defined by the rate of absorption of the desired constituents from the drug and their availability at the desired location in the body. Our further discussion is divided into two parts, including various possible routes of drug delivery and application of nanotechnology and functionalization in drug delivery.

10.4.1 Routes of Drug Delivery

On the basis of application location, routes of administration can be classified whether the effect is local (e.g. topical administration) or systemic (in enteral or parenteral

administration) as follows:

Topical/local effect: when the medication is administered directly to the desired location, that is, to the localised region in or onto the surface of a body part.

Systemic effect: when the response of medication is systemic (non-local), that is, the desired effect is into the circulatory system, which affects the entire body.

Different local and systemic routes of drug administration are as follows:

10.4.1.1 Gastrointestinal System (Enteral). Enteral/enteric administration of drug includes the administration of drug through the gastrointestinal (GI) tract, strictly meaning "through the intestines," and it has the systemic effect. Enteral administration of drug is possible orally (through the mouth), rectally (through the rectum) or by gastric feeding tube or gastrotomy. Gastric introduction involves the administration of drug directly to the stomach using a tube via nasal passage or belly.

Administration through the GI tract depends largely on two factors: the degree of solubility of drug and the degree of penetration of drug through the intestinal mucosa. Solubility of the drug depends on many factors such as surface area of drug particle, pH of GI content as well as their diffusivity and solubility in the solvent. In the intestine, the process of drug absorption is passive transfer in which the drug diffuses through the lipid membrane within the intestine.

10.4.1.2 Oral Drug Delivery. Historically, the oral route for medication is most commonly accepted amongst the patients because it is easier, safer and inexpensive amongst the enteral administration. Oral medication may be in the form of suspensions, tablets, capsules or chewable tablets. In the beginning, orally administered drugs may get absorbed in the mouth and stomach while mostly in the small intestine.

10.4.1.2.1 Advantages. The oral route of administration is an easy, safe, convenient and portable route. It is cheap because of the compact nature, no need of sterilization (but must be hygienic of course), and also tablets formation is commercially easy.

10.4.1.2.2 Disadvantages.

1. It is not reliable in case of unconsciousness, GI problems such as vomiting and also in serious conditions because of delayed effect due to its administration through the GI tract.
2. Due to first-pass effect, that is, administration of drug through the GI tract, digestion (inactivation) of many drugs occurs, decreasing the bioavailability of drug in the blood stream. For example, ingested proteins, insulin, penicillin, adrenaline and so on, are degraded by the GI enzymes.
3. The systemic effect of this route makes it unsuitable in case of drugs that are specific to certain organs.
4. Irritant drugs cannot be administered orally, as they can damage the stomach and intestine, leading to vomiting as in case of aspirin.

10.4.1.3 Rectal Drug Delivery. The rectal route includes administering drugs into the rectum, and through the absorption by blood vessels in the rectum, they go into the circulatory system of the body. Bioavailability of drug depends on their location in the rectum. The drug in the uppermost part of rectum will undergo the first-pass metabolism, as the upper vein drains into the portal circulation, while absorption in the lower and middle regions of rectum leads to direct enter into the systemic circulation. Rectal dosage forms are suppositories (solid), creams, and enemas. Glucose, aspirin and glycerine suppositories may be administered through this route.

10.4.1.3.1 Advantages.

1. It is safe, convenient and useful for unconscious patients as well as cases where oral administration is not possible, that is, in case of vomiting tendency, stomach upset and upper GI tract disease.
2. It is useful because of immediate response, higher bioavailability and reduced first-pass effect, because two-thirds of the veins in the rectum route the drug direct to systemic circulation.
3. It shows quicker absorption, and the lower digestive tract is less harmful to the administered drugs than the stomach and the small intestine due to the lower enzymatic activity and neutral pH.

10.4.1.3.2 Disadvantages.

1. Some discomfort may be possible using this route and is therefore uncommon amongst adults.
2. The absorption of drug is unpredictable and uncontrollable.
3. Irritant drug may sometimes cause damage and bleeding. Suppository form of drug generally shows incomplete absorption and erratic behavior.

10.4.1.4 Parenteral (Injection) Drug Delivery. Routes of systemic administration of drug other than through the GI tract are called parenteral. Introduction of medication and nutrition is via infusion, injection and implantation, but it practically refers to administration via injection by sub-cutaneous (SC), intramuscular (IM), intravenous (IV) and intra-arterial routes. This route is mostly used because the administered drug directly reaches blood. For targeted drug delivery, the drug could directly be injected into the specific organ.

10.4.1.4.1 Advantages.

1. Almost complete bioavailability and quick action due to avoidance of first-pass metabolism as compared to oral route, that is, same amount of drug would give the stronger effect.
2. It is useful in case of unconscious, non-cooperative patients, irritant drug (anti-cancer) and cases where oral administration is not possible such as in case of vomiting and diarrhoea.

3. This route of administration does not affect the mucous membrane and lungs.
4. Certain injections can last for days and sometimes even months, for example Depo-Provera, a birth control medication, is effective for 3 months.

10.4.1.4.2 Disadvantages.

1. This is not an ideal method because of cost and pain, and moreover, sometimes there is a danger of adverse reactions, which can even cause death.
2. Technical skill and aseptic measures are required, and also self-administration is not possible.
3. Administration of protein-based medications is some of the major limitations of injections.
4. In some cases, it is a dangerous route of administration because it bypasses first-pass metabolism, that is natural resistant in the body, causing hepatitis, infections and accumulation of unabsorbed particles.

10.4.1.5 Intravenous Injection. This route of administration is the most successful way to administer an accurate dose immediately when required in a controlled manner everywhere in the body as the drug is immediately delivered into the blood stream. IV administration of drug involves the introduction of drug directly into the peripheral vein for immediate action in a single dose via needle or by continuous infusion for longer effect. For infusion, the drug solution moves itself by gravity or with the help of infusion pump through catheter, which is a thin flexible tube. This route is used for targeting the drug to different organs, as particles larger than 7 μm get captured in the lungs and particles with particle size less than 0.1 μm are gathered in the bone marrow. Particles of sizes between 7 and 0.1 μm are absorbed by the liver. In case of paediatric HIV and asthma (immune deficiency), a blood product intravenous immunoglobulin (IVIG) is given only by this route. Some other examples are plasma, glucose, saline and so on.

10.4.1.5.1 Advantages.

1. Bioavailability is theoretically 100% after IV administration, and therefore, lesser amount of dose is needed.
2. Desired dose or large dose with controlled rate may be given in large volume for immediate and continuous effect.
3. Since veins are relatively unaffected by the irritant drugs, they may be administered intravenously in contrast to the SC or IM administration, which leads to pain and tissue damage in response to the irritant drug.

10.4.1.5.2 Disadvantages.

1. Higher skills and aseptic precautions are needed to overcome adverse effects of air embolism, hypothermia and phlebitis.

2. Several problems such as toxicity, local tissue damage and infection are supposed to be faced during continuous drug administration.
3. Expensive because of greater cost for preparation, transport and storage.
4. Difficulty in inserting a needle into a vein, as in case of a obese person, it makes it less convenient than IM and SC route.

10.4.1.6 Intramuscular Injections. Drugs are introduced deep into the muscle lying below the skin and fatty tissue. Drugs are usually injected into the deltoid, lateralis and gluteal muscle of upper arm, leg and buttocks, respectively. For the introduction of larger volumes of a drug product and for more rapid action, IM route is preferred over SC route, although the onset of action is slower than with the IV route. It is the most preferred route for administration of insoluble, irritant and oily substances. There may be adverse effect on muscle fibres at the site of injection, nerve damage and air embolism in the vein of the muscle and even death. The rate of absorption of drug depends on the chemical composition of drug injected and blood supply to the muscle and dissolution of drug in product form.

10.4.1.6.1 Advantages.

1. Larger volume of medication can be administered by IM with respect to SC route and provides easier administration such as in case where the patient is obese.
2. This route provides a sustained release effect, that is, a constant drug level for a specific time span, for example, procaine penicillin.

10.4.1.6.2 Disadvantages.

1. The site of injection (mass of muscle available) will determine the amount to be injected, as deltoid muscle has immediate and complete absorption.
2. This route is not suitable for poorly soluble drugs, for example, diazepam is erratic and painful, and degradable drugs such as peptides.
3. Precipitation of the drug occurs at the site of injection due to difference in the rate of absorption of the solvent and drug.

10.4.1.7 Sub-Cutaneous Route. The drug is injected into the fatty tissue beneath the skin from where it is slowly absorbed into the blood stream through capillaries. This route is not suitable for irritant drug, which could cause necrosis. This route is very useful in administering protein drugs such as insulin, which would be ingested in the digestive tract when orally administered. Certain drugs may be implanted underneath the skin in the form of capsules for long and sustained effect, for example implanted contraception drug etonogestrel may last up to 3 years.

10.4.1.7.1 Advantages.

1. Predictable and complete absorption and self-administration as in case of insulin make this a promising route.

2. Aqueous solution gives rapid response due to its easier absorption but opposite in case of depot formulations.
3. Massage or heat helps improving absorption, thus giving a long therapeutic effect.

10.4.1.7.2 Disadvantages.

1. Irritation, pain and local unwanted effect at injection site due to accumulation of unabsorbed drug.
2. Limited amount of drug (maximum 2 ml) can only be administered.
3. Comparatively slower absorption and delayed response.

10.4.1.8 Intrathecal or Intraspinal Injection. Intrathecal injection involves the administration of drug in cerebrospinal fluid via the space between two vertebrae in the lower spine and through the space around spinal cord in the sub-arachnoids cavity. This route is used to administer antibiotics on an urgent basis, as they can easily move to cerebrospinal fluid as compared to the IM injection. This route is used for medications that act specifically on the brain, spinal cord and tissue around them such as anesthetics and analgesics.

10.4.1.9 Inhalation. Using this method, drugs in the form of particles are introduced by inhalation through the wind pipe into the lungs. Frequent absorption and immediate response can be seen using this method. Volatile (anesthesia and O_2) medication can be simply inhaled, while non-volatile (penicillin) medication can be inhaled in spray form using aerosol therapy. Absorption of drug is size dependent, as smaller drops can easily get absorbed into the blood stream via lungs. This route is usually used for drugs that are specific to lungs as anti-asthmatic drugs aerosol form and gases of anesthesia.

10.4.1.9.1 Advantages.

1. There is relatively efficient absorption of gases in comparison to liquid and solids smaller than 20 μm, in which only 10% of the drug is absorbed.
2. It shows rapid absorption due to by-passing the liver.
3. This route is useful in providing local (e.g. bronchodilators) as well as systemic effect (e.g. general anesthesia).

10.4.1.9.2 Disadvantages.

1. Size-dependent administration limits its use for medication.
2. Carefully monitoring is needed to provide the desired quantity of medication in a definite period.
3. Specific equipments are required to administer drug via this route.

10.4.2 Application of Nanotechnology and Surface functionalization in Drug Delivery

Nanotechnology has helped bring a number of new advances in biomedical applications as new vectors for the diagnosis and treatment of disease. The unique properties of nanomaterials including good penetration across membrane and reduced toxicity and side effects have been crucial in their acceptance in the biomedical field. The application of nanomaterials is set to spread rapidly because of their unique features such as large surface-to-volume ratio, settling velocity, fine drug and probe absorption and carrier ability and specific magnetic and optical properties. In most biomedical applications, nanomaterials are used as drug/gene carriers in the delivery of therapeutics and as imaging contrast agent in disease diagnosis. Apart from using a nanocarrier for the delivery of therapeutics, the drug can itself be developed as a nanoparticle. Relevant biomedical application of nanomaterials depends on their non-toxicity, biocompatibility and biodegradability. Hence, organic bio-nanomaterials such as liposomes and biodegradable polymers are of great interest in therapeutics and diagnosis. However, safety concern related with inorganic nanomaterials such as fullerenes and metal nanoparticles limits their application. A recent cytotoxicity study denies the dependency of biocompatibility on size, shape and material but attributes it to the surface properties, making surface functionalization a significant step. Surface functionalization of nanomaterials is a method of introducing a chemically functional group (–COOH, –OH, $-NH_2$ etc.) onto the surface of the nanomaterial with inert molecular chain such as polyethylene glycol (PEG) between the surface and functional group. PEG, a hydrophilic molecule on the surface of nanomaterials, protects them from antibody as drug binding to the antibody becomes weak. Thus, PEG-modified drug has increased the half-life in the systemic circulation [40]. Surface functionalized nanomaterials are able to penetrate the lipid bi-layer of the cell membrane and therefore provide targeted drug delivery. Therefore, a wide range of surface functionalization and control over size and shape makes inorganic nanoparticles more useful over bio-nanomaterials. The main concerns regarding proper nanocarriers for drug delivery are safety (non-toxic and non-inflammatory), stability, mass production, low cost, biodegradability and compatibility with both drug and cells.

Nanocarriers for Application in Biomedicine

1. Liposomes
2. Micelles
3. Dendrimers
4. Fullerene
5. Metallic and semi-conducting (quantum dot) nanoparticles.

10.4.2.1 Liposomes. A *liposome* is a bubble-like bi-layer structure made by phospholipids in an aqueous solution with hydrophobic end outside and hydrophilic end inside the bi-layer membrane. Unique features of liposomes such as biocompatibility and their fusion with other bi-layer membranes make it useful in drug delivery applications as well as diagnosis. When liposomes are prepared in solution of drug, they encapsulate

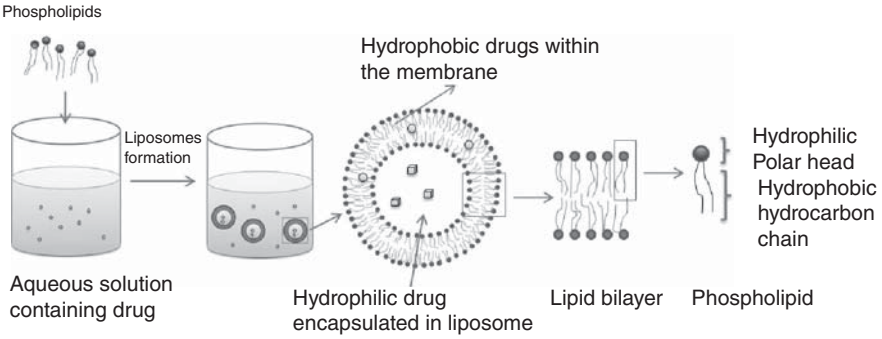

Figure 10.16. Formation of liposomes in an aqueous solution.

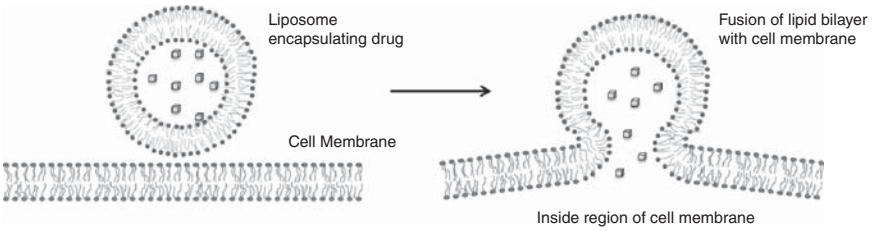

Figure 10.17. Fusion of liposomes into the bi-layer of cell membrane for drug delivery.

some amount of solution containing hydrophilic drug and does not let it pass through the lipid bi-layer (Fig. 10.16).

In addition, hydrophobic drugs can be dissolved in the membrane itself. Liposomes may be prepared to deliver drugs in different ways, one of which is by fusion with other cell membrane (Fig. 10.17).

Other than fusion, liposomes can also deliver drug by diffusion that could be possible only by controlling the pH. Endocytosis process can also help in releasing the drug, as liposomes in specific size range are digested by macrophage. Due to their highly reactive surface, covalent addition of ligand (to activate endocytosis), antibody, cell receptors specific to the target and so on are possible. Few hundred nanometre sizes of liposomes enable them to encapsulate multiple nanoparticles as well as responsive materials such as optically detectable fluorescent dyes through transparent membrane, which made liposomes useful as a contrast agent in imaging techniques. For targeted drug delivery, magnetically targeted nanoparticle can also be loaded along with the drug, in which binding to the drug is not required in contrast to other nanocarriers.

10.4.2.2 Micelles. Micelles are formed by the aggregation of amphiphilic molecules such as a salt of a fatty acid (soap), phospholipids and so on in water, with the polar hydrophilic end facing toward the solvent, and the non-polar hydrophobic chain gets assembled into the interior of the structure (Fig. 10.18).

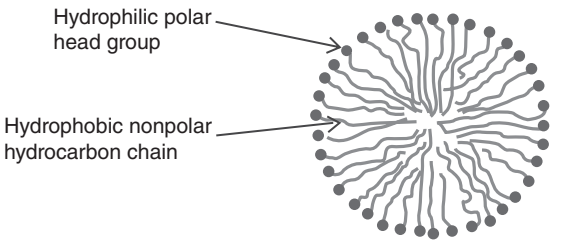

Figure 10.18. A schematic showing micelle, which forms over a certain concentration of amphiphilic molecule.

Critical micelle concentration (CMC) sets the limit above which micelles formation of amphiphilic molecules are possible. Hydrophobic drugs can be encapsulated into the inner core of the interior. Since water concentration drops as we move from the surface toward the core of the micelle, the polarity of a dissolved drug in a micelle will determine its site of dissolution; non-polar drug will accumulate in the inner core, and polar material will lie in certain intermediate positions between the surface and the core, depending on their polarity. Depending on different features such as head group size, ionic strength and hydrophobic tail, the micelles may be of different sizes and shapes (spherical, ellipsoidal and cylindrical). Reverse micelles are formed in non-polar solvent. The wetting property of micelles increases the adhesion between the drug and the cell membrane.

10.4.2.3 Dendrimers. Dendrimers are a new class of polymeric materials. They are a spherically symmetric tree-like structure with functional terminal surface and void core (Fig. 10.19).

Dendrimers have their own importance in the field of targeted drug delivery and sustained drug release due to their unique characteristics involving water solubility (in case

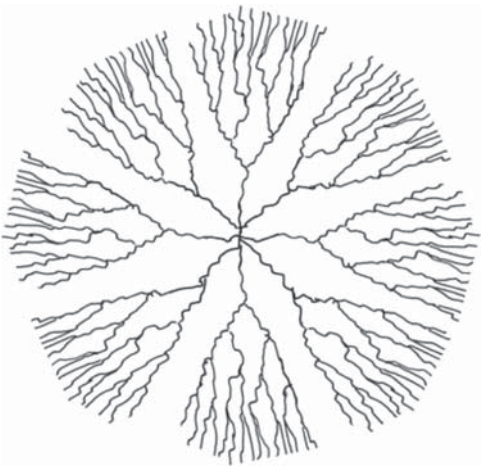

Figure 10.19. A schematic showing a dendrimer.

of hydrophilic group attached to the terminated surface), monodispersity, low molecular weight, specific size and shape and so on. In addition, the interior void space and large number of functional peripheral groups make these structures to be useful as hydrophobic and hydrophilic drug carriers, respectively. Two methods of drug delivery mechanisms using dendrimers include (i) encapsulation of drugs in the interior void space of dendrimer exhibiting micelle-like behavior and (ii) dendrimer–drug conjugation at functional terminal groups. Since dendrimers have a large number of active sites on their exterior surface, the terminal functional groups on the surface can be modified to enable the conjugation of imaging agent, targeting moieties, biocompatibility group, solubility-enhancing agent and so on along with the therapeutics.

10.4.2.4 Fullerenes. Buckminsterfullerene (C_{60}) or buckyball is an inorganic football-like structure, 0.7 nm in diameter, containing 60 carbon atoms with 20 hexagons and 12 pentagons. The physical, chemical and biological activities of fullerenes have attracted major attention in the field of biomedicine. Due to poor solubility in physiological media, they tend to aggregate, which limits their application as a drug carrier. This problem has been resolved by chemical functionalization of fullerene, increasing its hydrophilicity, for example using amphiphilic polymers and so on, which makes it capable of carrying drug [41]. Their small size, three-dimensional, cage-like structure and chemical functionalization make them an efficient and safe carrier in therapeutics as well as diagnostics. The fullerene activity as carriers is defined by its core and surface properties. Cellular drug delivery, that is, transportation of the drug to the nucleus, is a major concern as it has to penetrate the membranes. It is found that fuctionalized fullerenes penetrate across the cell membrane and become soluble in physiological media. Thus, scientists are attracted toward derivated fullerenes as promising carriers due to their unique features such as biocompatibility and targeted and sustained release of drug. Derivated fullerenes are found to possess anti-viral activity due to their architecture and other chemical properties. They can be used as therapeutics in acquired immunodeficiency syndrome (AIDS), as they delay the virus replication by forming a complex with HIV protease [42]. The presence of double bond and low lying lowest unoccupied molecular orbital (LUMO) in fullerene is facilitating its interaction with electron, leading to an anti-oxidant property. Single fullerene molecule can react with 34 methyl radicals. Therefore, fullerenes act as radical scavenger in the diseased cell that produces free radicals. Metallofullerenes, that is fullerenes carrying metal atom in their cage, are useful as contrast agent in MRI and X-ray imaging due to the fact that fullerene cage is non-toxic and protective against immune destruction.

10.4.2.5 Metallic and Semi-Conducting Nanoparticles. Metallic and semi-conducting nanoparticles (MSNs) have attracted great attention from scientists in the field of diseases diagnosis and treatment, examples including application in biomedicine as drug nanocarriers in targeted drug delivery, contrast agent in MRI, fluorescent particle in optical imaging and therapeutic in cancer treatment by heat ablation of target cells. Nanoparticles are required to be biocompatible and sometimes surface functionalizable for the above-mentioned applications.

Metallic nanoparticles have different pharmaceutically relevant properties, including large surface-to-volume ratio, thermal stability, penetration across membrane and

exceptional optical properties. Gold, silver and iron oxide nanoparticles are useful choices in biomedical applications. Amongst these, gold nanoparticles (GNPs) have attracted significant attention due to their capability of being functionalized and having relatively less chemical reactivity and toxicity.

For targeted delivery of therapeutics and highly sensitive diagnosis, targeting moieties that are specific to receptors present on the diseased targeted cell have to be attached on the surface of GNPs to increase their sensitivity toward the targeted cell. Surface functionalization of GNPs with a biologically relevant ligand such as PEG having a thiol group and a functional group on two different ends enables the conjugation between targeting moieties and GNPs surface. Different interactions between targeting moieties and their specific receptors that are responsible for increased sensitivity are antibody–antigen interaction, enzyme–substrate interaction and DNA complementary interaction. In addition, surface-modified GNPs with PEG avoid macrophage event and can stay in the systemic circulation for a longer time span [43]. The anti-oxidant property of functionalized GNPs is useful in cancer treatment, as they absorb a large amount of free radicals produced in the targeted cell. Hollow GNPs when irradiated with near-infrared light can release drug as well as kill cancer cells due to localize thermal ablation [44].

Silver nanoparticles are useful in biomedical applications including infections and wounds treatment because of their anti-microbial activity as well as HIV-1 infection treatment [45]. Semi-conductor nanoparticles, also known as *quantum dots* (2 –10 nm), have captured great attention in imaging and drug-targeting applications, because they possess surface modification ability and superior tunable optical properties, including sharp emission and broad band excitation. Small size and surface conjugation with targeting moieties specific to the target such as antibody enable the targeted delivery of therapeutics.

Apart from the nanocarriers discussed previously, there are many more that are being used in biomedical and biotechnological applications, including carbon nanotubes, hollow and porous inorganic nanoparticle and magnetic nanoparticles. In addition, some drugs themselves can be made in nano form and can serve a as self-carrier.

QUESTIONS

1. Define the term “bone” with a neat sketch and chemical composition.
2. What is the role of hydroxyapatite in bone formation?
3. Define the various modes of facture in bone with schematic diagrams.
4. What are collagen fibers and what is their significance?
5. Define the terms “bone grafting” and “Osseointegration”.
6. List out the basic properties of any material for bone implant applications.
7. How do implant materials bond with natural host bone?
8. How X-rays are useful in biomedical applications (X-ray imaging)?
9. What is the role of gold and silver nanoparticles in drug delivery?
10. What is the effect of PEG-modified surface functionalization on drug delivery?

11. Explain the role of magnetic nanoparticles in disease diagnosis and targeted drug delivery?

12. What are the advantages of organic bio-nanoparticles over inorganic nanoparticles?

13. Explain the role of surface functionalization in targeted drug delivery?

14. Peek into the history of CAD and find out the following:

(a) What are the major contributors to the development of angioplasty and stents?

(b) What techniques and materials were used for its treatment before the advent of modern stents?

15. When developing materials for stents, what kind of biological testing is carried out? Similarly, what kind of studies is undertaken to ensure the reliability of the design and expansion mechanism? Hint: for the first part of the question, refer Chapter 5.

16. An area of focus today in stent materials is the use of smart materials such as the nitinol-shape memory alloys. What are the advantages of the "smartness" of these materials that researchers foresee in terms of stenting?

17. Are all regular materials and designs also applicable for branched stents? What is the procedure for stenting in such a case?

18. In addition to coronary applications, where else are stents used as prosthesis? What materials are used for their construction?

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