



Drug delivery system in bone biology: an evolving platform for bone regeneration and bone infection management

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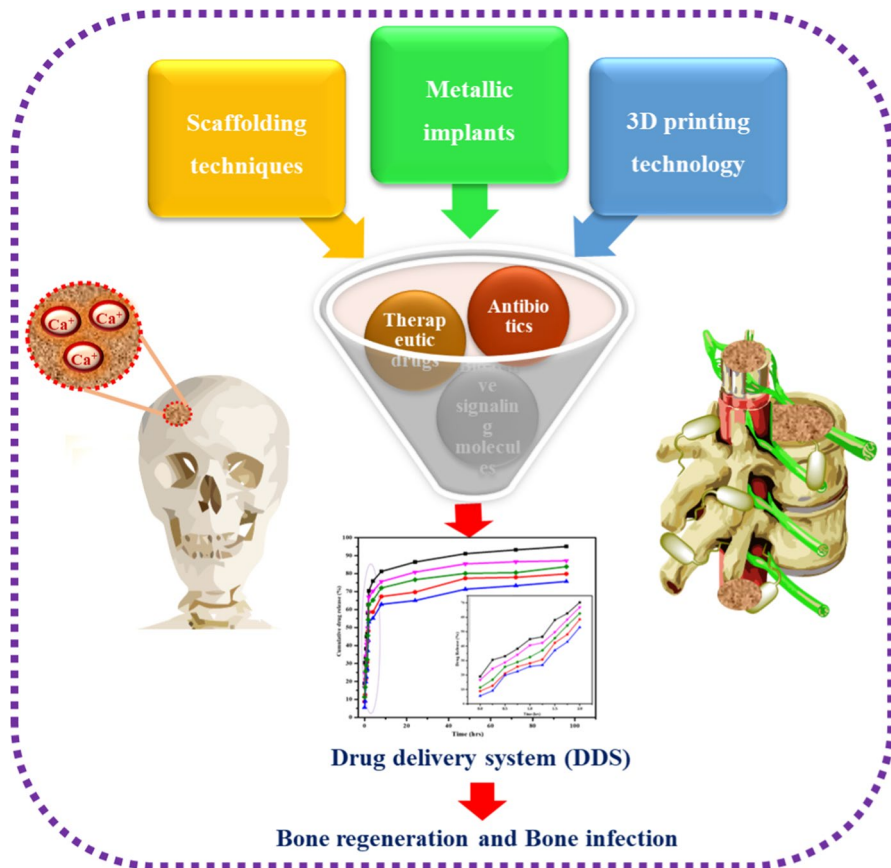
Abstract

Human osteology is the biomechanics science that deals with the study of minerals and non-collagenous organic components that shield human organs and aids in the production of blood cells. A bone follows a specific regenerative pattern after injury or defect. Direct healing ability is still a substantial medical challenge in pathological or nonunion conditions. Such bone defects often necessitate a choice of biomaterial matrix (polymer/ceramic/bioglasses/metallic implants) with the combinations of bioactive signaling molecules (drug molecules) in a spatiotemporal pattern. In this regard, we address the development of a drug delivery system and also outline the interactions of drug molecules with the scaffolding surface that could further trigger the regeneration process. Eventually, the review highlights the notion of drug embedded onto the three-dimensional scaffolds and the release profiles surface coated metallic implant that creates a new window for bone tissue engineering. Besides, a systematic review was performed for literature regarding the role of antibiotics and dual drug delivery strategies that would have a potential utilization of bone-related infection control.

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Graphical abstract



Keywords Drug delivery system · Bioactive signaling molecules · 3D technology · Anti-infection strategies · Dual drug delivery system · Bone regeneration

Introduction

Bone related defects typically originate as a result of fractures (trauma), disease (osteoporosis, osteogenesis imperfecta), or at times induced by surgeries (removal of tumors and infections) are often sequelae in bone biology. Following the bone healing biology, Jakob et al. [1] proposed that bone tissues have a low intrinsic regenerative capacity or even develop an unfavorable anatomical position. The option of direct bone treatment offers many biological and surgical remodeling strategies. In addition, it also requires defect management such as bone transport/replacement, bone tissue regeneration, and other surgical reconstruction procedures. The current surgical procedures which are employed to treat long bone defects are (1)

Reamer–irrigator–aspirator (RIA) system, (2) Masquelet technique, and (3) bone transport using the Ilizarov technique. Parallely, Cirstoiu et al. [2] had proposed that these techniques are a complicated process that leads to slow healing, high risk of infection, and unclear guidelines.

A famous prehistoric painting belonging to the Egyptian and Greek civilization (ca.1395-1455) “The Healing of Justinian by saint Cosmos and saint Damian” has been evidenced by Dorozhkin et al. for the homograft transplantation of an injured soldier [3]. In this regard, bone tissue engineering plays a high-energy impact on bone defects to develop an alternative solution. As an emerging domain, it is considered to be an optimal approach to root the utilization of autograft, allograft, and synthetic biomaterials. Among the available bone augment, autologous grafting is still considered as a “gold standard” due to its low immunological property. However, a study by Dimitriou et al. [4] had suggested that the choice of autografting could result in less osteoinductive and cause stress at the donor site consequently limiting its applications. On the account of overcoming these constraints, bone tissue engineering (BTE) synergistically use bioceramics, bioactive glasses, and biological or synthetic polymers to form a highly porous scaffold material. Such scaffolds/templates are significantly designed as a replacement to improve, maintain, or restore tissue functions. Matassi et al. [5] had recommended that modern biomaterials lack in mimicking the native extracellular matrix environment.

Researchers have combined the scaffolds with biological strategy (e.g., growth factors, therapeutic drugs, peptides etc.) to advance bone tissue healing via vascularization (osteoinductivity) by regulating regeneration and strongly defend the migration of mesenchymal stem cells. Besides, bioactive molecules would boost the cellular level mechanism, influences in regeneration and healing process specially for longer bone defects. We retrospectively reviewed the prevailing development of drug delivery systems in bone regeneration applications and proper attention has given to bioactive materials that could be a promising agent for future bone applications. This review also highlighted the contemporary research on the interaction of drug molecules with scaffolds and dual drug delivery system as a future driving force in bone regeneration applications.

Principles of drug delivery system (DDS)

Hanes et al. had defined a drug delivery system (DDS) as process of administrating a pharmaceutical compound to specific target sites [6]. Local drug delivery aims to deliver the minimum concentration of drug locally to the affected site/tissue at desired rate over a specific period. The effective local drug delivery systems with controlled kinetic can suppress off-target side effects to treat inflammatory diseases or osteoporosis. The traditional systemic drug administration into the body is initially absorbed into the bloodstream and distributed all over the body which may roots to renal and liver problems. Henceforth local drug delivery could minimize the side effects and improves bioavailability by reducing the dosage of drug. For bone infections, target drug delivery or smart drug delivery aims to deliver the therapeutic agents (can also be nanoparticles, proteins, antibodies, peptides) to the involved regions (i.e., specific cells/organs)

thereby release in a dosage manner. The reduction in side effects with improved activity against bacteria been advantage of this system, whereas high cost and productivity makes more complicated. Henceforth, it can be designed by controlled composition, shape, size, morphology, orientation to increase the solubility, immuno-compatibility, and potential cytotoxicity. The dramatic expansion of designing drug carriers such as nanocarriers, pills, microneedle injections, transdermal delivery systems, and micro-particle-based depots that should trigger the biological systems. Due to this off-target drug adsorption, bone tissues will employ very little doses and negatively narrows therapeutic functions. This can be achieved by binding the drug molecules with synthetic or natural moieties. The drug delivery system requires a new biomaterial design which ensures the effective delivery of macromolecules (proteins, drugs, and nanoparticles) from the tortuous network in a sustained or controlled manner.

In that case, drugs are physically trapped within polymeric shell or matrices, or also covalently attached with polymer backbone. Once the drug is systematically absorbed by the body, it penetrates through the bloodstream to the tissues and intracellular fluids and binds with the receptor. This network then releases the drug molecules from the receptor, further it can distribute via a circulatory pathway and it has been proposed in the study of Ghosh et al. [7]. Figure 1 illustrates the integration of drug molecules in diverse biomedical devices. The drug transporting process hence being a new era for (i) controlling pharmacokinetics and pharmacodynamics, (ii) to reduce non-specific toxicity, (iii) immunogenicity, (iv) biorecognition, (v) efficacy of drugs, (vi) improves bioavailability, and also (vii) empowers therapeutic agent stability against enzymatic degradation.

The rational designing of a hybrid drug delivery system not only improves therapeutic activity but also improves biodistribution, biodegradation, and drug encapsulation. Drug release can be controlled by diffusion, partitioning, dissolution, swelling process, matrix erosion, and osmosis (i.e., hydrophilic drugs undergo diffusion and hydrophobic drug undergoes swelling or erosion process). Besides, if the penetration process of the drug molecules becomes poor (i.e., poor diffusion coefficient) it may create an adverse toxic effect.

In such complexity, the drug release profile can be justified by mathematically derived statistical methods called the model-dependent method. The common mechanism of drug delivery from existing bone substitute materials is primarily occurred by Fickian diffusion or desorption of the observed drug or a combination of erosion and diffusion process. Lee et al. had reported in his study that an intracellular drug release kinetic models are zero-order, first-order, Higuchi model, Ritger-Peppas model, and Kopcha model, Hixson-Lonsdale, Weibull, Hopfenberg, and Grompertz. The DDS should hold the fundamental criteria that include (i) Loading capacity, (ii) Homogeneous distribution of the drug, (iii) Binding affinity of the drug with the scaffold, (iv) Stability of the loaded drug, (v) Kinetics of drug release with time [8].

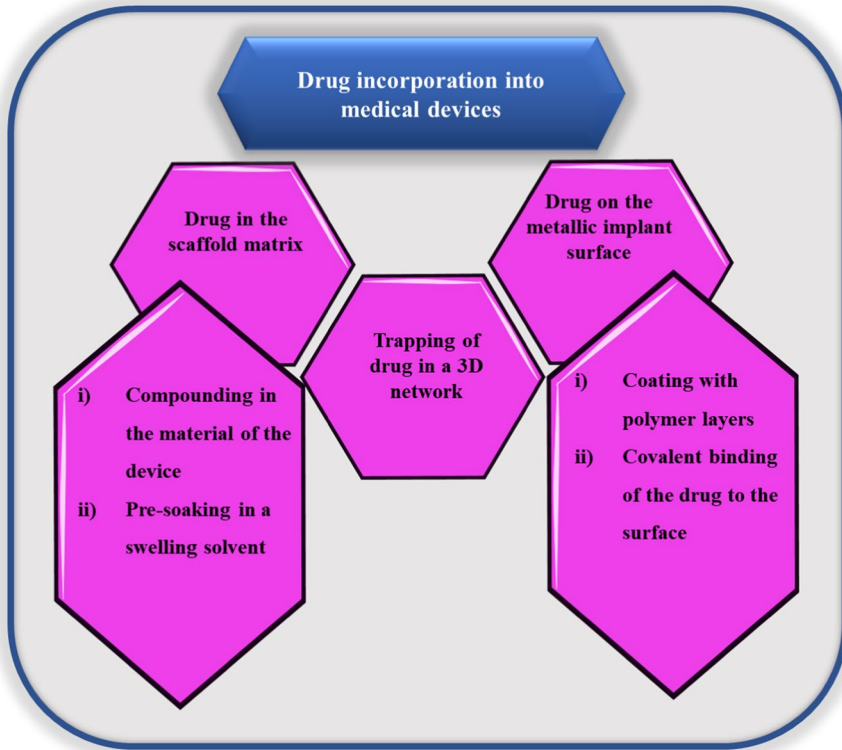


Fig. 1 Illustrates the drug incorporation into the drug-carrying vehicle for biomedical applications

Bone targeting drug delivery

Bone targeting drug delivery technologies has been developed to resolve the difficulty of reaching the desired foci and minimizing the toxicity created by poor drug activity. The drug penetration process through multi-pathway is an imperative concern of bone defects, bone infections, and also stimulating regeneration. Drug molecules that include antibiotics which could resolve the problem and so-called specific bone-targeting drugs. Also, bone gene therapy is still being at the research stage and hence it is not equipped to be used for clinical applications. Most of the bone-targeting drugs are designed for treating musculoskeletal diseases such as osteoarthritis [9], osteomyelitis [10], osteoporosis [11], osteosarcoma [12], and metabolic skeletal dysplasia [13]. In general, bone-specific drug targeting moieties provide a vital impact on specific cell types or the entire skeletal system that could regulate the bio functions of bone cells. Figure 2 illustrates the osteoconductive of bone enhanced by bone targeting drugs.

Drug incorporation can be done in the polymeric/ceramic matrix, three-dimensional matrix, and on the surface of coated metallic implants. Bone repairing drug

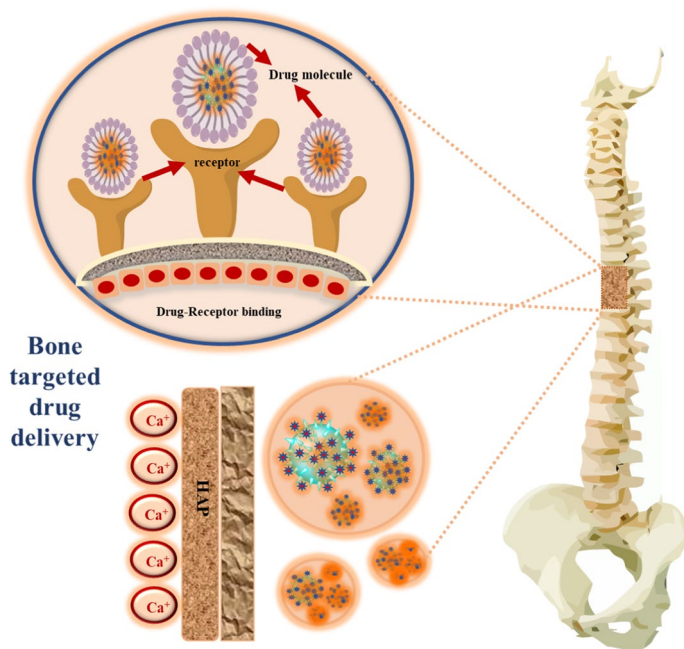


Fig. 2 Osteoinduction of bone via drug delivery system

can be integrated by using two different methods (i) the prior mixing of drug solution with biomaterials before fabrication, i.e., where the drug molecules are covalently bonded with the functional groups of biomaterials, (ii) the fabricated scaffold are immersed in the appropriate concentration drug solution, i.e., where the drug molecules are not covalently bonded with biomaterials. The encapsulated drug on the surface or within the material matrix may initially release by diffusion or degradation (i.e., polymer degradation) and also by the porosity of the material. Hence, the degradation rate of the polymer is mainly due to the hydrophilic nature of the bone scaffold. The drug attached on the surface may undergo initial burst release, whereas the encapsulated drug may undergo sustained drug release for the long term. The *in vitro* drug release kinetics and duration with time intervals can be controlled by the drug integration process or also by composition.

Bioactive signaling drugs in bone regenerations

Bioactive signaling molecules (also called biological mediators) create a biological signal that could further regulate cellular activity and develop a tissue that binds with receptors on the target cell membrane (Fig. 3). Each category of signaling molecules possesses a multitude of growth factors such as bone morphogenetic protein-2 (BMP-22), BMP-7, vascular endothelial growth factor (VEGF), and fibroblast growth factors-2 (FGF-2). Glassman et al. had reported the efficacy of

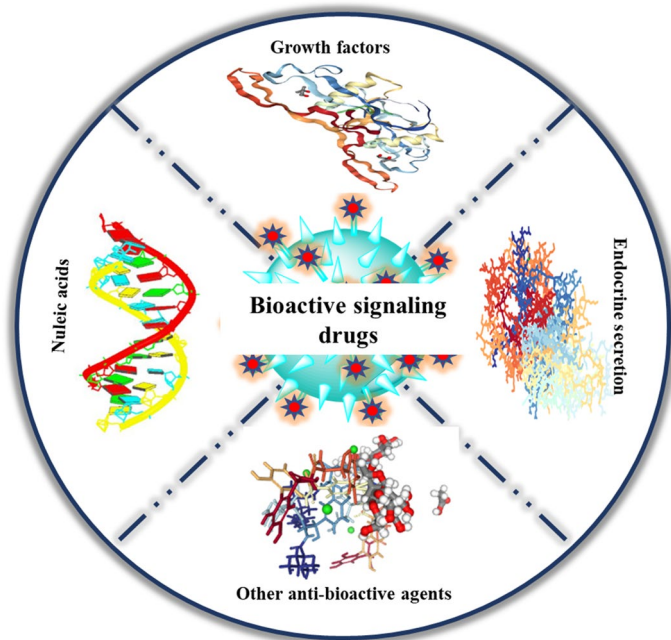


Fig. 3 Bioactive signaling molecules for bone formation

rBMP-2 in posterolateral lumbar spine fusion [14]. The studies of Hirata et al. and Koh et al. had proved that BMP-7 and BMP-2 have been successfully used in dermal fibroblasts for bone regeneration [15, 16]. Kawaguchi et al. had described in his preclinical study that gelatin containing recombinant human (rh) FGF-2 hydrogel accelerated the tibial shaft fractures. Unfortunately, using BMP concerns about the heterotopic bone formation, BMP-2 increases the risk of cancer and VEGF induces hypotension [17]. These current growth factors in clinical settings create many therapeutic complications and negative side effects.

Endocrine secretion molecules (e.g., Hormones by glands) are the next class of signaling molecules that regulates tissue growth, function, and development. Parathyroid hormones (PTH) are a bone remodeling hormone (i.e., bone-building agent) has been investigated in the recent study by Dang et al. which is used to improve bone resorption of osteoporosis treatment in the US. Nucleic acids also play an important role in signaling cellular functions at the genetic level [18]. For example, Basu et al. and Yong et al. had investigated DNAs and mRNA encode the BMPs, FGF-2, and VEGF to induce regeneration. Owing to this, noncoding genes such as siRNA, miRNA have also been used to regulate gene expression [19, 20].

Additionally, a series of other anti-bioactive agents are also been used in combination with scaffolds. Kalhapure et al. and He et al. had reported an antibiotic and an anti-inflammatory drug are effective in controlling infections at the bone site and minimize the effect of bacterial colonies [21, 22]. Meng et al. had developed an aspartic acid modified BMP-2 peptide (P28) incorporated mineralized

tissue-derived ECM modified scaffold (MSIS/TBC) to induce osteogenic activity. The release profile of the SIS/TBC scaffold followed sustained release of BMP peptide whereas showed controlled release in mineralized SIS/TBC due to the affinity multiple sequence of aspartic acid with apatite surface [23].

Similarly, Sun et al. had investigated a sequential delivery system of BMP2 and Apt19s (aptamer) from ECM based scaffold. The work proposed that the novel PCL/SIS-PBMP2-Apt19s scaffold enhanced osteogenic differentiation during slow sequential release and also induced higher degradation over prolonged time [24]. A large number of bioactive growth factors have been utilized as a crucial regulator of skeletal formation, bone, and cartilage regeneration. The use of the drug delivery system would build an efficient integrative approach for targeting tissue engineering in a temporary and spatially controlled manner.

Scaffolding: as a tool for modulating drug delivery

An artificial extracellular network of the scaffold facilitates a porous biodegradable three-dimensional structure, which fits for cell attachment, cell proliferation, cell differentiation, and cell migration. It serves as a three-dimensional tissue arrangement, high pore interconnectivity, and accessibility for drug/medication delivery to the targeted site. Scaffolding assumes a vital part in tissue engineering that advances biological activity (by enhancing the nutrient and fluid diffusion rates), convey drugs via vascularization, and also gives a platform for bone regeneration. An optimal scaffold should have a desired volume, shape, and mechanical architecture with non-toxic, biocompatible, and manifest degradation.

There are four types of ideal scaffolds such as (i) highly well-interconnected porous scaffolds prepared by freeze drying, (ii) nanofibrous matrix fabricated using electrospinning/3D bioprinting, (iii) injectable matrices (i.e., hydrogels), and (iv) porous microspheres. However, desired scaffolds are prepared by naturally derived and synthetically derived polymers that have been demonstrated which are seen as likely biomaterials for engineering scaffold. Such polymers help in dispersing the biological fluid via a cellular system that holds the properties of biocompatible, biodegradation, high cell adhesive, and mechanical stable. Hence, the scaffolding biomaterials are largely categorized into further groups such as ceramics, natural and synthetic polymers, metals, and composites of these three or either two of them.

Haider et al. [25] had proposed that diverse techniques have been developed to fabricate a scaffolding lattice including (1) fiber bonding, (2) emulsion freeze-drying, (3) solvent casting/particulate leaching, (4) high-pressure processing, (5) gas foaming/particulate leaching, (6) thermally induced phase separation (7) electrospinning and (8) rapid prototyping. The release rate of incorporated drugs or encapsulated drugs into matrices/microcapsules can be controlled by diffusion, polymer erosion, biodegradation, and swelling. Porosity can contribute to drug release by diffusion and degradation property used to achieve suitable control and that synchronized with the rate of tissue growth. The chemical and physical properties of the polymers are of the utmost importance to achieve controlled drug release or sustained drug release. These rational factors along with the scaffolding technique

offer the prospects of developing a prosthetic drug delivery device for bone-related treatment.

Polymers: an integral role in the drug delivery system (DDS)

Polymers are macromolecules which are composed of repeating units called monomers that can be controlled via polymerization or by functionalization of polymeric units. Interestingly, polymers are found in both living (proteins, lipids, cellulose, and nucleic acid) and non-biological systems (synthetic polymers). Polymers in combination with ceramics, bioglass, or metals form a strong bio-responsible material that could elute the drug molecules depending on its physicochemical properties such as swelling/shrinking, degradation, or porosity. Polymer-based nanocomposites are the smart conventional drug delivery device that allows for spatiotemporal releases of bioactive molecules via the biological mechanism. The advances of such polymers are generally represented into two main classes: (i) Natural polymers (organic macromolecules derived from a natural source) and (ii) Synthetic polymers (artificial macromolecules).

Bone drug delivery applications have been emerging with both natural and synthetic polymers that originated from biologically derived materials that exhibit excellent biocompatibility and controlled enzyme degradation. In the aforementioned perspective, the DDS constructed using various biodegradable polymers breakthrough in controlled drug delivery systems (CDDS) and sustained release drug delivery systems (SRDDS). Figure 4 shows the drug diffusion from polymer/ceramic-based scaffolds that have fabricated by different scaffolding techniques.

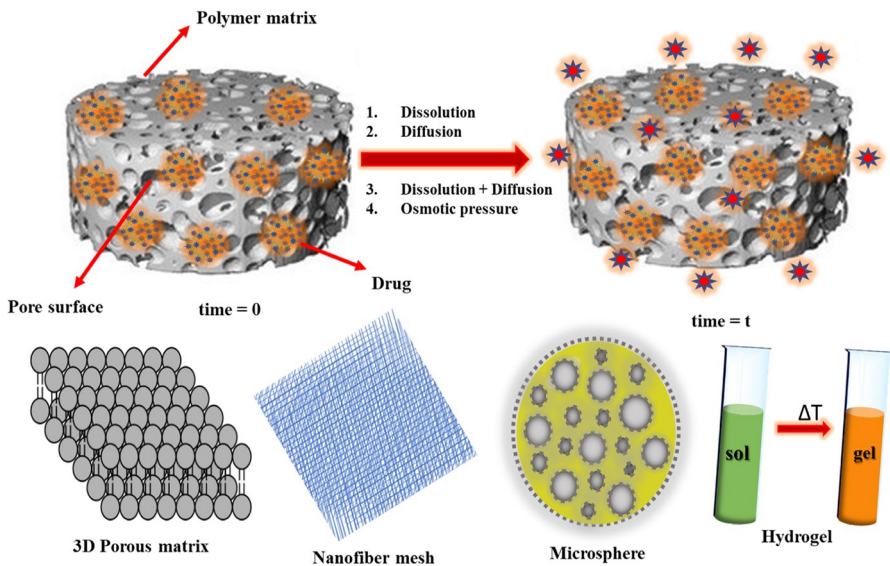


Fig. 4 Graphical representation of polymer/ceramic composite-based drug delivery system

(i) Natural polymer

Silk fibroin-based drug carriers

Silk fibroin (SF), the core protein with high molecular weight obtained from the cocoon of the domesticated silkworm (*bombyx mori*). SF is a particularly beneficial material in biomaterial applications due to its biocompatibility, biodegradability, mechanical conformity, and low adverse immune effect by Ma et al. [26]. The silk-based drug delivery system provides an ideal reservoir for specific drug targeting, intracellular transport, and biocompatibility. Silk fibroin possesses a unique drug system for modulating drug-releasing effects by the tissue-specific target, especially in the case of anticancer drugs.

Drugs were loaded into silk fibroin scaffolds which have been fabricated by various forms including nanofiber, hydrogels, films, three dimensional (3D), microsphere as well as SF coated polymer particles. Engineered SF scaffolds with modified drug carriers have multiple advantages such as improving mechanical properties of the formulation, modifying drug release kinetics, and enhance cell adhesion. Drug distribution of small molecule drugs, biological drugs, and genes in the SF-based scaffold was widely used as therapeutic agents. Entrapping the drug molecules was expected to stabilize them by different mechanisms including adsorption, covalent interaction, and entrapment. Pritchard et al. had deliberated that encapsulation of antibiotics with SF sponges show antibacterial activity for up to 31 days against staphylococcus Aureus. The active groups and tyrosine residues of SF bind with anticancer drugs to treat desired tumor tissue [27].

Rama et al. had studied a detailed examination of the effect of silk fibroin in two different scaffold matrix and its in vitro sustained drug release of CEM antibiotic for bone-related infections and osteo-regeneration applications. The progress of in vitro drug delivery on the bone the matrix was influenced by the addition of silk fibroin, where the drug may be a trap into the SF network that resulted in effective intracellular drug release [28]. Bhattacharjee et al. had developed a non-mulberry silk fibroin (NSF)/PCL/HA with combinations of bone morphogenic protein (rhBMP-2) and transforming growth factor (TGF- β) to enhance the osteoinductive [29]. Growth factors (rhBMP-2 and TGF- β) were loaded on the NSF-PCL/n25 nanofibrous scaffolds and the release kinetics showed only 21.34% and 22.6%, due to the strong bonding between growth factors and the functional group of SFs. Seib et al. had designed lysosomotropic SF nanoparticles for the pH-dependent release of the anticancer drug (doxorubicin) to overcome drug resistance. This study revealed that the release rate was higher of the sample which holds pH=4.5 compared to the other pH conditions [30].

Chen et al. had prepared paclitaxel (PTX)-loaded SF nanospheres (ranging from 270 to 520 nm) with controllable size and the release of PTX depends on the SF concentration as anticancer drug nanocarrier for chemotherapy [31]. Similarly, Shuying Yu et al. had prepared floxuridine (FUDR)-regenerated silk fibroin (RSF) nanoparticle (210–510 nm) for anticancer activity. The loading efficiency of FUDR labeled RSF nanospheres increased with an increase in the SF concentration [32]. A

3D-printed scaffold of biomineralized hydroxyapatite nanocomposite on silk fibroin was prepared by Huang et al. [33]. He reported that bovine serum albumin (BSA) was released in a sustained manner from SF/HAP-SA scaffolds and could support hBMSC proliferation and osteogenic differentiation.

SF has hydrophobic β sheet (amphiphilic co polymer block), it improves the mechanical strength of the scaffolds thereby improves the biological actions in bone tissue growth. Drug embedded SF scaffolds showed excellent drug release kinetics (controlled/sustained release or sequential release), areal natural signals and deliver therapeutic drugs due to its slow bio-degradation rate. Incorporated drug from silk scaffolds can be released by diffusion, dissolution, solvent penetration or stereotypically by polymer degradation. Though the release mechanism from silk fibroin-based scaffolds are suspected to be fickian-diffusion model in most cases, there is no clear mechanism pattern mentioned and must be investigated in detail.

Chitosan-based drug carriers

Chitosan (CS, aminogluco-pyran/poly- β -1,4-glucosamine) is composed of a long biopolymer chain of *N*-acetylglucosamine and β -(1,4)-linked glucosamine residues. Chitosan and its derivatives are the deacetylated form of chitin, which is naturally found in exoskeletons of arthropod, marine crustaceans, shellfish, and some fungi. As reviewed by Tao et al. chitosan is biodegradability, biocompatibility, anti-oxidant activity, bioadhesive property, anti-inflammatory activity, and immune-stimulating activity [34]. Besides, the combinations of chitosan/chitin and other polymers/ceramics with chemical modifications are used as drug carriers in bone-repairing applications. Furthermore, the interactions of the amino group present in the chitosan and functional group of drug molecules create a tight junction that enhancing the delivery process by diffusion.

Anjaneyulu et al. had prepared a multiphase 5%@Ag:HAP-Fe₃O₄-Cs nanocomposite using a ball milling method for bone regeneration [35]. The biological study of the nanocomposite revealed that the presence of chitosan in the metal doped composite showed high hemocompatibility and NIH-3T3 cell proliferation. Saber-Samandari et al. had prepared a chitosan-graft-poly (acrylic acid-co-acrylamide)/hydroxyapatite nanocomposite and celecoxib-loaded to the scaffold where the cumulative release of celecoxib showed a maximum amount of celecoxib (95.2%) [36]. Furthermore, it was found that with the increase in Hap the decrease in the amount of drug release from chitosan-graft-poly (AA-Co-AAm)/Hap scaffolds. Hence, the amount of drug released depended on the morphology and composition of the designed scaffold. Sara Azizian et al. [37] had reported a chitosan–gelatin porous scaffold incorporated with chitosan nanoparticles loaded with basic fibroblast growth factor (BFGF) along with bovine serum albumin (BSA). The sustained release of the entrapped growth factors from the chitosan–gelatin scaffold enhanced fibroblast cell proliferation.

An ursolic acid loaded mesoporous bioglass/chitosan scaffold (MBG/CS/UA) as a drug delivery vehicle was developed by Ge et al. [38] has enhanced bone regeneration. The as-released UA drugs from the mesoporous scaffolds showed a long-time controlled release performance. This may be due to the microstructure with

interconnected macropores and functional groups of the MBG/CS/UA scaffold that could enhance the mineralization rate of new bone tissue. Malek-Khatibi et al. had proposed a review on chitosan as a drug carrier of growth factors in bone tissue regeneration. He described that the chemical and physical modification of chitosan is an essential factor for modulating drug incorporated scaffolds and regulating bone metabolism [39]. Recently, Archana et al. had achieved a sustained release profile (3–4 days) from biodegradable vitamin D incorporated (10–60 mg/ml) chitosan based lyophilized scaffold to modulate bone regeneration [40].

Due to its weak mechanical property and less solubility, it has been limited in clinical practice until it is functionalized. On a cautionary note, chitosan derived or functionalized scaffolds has shown an effective absorption and delivery of macromolecules in targeted site and stimulates response in corresponding tissue site. Hence, chitosan-based ceramic in drug delivery system is an excellent vehicle with prolonged release and desired elution kinetics in bone biology.

Gelatin-based drug carriers

Gelatin, a single-stranded protein which is prepared by thermal denaturalization of collagen. Gelatin is reported to consist of glycine, proline, and 4-hydroxy proline residue linked together in a particular ordered fashion by Chen et al. [41]. As a drug delivery carrier, gelatin can preserve the intrinsic features in tissue engineering, cancer therapy, and therapeutic angiogenesis. The inclusion of gelatin in the composite system has evoked the pharmacokinetics profile and drug efficacy. Shahrezaee et al. [42] had investigated a metformin loaded gelatin (MET/GNs) coated PLA/PCL scaffold to critical-sized bone defects in a rat model. Due to long-term sustained release of MET/GNs showed an impact on increasing the osteogenic activity and angiogenic activity of progenitor cells. MC3T3-E1 cells (mouse osteoblast cells) incorporated in covalently cross-linked gelatin macroscopic scaffolds (ccG-MSc) were prepared by Fan et al. had to facilitate osteogenic differentiation [43]. The MC3T3-E1 cells loaded scaffolds showed a promising potential acting vehicle toward a drug delivery application. Recently, Govindan et al. had developed a 3D porous ciprofloxacin loaded phosphate glass-reinforced gelatin composite (GPG1 and GPG2) scaffolds. The prolonged release behavior of ciprofloxacin was observed in a sustained release manner which was due to the strong interactions between PG-Gelatin-ciprofloxacin via fickian diffusion mechanism [44].

Saber et al. had proposed a review on surface modification of gelatin-based nanoparticles and its effect on various drug targeting applications [45]. In his regard, gelatin as bio-based nanoparticles has shown the greater potential of drug delivery via self-diffusion process, liberation due to degradation, surface erosion of the matrix, or combinations of two or more. Subsequently, Habraken et al. had embedded calcium phosphate cements (CPCs) in gelatin particles to generate porous microparticles [46].

This macroporosity of the material facilitates sustained drug release to encourage tissue integration. At the end of the investigation, gelatin-based composite materials have been successfully designed to utilize in musculo-skeleton tissue engineering due to its favorable biodegradation profile.

Collagen-based drug carriers

Collagen is the dominant fibrous protein present in the ECM (extracellular matrix) and the mineralization cartilage of the epiphyseal growth plate. The pattern of collagen is made up of a triple-standard superhelix structure which holds three polypeptides twined by hydrogen bonding by Liu et al. [47]. This heterotrimeric protein structure plays an important role in drug carrier applications. The interchain hydrogen bonding and electrostatic interactions between residues could hold drug molecules and release in desire site. Additionally, collagen has tendency to activate osteogenic differentiation by stimulating extracellular protein kinase and phosphatidylinositol kinase. The major integrins such as $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, $\alpha 11\beta 1$ could bind with collagen to induce cell adhesion and thereby regulate osteoclast differentiation. Eventually, collagen activate osteoclast receptors and leukocyte-associated receptor which generate signals to inhibit osteoclast formation hence prevents the premature absorption of osteoblast-like cells [48, 49].

Farahnaz Fahimipour et al. had fabricated an $n\beta$ -TCP (nano β -tricalcium phosphate) particles reinforced 3D bilayer collagen (COL) scaffold further investigated for delivery of leukocyte platelet-rich fibrin (L-PRF) cells and growth factors to initiate bone regeneration. The addition of $n\beta$ -TCP increased the compressive modulus in turn decreased the porosity and porosity has increased the cell viability of the bilayer scaffold [50]. A novel multifunctional 3D-printed PLA-collagen-minocycline (MH)-citrate HAp scaffolds with bioinspired coatings of human bone marrow-derived mesenchymal stem cells (hMSCs) were engineered by Victor Martin et al. The release of MH from PLA-COL-MH-CHAP scaffolds had improved antibacterial activity against *S. aureus* which could prevent bone infections and hMSCs depicted increase in osteogenic activity of the 3D scaffold [51]. Manami Ozati et al. had evaluated a subsequent effect of a bioabsorbable collagen membrane (BCM) containing osteogenic protein-1 (OP-1) to facilitate bone regeneration in a mandibular bone defected rat model. The delivery of rhOP-1 from BCM has significantly increased the potency of osteoinductive/osteogenesis in a sustained manner [52].

Didem Mumcuoglu et al. had designed a novel BMP-2 delivery system using recombinant protein-based human collagen I (RCP) microspheres. He studied the influences of BMP-2 release kinetics from RCP microspheres along with the degree of cross-linking and sphere size [53]. The resulted findings showed that HMDIC or DHT cross-linked microsphere released in a sustained manner (10–20%), this may due to the higher affinity of BMP-2 and RCP. Marelli et al. had prepared a bioglass-collagen nanocomposite that would have the potential to support the biomineralization of osteoinductive cells [54].

From the above discussion, different strategies have been investigated for collagen-based scaffolds that exhibits significant protein/drug transfer and improves osteoblast proliferation. A combination of collagen with other polymeric matrix could allow the non-steroidal drug molecules (i.e., antibiotics and anti-inflammatory drugs) in a sustained release manner and improve its performance. Moreover, incorporation of collagen not only possess the ability to deliver drug molecule, but it also controls the evaporation of fluids, promotes granulation tissue, diminishes pain, and protect from bacterial infections. Collagen-drug system can be chemically modified

by using cross linkers to alter the desire water absorption property where diffusion takes place. This chemical bonding of drug molecules with collagen system might be the reason for prolong drug release from scaffold matrices.

Alginate-based drug carriers

Alginate/alginate acid (Alg) is a hydrophilic, linear carbohydrate (anionic polysaccharides) composed of β -[1-4]linked D-mannuronic acid residues (M block) and α -L-guluronic acid residues (G block). It has been isolated from the cell wall of brown seaweed (*Laminaria hyperborea*, *Laminaria digitata*, *Macrocystis pyrifera*) and bacterial source (*Azotobacter vinelandii*). Alginate can ionically form strong hydrogels in various medical applications including cell encapsulation, wound dressing, and also it regulates the drug delivery system and has been proposed by Fernando et al. [55]. Alginate is of particular interest in mimicking many functions of the extracellular cellular matrix (ECM) which provides the efficacy of the drug-delivering matrix and biological performance. The hydrophilicity of the alginate is the reason for creating a temporary platform to support the drug distribution and also allows the retention of metabolic functions.

Jingxuan Yan and Yuting Miao et al. [56] had reported a drug-loaded injectable alginate-based composite gel scaffold doubly integrated with hydroxyapatite and gelatin microspheres (GMs) were cross-linked via in situ release of calcium cations. Tetracycline hydrochloride (TH) was loaded onto alginate/HAP hydrogels showed cumulative drug release mode and gelatin microsphere showed delay releasing rate of TH. Jisun Park et al. had fabricated a 3D cell-laden alginate hydrogel with controllable features for drug delivery and bone tissue engineering (BTE) [57]. Compared to alginate bio-ink, the inclusion of alginate-sulfate bio-ink enhanced osteogenesis stimulation by offering a prolonged BMP-2 activity. Yong-guang Bi et al. had investigated a hydroxyapatite/sodium alginate/chitosan (HAP/SA/CS) composite microsphere that might have a potential for carrying drugs in a pH-controlled drug release system [58]. To minimize the osteoporotic (OP) fracture risk, Segredo-Morales et al. studied an injectable BMP-2 and plasma rich growth factor (PRGF) loaded tetracycline alginate composite thermogel [59]. He reported that the presence of alginate to tetracycline acid reinforced the stability and BMP-2 delivery showed a response to 17 β -estradiol compared to PRGF.

On focusing on osseous defects, Kolambkar et al. had introduced an electrospun nanofiber mesh tube with peptide-modified alginate hydrogel for a growth factor (rhBMP-2) sustained release delivery system [60]. Fereshteh Ahadi et al. had prepared a hydrogel/fiber scaffold of silk fibroin/oxidized pectin (SF/OP), the presence of aminolyzed PLLA-drug fibers resulted in the sustainable release of vancomycin HCl [61]. Zhang et al. [62] had prepared a vancomycin loaded alginate hydrogels to achieve a sustained drug activity for osteoblast proliferation.

Based on the above discussion, the alginate composite scaffold systems stand out for its ability to encapsulate cell/bioactive molecules and allowing them to specific applications that could promote steady and long-term delivery. In addition, the clinical study of alginate composite based bone drug carriers in bone regeneration is still low and rare, only few preclinical animal studies have been reported.

Hyaluronic acid-based drug carriers

Hyaluronic acid (HA), also known as hyaluronate is its conjugated base, is a non-sulfated linear glycosaminoglycan composed of subunits of d-glycuronic acid and *N*-acetyl-d-glucosamine. HA is perhaps the best-known linear polysaccharides found in all the connective tissues (ECM) such as epithelial, neural tissues, the dermis, synovial fluid, the vitreum. HA plays a major role in biomedical applications including osteoarthritis surgery, plastic surgery, ocular surgery, drug delivery, and biopolymers in tissue engineering. This wide range of applications is due to its excellent biodegradability, biocompatibility, non-toxicity, highly hydrophilic, and non-immunogenicity [63]. Besides, chemical modification or cross-linking effect on hyaluronic acid functional group with composite could improve the antibacterial activity of the scaffold. This inhibitory effect could also reduce the bacterial adhesion by creating an electrostatic interaction that has ability to kill negative cell walls of bacteria. The bio-degradation of HA in microenvironmental condition favors the sustainability of drug molecules and results in prolong stable release to increase osteointegration.

Jungju Kim et al. had prepared a hyaluronic acid-based hydrogel with bone morphogenic protein-2 and human mesenchymal stem cells (hMSCs) for rat calvarial defect regeneration. HA scaffolds showed a promising growth factor carrier for bone differentiation [64]. A chondrocyte encapsulated gellan gum-based hyaluronic acid blended hydrogel was evaluated by Won Kyung Kim et al. [65]. A physically blended GG/HA hydrogel showed higher encapsulation and cartilage-specific protein and gene. Jinlei Dong et al. had designed a novel hyaluronate-modified nanoparticle for combo-delivery of curcumin (CUR, a bone formation agent) and alendronate (ALN, anti-resorptive agent) to treat the osteoporosis defect [66]. The CUR/ALN decorated hyluronate nanoparticle showed greater ability to stimulate bone formation and harmonized a drug nanocarrier-based formulation to treat bone erosion disorders.

Hemshkhar et al. had reported the role of hyaluronic acid bio-scaffolds in therapeutic applications such as organ-specific tissue engineering, regenerative medicines, and drug delivery applications. Further investigations of HA-base biomaterials/nanoparticles have been used for delivering growth factors and antibiotics in a controlled release manner [67]. In such a case, Ansari et al. had developed an alginate/hyaluronic acid hydrogel loaded with TGF- β 1 ligand (Transforming growth factor-beta) encapsulated periodontal ligament stem cells (PDLSCs) for regulating the periodontal differentiation [68]. Hydrogel showed a continuous release of TGF- β 1 toward the chondrogenic differentiation of mesenchymal stem cells (MSCs). The hyaluronic acid-based composite found to bond electrostatically with drug molecules and thereby modulate drug delivery ability and enhance bone formation.

(ii) Synthetic polymer

Poly(lactic acid)/polylactide (PLA)-based drug carriers

PLA perhaps the well-known biodegradable aliphatic semicrystalline polyester that can be produced from the monomer of lactic acid by direct polycondensation (DP) route or ring-opening polymerization (ROP) route. PLA can be derived from 100% renewable bioresources such as rice, wheat, and sweet potato via a fermentation process. Due to its biocompatibility and biodegradability and bioresorbable, PLA has been used in the biomedical-pharmaceutical field. Farah et al. had reviewed that erosion, diffusion, and high swelling rate of PLA would maximize the drug release and minimize the toxicity [69]. The erosion of PLA polymer occurs through hydrolytic ester cleavage which makes them a stellar candidate as a drug delivery layout. PLA also holds poly(lactic-*co*-glycerol) PLGA (copolymer of PLA) and stereo-isomers poly(L-lactide) PLLA, poly (D-lactide) PDLA, poly (DL-lactide) PDLA.

Mary Stella et al. had designed a chemically modified (alkaline treated) novel luffa electrospun nanofibers from luffa cylindrica for bone regeneration applications [70]. The study investigated the influence of natural cellulose in PLA/HAP composite enhanced the mechanical property and cell viability. In the study of Birhanu et al. had prepared a multilayer PLLA/pluronic P123 electrospun nanofibers and examined drug release using dexamethasone, where the drug was loaded into the middle layer [71]. The single-layer showed a burst drug release profile and the multilayer showed a controlled release and better osteogenesis. Li et al. had constructed a bone morphogenetic protein-2 and protein-7 (BMP-2 and BMP-7) loaded polylactide-poly (ethylene glycol)-polylactide (PELA) microcapsule-based scaffold to promote osteogenesis [72]. Likewise, Baek et al. utilized a layer aligned human meniscus cell embedded PLA electrospun (ES) that would support meniscus tissue formation [73]. A PLA/PGA scaffold delivers human cartilage-derived morphogenetic protein-2 (hCDMP-2) to facilitate meniscal repair by fibrocartilage-like tissue regeneration.

Recently, Lukmanul Hakim et al. had prepared a PLA/PCL microsphere with the compositions of 60:40 using span 80 as an emulsifier. His study concluded that particle sizes of microspheres were suitable for controlled drug delivery carriers [74]. Similarly, Herrero et al. had fabricated PLA/PCL electrospun membranes of systematically tailored fibers diameter and the membranes were loaded with bovine serum albumin (BSA) [75]. As a result, the PLA/PCL membranes with above micron fiber diameter showed the most effective BSA released in a controlled manner.

Poly(ϵ -caprolactone) (PCL)-based drug carriers

PCL is a bioresorbable aliphatic semicrystalline poly (α -hydroxy ester) with a low melting point (60 °C) and that undergoes hydrolytic degradation (i.e., hydrolytic cleavage of ester group) under physiological conditions. In recent review by Abrisham et al. it has been proposed that due to PCL good dissolution tendency, tissue compatibility, low melting point ($T_m = 59\text{--}64$ °C), and good mechanical property which makes it suitable material in artificial scaffold for regenerative therapy and drug delivery applications [76]. Due to the hydrophobic nature, PCL enables cell proliferation and restricts other cellular interactions. Fereshteh et al. had studied the effect of coating type and controlled drug release of PCL/Zein coated 45S5

bioactive glass scaffold for bone regeneration [77]. The release rate of absorbed TCH (tetracycline hydrochloride) from the PCL/Zein coated scaffold was released in a sustained manner.

McNeil et al. had prepared a poly (ϵ -caprolactone) fibers using gravity spinning techniques, in which the collagen was either incorporated or coated onto the as-spun fiber as a potential delivery system to support bone regeneration [78]. The entrapped collagen enhanced cell proliferation compared to the coated fibers. Chang et al. had reported an oxalate-connected oligocaprolactone multiblock co-polymer (PCL-OX) microspheres as a fast-degradable PCL for drug delivery. The PCL-OX microspheres loaded paclitaxel and PLGA microspheres showed that the paclitaxel release was slower rate from the PCL-OX microsphere than from the PLGA microsphere [79]. Similarly, Palamà et al. had designed a microporous PCL scaffold incorporated with dexamethasone (DXM) for reparation of resected osteosarcoma defect. In vitro sustained drug release of anti-inflammatory (DXM) was higher in acidic medium and slower release at pH 7.4 [80]. Recently, Li et al. had fabricated and characterized a hybrid 3D-printed aspirin-laden liposomes composite scaffold (PCL-Asp @ Lipo) using film dispersion method for bone tissue regeneration [81]. The cumulative aspirin-laden liposomes release profile followed a sustained release rate that could endow the promotion of cell-based tissue growth. Considering the success of the therapeutic molecule delivery system of PCL-based biomaterials is still limited because of low encapsulation efficiency and low bioactivity.

Polyethylene glycol (PEG)-based drug carriers

Polyethylene glycol (PEG), often also called polyoxyethylene (POE), is a linear or branched synthetic polyether (or an oligomer) with the major characteristic of biocompatibility, hydrophilicity, non-immunogenicity, easy processability and it has been reviewed by Wang et al. [82]. It has numerous applications including drug/gene/cell delivery, tissue engineering scaffolds, and utilized in medical devices and implants. Of late, Leila Moradkhannejhad et al. studied the effect of molecular weight (6000, 3350, 1500, 600, 400) of PEG on in vitro drug release of electrospun curcumin loaded PLA-PEG nanofibers. The as-released amount of CUR from the sample without PEG showed a minimum release value, while the value increased systematically with the increase of PEG content [83]. This is because PEG with low molecular weight are most hydrophilic that allows the nanofiber to release more drug content. A PEG-silk hydrogel combining with polymeric particles (PLA/PLGA) loaded rhBMP-2 composites were evaluated by Rezaei et al. for modulating osteoinductive property. PEG reinforced the silk gel network that accomplished the local release of BMP-2 with an increase in the retention time [84].

Kavas et al. had studied a raloxifene-/raloxifene-poly (ethylene glycol) conjugate-loaded microspheres prepared with PCL or with the blend of PCL and PLGA for drug delivery to bone-forming cells. Ral released from Ral-PEG loaded PCL:PLGA (1:1) microspheres showed a higher release rate than observed from Ral loaded PCL, PCL:PLGA microspheres and Ral-PEG loaded PCL microspheres [85]. Leite et al. had developed two nanoparticle drug delivery systems based on monomethoxy Polyethylene glycol-poly (trimethylene carbonate) (PEG-PTMC) and poly

(lactide-*co*-glycolide) as hydrophobic drug (dexamethasone) carriers to modulate osteoblastic activity. Because of the PEG hydrophilicity, the release of DEX was higher amount compared to PLGA in a controlled manner [86]. Hong zhang Deng et al. proposed a review on injectable thermosensitive nanoparticles assembled with an amphiphilic polymer of PEG/PCL-based targeted and sustained released system [87]. Due to the presence of the hydrophilic nature of the polymers, the hydrogel matrices showed better drug release kinetic profile via diffusion.

Polyvinyl alcohol (PVA)-based drug carriers

Polyvinyl alcohol (PVA or PVOH) is a linear synthetic vinyl polymer derived from polyvinyl acetate, having biocompatibility, hydrophilicity, and strong cohesiveness. The solubility of PVA depends on the degree of hydrolysis, i.e., low degree shows high solubility and vice versa. Interestingly, the presence of strong inter- and intra-hydrogen bonding of –OH group makes the PVA completely dissolves in water (above 70 °C). This particular bonding in PVA increases the hydrophilicity, biodegradability, swelling, blending nature, and biological property, which has been reviewed by Tran et al. [88]. On owing these properties, PVA-based biomaterials have been used in cartilage replacement/transplantation and drug carrier systems. Jensen et al. [89] had developed a spontaneous eroding physical hydrogel based on PVA by the non-cryogenic method under physiological condition. The hydrogel was subjected to multi-triangle characterization for the effect of the inflammatory response (macrophages), antiproliferation activity (myoblasts), cell proliferation (endothelial cells), and delivery of cytotoxic drugs (liposomes and growth factors).

Taoyu wan et al. had prepared a PVA/PCL and PVA/HAP (PEG)-based nanocomposite membrane by freeze/thawing process and investigated a new drug delivery of cefuroxime sodium in the context of bone infections [90]. This membrane achieved the prolonged controlled and effective release of cefuroxime sodium. He concluded that due to the molecular weight discrimination of PVA, HAP-based system released complete elution and PCL-based system showed steady release of the drug. Kaleem Ullah et al. had fabricated a cross-linked carboxymethyl chitosan (CMCh)- PVA hydrogel by the free radical polymerization for delivering an anticancer drug [91]. Oxaliplatin (OXP) release behavior of the cross-linked hydrogel was precisely shown controlled release system. Yong Hou et al. had developed an injectable degradable PVA microgel loaded with hMSCs (a regenerative medicine) and growth factors by using high-throughput (HT) microfluidic technology [92]. This microgel showed the long-term sustained release of BMP-2 to promote osteogenic differentiation of mesenchymal stem cells.

Ceramic as an active drug carrier

Calcium phosphate (CaP), a family of calcium salt of phosphoric acid is the main biocompatible inorganic component of bone minerals. On owing to their composition of calcium and phosphate, it has been utilized as an ideal bone graft substitute material/scaffold. In this regard, CaP ceramics cover a wide

range of components such as monocalcium phosphate (MCP, $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$, $\text{Ca}/\text{P}=0.5$), α -tricalcium phosphate (α -TCP, α - $\text{Ca}_3(\text{PO}_4)_2$, $\text{Ca}/\text{P}=1.5$), β -tricalcium phosphate (β -TCP, β - $\text{Ca}_3(\text{PO}_4)_2$, $\text{Ca}/\text{P}=1.5$), hydroxyapatite (HAP, $\text{Ca}_{10}(\text{PO}_4)_6 \cdot (\text{OH})_2$, $\text{Ca}/\text{P}=1.667$ which has been mentioned by Xavier et al. [93], and biphasic calcium phosphate (BCP) has reviewed recently by Salimi et al. [94]. These calcium phosphates are varying in different forms such as powders, granules, blocks, ceramics, cements, and coatings which depend on their selectivity toward bone defects. Ionic exchange of calcium and phosphorus ions into the surface of the tissues regulates the vesicular transport that activates the osteoblast/osteoclast for bone mineralization. In recent years, several studies have been actively carried out using a polymeric matrix with the incorporation of ceramic particles with encapsulation of therapeutic agents (TA) for its osteoconductive and osteoinductive features.

- (i) *HAP-based composite as drug carriers* Zhongchao Yi et al. had prepared a porous HAP fiber using an electrospun technique by facile ion-exchange approach as drug delivery carriers [95]. He proposed that because of the hollow structure the fabricated fiber supported the cumulative release of the BSA (bovine serum albumin) protein in a controlled manner. Priyadharshini et al. had synthesized multi-ion co substituted HAP (Ce/Si-HAP) nanopowders for bone regeneration [96]. The combinations of Ce^{4+} and Si^{4+} co-doped HAP powder showed excellent metabolic activity toward MG63 cells and resistance against bone-related microbial organisms.

Sudip Mondal et al. had fabricated a novel multifunctional nanostructured hollow carbon template coated HAP to enhance the drug delivery profile, where DOX-loaded HAP (HAP-DOX) and H-HAP-DOX were prepared by a facile adsorption method [97]. The drug and BSA protein release kinetics (Higuchi model) of the synthesized nanostructure material enhanced the drug delivery system (sustained manner) compared to conventional HAP. Nimmy Mohan et al. had used a novel surfactant free hydrothermal method for preparing a porous HAP scaffold from a ‘coral-like’ synthetic inorganic precursor for bone substitute applications and as drug vehicles [98]. The prepared gentamicin loaded HAP microbeads showed a promising drug carrier activity and hence could be used for treating osteomyelitis.

Dual functions and adsorption behavior of DOX (doxorubicin) in the hollow HAP microspheres and HAP nanoparticles were investigated by Qing Zhao et al. [99]. According to his observation, both drugs loaded HAP materials exhibited low loading efficiency when compared to nanoparticles, hollow microspheres showed better-sustained release of DOX. Moreover, Ram Prasad Sekar et al. had investigated HAP-PVA core-shell nanoparticles for dual delivery of methotrexate (MTX) and gemcitabine (GEM) [100]. The reason behind this study was to improve the structural integrity and polymer-NPs interactions. A ceramic core and polymeric nanoparticle system showed the GEM release followed by the release of MTX in a sequential fashion for sustained delivery of anticancer drugs to treat the bone disease.

- (ii) *β -TCP-based composite as a drug carrier* Gokhale et al. had prepared the β -TCP microsphere via a solid-in-oil-in-water (S/O/W) emulsion method to facilitate the tendon-to-bone-repair process [100]. Henceforth, further research is necessary to refine the accelerated effect of recombinant hBMP-2 delivery in a rabbit model.

A porous multifunctional β -TCP based gelatin with zoledronic acid (ZA) loaded scaffold was investigated by Mehdi Rahmania et al. [101]. From his findings, due to the agglomeration of the drug with a scaffold matrix, the releasing efficacy of ZA could increase cell proliferation. Besides, the incorporated higher concentration of β -TCP increases the amount of ZA release.

Bastami, Farshid et al. had designed a highly porous three-dimensional β -TCP/gelatin with chitosan-based nanoparticle via foam casting technique [102]. The sustained release of BMP-2 on the porous scaffold was achieved by using an enzyme-linked immunosorbent assay (ELISA).

- (iii) *Octacalcium phosphate (OCP) and Biphasic calcium phosphate (BCP)-based composite as a drug carrier* Ito Natsuko et al. had prepared a spherical octacalcium phosphate (OCP)/HAP porous granule in which the methotrexate was loaded [103]. He achieved a spherical OCP by treating the spherical β -TCP granules in a buffer solution and his study implied that human osteosarcoma (HOS) cells were proliferated only by the release of methotrexate (MTX).

Lee et al. had reported a novel porous scaffold of calcium phosphate cement (CPC) incorporated alginate for drug delivery and bone tissue engineering. His pilot study is to prove the CPC-alginate scaffold as a desired candidate for drug release [104]. Seong et al. had reported a porous biphasic calcium phosphate (BCP)/Collagen microsphere by using a water-in-oil-emulsion technique followed by dip coating. The drug release system was estimated by the incorporation of human bone morphogenic protein (hBMP-2) to improve the osseointegration potential of the scaffolds [105].

Based on the above discussion, Ceramic particles/microbeads with superior biocompatibility showed two major advantage in bone DDS. First, the degradation of Ca/P ions will not create adverse effect, meanwhile accumulate by-products in the targeted site. Secondly, the inorganic ceramic particles may trigger an immunogenic tissue response by electrostatically binds with bioactive molecules such as RNA and DNA. In addition, ceramic coated orthopedic implants often resulted in gradual release of metallic ions and hence leads to adverse effect to the patients. In the case of ceramic-based 3D scaffolds, it showed high surface area and porosity for better cell adhesion, cell proliferation and transfers nutrients/drug to the detected site.

Bioactive glasses as a drug carrier for bone regeneration

Bioactive glasses (BGs), a series of non-crystalline solids composed of silicon dioxide (or silicate) network which is modified by the incorporation of sodium dioxide (Na_2O), calcium oxide (CaO), and phosphorous (P_2O_5). Since the development of 45S5 bioglass by Hench et al. [106], it has been received greater attention due to

its high bioactivity, biocompatibility, stimulation of gene expression, osteoconductive capacity, antibacterial property and avoid brittleness. Bioglass glasses form a biomimetic surface layer of calcium hydroxy-carbonate apatite (HCA) or crystalline phase HAP when exposed to body-fluid via nucleation and has been reported by Vijayalakshmi et al. [107]. Bioactive materials are another choice of excellent candidate in two main applications namely (i) BTE scaffolds to repair or regenerate tissue (ii) de Mesoporous particles (micro to nano) such as ball-shaped, rod-shaped, sheet-shaped and hollow-shaped are synthesized using different methods such as sol–gel, hydrothermal, microwave, precipitation method, room temperature method and non-aqueous method. Mesoporous silica particles are synthesized through sol–gel technique using supramolecular surfactant as a template or surface-directing agent (e.g., cetyltrimethylammonium bromide (CTAB) and tetraethoxysilane (TEOS, silica source) in alkaline medium). The reaction medium undergoes nucleation of TEOS, hydrolysis, co-condensation of negatively charged silanes (Si–O⁻) and positively charged $-N+(CH_3)_3$ micellar packings through electrostatic molecular interactions to form a highly ordered microscopical silica architecture [108]. MCM-41 (mobil crystalline material, 2D hexagonal phase) was first synthesized in 1990s using anionic surfactant as a template, later 3D cubic phase MCM-48, lamellar MCM-50, Santa Barbara Amorphous (SBA-1, SBA-15, SBA-16) was synthesized. Its controllable particle size (7–300 nm), pore size distribution (2–30 nm), large surface area ($> 700\text{m}^2/\text{g}$), pore volume ($> 1\text{cm}^3/\text{g}$) and abundant active silanol groups. MSNs seems biocompatible, supports cell proliferation but unfortunately low mechanical strength. Besides, more silanol groups in the external surface of porous silica combines with organic moieties (e.g., proteins/peptides and growth factors) to form strong chemical bonds that enhance osteoinductive signals, induce biomineralization, drug delivery and cellular level functions [109, 110]. Due to its tunable pore size and larger surface area, mesoporous silica is being used to enhance cellular internalization, drug delivery vectors including multiple drugs, biomolecules (proteins and genes) and mass delivery of therapeutic drugs (hydrophilic or hydrophobic drugs) liver protein/biomolecules for therapeutic effects.

Yudong Wang et al. had prepared a hollow mesoporous bioglass (HMBG) nanoparticles, it possessed stable drug release behavior that could modulate bone tissue regeneration [111]. A co-delivery approach of therapeutic molecules such as Sr ions and drug incorporated mesoporous bioglass nanoparticle (MBN) was investigated by Jung-Hwan Lee et al. for hard tissue regeneration [112]. The cumulative release of ions (Si, Ca, and Sr ions) from the nanoparticles (Sr-MBN) and phenamil which active BMP-2 smad signaling pathways. Thus, Sr ion from Sr-MBN showed a significant effect on osteo/odontogenesis of MSCs, whereas phenamil drug release could stimulate MSCs cells. Wei Li et al. had prepared a PHBV (poly(3-hydroxybutyrate-co-3-hydroxyvalerate)) coated on highly porous 45S5 bioglass ($\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5$)-based glass–ceramic scaffolds with a drug (vancomycin) [113]. He relieved that the encapsulated drug in an uncoated scaffold was released in a sustained manner as compared to an uncoated scaffold. This hypothesis may be due to the hydrophilic drug not efficiently encapsulated inside the hydrophobic surface of the coated polymer (i.e., poor diffusion).

He Xu et al. had used icariin loaded-hollow structural bioglass/chitosan (ICA/HBG/CS) hybrid scaffolds to enhanced osteogenic related protein/gene expression. Because of the hydrogen-bonding interactions between the scaffold and drug molecule, the drug was released in a controlled manner [114]. As similar to the previous study, Yang et al. had developed an ophiopogonin (quasi-NGF activator) loaded bioglass–collagen–phosphatidylserine scaffolds (BG–COL–PS) by using chemical-cross-linking followed by the freeze-drying method [115]. The reason behind the incorporation of ophiopogonin drug was to stimulate the neonatal nerves which could further regulate the bone functions/bone healings. Franceson Baino et al. had attempted a multifunction system of mesoporous bioactive glass membrane containing $\text{SiO}_2\text{--P}_2\text{O}_5\text{--CaO}$ (ternary system) and pluronic copolymers (P123) [116]. The as-released ibuprofen showed similar kinetics that was observed from pure silica mesophase in a controlled manner.

Metallic implant coated drug delivery system

Metal and its alloy as biomaterials have been used in different forms (ions, screw, plate, film forms) and its coating forms also play a major role in orthopedic repairing applications. Unfortunately, traditional drug treatments fail due to the poor effect and economically unfavorable condition. Therefore, greater efforts have been employed to coat a metallic surface using various techniques such as dip coating, electrospun coating, spin coating, and electrophoretic deposition. The concept of employing drug-eluting on the metallic surface serves a biological role in the course of bone healing and enhances bony integration behavior.

Drug/therapeutic agent coatings require a polymeric phase for well dispersion and diffusion via degradation whereas ceramic coating provides a porous environment for eluding drug molecules (Fig. 5). In detail, the permanent metallic implant (stainless steel, titanium and its alloys, magnesium alloy) with drug embedded polymer/ceramic composite coating could regulate the biological metabolism of bone-related cells thereby promotes the bone regeneration process on the surface of the implant by Bagherifard et al. [117]. On the other hand, implant-related infections (IRIs) are still remains failure of orthopedic implants often caused by microorganisms which can lead to serious revision procedure with prolong hospitalization and the need for secondary surgery. Antibacterial agents can prevent the surface infection during surgery, this drives an idea for researchers to coat the antibacterial drug on the metallic substrate.

Dexamethasone loaded graphene-oxide-coated titanate on titanium foils were prepared by Na Ren et al. [118], the sustained release of DEX on coated Ti foils could promote the osteogenic differentiation and proliferation to rat bone mesenchymal stem cells (rBMSCs). Jiabing Ran et al. had designed a silk fibroin-dexamethasone@zeolitic imidazolate on a titanium implant framework in bone implants. The sustained release of DEX from the SF-DEX@ZIP on the surface of the Ti implant could support calcium deposition and osteogenic differentiation of adherent cells [119]. Chul Ho Jang et al. had developed a BMP-2 loaded collagen/HAP coated on titanium implant screw to accelerate osteointegration.

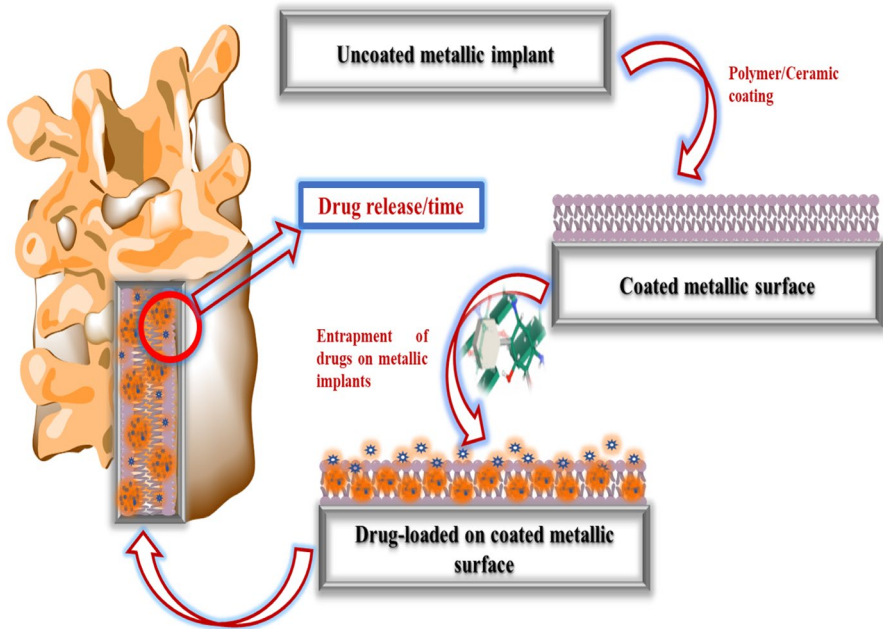


Fig. 5 Schematic representation of Metallic implant-based drug delivery system

The release of BMP-2 from implant surface improved cell proliferation and peri-implant osteogenic activities [120]. Guoyuan Li et al. had studied a dual modulation of bone formation and resorption with zoledronic acid-loaded PLA/brushite coated on magnesium alloy implants to improve osteoporotic fracture healing. The release of ZA from the coated implant showed a controlled manner which could increase bone regeneration rate [121].

Kiran et al. studied a rifampicin/HAP loaded PCL electrospun nanofibers coated on titanium for implant-related infections. The as-released antibiotic drug showed initial burst release followed by a sustained release on PCL/HAP/Rf coated implant to enhance an antibacterial property [122]. Maohau Chen et al. had designed a biofunctional multilayered molecular reservoir using β -cyclodextrin (β -CD) grafted onto chitosan loaded with calcitriol (VD3) on Ti6Al7Nb substrate to promote osseointegration property in osteoporotic conditions. In vitro sustained drug release of VD3 showed a burst release manner to modulate bone-related cells and could also heal the damaged tissue [123]. Coating on metallic implant are becoming tedious for sorting bone infections to improve bone regeneration along with the modification of the surroundings for achieving bioresorbable material and more potential drug eluting system. An antibiotic/therapeutic drug coated on an orthopedic implant offers a controllable initial burst release followed by a slow continuous release for long-term applications. As said before, the phenomenal concept on the scaffolding technique where the drug molecules form a covalent attachment with polymer/ceramic phase by creating osteogenic integration.

Three-dimensional printing (3D technology) for bone targeting drug delivery

Three-dimensional printing (3DP) or additive manufacturing (AM) or rapid prototyping (RP) is a unique technology of digital fabrication process wherein drug loading and controlled release can be attained. Among other methods, 3D printing has been a growing interest due to the ability to design a porous interconnected network with a flexible structure and controlled porosity. Bio-printed scaffolds are widely used for customized medical treatments for bone fractures/defects. The additive manufacturing technology with computer-aided design (CAD) comprises vat polymerization, powder bed fusion, binder jetting, and material extrusion technologies. Additionally, the drug molecules added flavor to the three-dimensional scaffold as a drug delivery vehicle for biomedical research and tissue engineering (Fig. 6). The three-dimensional structure provides a suitable microenvironment for cell proliferation and is a bridging architecture in tissue engineering. Hence delivers pharmaceutical active ingredient (API) at the site of action that includes proteins, growth factors, therapeutic agents, and biological nutrients.

Bioprinting technology follows inject printing, laser-assisted printing such as selective laser sintering (SSL, a powder-based pattern) and stereolithography (SLA, a solid-based pattern), and extrusion printing such as fused deposition modeling (FDM, a liquid-based pattern). SLS method is the heating process of powder particles to glass transition temperature using CO₂ laser beam for sintering the particles, where the particles directly form a solid model (i.e., fabrication of direct metallic implant). SLA is the first commercially used RP technique that uses the ultraviolet

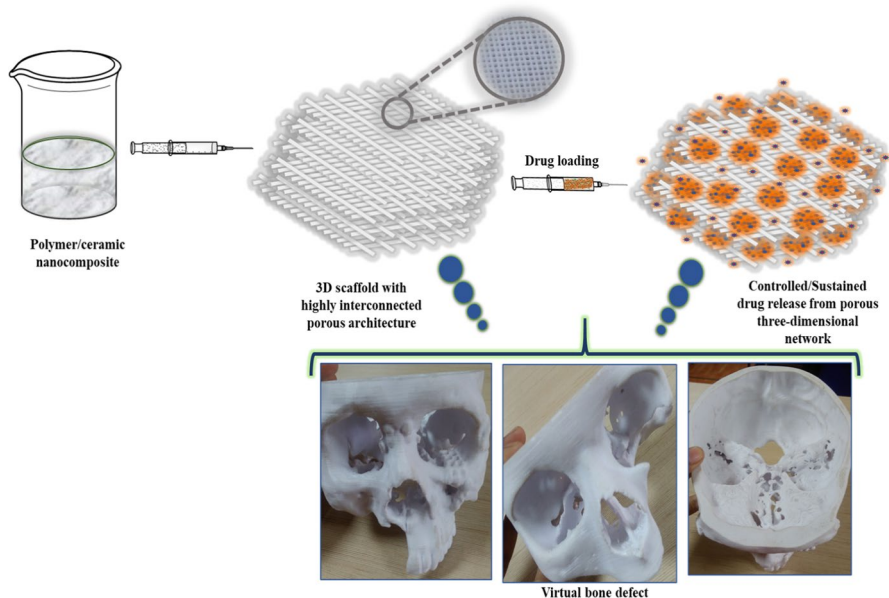


Fig. 6 Application of three-dimensional technology in drug delivery system

laser beam as light sources to irradiate to fabricate layer by layer solid models. FDM is the simple process based on extruding fused material onto the x - y - z platform via a computer-controlling nozzle to fabricate mesh-like porous scaffolds. Aerosol jet printing is one such type of fabricating layer by layer 3D structure scaffold using aerosol stream by atomization of composite suspension (polymer/ceramic/metal nanoparticles).

Alaitz Etxabide et al. used three-dimensional (3D) technology to fabricate lactose-cross-linked gelatin-based scaffolds further loaded with dexamethasone sodium phosphate (DSP) for targeted drug delivery system [124]. Pariksha et al. designed a 3D bio-printed pseudo-bone drug delivery scaffold comprised of polypropylene fumarate (PPF), polyethylene glycol-polycaprolactone (PEG-PCL-PEG) and pluronic (PF127) scaffold loaded with simvastatin [125]. This computer-aided (CAD) designed scaffold showed a sustained release manner which could further promote the butterfly fractured bone damage/bone healing. Zhu et al. designed a drug delivery model using 3D technology to fabricate a growth factor embedded in gelatin/platelets-based scaffolds. The as-released growth factor from a three-dimensional matrix showed a massive sustained-release on the gelatin-based scaffold when compared to platelets scaffolds [126].

On owing to the geometrical characteristics (i.e., depending on the lattice structure) and mechanical performance, 3D printing technology utilized Triply Periodic Minimal Structure (TPMS). TPMS is an emerging class of structure-based scaffolds/model in the ease of geometry manipulation (i.e., designed macro porous structure), which has superior mechanical properties and random porous architecture that mimic bone internal structure. Though, alloplastic graft provides a long-term structural support, nevertheless, it should also support new tissue growth such as cellular proliferation, migration and proliferation after implantation. This designed graft can be modulated by nano to macroscale intricate architecture (also considered as biomorphic) based on six TPMS that includes Gyroids, Diamonds, Neovius, Face-centered cubic rhombic dodecahedron (FRD), I-graph-wrapped package (IWP) and Primitives. Riccardo Salaa et al. had proposed the insights of parameters and characterization of thermoplastic polyurethane (TPU) on TPMS models to mimic the honeycomb lattices in biomedicine and tissue engineering. The study portrays the effectiveness of the printing parameter of hybrid structures which could explore in pharmaceutical applications for controlled drug delivery systems [127]. These findings could support the proliferation of pre-osteoblast cells. Though the three-dimensional technique has opened a new door for long-term regeneration of anatomic structure and drug delivery, it is still under developing stage in clinical applications.

Anti-infection strategies for bone infections and regeneration

The one celled bacterium encased by peptidoglycan or murein composed of mesh-like peptide-linked β -(1-4)-*N*-acetyl hexosamine layer and classified as gram-positive and gram-negative bacteria, respectively. About 20–80 nm thickness of peptidoglycan plasma layer depicted to gram positive bacteria (contains many layers) whereas 7–8 nm thickness of lipopolysaccharides layer depicted to gram-negative

bacteria. Such bacteria can detrimentally affect skeletal growth and bone loss at infected site after implantation leads to osteomyelitis (also referred as bone infection) or dysregulation [128]. Osteomyelitis are serious complications in orthopedic trauma-related surgery, caused by bacterial colonization surrounded at bone tissue and its marrow. Though modern scaffolds have enriched in their design, adhesion of bacterial colonies on the implanted area can cause severe infections and collapse the propagation of bone growth as mentioned above. This may lead to urgent surgery or replacement of implant or scaffold. Controversially, anti-infection strategies can reduce the infectious defect near targeted site and improves bone regeneration by regulation osteoblast formation and osteoclast resorption.

In detail, anti-infection strategies involve antibiotic-mediated cell death which may triggered by electrostatic interactions between drug molecules and negatively charged bacterial site. Antibiotic therapies help in bacterial inhibition that can destruct the cell wall of bacterium or block reproduction of bacterial growth by destroying DNA. Antibiotic drug interacts with ribosomes and DNA gyrase stimulate an oxidative environment to inhibit cell wall synthesis of bacteria. Hence, bactericidal antibiotic can exclusively increase the efficacy of biomaterials in bone tissue regeneration. Many anti-infection strategies are employed to eradicate bacterial adhesion and to facilitate bone growth via releasing antibiotics from the matrices. Indeed, the release of antibacterial agents/drugs from scaffold matrix/ coated implant materials can promote cellular functionalities and improves osteoconduction.

The drug delivery system offers an active device that allows the prolonged release of antibiotic molecules to treat persistent pathogenic diseases. The integration of antibiotics into the 3D polymeric matrix (scaffold)/coated implant passes through the spectrum of colonized microorganisms at the targeted site has more advantages to prevent any infections rather than injecting or oral consumptions by Rotman et al. [129]. Table 1 illustrates the literature appraisal of an antibiotic integrated composite-based system to overcome bone pathological infections caused by gram-positive and gram-negative bacteria for regeneration applications. Indeed, antibiotic drug delivery system (ADDS) that includes gentamicin, ciprofloxacin, vancomycin, levofloxacin, and amoxicillin are currently used to combat bone related infections and also has an osteoinductive property that exploits new bone formation (Fig. 7).

Recent strategies of dual drug delivery system (DDDS)

Natural bone regeneration phenomena involve a complex physiological process driven by multiple biological factors that include inflammation and cellular activities of bony callus. Typically, designing/functionalizing bone scaffolds with multiple growth factors, therapeutic drugs, bioactive signaling molecules, and bone-related cells can mimic the natural microenvironment for bone tissue formation. However, the efficacy of drug molecules, short half-life periods of growth factors, slow penetration, and insufficient vascularization of bioactive molecules may cause unsuccessful regeneration or ectopic bone formation. Kim et al. had reviewed the utilization of dual drug delivery with appropriate kinetics has more potential toward osteogenic differentiation than a single use of biomolecules drug delivery system [159].

Table 1 Illustration of the literature appraisal of an antibiotic integrated composite-based system

Author name (year)	Antibiotics names	Drug embedded composite	Explanation	Bacteria	Application	References
Puga et al. (2012)	Ciprofloxacin	PCL/Poloxamine	Sustained-release showed < 50% efficiency against bacterial growth	<i>S. aureus</i>	Bone infections and bone regeneration	[130]
Balmayor et al. (2012)	Gentamicin	Starch-conjugated chitosan microparticles	A long-term sustained release showed that the increased in the concentration of gentamicin (from 50 to 150 mg/ml) led to a decrease in the encapsulation efficiency profile (from 67–55%)	<i>S. aureus</i>	Bone infection	[131]
Zongping Xie et al. (2013)	Gentamicin	Borate bioactive glass pellets	The study showed the eradication of bacterial infections was about 81.82	<i>E. coli</i>	Osteomyelitis and bone regeneration	[132]
Lian Xiaojie et al. (2013)	Vancomycin	Nano HAP/collagen/PLA scaffold	The release of antibiotic showed long-term sustained release from composite and also reported that vancomycin was safe in rabbit marrow stromal cells	<i>S. aureus</i>	Bone-defect related infections	[133]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded composite	Explanation	Bacteria	Application	References
Lucja Rumian et al. (2016)	Gentamicin	TiO ₂ /PLGA microparticles	A sustained release was observed after 10 days which was then about 90% in 50 days (decsive period) and low concentrated cross-linked sodium alginate was effective	<i>Staphylococcus. spp</i>	Perioperative bone infection	[134]
Mantripragada et al. (2016)	Vancomycin and Cefazolin	Chitosan/Tripolyphosphate microparticles	The minimum concentration (21.5 µg/ml) of cefazolin might enhance the osteoblast proliferation and showed about ~ 85% inhibition whereas vancomycin at 30 µg/ml showed ~ 80% inhibition against bacterial growth	<i>S. epidermidis</i>	Osteoarticular infections	[135]
Li Haibin et al. (2016)	Vancomycin	Strontium/HAp incorporated alginate composite	Incorporation of SrHAp into alginate microsphere increased the sustained release of composite microsphere	–	Bone regeneration	[136]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded com- posite	Explanation	Bacteria	Application	References
Butini Maria Eugenia et al. (2017)	Gentamicin	Biphasic gentamicin loaded beads/HAp	A sustained release of high gentamicin concentration showed prolonged exposure on bacteria that facilitates a local immunity and new bone formation	<i>S. agalactiae</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. faecalis</i> , <i>E. coli</i>	Bone and implant infections and bone regeneration	[137]
Dorati Rossellia et al. (2017)	Gentamicin	Chitosan thermosetting hydrogel	The higher concentration of gentamicin was achieved in short time release (4 h)	<i>E. coli</i>	Anti-osteomyelitis	[138]
Pierchala Malgorzata Karolina et al. (2017)	Gentamicin	PLGA/Halloysite porous membrane	The study showed that about 90% of release in set 2S which was higher than layer 2S and lower than layer 1S and 3S	<i>S. aureus</i> , <i>E. coli</i>	Bone regeneration	[139]
Magda Ferreira et al. (2017)	Levofloxacin	PMMA/lactose	The study reported that the release of the antibiotic from bone cement matrices that could penetrate the osteoblast cell membrane and highly effective against intracellular of <i>S. aureus</i> strains	<i>S. aureus</i>	Bone infections	[140]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded composite	Explanation	Bacteria	Application	References
Somruethai et al. (2017)	Gentamicin	Oligolactide hydrogel	The prolonged-release at the level higher than the minimum inhibitory concentration of bacteria for 2 weeks	<i>S. aureus</i> , <i>E. coli</i>	Bone infection and bone scaffolding applications	[141]
Budiatin et al. (2021)	Gentamicin	Bovine hydroxyapatite-gelatin based scaffold	The VEGF with gentamicin in the scaffold resulted in intact effect and stimulated osteogenic ability. The in vivo studies on BHA-GEL-GEN implanted scaffold proved the acceleration of bone tissue vascularization which could treat osteomyelitis and bone infections	–	Bone regeneration and bone infection	[142]
Lin Du et al. (2017)	Vancomycin	PLGA microsphere/scaffold	Initially, the controllable drug release rate of the scaffold showed lower than microsphere and when the temperature increases (37–42 °C), the drug release from scaffold attained cumulative jump (5%–10%)	–	Bone infection and regeneration	[143]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded composite	Explanation	Bacteria	Application	References
Weizong Weng et al. (2017)	Vancomycin	Graphene/nHAp scaffold	Due to the physico-chemical property of graphene in the 3D porous architecture of the scaffold which extended the drug release duration	<i>S. aureus</i>	Infected bone defects and bone regeneration	[144]
Nadir Laghmonche et al. (2017)	Fluoroquinolones	Study of antipseudomonal drugs	The comprehensive analysis depicted that antibiotic treatment for patients about 87% ensues in short-time therapy over 42.5 days. Initial intravenous therapy over 15 days showed less efficacy. Hence, the study suggested that the oral antibiotic therapy could be potentially effective before six months	<i>P. aeruginosa</i>	Chronic Osteomyelitis	[145]
Xiaojun Zhou et al. (2018)	Vancomycin	Mesoporous silica/gelatin scaffold	A sustained-release showed no unfavorable effects on proliferation and differentiation of BMSCs	<i>S. aureus</i>	Bone-defects related infections and bone regeneration	[146]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded composite	Explanation	Bacteria	Application	References
Ezazi et al. (2018)	Vancomycin	HAp/mesoporous silica/gelatin-poly pyrrole-based scaffold	The burst release was due to the vancomycin trapped in a gelatin matrix	–	Infected bone defects and bone regeneration	[108]
Prasana et al. (2018)	Amoxicillin	PVA/HAp/sodium alginate nanocomposite	The observed sustained release was about 30 days and showed good antibacterial activity	<i>Bacillus subtilis</i> , <i>Klebsiella pneumoniae</i>	Bone infections	[147]
Sreeja et al. (2019)	Ciprofloxacin	Phosphorylated PET fibrous coated PHEMA	The cumulative release of antibiotic showed ~60% within 120 h and facilitates self-biom mineralization leading to osteoinduction	<i>S. aureus</i> , <i>E. coli</i>	Bone specific infection and bone regeneration	[148]
Bakhsheshi et al. (2019)	Ciprofloxacin	Monticellite scaffolds	Sustained release of the drug increased the cell viability with the increase in the incubation time (24 h)	<i>S. aureus</i> , <i>E. coli</i>	Bone infections	[149]
Wang et al. (2019)	Levofloxacin	Mesoporous silica/nHAp/PU scaffold	The loaded antibiotic penetrates through the porous network of MSNs and resulted in a sustained release that could treat chronic osteomyelitis	<i>S. aureus</i> , <i>E. coli</i>	Bone defect healing and osteogenesis induction	[150]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded composite	Explanation	Bacteria	Application	References
Xiaolin Lu et al. (2019)	Gentamycin	Bovine serum albumin-manganese dioxide-ubiquitin-indocyanine green (ICG)-gentamicin (BMUIG)	A strong fluorescence signals from antibiotic/photodynamic of BMUIG showed synergistic effect for bone healing. This study depicted that combinations of low dose drugs could enhance antibacterial effect toward osteomyelitis	<i>S. aureus</i>	Osteomyelitis	[151]
Mohammad Yousef Memar et al. (2019)	Gentamycin	Gentamicin loaded CaCO ₃	The study depicted that the biocompatible gentamicin composite potential favored against osteomyelitis	<i>P. aeruginosa</i>	Chronic Osteomyelitis	[152]
Gunday et al. (2020)	Ciprofloxacin	PLGA/PCL nanoparticles	The study suggested that the use of antibiotics was safer and effective against bacterial growth	<i>S. aureus, P. aeruginosa</i>	Bacterial infections and regenerative medicine applications	[153]
Ferreire-Ermita et al. (2020)	Ciprofloxacin	HAp/Fe ₃ O ₄ nanoparticles	Ciprofloxacin used to avoid infections regarding in vivo rabbit model	–	Bone infections and bone regeneration	[154]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded composite	Explanation	Bacteria	Application	References
Shue jin et al. (2021)	Baicalin	Multifunctional baicalin-loaded coaxial nanofibers	The study proposed that the continuous release of antibacterial drug from the middle layer followed sustained release which could be beneficial to regulate cell functions and inflammatory response	–	Vascularized bone regeneration	[155]
Guliz Ak et al. (2021)	Gentamicin	Getamycin-loaded magnetic gelatin nanoparticles (GMGNPs)	The controlled drug release from the developed biocompatible GMCNPs exhibited fast recovery compared with free gentamicin for magnetically targeted osteomyelitis	<i>S. aureus</i>	Chronic Osteomyelitis	[156]
Tatiana Padrao et al. (2021)	Vancomycin	Heparinized biocomposite if Vancomycin-loaded nanohydroxyapatite/collagen granules	This biocomposite allowed sustained release of vancomycin from interconnected macroporous for 19 days, resulting in positive bacterial inhibition and bone regeneration	<i>S. aureus</i>	Chronic Osteomyelitis and bone regeneration	[157]

Table 1 (continued)

Author name (year)	Antibiotics names	Drug embedded com- posite	Explanation	Bacteria	Application	References
Surajit Misry et al. (2022)	Vancomycin hydrochloride and tobramycin sulfate	PLGA coated Bioactive glass/Calcium Sulfate-based composite cement	The designed biodegradable scaffolds followed slow prolong release via diffusion through semi-porous network to repair bone infection and combat chronic osteomyelitis	<i>S. aureus</i>	Chronic Osteomyelitis	[155]
Shixiong Zhang et al. (2022)	Vancomycin	Vancomycin loaded Oligochitosan nanoparticles with PLGA-PEG-PLGA gel	The sodium triphosphate (TPP) cross-linked scaffolds showed excellent antibacterial effect toward in vivo rat model and prolong release/ degradation of TPP enhanced osteogenic differentiation	<i>S. aureus</i>	Bone regeneration and treat Osteomyelitis	[158]

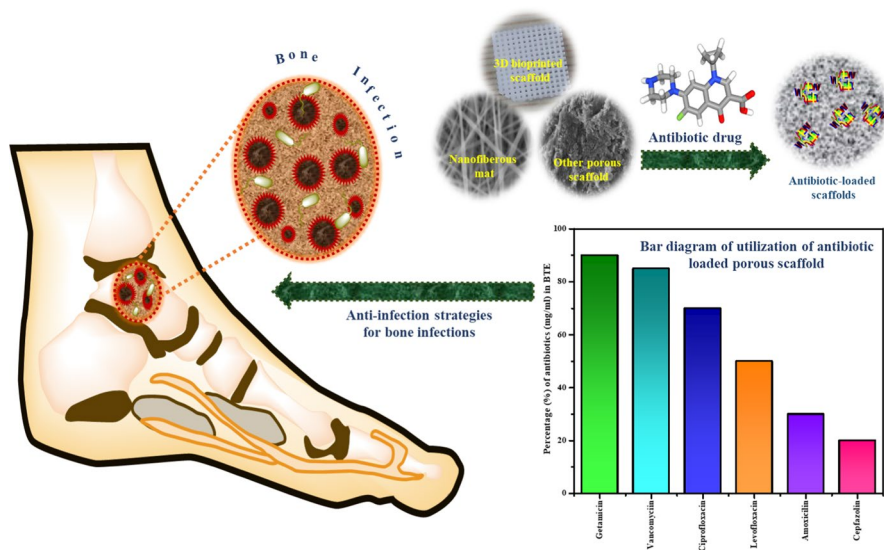


Fig. 7 Schematic of antibiotic treatment for bone-related infections

In this regard, Qingqing Yao et al. had developed a tunable novel mesoporous silica nanoparticles (MSN) incorporated 3D gelatin nanofibrous (GF) scaffold-mediated dual drug delivery of BMP-2 and deferoxamine (DFO) to activate angiogenesis by using hypoxia-inducible factor-1 alpha (HIF-1 α). Incorporation of MSN and DFO onto porous 3D GF scaffold engineered covalently mimic osteogenic micro-environment in both mouse and human stem cell models [160]. The initial release of VEGF from the outer layer followed by the sustained release of BMP-4 from the inner layer of double cryogel promoted osteogenic induction in a critical-sized cranial defect model.

Similarly, Hyeran Cho et al. had designed a coacervate (Coa, a tertiary complex of poly (ethylene arginine-laspartate diglyceride) PEAD) embedded composite hydrogels for dual delivery of stem cells and insulin-like growth factor-1 to enhance cartilage regeneration in osteochondral defects. The exogenous dual delivery of progenitor cell and therapeutic growth factors (IGF-1) from Coa has enhanced chondrogenic differentiation in the rabbit model [161]. The *in vivo* animal model proved that the chondral and subchondral layers were improved in 12 weeks via dual delivery of ADSC and IGF-1 from Coa encapsulated in gelatin-SH/PEGDA IPN hydrogels. Nopphadol Udomluck et al. had attempted a surface functionalization technique using dual growth factors (BMP-2 & FGF-2) on hydroxyapatite-coated porous gelatin nanofibers and functionalized by avidin (to facilitate binding with biotinylated growth factors for bone tissue engineering. The study anticipated that the delivery of multiple growth factors from HAP coated nanofibers were effectively increased osteogenic gene markers (RunX2, COL1 α 1, and OCN) [162].

Yoshie Arai et al. had designed a hydrophilic bile acid (Ursodeoxy cholic acid, UDCA) based on dual-functional prodrug nanocomposite for bone regeneration

through hydrogen peroxide (to regulate pro-inflammatory cytokines) scavenging and inhibits the osteogenic differentiation of mesenchymal stem cells (by suppressing their adipogenic differentiation) [163]. The rat bone defect model of the study evidenced that the collagen sponges loaded PUDCA significantly improved regeneration capacity in the epiphysis and anti-inflammatory effects. Chong Wang et al. had developed a cryogenic 3D printed β -TCP/PLA scaffold which was spatially loaded with AP (angiogenic peptide) and OP (osteogenic peptide) for improving bone regeneration via vascularization. The dual delivery of the scaffolds was mechanically similar to human cancellous bone and showed a sequential peptide release (i.e., quick release of AP and a sustained prolong the release of OP) [164].

The robust potential of dual drug delivery strategies Fig. 8 (dual drug incorporation and its functionalization of scaffold designing) can be controlled in a sustained release manner by co-delivery or sequential delivery. It was noted that successful key findings of dual delivery in both in vitro/in vivo models can maintain the temporal and spatial connections between bone and blood vessels which significantly stimulate osteogenesis and angiogenesis. Dual growth factors can also promote the endochondral and intramembranous ossification by increasing the interconnectivity of bone architecture. Further, review by Farokhi et al. [165] had described that a dual antibiotic delivery via a prolonged sustained release in the co-delivery manner of metal nanoparticles (e.g., Silver nanoparticles) can increase the antimicrobial activity of the scaffolds.

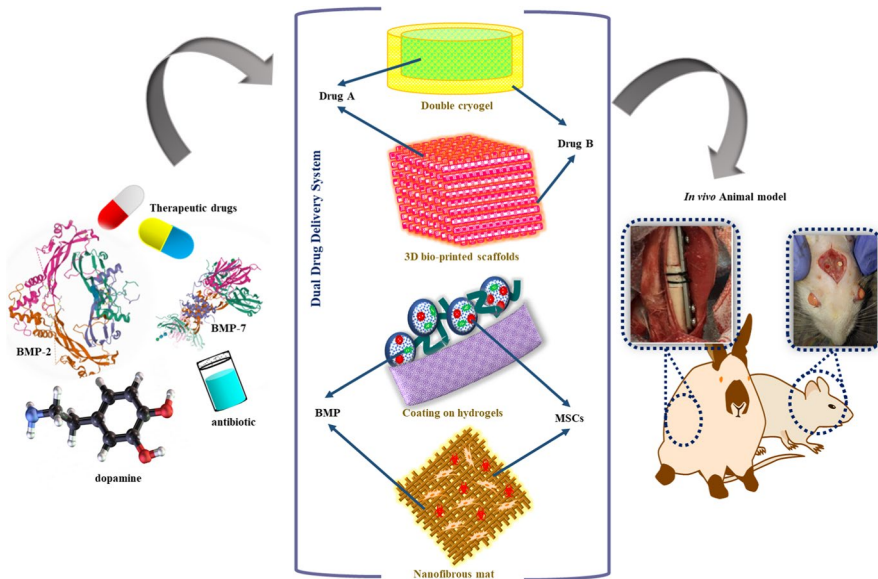


Fig. 8 Strategy and design of dual drug delivery system for bone tissue engineering

Summary and future perspectives

Despite progress in regenerative orthopedics, the innovations and development of the drug delivery system contribute to the improvement in bone healing and new bone formation. In such a condition, lack of specific targeting mode, the drug delivery may result in poor distribution, less efficiency, and undesired burst release at the site of action. Hence, it is necessary to follow a specific targeting strategy with porous architecture that allows controlled or sustained long-term release effect and in turn promotes cell proliferation, migration, and differentiation. Moreover, the drug release can be controlled by the scaffolding technique or altering the compositions of the material and also by drug integration methods. From the recent literature study, it is clear that different kind of composite shows different release efficiency that occurs via diffusion followed by degradation. Besides, drug molecules stimulate cellular adhesion to expedite osseous regeneration and minimize bacterial infections. The current research on bone targeting drug delivery has focused on incorporating dual/multidrug into the matrix for sequential/co-delivery system. Further investigation on this topic needs to deepen on using different drug integration methods such as core–shell technology and layer by layer technology, drug release kinetic studies using animal models, and to design spatiotemporal dependent drug carrier. Concurrently, synergize bactericidal effect of multi-antibiotic loaded drug delivery system can reduce osteomyelitis (i.e., infections of bone and its marrow) and endow clinical challenges. The multiple antibacterial therapy and its extensive prolong release could provide a wider coverage of bactericidal resistance in desired clinical outcomes. Though, there is limited case studies on clinical experiences, further investigation and findings on in vivo/case study are needed to prove the rationale theory on synergistic potential. Multifunctional scaffolds with therapeutic agents and its designing strategy should be highly considered to eliminate bone-implant associated infections which give route to effective bone tissue growth. Considering the above introspection, the field of dual/multi drug delivery in bone tissue engineering makes a potential zeal for bone functions, bioimaging, and bone regenerative medicine.

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