Section A-Research paper

Titanium Implants for Localized Drug Delivery: A Drug-Eluting Approach

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Abstract

Orthopedic and dental implants are commonly fabricated by titanium and its alloys. While these implants generally exhibit a high success rate, there are instances where they fail due to issues such as insufficient osseo-integration, bone resorption, and postoperative infections. In light of these challenges, localized drug delivery through implants is a promising approach. It offers advantage of delivering medications directly to the target area while managing potential side effects associated with systemic drug administration. To achieve drug release from titanium implants, surface modification techniques involving coating or adsorption have been developed. Currently, there are two main methods being employed. The first method involves modifying the implant's surface or pore structure by incorporating a drug-loaded carrier made of polymers, ceramics, or composites. This carrier acts as a reservoir for the medication and releases it gradually over time. Alternatively, drugs can be directly injected into the implant material itself. The primary focus of research in this field revolves around achieving controlled medication release and ensuring adsorbed or coated materials stability physical and mechanically. These aspects are critical to ensure the effectiveness and longevity of the drug delivery system. Recent advancements in both methods have set the stage for titanium implants development with multiple functionalities, specifically designed for targeted medication administration. In summary, titanium implants are widely used in implants, but complications can arise, leading to failure. Localized drug delivery through surface modification or direct drug injection into the implant material has gained significant attention. Ongoing research aims to enhance the control of drug release and optimize the stability of the coating or adsorbed materials. This review highlights the latest developments in these methods, contributing to the advancement of titanium implants with enhanced capabilities for targeted medication delivery.

Keywords: Polymer, Ceramic, Bulk delivery, Local drug delivery, Growth stimulants

Introduction

Several studies have presented compelling evidence pointing to a significant increase in the demand for knee arthroplasty, primary and revision hip surgeries between the years 2030 and 2035 [1, 2]. The escalating demand for hip and knee arthroplasty procedures underscores critical and pressing requirement for advancements in implant materials and treatment techniques. Scientists have extensively investigated a range of materials to tackle challenges in hard tissue applications. Notably, bio-active polymers like poly(L-lactide) (PLLA), polyglycolic acid (PGA), collagen, and chitin have garnered attention due to their potential to promote bone or tissue formation when used in biocompatible implants. These polymers have shown promising results in various studies (3-8) and offer advantages such as biodegradability, mechanical strength, and the ability to support cellular growth and regeneration. However, these materials often exhibit poor mechanical characteristics; high brittleness and low strength to fracture .In

contrast, metal-based implants, such as orthopaedic prostheses, pins, screws etc. are more commonly used in dentistry and orthopaedic applications due to their favorable mechanical and biological properties [9-14]. These metal implants possess structural qualities that are comparable to or even superior to natural tissues [15].

Among the metal-based materials, titanium based alloys stand out as most promising choices to make implants. Titanium implants offer high biocompatibility, strong resistance to corrosion, and other properties including mechanical that closely resemble human bone. The use of titanium and its alloys in implant manufacturing is particularly advantageous due to their ability to provide both mechanical stability and biological integration. The mechanical properties of titanium allow it to withstand the forces exerted on the implant during daily activities, while its biocompatibility ensures favorable interactions with the surrounding bone tissue. The corrosion resistance of titanium implants prevents degradation over time, ensuring their long-term functionality. Moreover, titanium exhibits excellent osseo-integration properties, facilitating the formation of a strong bond between the implant and the surrounding bone. The development of new implant materials and treatment methods is essential to meet the growing demand for hip and knee arthroplasty and to improve the long-term success and functionality of these implants [16].

Now days, focus has been shifted from traditional thick metal implants to the development of porous implants, which offer a unique combination of physical as well as mechanical characteristics that are essential for successful implantation. Porous implants are designed with interconnected pores and voids throughout their structure, creating a three-dimensional network that closely resembles the natural architecture of bone. This innovative design has several advantages over solid implants. One significant advantage of porous implants is their ability to facilitate bone ingrowth, which contributes to the strengthening of the implant's anchorage within the surrounding bone tissue [17].

The interconnected porosity of these implants allows bone cells, such as osteoblasts, to infiltrate and grow into the implant structure. This process, known as osseo-integration, promotes the formation of a strong and stable interface between the implant and the bone, improving the implant's longevity and functionality. Furthermore, the network of linked holes present in porous implants serves another crucial purpose by promoting cell growth and facilitating the movement of bodily fluids [18]. The porous structure provides an ideal environment for the attachment, migration, and proliferation of cells involved in bone regeneration. This cellular activity is crucial for the integration of the implant with surrounding bone tissue and supports the overall healing process. Additionally, the interconnected porosity allows for the passage of essential fluids, such as nutrients and waste products, promoting a healthy physiological environment in the implant site. To fabricate porous implants, researchers have explored various manufacturing techniques, taking into consideration factors such as the chosen material, desired pore size and distribution, and complexity of the implant design. Among the most extensively researched techniques for porous implant fabrication are solid-state foaming, additive manufacturing, powder metallurgy etc. [19]. These methods offer control over the size, shape, and pore distribution, enabling production of implants with tailored properties to meet specific clinical requirements. The shift towards porous implants signifies a significant advancement in implant technology. Their ability to support bone ingrowth and promote cellular activity makes them highly desirable for applications in orthopedic and dental fields. By mimicking the natural structure of bone and facilitating osseo-integration, porous implants offer improved implant stability, reduced risk of implant failure, and enhanced long-term outcomes for patients.

The success rate of implant insertion has significantly increased, thanks to advancements in material science and manufacturing technology, by approximately 90% [20]. However, challenges remain regarding early implant failure caused by improper bonding of bone-implant, immune responses to external materials, and bacterial infections which increase the cost of therapy, prolong hospital stays, necessitate additional procedures, and in severe cases, can lead to amputation or life-threatening sepsis. Traditionally, systemic administration of medications such as osteogenic, anti-inflammatory, analgesic, and antibacterial drugs has been employed following implantation. However, there are several drawbacks to systemic medication administration for treating implant rejection. Systemically delivered drugs must travel through the bloodstream to reach their target site [21]. Due to the limited blood supply to bone tumors, only a small fraction (1%) of the systemically injected medication reaches its intended destination [22]. Moreover, compromised drug availability at the target site necessitates higher concentrations and longer durations of drug administration, which can have detrimental effects on other tissues [23].In contrast, local drug delivery (LDD) has emerged as a prominent area of focus in the realms of orthopedics and dentistry. LDD provides distinct advantages when compared to systemic drug delivery methods in the context of implant-based therapy. Firstly, it avoids the harsh conditions of the gastrointestinal tract when delivering various types of medications [24]. Secondly, it enhances drug concentration in the bone microenvironment, reducing negative impacts on other organs and tissues. Thirdly, LDD allows for personalized care tailored to the unique needs of each patient [25]. Lastly, due to its proximity to the target area, LDD exhibits a high level of effectiveness. In recent years, there has been a notable emphasis on the utilization of titanium-based drug-eluting implants in local drug delivery (LDD) for a wide range of therapeutic applications, aiming to address post-implant complications and facilitate the healing process. These studies examine the state of the art in titanium-based drug elution implants over the past three years, highlighting their potential in LDD for managing implant-related issues and promoting successful outcomes.

Implementing medications through titanium implants for LDD

Drugs of four types have been delivered locally in titanium implants. These include chemotherapeutic treatments, growth stimulants, antibacterial pharmaceuticals, and anti-inflammatory medications.

Antimicrobial drugs

Even with meticulous maintenance of aseptic and sterile conditions during implant placement, there is still a risk of bacterial infiltration. Statistics show that approximately 2.5% of primary knee and hip implants and 20% of revision joint replacements encounter complications due to bacterial infections [26]. Bacteria can enter the body through various means, including deep tissue following fractures or open trauma, the bloodstream due to existing bacterial infections, during surgery, or via the implant surface. Bacteria on implant location can proliferate and cause challenging infections [27, 28].After implant insertion, a battle for surface space occurs between invading bacteria and bone cells. If bone cells can initially grow and multiply on the surface, it can resist the adhesion and bacteria colonization. Still, if bacteria prevail, a biofilm may form on the implant's surface, providing protection against antibiotics and potentially leading to implant rejection and infection. Bacterial species such as Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, and others have been associated with infections in titanium implants. Local drug delivery (LDD) using titanium implants has emerged as an effective approach for combating bacterial infections. LDD devices can employ contact killing or elution strategies to

combat bacteria around the implant. Moreover, these devices enable the release of potent antibiotics at concentrated levels, enabling deep penetration into bone tissue and biofilm to effectively combat bacterial infections. Studies conducted both in laboratory settings (in vitro) and living organisms (in vivo) have demonstrated the effectiveness of various antibiotics, including vancomycin, gentamicin, aminoglycosides, quinolones, and glycopeptides when administered locally through titanium implants [29].

Anti-inflammatory medications

Inflammation is a localized response of vascularized tissue that occurs following implant implantation, often as a result of infection or tissue injury. When an injury occurs, the body's defense mechanism is triggered, and inflammatory cells such as lymphocytes etc. are sent to the site of damage. These cells produce inflammatory mediators such as reactive oxygen species and prostaglandins. These molecules act as signals, attracting additional macrophages and phagocytic cells to the site to eliminate toxins, pathogens, and tissue debris, thereby creating a conducive environment for tissue repair [30, 31].. While the body's inflammatory response is essential for establishing skin homeostasis after an injury, prolonged inflammation is considered an indication that the wound may not heal properly. It is believed to impede the healing process and requires prompt attention [32]. Natural anti-inflammatory medications like curcumin and others are often used to address this issue.

Growth stimulants

Osseo-integration, which involves bone ingrowth and adhesion to titanium implants, has a vital role in implant success At the onset of osseo-integration, the process commences with the absorption of various substances such as proteins, proteoglycans, polysaccharides, and ions. These components are involved in the initial stages of creating a conducive environment for the integration of the implant with surrounding bone tissue. This leads to the movement of fibroblasts, osteoblasts, neutrophils and macrophages to establish contact between bones and implant [35]. Chemical modifications or surface treatments of implants can influence the osseo-integration process by affecting the absorption of proteins based on surface chemical composition and features [38].Growth factors such as vascular VEGF, FGF), and TGF-β play a crucial role in promoting osseo-integration and accelerating bone formation. They stimulate angiogenesis, the formation of fresh blood vessels, and the accumulation of extracellular matrix (ECM). This facilitates nutrient flow, waste removal, and the recruitment of precursor cells for tissue repair, supporting osteoblast, fibroblast, and endothelial cell proliferation [37]. The ECM also regulates various cellular processes, including protein synthesis, cell migration, and proliferation [38]. In recent years, the local drug delivery (LDD) method using titanium implants has been proposed for efficient and accelerated recovery. Various growth factors, including growth factors such as FGF, VEGF, TGF-β), systemic factors and transforming growth factors (Bone morphogenetic proteins, or BMPs), has been effectively supplied locally through implants to enhance osseo-integration [39].

Chemotherapy substances

Titanium-based implants find diverse applications, including their utilization in the restoration of bone tissue functionality following the removal of bone tumors. As part of the treatment for bone tumors, surgical excision is performed along with systemic chemotherapy or radiation therapy [40]. Due to the limited blood flow and altered bone architecture caused by tumors, a high dose of chemotherapy drugs is required to achieve an effective concentration at the target site [41].

However, such systemic administration may have negative effects on other tissues. To address this, a novel treatment approach has been proposed: a local drug delivery system utilizing titanium implants. Along with support at the site of the defect these implants also deliver chemotherapeutic or antitumor drugs such as cisplatin, curcumin, and doxorubicin directly to the targeted area at the required concentration [42, 43].

Methods used to make titanium implants that release drugs

Current advancements in medicine aim to achieve deep incorporation of the drug payload within implants to ensure effective and sustained drug delivery. This approach not only improves treatment efficacy but also enhances therapeutic outcomes. One development is techniques for modification of surface. This involves surface coating or adsorption of drugs onto implant surface. Surface coatings have been extensively researched for drug/implant combinations. Drugs can be integrated into biodegradable polymers that are coated onto the titanium implant or directly applied onto the implant surface. The latter method allows for prolonged release of the drug. The two main drug/implant combinations involve ceramic coatings loaded with drugs and polymer matrices coated metallic implants containing dispersed drugs.

The drugs enter into tissue through diffusion, erosion, and degradation mechanisms as they are liberated from the coating. However, coated implants have limitations, such as limited mechanical stability and potential for injury during insertion of the polymer coating. There is also a risk of toxicity or unintended side effects from the added agents. Ceramic coatings require high pressure and temperature for formation, leading to many drugs being delivered through surface absorption or adsorption at a later stage [44, 45].Drug release from carriers (polymer or ceramic) typically occurs in two stages: an initial burst release and a subsequent controlled release. Physically adsorbed drugs have a fast release with rapid breakdown, while chemically adsorbed drugs are tightly bonded and release slowly. Carrier-based delivery, especially in ceramics, often results in loose binding of drugs, causing a majority of the drug to be released in an early burst. However, the ability to customize a controlled release mechanism is limited. Another approach is bulk delivery, which takes advantage of the inherent antibacterial properties of implant materials such as copper, silver etc. However, drawbacks of this technique include rapid temperature loss, hydrogen release and excessive metal concentration in the tissue, which may be toxic. Porous implants created through additive manufacturing processes can serve as drug carriers, but it has been found that the pores mainly act as a container for the drug without significantly influencing its release rate.

Fabricating titanium implants with drug elution: carrier-based delivery

Researchers are actively engaged in extensive studies exploring bioactive and biocompatible materials for the LCD system based on titanium implants. These materials are potential drug carrying medium for various types of medications. The various factors affecting selection are type of drug, dosage required at the infected site, the desired discharge duration, the potential toxicity to surrounding tissues, and any impact on implant functionality. Among the commonly used drug carriers for titanium implants, polymers and ceramics are particularly popular. Figure 1 provides a schematic illustration depicting the loading site and therapeutic release from titanium implants utilizing a carrier for drug delivery.

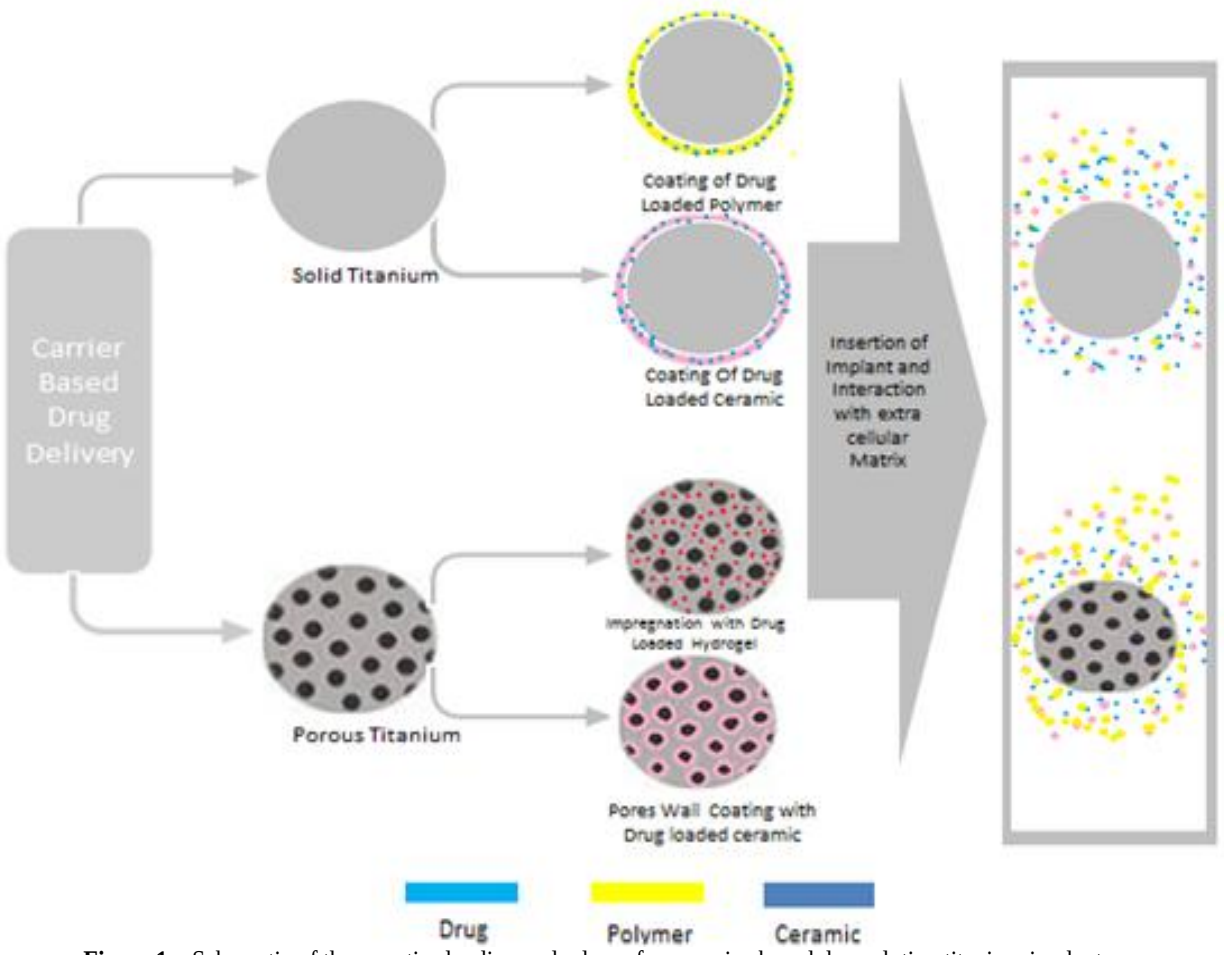

Figure 1: Schematic of therapeutics loading and release from carrier-based drug-eluting titanium implants.

Drug delivery using polymers

According to research, hydrophilic or hydrophobic are classifications of polymers based on water solubility along with biodegradable or non-biodegradable based on their susceptibility to deterioration (chemically or physically). Some commonly used biopolymers include chitosan, polycarprolactone, poly (glycolic acid), poly (D, L-lactide), poly (l-lactic acid), and polyphosphoester. Medications can be mixed with polymer melt to apply them on polymer. Alternative approaches can be employed for therapeutically sensitive drugs that undergo degradation at elevated temperatures. Drug is added into solution made by polymer and suited solvent which may form an emulsion or dissolve. The drug-loaded polymer solution is then applied to titanium-based implants. Though, it may result in less adhesive strength, which can be addressed through surface treatment procedures such as electrolytic plasma oxidation and anodization [46, 47]. Heating or Air in drying removes the solvent. Otherwise, coating of nanofiber made by electrospinning can be used for implants [48]. Various drug carrying polymers in implants allows for customization and controlled of drug release. Diffusion or erosion releases drugs from the polymer matrix when exposed to body fluid. On-biodegradable polymer matrices primarily rely on diffusion for drug release, while biodegradable matrices employ both diffusion and erosion mechanisms. Drug release can last for days to weeks depending on the content after initial burst release. By coating polymers on the titanium implant using a layer-by-layer approach facilitated by electrostatic interaction, the drug release characteristics can be tailored [49, 50]. These techniques enable the creation of defined and

uniform coatings containing drugs and control its release rate. For example, anionic poly(acrylic acid) can be coated on surface of implant followed by cationic polyelectrolytes [49]. However, such implants may exhibit an initial burst release, which can be controlled by combining beta-cyclodextrin (-CD), an amphiphilic molecule, with the layer-by-layer PAA-PLL coating [49]. Complex formation between drug molecules and CDs helps prolong the drug release. Researchers investigated the layer-by-layer assembly of strontium-doped hydroxyapatite (ceramic) and drug-loaded polymer (alginate) [51]. It's with other Local drug delivery methods showed controlled release of gentamicin (GS), with 30% released during the initial burst phase [52-56]. Additionally, responsive polymeric coatings have been explored for titanium implants that release drugs in response to external stimuli [56]. Alenezi et al. developed a clever coating called Poly(N-isopropylacrylamide) (PNIPAAm) that exhibits temperature-responsive behavior, allowing it to alternate between hydrophilic and hydrophobic states. The researchers suggested using near-infrared light as a potential stimulus. This unique characteristic offers the potential for precise control over drug release, particularly in the initial drug delivery phase.

Tissue engineering experts are intrigued by the ultrafine polymer fibers produced through electrospinning. This technique has significant potential for scalability and can generate fibers ranging from the nano to micro size using various combinations of polymers and solvents. The tissue growth is enhanced by interconnected pores fabricated by nano-fibers using electrospinning. The surface area/Volume ratio is also very high [57]. Diversity of polymer and solvent in electrospinning allows for the incorporation of numerous drugs into the polymer fibers, making them effective drug carriers. The choice of polymer, fiber porosity, and shape can all impact the release of drugs from micro or nano-fibers [57, 58]. Composite nanofibers consist of a polymer (PCL) matrix that incorporates dispersed ceramics (HA) and drugs have demonstrated controlled drug release while enhancing mechanical properties [58]. Various biopolymers and their composites, which exhibit improved hydration and physical and chemical properties, have been extensively studied. Biopolymer-based hydrogels, such as those made from fibrin, chitosan, dextran, alginate and gelatin offer additional functionalities for localized drug delivery (LDD). Synthetic polymers based cross-linked hydrogels encapsulating drugs are potential carriers in the LDD system. Encapsulated antibiotics on alginate or gelatin based [59] cross-linked hydrogel demonstrated that the release of drug is related to degree of cross-linkage. The study showed that a drug-loaded hydrogel could gradually release antibiotics, preventing bacterial biofilm formation and colonization at the site of a titanium implant. Porous titanium implant fabricated by 3D-printed and a biodegradable hydrogel loaded with an anti-tumor drug, the drug release was directly correlated with the degradation of the hydrogel. The hydrogel is composed of poly(D,L-lactide-co-glycolide)-poly(ethylene-glycol)-poly(D,L-lactide-co-glycolide). [60]. Researchers are also exploring drug-loaded polymers as a shielding layer for degradable ceramic coatings of implants [61]. These coatings not only release medication but also regulate the different ions release from the degrading ceramic layer. Titanium implants are typically coated with calcium and silicon-based ceramics (CS) to enhance osseo-integration by releasing calcium and silicon ions [62]. However, excessively high levels of these ions inside and outside cells are also harmful. The local drug delivery system demonstrated reduced NCS breakdown and antimicrobial effects. Another study [43] investigated electrochemical deposition as a method for ceramic (HA)-coated titanium samples with a composite layer composed of doxorubicin and polymer (chitosan). The electrochemical deposition method improved drug loading and release time for both substrates. The beneficial interaction between HA and chitosan, facilitated by hydrogen bonding, influenced the titanium's HA coating, enabling continuous drug

release while preventing chitosan swelling. Table 1 provides a list of titanium implants with drug-eluting polymer-based materials.

TABLE 1: Polymeric drug-eluting titanium implants.

Loading agent	Name of Drug	Technique	Key observations
Poly(lactide-*co*-glycolide) (PLGA) poly-L-lysine (PLL) and Poly(acrylic acid) (PAA)	Amoxicillin Tetracycline (antibiotic drug)	Dip-coating	Research has indicated that the polymer coating is beneficial for promoting attachment of bone cells [64].significant burst release of tetracycline within 24 hours of incubation [52].
Gold nanorods integrated Poly(*N*-isopropylacrylamide)-*co*- acrylamide (PNIPAAm-AAm).	Vancomycin (antibiotic drug)	Spin-coating	Exhibited responsive drug release triggered by near-infrared irradiation, as demonstrated in [58].
Polyacrylic acid (PAA)	Gentamicin (antibiotic drug)	The deposition process involved layer-by-layer assembly through electrostatic interactions	As reported in [52], the material demonstrated significant antibacterial activity against S. aureus and E. coli. It exhibited an initial rapid release of the substance within a 24-hour period, followed by a sustained and gradual release over the course of 11 days.
Chitosan (CH)	Doxorubicin (Dox) (chemotherapeutic drug)	Electrochemical deposition	The HA coating and drug hydrogen bonding resulted in the inhibition of chitosan swelling, as indicated in [65]. In comparison, the Dox-CH/HA coating exhibited a slower drug release rate as opposed to the Dox-CH/Ti coating.
Chitosan (CH) impregnated in HA	Gentamicin (antibiotic drug)	Vacuum Impregnation	The inclusion of the polymer improved the fracture toughness, as stated in [65]. Furthermore, the implant surface loaded with the drug provided sustained release for duration of up to 180 hours.
poly-L-lysine and Poly(acrylic acid) (PAA) along with anionic beta-cyclodextrin (β-CD)	Tetracycline (antibiotic drug)	Layer-by-layer deposition by utilization of electrostatic interactions.	The multilayer system demonstrated its drug-delivery capacity through controlled release of the drug over a span of 15 days, followed by sustained release over 30 days, as evidenced in [50].
Chitosan (CH) was synergistically combined with zinc-coated halloysite nanotubes.	Gentamicin (antibiotic drug)	Electrophoretic deposition	The release of Zn+ ions promoted cell viability, as highlighted in [66]. Furthermore, apart from gentamicin, The antibacterial effect was enhanced through the interaction of Zn+ ions and the positively charged chitosan surface, which effectively interacted with the negatively charged bacterial membrane.
A composite material consisting of hydroxyapatite (HA) reinforced with polyvinyl alcohol (PVA).	Methotrexate (MTX) (chemotherapeu-tic drug)	Electrospinning	A composite material consisting of PVA reinforced with HA was investigated in [42].
Chitosan (CH)	Cefazolin	Electrophoretic deposition	Using a voltage setting of 10 V, a coating with a uniform thickness of 4.3 µm was successfully obtained. This coating consisted of a blended

			layer of chitosan (CH) and the drug, without any noticeable distinction between the two components. On the other hand, when the voltage setting was increased to 50 V, a different coating structure emerged. In this case, a layer comprising both chitosan and the drug was formed in close proximity to the substrate, while a separate layer enriched with the drug was observed on the top surface of the coating.
PCL (poly-mer)/Hydroxyapatite (HA) (ceramics) composite and Polycaprolactone (PCL) and	Rifampicin	Electrospinning	Within a span of 32 days, 61% of the drug was released. Titanium samples coated with a Nano fibrous layer exhibited antibacterial properties without causing any harm to cells. [58]
Alginate was employed as an agent to facilitate the handling and administration of the drug. This utilization of alginate was in conjunction with layers of strontium-doped hydroxyapatite.	Gentamicin (antibiotic drug)	The layer-by-layer deposition process was facilitated through spin-assistance.	In [51], it was observed that there was an initial minor burst release lasting for 9 hours, which was followed by a continuous and slow release over a period of 13 days.

Developing titanium implants with drug eluting properties: bulk delivery

This particular type of titanium implant depends on the inherent material capability to release therapeutic substances, eliminating the need for a drug carrier. Porous titanium implants have gained significant popularity in tissue engineering due to their superior mechanical and physical properties compared to solid metal, ceramic, or polymer implants. The porous structure facilitates bone ingrowth, enhancing the implant's stability. Moreover, Implant with pore interconnectivity implant support the growth of new tissue cells and enable the movement of bodily fluids [19]. Techniques like additive manufacturing [84]. The primary objective of bulk eluting titanium implants includes utilizing the extensive the porous implant surface area to distribute medication effectively, avoiding use of additional agents such as polymers or ceramics. The loading and release of therapeutic substances from bulk eluting titanium implants are illustrated schematically in Figure 2. Recently, researchers tailored pores with amphora-shaped using laser structuring technique on titanium implants surface [56]. The study demonstrated that these structured pores facilitate capillary action allowing drug loading by immersion directly. This technology offers the potential to directly load a sterile implant during surgery, tailored to the specific requirements of each patient.

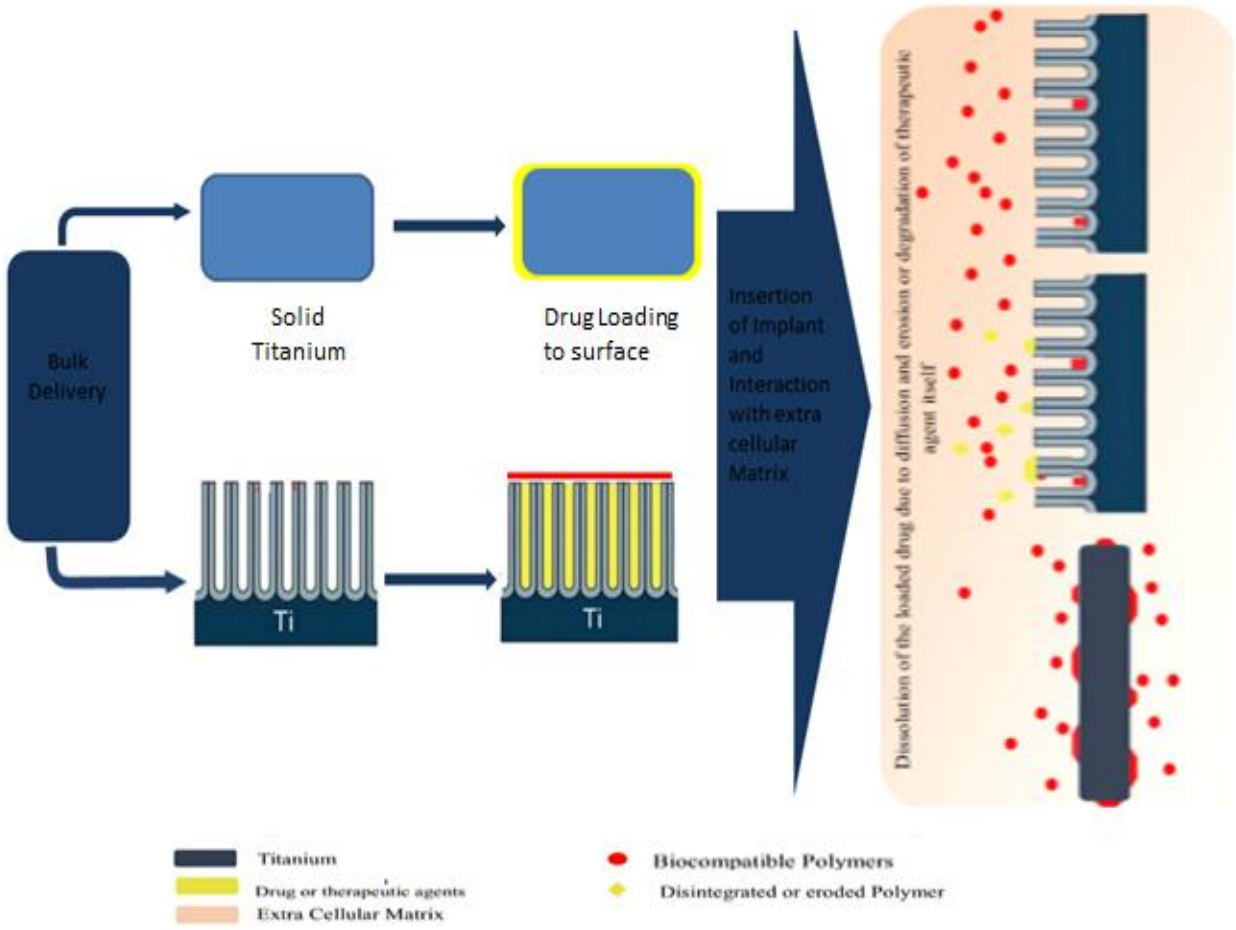

Figure 2: Schematic representation of loading site and release of therapeutics from bulk eluting titanium implants.

Additionally, researchers are exploring the use of nano-porous and nano-tubular surfaces coated with polymers as drug reservoirs, enabling drug loading [85, 86]. A notable approach in bulk drug delivery systems involves TiO2 nanotubes (TNTs). These TNTs possess a unique topography and a hollow, cylindrical shape that can accommodate drugs. He et al. [87] employed additive manufacturing to create vertically aligned TNTs loaded with 1, 25-Dihydroxyvitamin D3. They monitored the release of the drug by sealing the TNTs using Pluronic F-127. Their findings revealed that drugs loaded within nano-pores exhibited a slower release rate compared to deep adsorbed drugs in TNT reservoirs when coated with polymers (He et al., 2020).

Metal-organic frameworks (MOFs) have emerged as a promising titanium implant coating, particularly those designed to release metal ions in response to bacterial acid reactions [88]. MOFs possess a well-organized three-dimensional porous structure, consisting of metal ions connected by organic ligands. Among the various types of MOFs, those based on magnesium (Mg) and zinc (Zn) are commonly utilized due to their antibacterial properties, achieved through the controlled release of Mg2+ and Zn2+ ions at sites where bacteria are metabolically active [89, 90]. However, MOFs are susceptible to degradation in the presence of water, and their deterioration is accelerated by active bacteria created acidic conditions [88].In a recent study, researchers developed a coating using organic framework of Mg/Zn-metal on titanium implants, which demonstrated enhanced osteogenesis-promoting effects. Escherichia coli bacteria caused acidic environment degraded the Mg/Zn MOF coating on titanium. The released Zn2+ and Mg2+

ions effectively controlled early inflammation and exhibited bactericidal activity. While in vivo studies are limited, indicating ongoing investigation of MOFs in orthopedic applications, they have shown promising therapeutic potential. Table 3 provides an overview of titanium implants utilizing bulk eluting agents.

Loading agent	Drug	Technique	Important observations
Acid etched 3D porous surface	Ciprofloxacin and Metronida-zole	Immersion into an antibiotics solution	The porous structure of the material offered ample space for drug handling. In addition, it was discovered in [92] that the density, distribution and pore size, acted as parameters to control kinetics of drug release.
Anodized nanotubes 0f TiO_2	Doxycycline (osteogenic agent)	Nanotubes caped polymer	In an in vitro study, it was observed in [86] that the drug exhibited a slow and prolonged release over a period of 30 days.
Anodized nanotubes of TiO_2	Recombinant human bone morphogenetic protein-2 (rhBMP-2), isobutylphenyl propionic acid, sodium alendronate	Nanotubes	The concentration of the released drug was observed to be influenced by the pH of the surrounding environment. Specifically, rhBMP-2, isobutylphenyl propionic acid, and sodium alendronate were found to elute from the TiO2 nano-tubular surface for approximately 2.2 hours, 3.6 hours, and 3.1 hours, respectively. This suggests that the release kinetics of these drugs were affected by the pH conditions in which the TiO2 nano-tubular surface was immersed. This information is based on the findings reported in reference [93].
Nanoporous and Nanotubular surface	Gentamicin (Antibiotic)	Chitosan caped nanotubes	Extended drug release profile was reported in polymer-coated nanotubes, with 95% of the drug being released over a period of 21 days. In comparison, when the drug was loaded directly into the pores, 95% of the drug was released within 11 days [85].
Anodized nanotubes of TiO_2	Gentamicin	Nanotubes	Approximately 30% of the drug is released within the first hour. Furthermore, it was observed in [94] that nanotubes with larger internal diameters exhibit reduced bacterial adhesion.
Laser structured amphora-shaped pores	Gentamicin (Antibiotic)	Immersion into an antibiotics solution	Within the initial 30 minutes, a burst release of 96% was observed, as reported in [56].
Anodized TiO_2 nanotubes	Vancomycin (Antibiotic)	nanotubes with Electrospun silk fibroin layer caped	Observed that the implant exhibited a reduced initial burst release [95].

Drug delivery through ceramics

Ceramics are considered promising biomaterials because of excellent biocompatibility, resistance to corrosion and wear [70], which can be classified based on porosity, roughness, density, and smoothness.. Bioactive ceramics commonly used are calcium phosphate and Hydroxyapatite (HA). A bioactive ceramic is capable of regenerating new tissue and is completely resorbable. HA, coating osseo-integration due to its porous nature and chemical similarity to human bone [71].The plasma spraying technique is widely used to apply HA to titanium implants [72]. However, this method involves high temperatures, making it unsuitable for loading heat-sensitive medications. As a result, only surface absorption of certain drugs is possible, leading to early burst release and inadequate control over drug release [73]. To modify the drug release kinetics, researchers have coated drug-loaded ceramic coatings with polymers [74, 75].

Another method for applying HA to titanium implants is electrochemical deposition (ECD) [76,77]. This technique operates at lower temperatures compared to plasma spraying, allowing for the use of thermosensitive drugs. ECD has been utilized to create BMP-2 (bone morphogenetic protein) and coatings of HA on titanium alloy substrates [78]. ECD technique not only enhances drug loading rate also resulted in a slower release rate [79].Researchers mixed vancomycin hydrochloride with the base electrolyte to create a titanium coating containing strontium-doped hydroxyapatite, graphene oxide and vancomycin [80]. Release of drug exhibited an initial burst (55% within 5 hours) followed by a sustained release (71% in 14 hours) for vancomycin. Electrophoretic deposition is a coating process that occurs at room temperature and has been utilized to create composite coatings loaded with chemotherapeutic drugs, consisting of casein, hydroxyapatite, and κ-carrageenan, on titanium substrates [81]. The EPD technique ensured uniform distribution of all components within the composite layer. Renewing and healing by composite coating was also reported by study [82].Table 2 provides a list of titanium implants with ceramic-based drug-eluting materials.

TABLE 2 Ceramic-coated titanium implants for controlled drug delivery.

Loading agent	Drug	Technique	Important observations
Mg-doped hydroxyapatite	Alendronate (bisphosphonate medication)	Induction plasma spray	The application of the coating led to a slower initial burst release, followed by a sustained release, as stated in [72].
Pulsed electrodeposition	Chlorhexidine digluconate	Pulsed electrodeposition	The deposition process involving electrolyte demonstrated antibacterial activity when chlorhexidine digluconate concentrations exceeded 3 mM. This suggests that higher concentrations of chlorhexidine digluconate resulted in effective antibacterial properties. Furthermore, the pulsed electrodeposition method was found to be superior to the conventional dipping method in terms of facilitating sustained drug release. This finding, as reported in reference [78], indicates that the pulsed electrodeposition process was more efficient in delivering the drug over an extended period of time.
Hydroxyapatite	Bone morphogenetic protein-2 (BMP-2) (growth factor)	Electrochemical deposition (ECD)	It was observed that the ECD samples exhibited a slow release of the substance for duration of over 48 hours [74].
Hydroxyapatite	Vitamin C	Plasma spray Coating	After 7 days, the system demonstrated a remarkable suppression of in vitro osteosarcoma cell viability, reducing it by 2.5 times, as stated in [79].
Plasma spray Coating	Curcumin (antitumor drug) and	Plasma spray Coating	It was discovered that the material under investigation demonstrated significant cytotoxicity against osteosarcoma cells, indicating its potential as a chemo-preventive agent. Moreover, an initial burst release of the drug was observed, with approximately 17% of the total drug being released within the first 24 hours. This finding, reported in reference [36],

			suggests an immediate release of a portion of the drug followed by sustained release over time.
Hydroxyapatite/chrysin (ceramiccomposite)	Extract of garlic and ginger paste, along with the antibiotic drug gentamicin, was utilized.	Electrophoretic deposition	The composite material was reported to possess non-toxic properties, exhibit antimicrobial activity, and promote osteoblastic behavior [76].

Pharmacological mechanisms

In local drug delivery (LDD) using titanium-based implants, there are two primary approaches: porous reservoirs or the use of a carrier (such as polymer and/or ceramic) to retain the medication. These drug-eluting implants begin releasing the drug at a predetermined rate upon contact with extracellular fluid after implant insertion. Several factors such as carrier properties influence the drug release rate drug type, physical and chemical characteristics of the carrier, the thermochemical state of extracellular matrix, method of drug loading, drug concentration, and external stimuli affects drug release. Typically, the drug release pattern in LDD systems involves "burst phase," and then gradual drug release for long time. During the burst phase, there is a rapid release rate that can last from a few hours to several days. This phase is characterized by the direct dissolution of the surface-bound medication into the surrounding biological solution [53].The initial phase of burst release, occurring within the first few hours after implant insertion, plays a crucial role in eradicating bacteria, controlling local infections, and reducing inflammation [98]. Subsequently, a prolonged and sustained drug release takes place as the drug carrier matrix gradually weakens and erodes over time, releasing the embedded drug molecules [99]. This extended release period is beneficial for treatment of bone cancer treatment and regeneration of bone [85].

Osmosis, matrix erosion, diffusion and controlled swelling are four primary mechanisms by which drugs are released in local drug delivery systems [100]. Diffusion involves the movement of drug molecules to from higher lower concentration, until equilibrium is reached. Drugs loaded through simple surface adsorption were released at quickly than embedded deep in matrix. Osmosis occurs when the solvent, typically water, moves from lower to higher concentration through a semipermeable to achieve equilibrium. Controlled swelling involves the expansion of the matrix as the solvent (water) enters, resulting in the formation of new chemical or physical linkages. A lower affinity to water and higher cross-linking level in the matrix result in reduced swelling [101]. Matrix swelling has important role in controlling the release of drug from polymer. Immobilized drug molecules from matrix carrier are released through degradation mechanisms, which can be caused by oxidation, hydrolysis, or physical degradation, or oxidation in the extracellular matrix [102]. Hydrophobic matrix materials exhibit surface erosion due to hydrolysis, resulting in delayed degradation and slow drug release as they shield the bulk from water intrusion. On the other hand, rapid water infiltration leads to widespread internal degradation, known as bulk erosion. As the degradation progresses, the drug release initially occur slowly, followed by a rapid release. Polymers can degrade through hydrolysis of ester linkages, enzymatic breakdown of amide bonds, and physical pressures induced by swelling that disrupt cross-linking connections [103, 104]. The by-products of biodegradable polymer degradation are resorbable or eliminated through physiological processes, and they are non-toxic [101]. Degradation may vary in patients of these polymers can vary among patients due to in vivo variables such as temperature and pH [105].

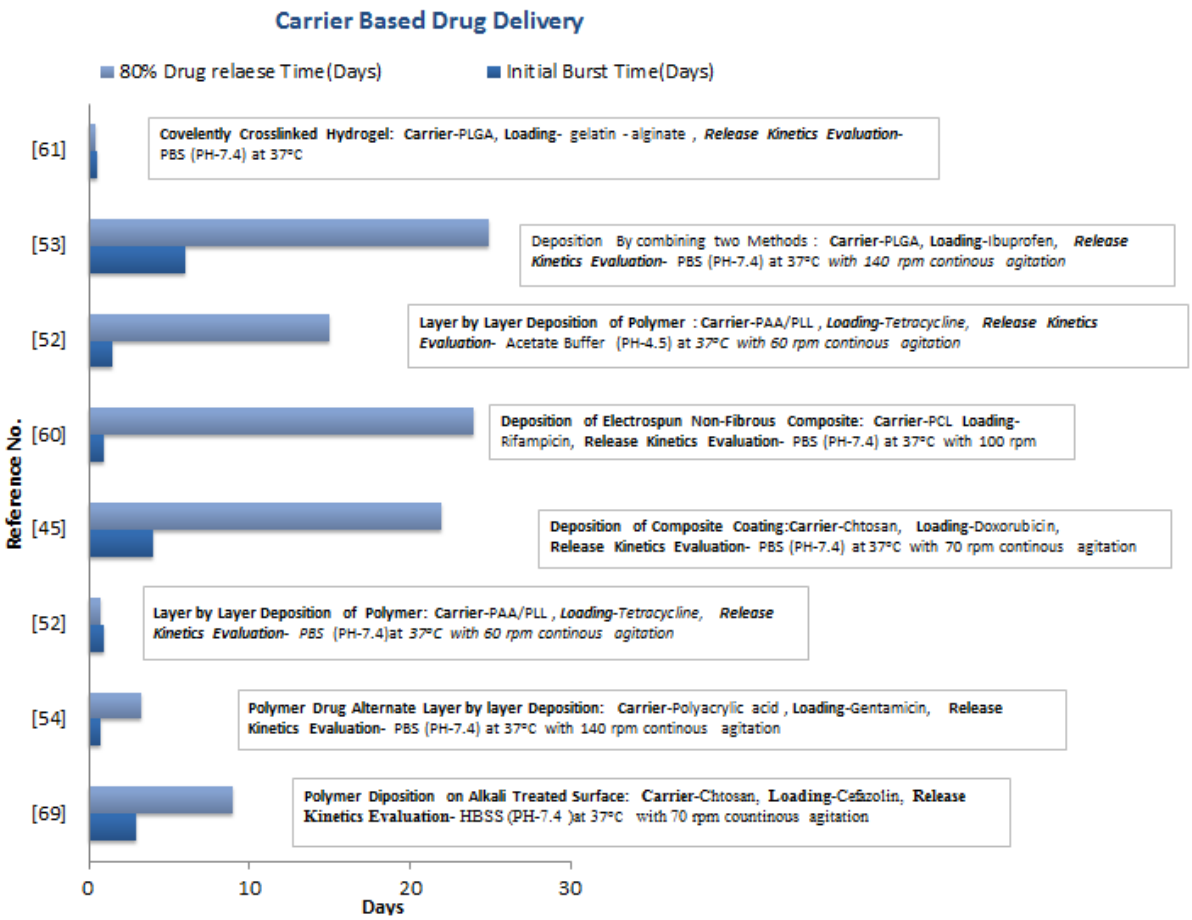

Figure 3: Drug release characteristics various polymer-based drug eluting implants.

Comparing drug release kinetics across studies presents difficulties due to variables such as the polymer's molecular weight, the size of the drug molecule, and the concentration of the drug utilized. [104]. Proper preparation of implant surface is crucial for the adherence of substrate and polymer coating [66, 69]. The alkali-treated titanium coated with chitosan coating was examined using the electrophoretic deposition technique, which result in thick coating with extended drug release. Figure-3 illustrates the relationship between processing parameters and the cumulative drug release[69]. The loading of Gentamicin without cross linking on titanium substrate using alternatives was studied by researchers. The mechanism behaved normally when releasing drugs. Layering different polymers offers several advantages, including drug loading, degradation control of drug [52, 106]. The application of poly (acrylic acid) and poly-L-lysine in a layer-by-layer coating is evaluated under varying pH conditions to assess its performance in inflammatory and normal environments [52]. While normal tissue has a pH of 7.4, the extracellular matrix of inflammatory tissues or tumors can have a pH value below 5. Monitoring drug release at different pH levels helps in predicting implant performance. Figure illustrates the drug release behavior, showing that poly-L-lysine degrades more rapidly high pH delivering drug at higher rate, which controls diseases or inflammation that has already developed. Incorporating a drug-loaded polymer layer (chitosan) into a composite coating of titanium significantly reduces the initial burst release [45]. Initial burst was controlled by chitosan in coating. Figure also presents a comparison of medication release. Similarly, an alternate layer of hydroxyapatite and alginate in a composite coating demonstrated prolonged release of gentamicin over a 300-hour period [54]. For drug release, an electro-spun coating composed of nanofibers with a composition of polycaprolactone (PCL) and hydroxyapatite was studied [60]. In this specific application,

hydroxyapatite accelerated the degradation of the composite and improved the hydrophilicity of the nanocomposite fibers. This system counteracts PCL's hydrophobic properties, allowing degradation to occur simultaneously with bone development. To create a stimulus-based long-lasting drug release system, gold nano-rods were incorporated into a polymer coating of poly (N-isopropylacrylamide)-co-acrylamide [58].

The application of near-infrared (NIR) light induces local heating, leading to the physical breakdown of the polymer film and enabling on-demand drug release. As the crosslinks of the polymer degrade and the hydrogel undergoes degradation, swelling occurs. Through diffusion, the medication is released from the swollen hydrogel. Eventually, the polymer chains are released from the cross-linker. Various concentrations of transglutaminase (TG: 0, 0.5%, and 1%) were used to cross-link the hydrogel, resulting in significantly different outcomes. It has been reported that a non-crosslinked hydrogel would release all loaded medication within approximately 20 minutes. However, cross-linkage more than 90% using TG ()/1% exhibited sustained release for over 120 minutes. Ceramic-based local drug delivery (LDD) systems mostly used hydroxyapatite for titanium implants. Surface (Ca+2) with positive charge provides ultimate adsorption capacity [107].

Similar to polymers, hydroxyapatite coating employs a mechanism for drug release. However, the dissolution rate may be slower due to the higher porosity (micro and nano) of the hydroxyapatite coating compared to polymers. Various factors, such as crystallinity, extracellular environment and porosity, influence rate of hydroxyapatite coating degradation and drug release. In ceramic coatings, like in polymers, drug release typically exhibits an initial burst caused by the removal of weakly adhered molecules. The release characteristics of hydroxyapatite were examined at two distinct pH levels, representing physiological pH (7) and an inflammatory environment (5) [79]. An acidic environment led to a higher drug release rate from coating of hydroxyapatite as shown in figure 4. This difference was attributed to the increased rate of surface disintegration in acidic media, resulting in exposed pores and cracks. Fig illustrates the impact on drug release with method of processing. Electrochemical deposition was found to be more advantageous than the immersion method for fabricating drug-loaded hydroxyapatite coatings, with increased rate of drug loading and improved control on release during first 24 hours. The addition of a polymer layer on hydroxyapatite was suggested to enhance LDD system effectiveness and control drug release kinetics [72]. Fig. also demonstrates the successful suppression of the initial burst by the PCL coating on Mg-doped hydroxyapatite. Slow PCL degradation resulted in a higher concentration of polymer coatings (4%), releasing the drug slowly compared to lower concentration coatings (2%) or no polymer coating. Modifying hydroxyapatite with additives such as Ag, Sr, and graphene oxide improved its physical characteristics (elastic modulus and hardness) without harmful effects.

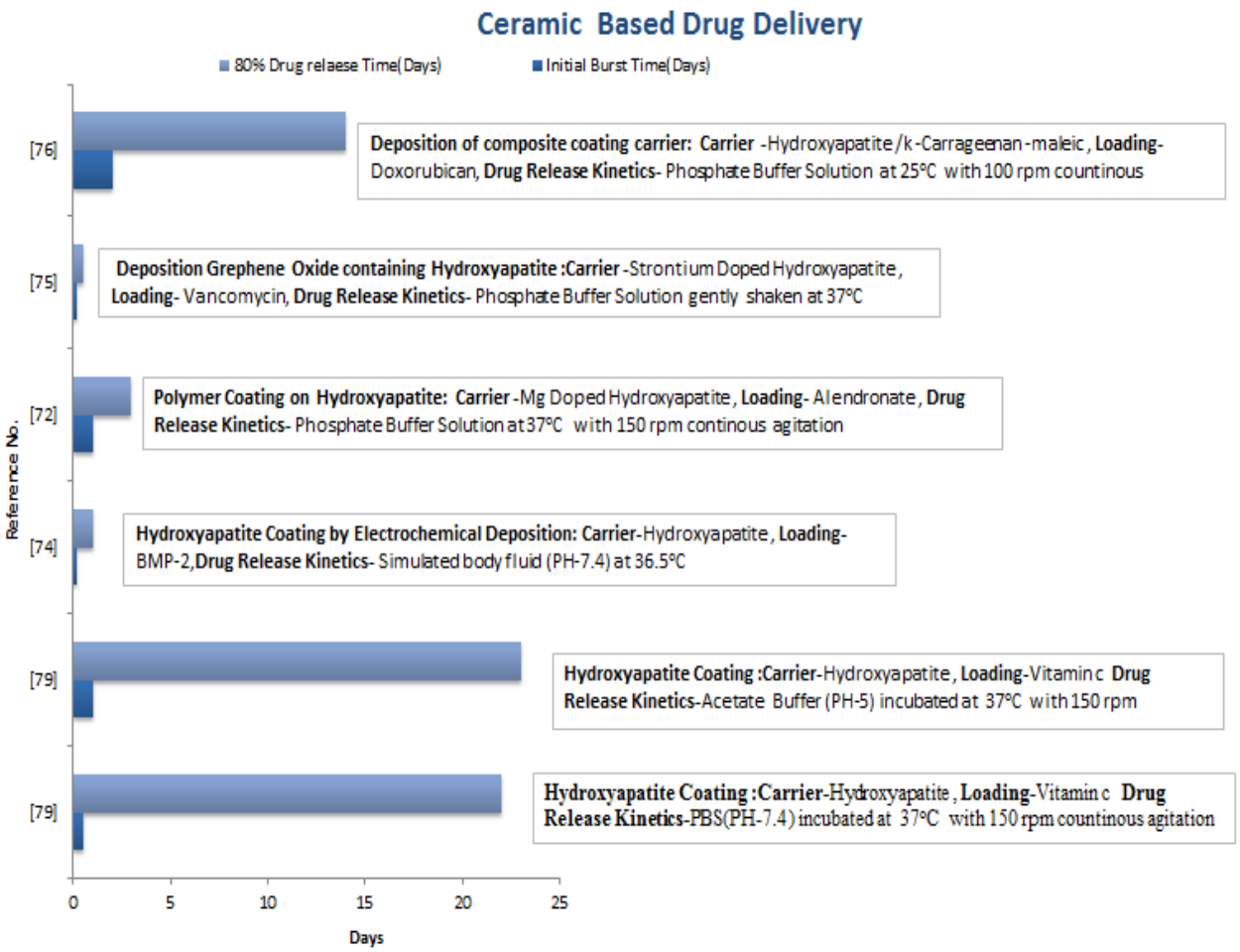

Figure 4: The drug release properties of diverse ceramic-based drug eluting implants

A composite coating made up of hydroxyapatite, carrageenan, maleic anhydride, and casein (HAP/Car-MA-CAS) was utilized to achieve a consistent and sustained drug release [76].The initial burst control was made by the strong electrostatically networked reservoir formed by HAP and Car-MA-CAS. Drug molecules escape from titanium surface and the openings of the micro reservoirs, resulting in the initial burst. However, deeper confinement within the micro reservoirs leads to slower release because of capillary action. The drug loading and release of titanium nanotubes as drug reservoirs were found to be influenced by the internal diameter [94]. The use of smaller inner diameter nanotubes was demonstrated to achieve delayed drug release due to their larger surface area for drug molecule storage. However, an initial burst release was observed within the first hour, resulting in approximately 30% of the medication being released. To modify drug release, polymer coating has been employed [86, 95]. A comparative study was conducted to evaluate the performance of polymer (PLGA)-coated nanotubes in comparison to bare drug-loaded nanotubes. The bare nanotubes with a diameter of 100 nm released around 80% of the medication within the first two hours. Surprisingly, when PLGA coating was done nanotubes loaded with drug), the drug release was effectively regulated.

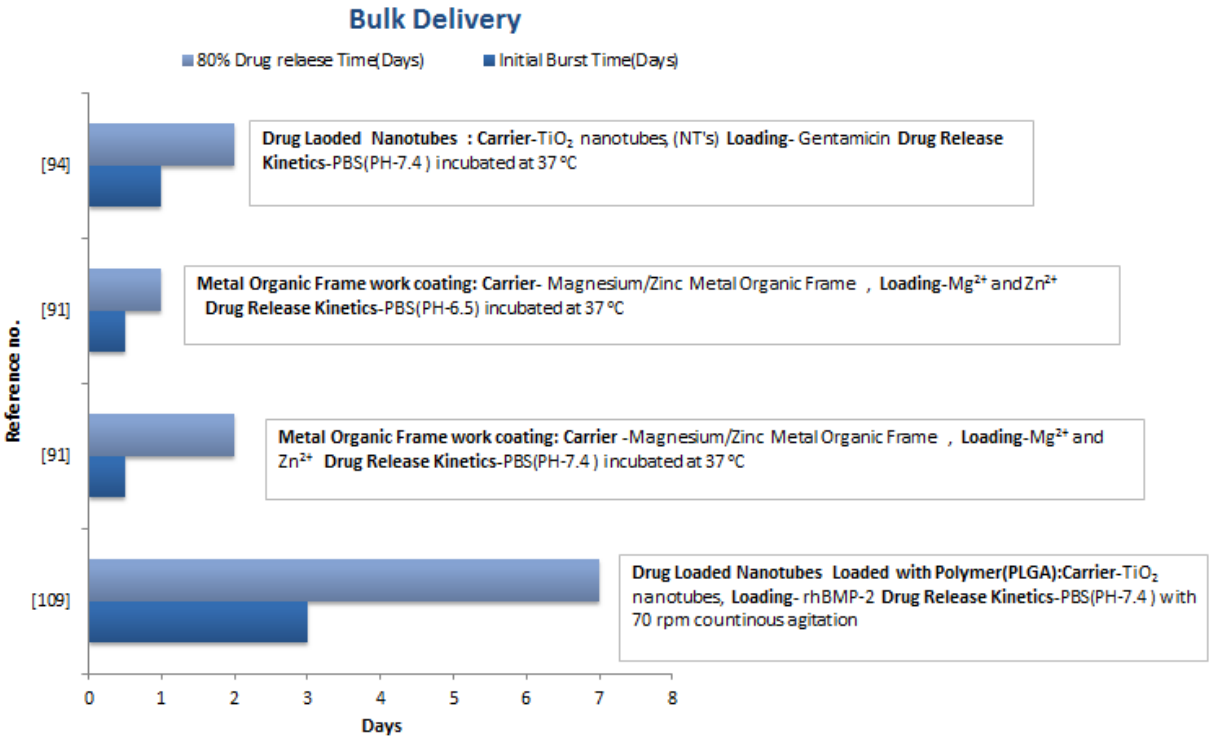

Figure 5: The drug release characteristics of distinct bulk eluting titanium implants

The medication was retained within the nanotubes for 28 days by a 10% concentration and 800 nm thickness of PLGA coating.The polymer coating on drug-loaded nanotubes acted as a barrier between the drug-loaded site and the extracellular media, resulting in drug release requiring diffusion through the polymer covering or dissolution into the polymer matrix due to polymer degradation [102]. In a separate study, drug-loaded porous titanium implants with TiO2 nanotubes on the surface were coated with a thermosensitive hydrogel for sustained drug release [87]. Figure 5 provides a comparison of drug release curves, indicating an initial burst release followed by sustained release in all samples. The absence of chemical cross-linking in the hydrogel led to faster degradation and consequently faster drug release and also avoids cytotoxicity. Electro spun coating extended the overall drug release duration from 10 to 40 days by acting as a barrier and mitigating the initial burst release. The release of metal ions from Metal-Organic Frameworks (MOFs) responsive to acidic microenvironments was also studied for their antibacterial effects [91]. MOFs degrade more rapidly in the presence of water due to interference by water molecules with coordination bonds, and acidic environments further accelerate the degradation process. Figure also demonstrates that MOF degradation occurs within the first 24 hours in an acidic environment, and an increase in Zn content in MOFs leads to a higher rate of Mg2+ ion release.

Conclusion

Implant-integrated medication delivery systems have gained attention in the fields of orthopaedics and dentistry, aiming to enhance various aspects such as osseo-integration, differentiation, cell adhesion, and proliferation, while also addressing local infection. However, this field is still in its early stages of development, with limited in vivo investigations and mostly promising in vitro research reported in recent years. Further studies are required to establish the superiority of coated or adsorbed medications in clinical settings and to ensure their physical and mechanical stability. One crucial aspect that demands attention is the appropriate release rate of loaded medications to ensure optimal recovery. Achieving the

desired release kinetics is essential to deliver therapeutic agents in a controlled manner and maintain their effectiveness. Extensive research is needed to investigate and optimize the release profiles of loaded medications, considering factors such as drug type, dosage, carrier materials, and implant design. Moreover, the exploration of newer materials and composites with enhanced drug loading capabilities is crucial. The development of safe and biodegradable materials is of paramount importance to ensure biocompatibility and minimize any adverse effects on the patient's health. Research efforts should focus on identifying innovative materials that possess favorable drug-loading properties while maintaining structural integrity and compatibility with the implant. In summary, while implant-integrated medication delivery systems hold significant potential in improving patient outcomes, further comprehensive studies are required. These studies should focus on establishing the stability of coated or adsorbed medications, optimizing release rates, and identifying novel biodegradable materials with superior drug-loading capabilities. Only through rigorous research can the full potential of these systems be realized, ensuring safe and effective treatments in orthopaedics and dentistry.

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