Engineered Science
DOI: https://dx.doi.org/10.30919/es1274

Novel Approaches to Alendronate Delivery Beyond Oral Administration- A Review

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Abstract

Alendronate is frequently prescribed among bisphosphonates for managing a range of conditions like osteoporosis, Paget's disease, and other bone-related disorders. By preventing bone resorption, it boosts bone density and lowers the chance of fractures. However, long-term alendronate use may be linked to possible side effects such as oesophageal ulcers, gastrointestinal irritation, and extremely rare cases of atypical femoral fractures and osteonecrosis of the jaw. Alendronate is still frequently prescribed for the treatment of osteoporosis and is regarded as a significant therapeutic option for enhancing bone health and lowering the risk of fracture despite these hazards. To overpower the limitations pertaining to the conventional administration of alendronate, many researchers have explored and developed formulations for delivering alendronate via controlled drug delivery systems. This review paper explores different formulations including hydrogels, transdermal formulations, microspheres, implants, and nanoparticles, devised to administer alendronate in a controlled manner, aiming to tackle the hindrances corresponding to traditional alendronate delivery strategies. In a pursuit to identify the best available formulation, an exhaustive literature survey was conducted, and a comprehensive review of the various formulations that have been developed to deliver alendronate in a controlled manner, was done.

Keywords: Controlled drug delivery; Alendronate; Biopolymeric formulations, Hydrogels, Osteoporosis.
Received: 25 July 2024; Revised: 27 September 2024; Accepted: 10 October 2024.
Article type: Review article.

1. Introduction

Bisphosphonates are categorized as stable pyrophosphate analogues, a class of drugs identified by a covalently attached Phosphorus-Carbon-Phosphorus (P-C-P) bond between two side chains, with a carbon atom in place of the central oxygen atom.[1-4] Unlike pyrophosphate, bisphosphonates can withstand enzymatic hydrolysis because of their P-C-P structure.[5] According to some reports, bisphosphonates can remain in bone for up to ten years after being administered. Their half-life varies from month to year. However, the impact on osteoclasts is lessened once fresh bone is deposited on top of bisphosphonate-containing layers.[6] Alendronate is an amino bisphosphonate,[7] which is a common oral drug prescribed for the avoidance and treatment of diseases such as osteoporosis, Paget's disease[8] and periodontitis.[9] Salari *et al.* in through their systematic review of the epidemiology revealed the prevalence of osteoporosis globally. The study comprised of 86 studies to understand the prevalence of osteoporosis across the globe. They analyzed data from more than 103 million people aged between 15 and 105. The overall prevalence of osteoporosis was found to be 18.3%, which means about 18 out of every 100 people possess this condition. By focusing on women, they analyzed 70 studies involving close to 800,500 women. They then established that the prevalence of osteoporosis in females was higher, standing at 23.1%. In the case of men, 40 studies showed that about 454,000 men had a lower prevalence at 11.7%.[10] The prevalence rate of osteoporosis in postmenopausal women and the trend of this prevalence,[11] as shown in Fig. 1.

In postmenopausal women with osteoporosis, consistent treatment with oral alendronate for 3 years considerably enhances bone mineral density in the spine, hip, and entire body. Alendronate has also been shown to demonstrate a trend toward fewer nonvertebral fractures and to decrease the occurrence of vertebral fractures, bone abnormalities, and height loss.[12]

Alendronate is currently available in the dosage forms of tablets, effervescent tablets, and solutions. By slowing down bone turnover, alendronate promotes secondary mineralization, which raises the amount of mineral content in

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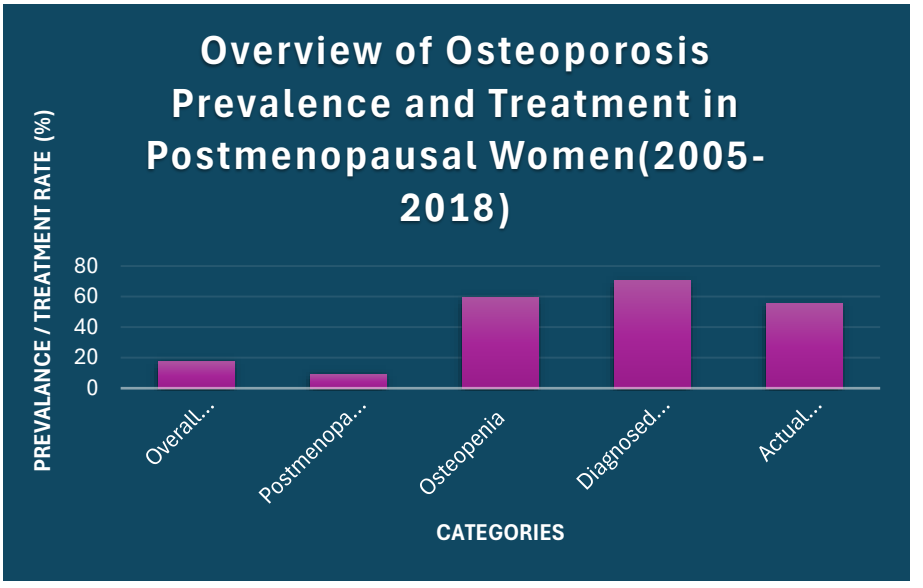

Fig. 1 Graphical Representation of predominance and treatment rate of Osteoporosis in postmenopausal women.

tissue.[13]

1.1 Mechanism of action

Alendronate has inhibiting effects on osteoblast apoptosis and osteoclast activity.[14,15] Alendronate functions by inducing cell death in osteoclasts which are the key cells involved in bone resorption. It binds to hydroxyapatite (HAP) in bone and is internalized by osteoclasts through fluid-phase endocytosis. Once inside, alendronate is released from acidified endocytic vesicles into the cytoplasm due to the acidic environment created by bone resorption. This release leads to a reduction in bone reabsorption.[16] The mechanism of action involves blocking the process of prenylation, which regulates the formation of the osteoclast's ruffled border (Fig. 2). Prenylation involves the covalent modification of guanosine triphosphatase (GTPase) signaling proteins with lipids, allowing these proteins to adhere to the cell membrane and form the ruffled border, thereby facilitating bone resorption.[17,18]

Alendronate binds to the enzyme farnesyl pyrophosphate synthase, or geranyl transferase, which is involved in the biosynthesis of terpenoids, and inhibits its action. A crucial step in the turnover process of osteoclasts is the synthesis of isoprenoid lipids, specifically farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which act as donor substrates for farnesylation and geranylgeranylation during

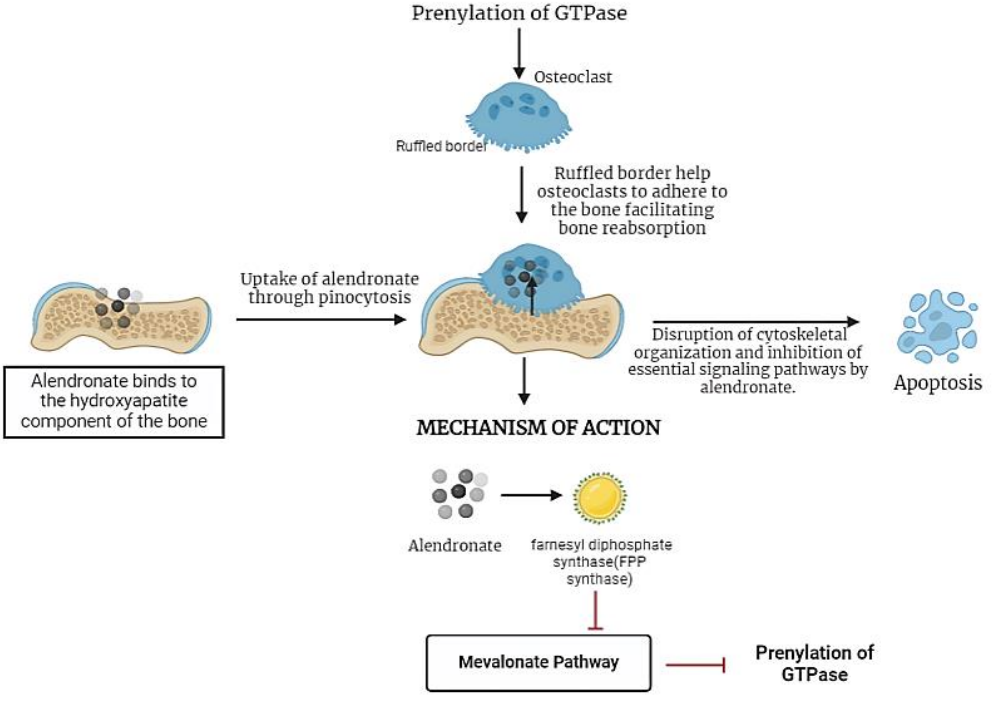

Fig. 2 Inhibitory action of alendronate sodium on osteoclast cells (Created using Bio render).

the post-translational modification of small GTPase signaling proteins. As a result, osteoclast activity is repressed, and bone resorption and turnover are diminished. A rate-limiting step in the cholesterol biosynthesis pathway that is necessary for osteoclast function can also be inhibited by alendronate.[19-27]

When compared to other bisphosphonates, alendronate has a very strong potency due to its four-carbon amino side chain, which enables it to effectively inhibit osteoclast-mediated bone resorption at doses that do not affect bone mineralization.[12] In vitro, alendronate decreased the expression of MMP-13 and ADAMTS-5, the two main metalloproteinases that break down cartilage, while increasing the expression of Collagen II (Col II) in chondrocytes.[28] In response to alendronate treatment, it was reported that human bone marrow stromal cells undergoing osteogenic differentiation had higher levels of certain proteins, including RUNX2 and osteocalcin.[29] Alendronate treatment of human bone marrow stromal cells also resulted in an increase in the expression of fibroblast growth factor 2 (FGF2), RUNX2, BSP2, and BMP2 mRNA.[30,31]

1.2 Drawbacks of alendronate

Although this ability of alendronate is utilized in the treatment of various bone-related conditions, these drugs are typically taken orally, in a systematic manner, and because of their poor bone-targeting effectiveness, frequent administration at high doses can have serious side effects.[32] It also has drawbacks, including limited bioavailability, cardiovascular risks, gastrointestinal discomfort, nausea, musculoskeletal pain, and jaw osteonecrosis.[33-35]

Alendronate is poorly absorbed in both people and animals, as is the case with other bisphosphonates; oral bioavailability in all examined species, including humans, is less than 2%.[7,36] It has a clearance rate of 71mL/min. Among the other commercially available brand names, alendronate is commonly available under the brand names Fosamax and Binosto. It has a molecular weight of 249.096 g/mol.[37] Alendronate, when given intravenously or orally, has the potential to cause musculoskeletal pain.

Oral administration of alendronate may also result in negative consequences such as upper gastrointestinal disorders, nausea, gastritis, dyspepsia, and abdominal pain.[38] Alendronate administered orally over an extended period causes considerable gastric damage. It elevates myeloperoxidase activity, and increases lipid peroxidation, while reducing tissue glutathione levels. Alendronate has been shown to cause oxidative gastric damage by irritating the surrounding tissue. Alendronate irritation has been connected to inflammation by means of oxidative tissue damage and neutrophil infiltration. Moreover, it has been noted that oral alendronate treatment raised collagen content, myeloperoxidase activity, malondialdehyde, and luminol levels.[39,40]

1.3 Controlled drug delivery

Drug delivery systems encompass formulations, systems, or technologies employed to regulate the drug's release in the body over a specified period and/or direct the drug to a specific tissue or cell type. Strong evidence indicates that patients who take once-daily medications adhere to their regimens much more than those who take multiple daily doses for different conditions, for example, bisphosphonates for osteoporosis.[41] Controlled drug delivery enables less frequent dosing without compromising therapeutic efficacy by enhancing drug pharmacokinetics, bioavailability, and efficacy by accurately directing drugs to specific locations at precise moments. This can enhance patient comfort, compliance, and conformity to treatment regimens, ultimately leading to better clinical outcomes.[42]

One way to accomplish controlled drug distribution is to create a polymer blend that can encapsulate the drug within its matrix in order to treat diseases such as cancer and COVID-19 more effectively and to minimize the adverse effects associated with conventional drug formulations.[43,44] The drug's release rate from the matrix can be customized by selecting the appropriate polymeric blend and adding crosslinking agents.[45]

To address the drawbacks of alendronate delivery through conventional methods, many researchers have investigated and created formulations for alendronate-controlled release. The focus of this review article is to analyze the same as a useful strategy to highlight the polymer combinations that worked best for controlled release. A compilation of the various polymer formulations developed by researchers up to date has been categorically reviewed and presented in the following sections.

2. Controlled release strategies - overview

Advancements in polymeric blends for controlled release of alendronate delivery were explored over time. The advantages and disadvantages of the several formulations and their impact on patient adherence across multiple diseases have been discussed. The different types of formulations, like gel-based, transdermal, microspheres, *etc.*, have been summarized, and every section concludes with a highlighted formulation that has the best-controlled release duration. The various studies that were discussed have also been summarized in the form of a table.

2.1 Gel-based formulations

Drug delivery through hydrogel-based polymeric systems might have therapeutic benefits. Given that hydrogels have flexible physical properties, they can protect unstable drugs from decomposition, and their degradability can be controlled. They can serve as a platform to study different chemical and physical interactions with encapsulated drugs for modulated release in the system.[46] Hydrogels have been shown to be promising templates for bone regeneration among the various scaffolds for bone tissue engineering applications owing to their similarity to the extracellular matrix found in nature.[47]

Hydrogels are comprehensively utilized in various fields, including intelligent, bionic, and biomedical devices, but their limited mechanical properties hinder broader applications.

Ma *et al.* developed biomimetic hybrid hydrogels comprising collagen, HAP, and alendronate utilizing a two-step procedure. These hybrid hydrogels showed improved mechanical properties and degradation resistance compared to collagen-based hydrogels, potentially offering enhanced treatments for conditions like osteoporosis.[48] Dual-crosslinked networks, combining physical and chemical crosslinks, can also offer a solution to the weak mechanical stability limitation. Chen *et al.* synthesized zeolitic imidazolate framework ZIF-8 and alendronate-ZIF-8 nanoparticles loaded with alendronate incorporated in a dual crosslinked hydrogel composed of polyacrylamide and carboxymethyl cellulose, enhancing the mechanical properties of hydrogels. These hydrogels exhibited superior tensile and compression properties, making them an appealing prospect for delivering alendronate in tissue engineering applications.[49]

In addition to focusing on enhancing mechanical stability, researchers sought to integrate biodegradable and biocompatible polymers. Pluda *et al.* produced a biocompatible and biodegradable drug-polymer derivative by functionalizing hyaluronic acid (HA) with alendronate moieties. This novel macromolecular drug delivery system combines the pharmacological activity of alendronate with the viscosupplementation and biological effects of HA, presenting a promising avenue for treating osteoarthritis.[50] Alendronate-based tetra-polyethylene glycol (tetra-PEG) hydrogel with good mechanical properties, easy injectability, and biocompatibility was developed by Li *et al.* Alendronate was incorporated and released steadily due to the hydrogel's structure, which was adaptable by varying the gel's solid content and molecular weight.[51]

In the context of periodontitis treatment, gel formulations of alendronate were explored to confine the drug to target locations, minimizing systemic side effects. The formulations incorporated various percentages of carbopol 934P, triethanolamine, methylparaben, and propylparaben. These formulations demonstrated efficacy and reduced adverse effects, thereby enhancing patient compliance.[52] The physical flexibility and controllable degradation of hydrogel-based delivery systems make them ideal for protecting unstable drugs and enabling controlled release, and they also offer promising therapeutic benefits. Furthermore, these hydrogels can also be improved by utilizing smart polymers.

The ability of stimuli-responsive hydrogels, also cited as smart hydrogels, to react to particular environmental stimuli has attracted an abundance of focus in the domain of controlled drug delivery (Fig. 3). The temperature, pH, enzymes, light, and magnetic fields are among a few of the stimuli that can alter these polymers' sol-to-gel transitions in aqueous solutions.[53,54]

In a research done by Nafee *et al.*, alendronate was encapsulated in a chitosan/β-glycerophosphate hydrogel, demonstrating thermoreversible gelation behaviour and controlled drug release for about 30–65 days, with minimal inflammatory reactions and enhanced tissue maturation.[55] Temperature-sensitive hydrogels, which swell or shrink in response to temperature changes, are classified as positive or negative based on their behaviour. Das *et al.* developed a thermogelling injectable or implantable gel system utilizing solid lipid nanoparticles to address alendronate's low bioavailability and localized effect. The addition of polymers Pluronic F-127 and Pluronic F-68 aided in drug entrapment and extended drug release due to their gel forming properties. These polymers have the ability to extend the drug's duration of contact with the intended tissue, which improves drug absorption. The formulated gel system was also found to be thermosensitive.[56] Shan *et al.* fabricated a temperature-sensitive hydrogel using poly(L-valine) polymer, incorporating alendronate and methotrexate for osteosarcoma treatment. This hydrogel rapidly gelled at body temperature, providing sustained local drug release.[57]

In order to enhance bone healing, Tang *et al.*, in their study

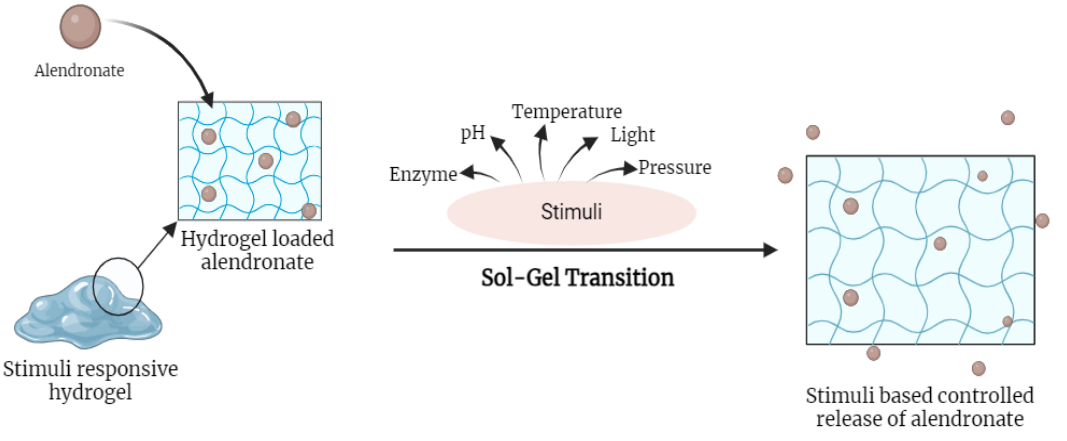

Fig. 3 General mechanism of action of stimuli responsive hydrogel (Created using Bio render).

developed a particular kind of drug-loaded scaffold that used a hydrogel known composed of alendronate-modified oxidized alginate network combined with methacrylated gelatin. This hydrogel was fabricated using a combination of photo-crosslinking and Schiff base reaction that mimics the environment found naturally in human bodies. A robust network is created when the reactive groups of methacrylate gelatin and oxidized alginate interact to form bonds. This bond gets stronger when it is exposed to UV light. This hydrogel can release drugs in response to pH changes and degrade in regulated ways because of the unique bonds that form, also referred to as Schiff base bonds. The properties of the structure facilitate the proliferation and viability of bone marrow-derived stem cells. The hydrogel at a pH of 6.5 released 97% of the drug within a period of 14 days, while at a pH of 7.4, 70% of the drug was released.[58]

Given that injectable hydrogels are easily placed into unevenly shaped bone lesions with minimal surgical intervention, they hold great promise. Unfortunately, the limited self-healing capacity and inadequate mechanical strength of many of these hydrogels restrict their usefulness as support materials. An innovative injectable hydrogel with strong support, self-healing properties, and the capacity to stimulate blood vessel creation and bone growth was developed by Wang *et al.*, using poly(l-glutamic acid)/MDex/CaP and poly-(γ-benzyl-l-glutamate) nanofiber, they created biomimetic nanofiber-reinforced dually cross-linked injectable hydrogels with self-healing, osteogenic, and angiogenic characteristics. These hydrogels showed strong self-healing properties as a result of being crosslinked by two reversible dynamic interactions, namely physical chelation and Schiff base reaction. The hydrogels exhibited good osteogenic function due to CaP and poly-(γ-benzyl-l-glutamate) mineralized nanofibers and alendronate sodium grafted on poly(l-glutamic acid).[59]

Table 1 summarizes the research on gel-based formulations for controlled drug delivery of alendronate. Temperature-sensitive synthetic hydrogels exhibit consistent mechanical properties, controlled degradation rates, and strong biocompatibility, making them promising prospects for

Table 1. Research on gel-based controlled drug delivery methods for various bone-related conditions across various domains.

Field	Condition	Formulation	Results	Reference
Dental	Bone resorptive lesions (Periodontitis)	Carbopol 934P hydrogel loaded with alendronate	Notable improvement in clinical outcomes such as gain attachment level, probing pocket depth, and gingival index. After seven hours of *in-vitro*-related studies, about 40% of the drug was released.	[52]
Orthopedic	Bone defect repair	Collagen and HAP-alendronate conjugate hydrogel crosslinked with genipin	Improved mechanical properties with variable collagenase degradation behavior.	[48]
	Osteoporosis	Thermogel composed of chitosan and β-glycerophosphate loaded with alendronate	Extended release of alendronate over a 30–65-day interval was achieved with the thermogel.	[55]
		Thermogelling system composed of alendronate and solid lipid nanoparticles	Enhanced drug encapsulation efficacy and 93.16% drug release after 102 hours	[56]
		Hydrophilic polyacrylamide, carboxymethyl cellulose hydrogel loaded with alendronate-zeolitic imidazolate framework	Improved mechanical properties with higher drug loading of 63.8% and controlled release up to 6 days.	[49]
	Osteosarcoma	Thermo-sensitive hydrogel composed of methoxy PEG and poly(L-valine) loaded with methotrexate and alendronate.	Approximately 40% of alendronate was released from gel-alendronate formulation after 30 days	[57]
	Osteoarthritis	HA conjugated with alendronate with the help of a linker	Within 10 days, less than 30% of the conjugate's total bound alendronate was released.	[50]
	Bone healing	pH sensitive hydrogel composed of alendronate-modified oxidized alginate network combined with methacrylated gelatin.	At 6.5 pH 97% of the drug was released in 14 days while at 74 pH 70% of the drug was released.	[56]

various biomedical utilization. Among the various gel-based formulations, the injectable thermogel composed of chitosan/β-glycerophosphate showed the best-controlled release of alendronate up to 30-60 days.[55] In aqueous environments, hydrogels can swell, which can cause changes in their volume and strength which can affect the drug's stability. The transdermal patch's adhesive matrix can aid in stabilizing the drug molecule by preserving its integrity and guarding against physical harm during application and wear. In contrast to gel-based formulations, which are typically injectable or implantable, transdermal patches offer a non-invasive method of administering drugs and improving patient compliance.

2.2 Alendronate loaded transdermal patch

Among innovative drug delivery systems, transdermal administration has become very popular because of its many benefits. Transdermal drug delivery is a controlled technique of administering drugs in which the prepared formulation is applied topically. The drug is contained within the formulation, which further permeates through the skin. Following the passage through stratum corneum, the drug reaches the epidermis and dermis, where dermal microcirculation enables systemic absorption, as shown in Fig. 4.[60] Transdermally delivered drugs circumvent liver metabolism by avoiding the gastrointestinal tract, which lowers the risk of both gastrointestinal discomfort and liver dysfunction. Furthermore, by utilizing the passive diffusion process and sustaining stable circulation levels, transdermal delivery maintains a constant rate of drug delivery over time. Transdermal drug delivery is an appealing option for pharmaceutical applications because of these factors that work together to enhance its safety and efficacy.[61]

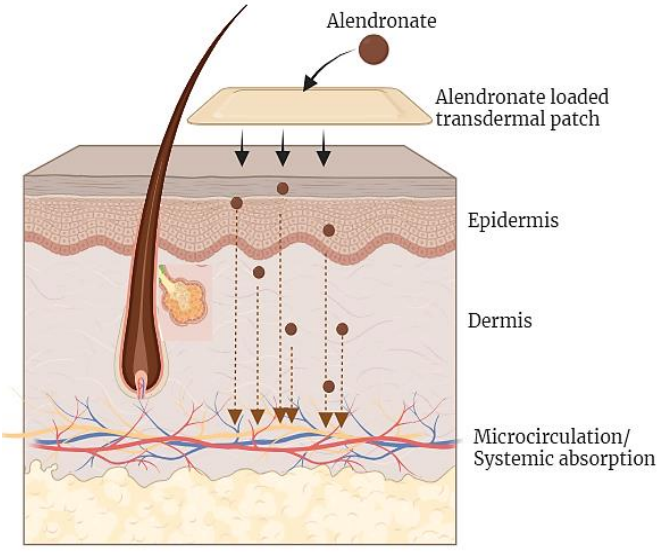

Fig. 4 Graphical representation of transdermal drug delivery of alendronate (Created using Bio render).

Alendronate has high polarity and hydrophobicity, which is why conventional transdermal absorption is limited by the skin's lipid layers. To improve the pervasion of alendronate, researchers have researched pressure-sensitive adhesive transdermal delivery systems containing caprylic acid and other amines. To achieve high alendronate penetration in the skin of hairless mice, Choi *et al.*(2008) developed a pressure-sensitive adhesive transdermal delivery system using Propylene glycol (PG) containing 6% caprylic acid.[62] Further in their investigation of alendronate absorption through transdermal delivery systems, Choi *et al.* (2010) looked at both human and rat subjects and found that the formulation containing 6% caprylic acid in PG showed better absorption and delayed half-life values when compared to oral administration.[63] On the other hand, Whang and Hyesun Gwak used pressure-sensitive adhesive transdermal delivery systems and solution formulations to study the impact of different amines on alendronate permeation. They discovered that PG containing 6% caprylic acid, 3% triethanolamine and 10% diethylamine showed the highest permeation rates.[64] Kusamori *et al.* evolved a new transdermal patch using a hydrophilic adhesive and glycerine containing alendronate. They observed maximum alendronate permeation fluxes through rat and human skin at 1.9 and 0.3 μg/cm² per hour, respectively. When applied as a patch, alendronate bioavailability in rats was about 8.3%, significantly higher than the 1.7% achieved through oral administration. This indicates that transdermal permeation could be effective for treating bone diseases. Applying the alendronate patch effectively reduced plasma calcium levels in rats with 1α-hydroxyvitamin D_3-induced hypercalcemia and inhibited bone mass decrease in rats with osteoporosis.[65]

Biodegradable polymer research and development offers possibilities for innovation and the development of new materials with enhanced characteristics and functionality. Biodegradable films for targeted alendronate administration in periodontal applications were fabricated using poly (lactic-co-glycolic acid) (PLGA) due to their biocompatibility. Long *et al.* incorporated an amphiphilic di-block copolymer as a plasticizer to enhance elasticity and regulate drug release rates, achieving uniform dispersion of alendronate particles within the PLGA matrix. Water penetration into the PLGA matrix facilitated controlled drug release, with the di-block copolymer increasing film porosity over time to ensure complete drug release and prevent cell toxicity.[66] Some research studies discuss the development of biodegradable films and nanoparticulate transdermal patches for the combined delivery of alendronate and other drugs like risedronate. Fanguo *et al.* investigated a novel transdermal patch combining risedronate and alendronate using PLGA, demonstrating its efficacy in maintaining normal plasma calcium levels in excised rat skin, suggesting its potential as an effective treatment for osteoporosis. These formulations show promise in effectively treating osteoporosis while minimizing side effects.[67]

Other innovative approaches that have been examined include the utilization of self-dissolving micron-size needle

arrays, hyaluronic acid gel sheets, and microemulsions to deliver alendronate transdermally. These methods aim to increase drug bioavailability, minimize gastrointestinal side effects, and improve patient compliance. In a study, HA was utilized to create self-dissolving micron-size needle arrays comprising alendronate, facilitating transdermal delivery through micron-scale pores in the skin. This method achieved approximately 90% bioavailability in rats, similar to subcutaneous administration, and effectively inhibited growth plate narrowing in an osteoporosis rat model.[68] Naito *et al.* developed HA gel sheets loaded with alendronate, demonstrating significant permeation across rat and human skin with minimal adverse effects, and enhancing alendronate bioavailability by approximately 20% in rats, suggesting their potential as a viable transdermal formulation for efficient alendronate delivery. Furthermore, a novel transdermal microemulsion carrier prepared by increasing the non-covalent interaction with the help of phosphoric acid for alendronate, demonstrated enhanced bioavailability and anti-osteoporotic efficacy compared to oral administration, highlighting its potential in preventing intestinal toxicity and improving therapeutic outcomes.[69] In order to prevent intestinal toxicity, Boche, M., and Pokharkar, V. identified transdermal microemulsion as an appropriate carrier for alendronate. They also demonstrated the anti-osteoporotic efficacy of transdermal microemulsion through comprehensive pharmacokinetic and pharmacodynamic analysis. In pharmacokinetic studies, transdermal microemulsion demonstrated a two-fold boost in bioavailability when contrasted to oral dosing.[70] Other novel technique based on β-cyclodextrin (alendronate-β-Cyclodextrin) was created and synthesized by Liu *et al.*, demonstrating a highly robust binding to hydroxyapatite with the aim to deliver a glucocorticoid drug named Dex to treat diseases like oral mucositis.[71]

The majority of the formulation's active ingredients have low skin permeability, due to which the application of transdermal patches in clinical settings is currently restricted. To get around this restriction, new approaches to skin penetration enhancement techniques are recommended.[72] Several studies have been reviewed, focusing on different strategies to improve transdermal delivery of alendronate, a drug used for treating bone diseases. These strategies include the use of nanocarriers, such as microemulsions and niosomes, to enhance permeability and prolong release. Villanueva *et al.* sought to create two submicron delivery systems for alendronate in osteoporosis treatment: solid-in-oil nanosuspensions and microemulsions, aiming to enhance permeation. They examined the effects of surfactant type and sonication time, revealing that microemulsions demonstrated quicker alendronate release and higher permeability through pigskin and synthetic membranes compared to nanosuspensions.[73] Alkilani *et al.* devised a transdermal delivery system for alendronate to improve its bioavailability and mitigate gastrointestinal side effects. They utilized nanocarriers to enhance permeability and prolong release, focusing on key characteristics such as particle size, polydispersity index, surface charge, drug entrapment efficiency, and in vitro release. This was achieved through niosomal formulations developed using the ether injection method.[74]

Li *et al.* fabricated a new transdermal drug delivery method utilizing sonophoresis, creating a patch containing chitosan-alendronate nanoparticles in hydroxypropyl methylcellulose-plasticizer. This innovative approach significantly increased encapsulation efficiency and bioavailability, achieving a six-fold enhancement compared to patches containing pure alendronate.[75]

Table 2 summarizes the research on transdermal formulations for controlled drug delivery of alendronate. Despite challenges posed by alendronate's high polarity and hydrophobicity, innovative approaches such as sonophoresis, nanocarriers, microemulsion and pressure-sensitive adhesive systems have shown promising results in enhancing alendronate permeation through the skin. Among the various transdermal formulations, transdermal film composed of PLGA with poly (DL-lactic acid)-block-methoxy PEG (diblock copolymer) showed the best release of alendronate over three weeks.[66] Small, lipophilic drugs that can successfully cross the skin barrier can usually be delivered with transdermal patches. This method may not be as effective for larger molecules or hydrophilic drugs. However, by using the appropriate blend and choice of polymers, microspheres can address this transdermal patch drawback.

Transdermal delivery of drugs is still less prevalent than other drug administration methods, like oral and intramuscular routes, even though it has several benefits. A key consideration in the therapeutic usage of drugs administered by this route is the variability in absorption that leads to uncertain results. Skin permeability, area, temperature, and skin metabolism all affect how quickly drugs are absorbed via the skin. A drug molecule must possess both non-ionic and lipophilic properties in order to effectively pass through the epidermal barrier. Another reason for their lack of popularity is that they are less effective for controlling symptoms quickly, like a fit of panic or an episode of severe agitation, due to their longer commencement of action as contrasted to intramuscular or intravenous methods.[76] Even though transdermal patches face obstacles in acceptability among adults, for older children and newborns who need lower doses than adults, transdermal distribution might be thought of as a practical, non-invasive delivery approach.[77]

2.3 Microspheres

Microspheres are spherical particles that are suitable and widely used for drug vehicles in the micron size range. The general release mechanism of the drug from the microsphere has been shown in Fig. 5. The microspheres are fabricated mostly using biodegradable and biocompatible polymers. In case of hydrophobic drugs, drug release is faster from

Table 2. Research on transdermal drug delivery methods for various bone-related conditions across various domains.

Field	Condition	Formulation	Results	Reference
Dental	Periodontal	Film formulations consisted of PLGA mixed with poly (DL-lactic acid)-block-methoxy PEG (diblock copolymer) efficiently encapsulated alendronate.	By lowering the glass transition temperature of PLGA, the formulation increased film elasticity and enabled better handling. Diblock copolymer was added, which accelerated the release of the drug for over three-weeks.	[66]
		Pressure-sensitive transdermal delivery system composed of PG containing 6% caprylic acid.	Improved drug permeation of the drug.	[62]
		Formulation with PG containing 6% caprylic acid.	Transdermal system's delayed half-life values in comparison to oral formulation, may allow less frequent dosing	[63]
		Alendronate-loaded PG with 6% caprylic acid and amines formulated as a pressure-sensitive transdermal delivery system.	Enhanced drug permeation due to the addition of amines	[64]
		Hydrophilic acrylic adhesive, glycerine, and alendronate were used to formulate transdermal patches.	Improved drug permeability and bioavailability	[65]
Orthopedic	Osteoporosis	Self-dissolving alendronate-containing micron-size needle array (microneedle array) made with HA as the building block using micromodeling technologies.	Transdermal formulation using a microneedle array fully dissolved and absorbed in the skin. The absorption of alendronate after utilizing an alendronate-loaded microneedle array was almost the same as that after subcutaneous administration, and its bioavailability was roughly about 90%.	[68]
		Alendronate incorporated transdermal microemulsion	Improved the skin permeation of the drug, improved bone mineral density, trabecular microarchitecture and bone health	[70]
		HA gel sheet that was made by simply utilizing polyhydric alcohol (propanediol and glycerine) and phosphoric acid to increase the noncovalent interactions between HA molecules.	Following a 24-hour application, the HA gel sheet did not cause any skin irritation for seven days. Bioavailability and drug penetration were both improved.	[69]
		Transdermal patches with sonophoresis assistance made of chitosan-alendronate nanoparticles	Improved encapsulation efficacy of 99.54%, indicating 82.7% drug release over a 12-hour period	[75]
		A dissolving transdermal microneedle containing alendronate niosomes	Enhanced patient compliance, decreased GI side effects, and improved drug penetration with a sustained 60-hour release of alendronate.	[74]
		Transdermal nanosystems utilizing solid-in-oil nanosuspensions, microemulsions, and alendronate	Enhanced skin penetration of alendronate and improved drug loading with small particle size and polydispersity index. Solid lipid nanoparticles showed a better sustained release compared to microemulsion.	[73]

microspheres with size fractions less than 50 μm, while bigger microspheres (>50 μm) exhibit slower release than smaller microspheres. One possible explanation for this could be that drugs with higher hydrophobicity slow down the impact of water inflow into the particles, which will cause drug breakdown to occur more slowly at larger drug-loading contents. In the case of hydrophilic drugs, a faster rate of drug release can be associated with higher drug loadings of larger microparticles, which can be outlined by an increased water influx. The drug's distribution within the microsphere could potentially have an impact on the release pattern. Smaller microspheres may exhibit a diffusion-like release curve due to a uniform drug distribution, but larger microspheres may exhibit a sigmoidal release curve due to a non-uniform drug

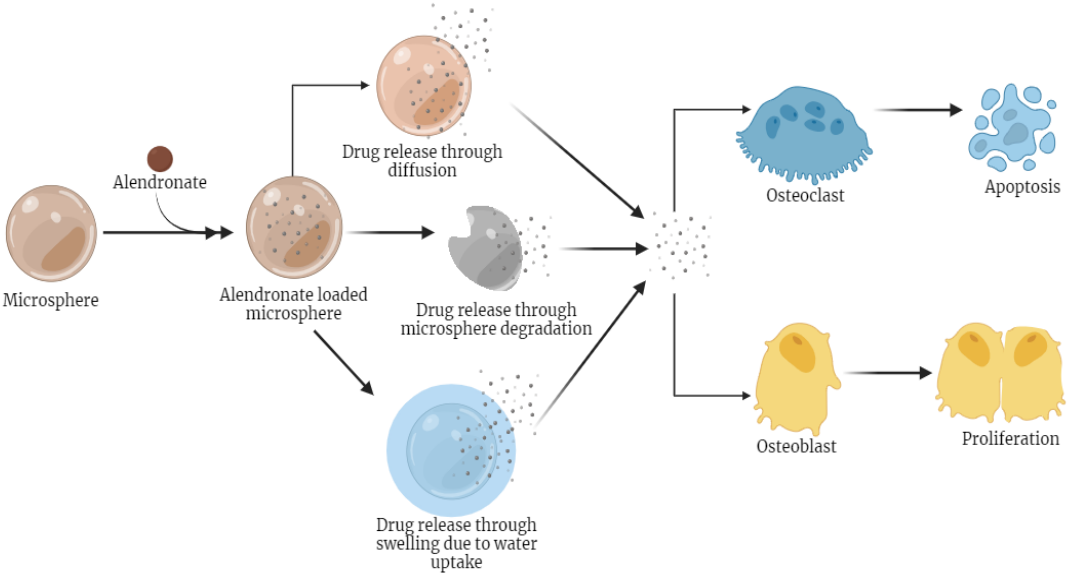

Fig. 5 General release mechanism and action of drug from microsphere (Created using Bio render).

distribution.[78] The porosity of the microsphere can influence the release of the drug. The development of pores in the matrix is influenced by several factors. From the perspective of the drug, as the hydrophilic drug loading rises, the microspheres' pore size will also increase.[79] Highly porous microspheres allow for deeper drug permeation, which causes the release kinetics to be delayed. The drug and polymer interact better over a larger surface area, which changes the rate of drug release.[80]

Many studies have centred on developing controlled-release drug delivery systems using microspheres for various biomedical applications, particularly targeting alendronate, used in osteoporosis treatment. Several approaches were explored to boost the encapsulation efficiency and sustained release of alendronate, considering its hydrophilic nature.[81]

A significant amount of study has been conducted on the development of alendronate sustained release formulations, with a particular emphasis on the use of PLGA-based microsphere systems because of the many benefits that PLGA systems provide, including biocompatibility, versatile formulation options, tunable degradation rate, and biodegradability. One approach involved hybridizing PLGA with HAP to create microspheres capable of efficiently encapsulating alendronate. HAP, similar in structure to natural bone minerals, exhibited high affinity for alendronate, thus enhancing encapsulation efficiency.[81] Wang *et al.* devised a controlled-release system using PLGA and HAP sintered microspheres to encourage osteogenic commitment of synovium-derived mesenchymal stem cells and to investigate the *in-situ* release of alendronate and dexamethasone, which could aid in bone regeneration therapy.[82] Deca *et al.* developed PLGA microparticles using the double emulsion method, containing a high concentration of alendronate, which released the drug steadily over an extended period, offering a novel strategy for treating metabolic bone disorders.[83] Lee *et al.* created an alendronate-releasing PLGA microsphere system with sequentially immobilized heparin and alendronate on the surface of mesoporous silica particles, aiming to bolster osteogenic differentiation and bone regeneration in vitro and in a rat model of critical-sized calvarial defects. This research collectively emphasize on the potential of PLGA-based microsphere systems for delivering alendronate to enhance bone repair and regeneration, offering promising alternatives to traditional bone grafts.[84]

In their respective studies, Shi *et al.* and Wang *et al.* explored the utilization of PLGA microspheres for controlled release of alendronate to promote osteogenesis and enhance bone repair. Shi *et al.* employed a mesoporous silica–HAP composite within PLGA microspheres to prompt *in vitro* osteogenesis in synovium mesenchymal stem cells (SMSCs), demonstrating successful bone formation.[85] Meanwhile, Wang *et al.* developed cross-linked PLGA microspheres containing alendronate for short-term controlled release, showing sustained release of alendronate over nine days and enhanced biomechanical characteristics and ultrastructure of newly formed bone.[86]

Xiong *et al.* and Liu *et al.* have extensively researched poly (L-lactic acid) (PLLA)-based scaffolds for bone tissue engineering, showcasing their better mechanical and biodegradable attributes contrasted to other scaffold material.[87,88] Additionally, PLLA scaffolds demonstrate better mineral deposition and bone ingrowth, indicating their potential for enhanced performance in bone tissue engineering applications.[89] Calcium phosphate microspheres were developed for alendronate delivery, offering controlled release through modulation of crystalline phases. Injectable microsphere-scaffold hybrid systems were also explored, incorporating chitosan/HAP microspheres loaded with

alendronate into PLLA)/nano HAP matrices for bone tissue engineering.[90] Wu *et al.* aimed to innovate by creating a microsphere-scaffold hybrid system for drug delivery and bone tissue engineering, incorporating chitosan/HAP microspheres loaded with alendronate (chitosan/nano-HAP-alendronate) into a PLLA/nano-HAP matrix.[91] Amino-modified polylactic acid (EPLA) nanofiber microspheres demonstrated elevated alendronate adsorption capacity and sustained release.

Chen *et al.* developed EPLA nanofiber microspheres, characterized by higher porosity, substantial surface area, potent adsorption capacity, and abundant active amino groups, making them ideal for drug delivery applications. These microspheres exhibited a remarkable alendronate adsorption capacity, which demonstrated an ideal release profile with steady release of alendronate over a period of roughly 15 days lacking any significant initial burst.[92] Guo *et al.* developed modified polylactic acid nanofibrous microspheres coated with nano HAP to enhance alendronate's sustained release and drug loading capacity. By combining aminolysis with emulsion and thermally induced phase separation techniques, they achieved enhanced hydrophilicity and potent adsorption capacity, enabling nearly five times higher alendronate loading compared to bare microspheres, thus presenting promising avenues for advanced drug delivery systems in bone tissue engineering applications.[93]

Chen *et al.* addressed the need for improved bone defect treatments by exploring injectable bone repair vehicles comprising poly(ε-caprolactone) (PCL)–HAP composite microspheres with controlled alendronate release. They achieved higher encapsulation efficiency and modulated release of the hydrophilic drug within spherical PCL/HAP–alendronate microspheres, offering potential for enhanced osteogenesis.[94] Koulouktsi *et al.* developed a biodegradable microsphere depot using PCL-Vitamin E d-α-tocopheryl poly (ethylene glycol) 1000 succinate copolymers, with anticancer properties. This depot aims to address tumor-induced hypocalcemia defects by prolonging the release of active pharmaceutical ingredients at the location of action, thereby improving stability, and enhancing pharmaceutical action.[95] Furthermore, Baniahmad *et al.* created a PCL-based delivery system incorporating layered double hydroxides (LDH) as a carrier to enhance the bioavailability of alendronate. By dispersing various concentrations of LDH/alendronate into a PCL matrix using the solvent evaporation method, they created a slow-release system for alendronate, offering potential improvements in therapeutic efficacy.[96]

Bone morphogenetic proteins (BMPs) are autocrine molecules primarily involved in bone formation, remodelling, and embryogenesis. They belong to the transforming growth factor-β superfamily.[97] Incorporating these proteins in polymeric formulation can enhance bone formation and regeneration. Lee *et al.* developed HAP microspheres capable of carrying both BMP-2 growth factor protein and alendronate, offering a therapeutic and osteoconductive effect. Utilizing an emulsification process, the microspheres were prepared to mimic the composition of mammal bones, primarily composed of highly biocompatible HAP, ensuring compatibility with biological tissues.[98] Jenjob *et al.* developed bisphosphonate-conjugated polyanionic HA microbeads for controlled delivery of bone morphogenetic protein 2 (BMP2). Methacrylated HA conjugated with alendronate, was photocrosslinked to form the microbeads. These microbeads exhibited sustained release of BMP2 over ten days, with a loading efficacy of up to 91.0% for cationic BMP2 absorption.[99] Meanwhile, Datta *et al.* addressed the fragility and instability of bone extracellular matrix (ECM) hydrogel by creating a hydrogel construct containing oleoyl chitosan and embedded microspheres. This construct facilitated the simultaneous delivery of BMP-2 and alendronate, for treating focal tibial irregularities in a rabbit model. These innovative approaches demonstrate the prospective of controlled drug delivery systems for enhancing bone regeneration and repair.[100]

Huang *et al.* formulated microspheres of poly(β-hydroxybutyrate-co-β-hydroxyvalerate) (PHBV) loaded with HAP and alendronate using a single emulsion technique, aiming for osteoporosis treatment.[101] In a study by Miyazaki *et al.*, magnetite microspheres were investigated for multifunctional biomedical applications, particularly in cancer treatment. These microspheres were created by aggregating iron oxide colloid in a water-in-oil (W/O) emulsion, with alendronate effectively incorporated into the porous structure of the magnetite microspheres under vacuum conditions. The microspheres exhibited mechanical integrity after three days of shaking in ultrapure water, suggesting their suitability for clinical use. The gradual release of alendronate from the microspheres in vitro was attributed to close ionic or covalent interactions between magnetite and alendronate, with the release rate being diffusion-controlled and dependent on the alendronate concentration.[102] Meanwhile, Wu *et al.* developed a microsphere system containing chitosan and nano HAP-alendronate particles using emulsification and cross-linking techniques. This system exhibited high loading efficiency and modulated release of the hydrophilic alendronate, making it suitable for regulated release locally in the bone microenvironment.[103] Wei *et al.* enhanced the osteogenesis-encouraging effect of injectable biomineralized microspheres for bone tissue engineering by incorporating alendronate during their formation in simulated body fluid.[104] Table 3 summarizes the research on microsphere formulations for controlled drug delivery of alendronate. These studies collectively highlight various strategies for developing microsphere-based drug delivery systems tailored for alendronate delivery, offering potential applications in bone repair, osteoporosis treatment, and bone tissue engineering. Among these studies, the microsphere composed of PCL incorporating LDH as a carrier showed the best release of alendronate for up to 60 days.[96]

Table 3. Research on drug delivery methods using microspheres for various bone-related conditions across various domains.

Field	Condition	Formulation	Results	Reference
Orthopedic	Bone Disorder	Alendronate-HAP loaded mesoporous silica composite encapsulated in PLGA microspheres.	The microsphere exhibited a controlled release for up to 30 days.	[85]
		Alendronate conjugated HAP encapsulated in the dexamethasone - PLGA microsphere	Good drug loading efficiency and controlled release of alendronate up to 30 days.	[82]
		Alendronate-containing bioabsorbable calcium phosphate microspheres	Enhanced drug loading and sustained release up to 40 days	[90]
		Alendronate encapsulated PCL–HAP composite microspheres	Microspheres showed a sustained drug release up to 21 days	[94]
		HAP microspheres loaded with BMP2 and alendronate	Improved absorption efficiency of alendronate and BMP2 of 84.1% and 79.2% respectively.	[98]
		Alendronate loaded chitosan/nano HAP composite microsphere	Improved loading efficiency and regulated release of the drug for 25 days	[103]
		Alendronate encapsulated PLGA microspheres	The microsphere exhibited encapsulation efficiency of 13.24% and 58% of the encapsulated drug was released for about 5 days with an initial burst.	[83]
		Alendronate-releasing porous microsphere made of PLGA	The microsphere demonstrated sustained release over a period of 15-30 days.	[84]
		Alendronate-loaded chitosan/HAP microspheres loaded into a PLLA/nano HAP matrix hybrid system.	A cumulative release of 90% in 3 days was observed from the formulated microsphere	[91]
		High porosity, alendronate loaded EPLA nano fibre microspheres	The microspheres demonstrated sustained release for a period of 15 days with a drug loading up to 503 mg/g	[92]
		Alendronate loaded PCL /Vitamin E d-α-tocopheryl poly (ethylene glycol) 1000 succinate copolymers microsphere.	Microsphere exhibited sustained drug release for 30 days	[95]
		Alendronate-loaded poly(β-hydroxybutyrate-co-β-hydroxyvalerate) microspheres integrated with HAP	The microsphere demonstrated a regulated release of the drug for 26 days	[101]
	Osteoporosis	A PLGA cross-linked alendronate microsphere	Microsphere exhibited a controlled release of 50–100 nM of alendronate for 9 days.	[86]
		Nano-HAP deposited on the surface of alendronate loaded EPLA nanofibrous microspheres	The microspheres exhibited sustained release for up to 15 days.	[93]
		Alendronate incorporated in LDH and PCL matrix	The microspheres showed sustained release up to 60 days	[96]

Differently micro structured microspheres still require optimization because of certain shortcomings. The barriers preventing the development of drug loaded microspheres with sustained release include poor encapsulation rate, difficulty in removal of pore-forming agent that is added to the porous microspheres, and the high initial burst concentration of microspheres. Excessive drug loading may cause burst release, in which a significant quantity of the drug is released rapidly and is followed by a prolonged release period. Long-term, controlled release is often achieved with lower pharmaceutical loading.[105]

2.4 Implant coating

Implant-based controlled drug delivery systems have garnered significant attention due to their ability to optimize treatment efficacy while minimizing adverse effects. When sustained, targeted, and accurate drug administration is required over an extended period of time, implant-based delivery might be optimal in some circumstances. With the potential to minimize systemic side effects, implants may be engineered to deliver drugs directly to the site of action, enabling targeted therapy. For the treatment of diseases like localized infections, tumors, or inflammatory disorders, this targeted drug delivery is very

advantageous. Drug loaded polymer matrix are coated or embedded onto implants such as bone plates screws, scaffolds etc to provide a more localized drug release. The release mechanism of the drug from the implant is shown in Fig. 6. Various medical conditions such as osteoporosis, bone defects, diabetes, cancer, and cardiovascular disorders have seen substantial improvements through the utilization of implants for controlled drug delivery.

Mesoporous titania has shown significant potential in drug delivery applications, offering sustained drug release within the therapeutic window. Its biomechanical stability enhances its suitability as an implant coating, particularly in bone fixation systems.[106] Furthermore, it has been demonstrated that drug delivery from coatings made of mesoporous titania is an affirmative way to improve the healing of implants that anchor bone.[33] Studies by Tarafder and Bose investigated the impact of site-specific alendronate delivery on bone formation from PCL-coated scaffolds and the impact of PCL coating on alendronate release kinetics, respectively.[107] Hur *et al.* developed a bone fixation plate capable of locally delivering alendronate in a controlled manner by coating it with chitosan modified with azidobenzoic acid and loaded with alendronate, crosslinked using UV radiation.[108] Bose *et al.* examined the influence of PCL coating on alendronate release from plasma-sprayed Mg-doped HAP-coated commercially pure titanium samples, aiming to reduce burst release.[109] Metal implants, commonly used in orthopedic surgery, can be modified for controlled drug delivery. Titanium alloys, renowned for their mechanical stability and corrosion resistance, can form a stable oxide layer, enhancing biocompatibility. Aryan *et al.* designed an experiment utilizing titanium oxide nanoparticles, strontium, silver, HAP, and chitosan to coat implants with alendronate, prolonging drug release for up to 16 days. Chitosan's large functional group regulates drug release and inhibits strontium release, contributing to controlled drug delivery.[110]

Under physiological conditions, magnesium alloys are prone to fast corrosion, which can be hazardous to nearby tissues. They are also vulnerable to bacterial colonization. To enhance the performance of magnesium alloys in medical applications, Zhang *et al.* created a smart coating for magnesium alloys. To increase corrosion resistance, a primary $Mg(OH)_2$ barrier layer was applied to the magnesium alloy. A light-sensitive mask was then used to construct a series of thin hydrogel patterns with alendronate for bone formation, dimethyl diallyl ammonium chloride for antibacterial properties, and poly(ethylene glycol) diacrylate for bonding. In order to prevent infection, they investigated various pattern sizes ranging from 5 to 80 micrometers and doped the material with berberine, an antibacterial derived from plants. In reaction to pH changes, the hyaluronic acid and berberine coating released the berberine quite quickly in bacterial conditions.[111]

Table 4 summarizes the research on implant-based formulations for controlled drug delivery of alendronate. These developments have a lot of potential to improve patient outcomes in orthopedic treatments by improving implant systems' drug delivery strategies. Among the various implant-based delivery discussed, a bone plate coated with a combination of alendronate and a biocompatible polymer, chitosan modified with azidobenzoic acid and photo-crosslinked using UV light showed the best-controlled release for up to 63 days.[108] Drug formulations, release profiles, and therapeutic indications are often taken into consideration when designing implant-based drug delivery systems. Their proficiency to adjust and change with the needs of patients, disease states, or treatment plans may be limited by this lack of flexibility. Drug delivery systems based on nanoparticles can be customized to target disease states, patient demographics, or treatment plans. Non-invasive or less invasive administration routes are also available for these, whereas implant-based drug delivery systems necessitate invasive surgical procedures that may decrease patient compliance.

There are various ways through which drug release rates can be modulated. Changing the cross-linking density of polymeric networks is a key strategy for managing the release profile of drugs incorporated in the coating. Numerous strategies, such as dip coating, electrospinning, layer-by-layer self-assembly, and electrochemical deposition, can be

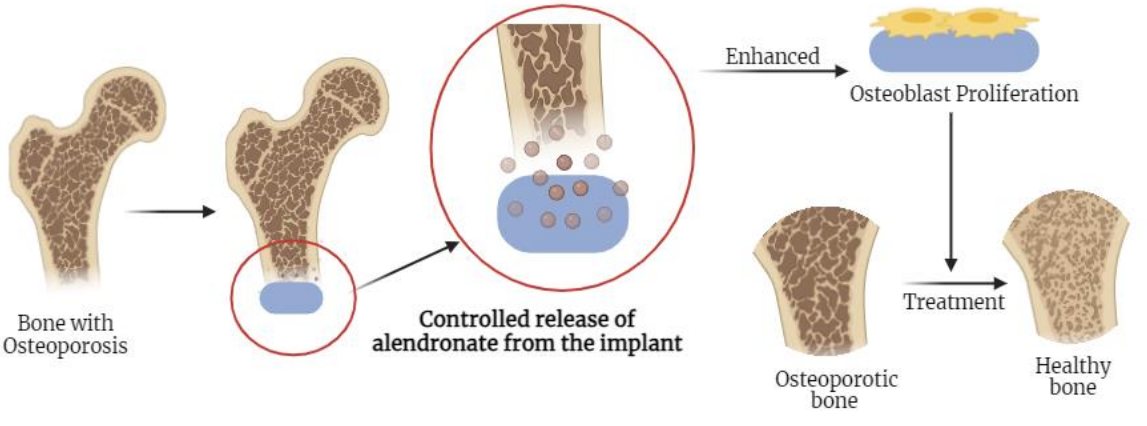

Fig. 6 Representation of controlled release of alendronate through implants (Created using Bio render).

Table 4. Research on drug delivery methods using implants for various bone-related conditions across various domains.

Field	Condition	Formulation	Results	References
Orthopedic	Musculoskeletal diseases	Alendronate integrated 3D printed interconnected macroporous tricalcium phosphate (TCP) scaffolds coated with PCL.	All the scaffolds with alendronate exhibited increased early bone growth.	[107]
	Bone Fixation	Bone plate coated with a combination of alendronate and a biocompatible polymer, chitosan modified with azidobenzoic acid and photo-crosslinked using UV light.	The drug was released from the coating for 63 days @ 4.03 µg/day in an *in vitro* drug release study. By the eighth week, there was a noticeable increase in the volume of newly formed bone in the group that had the plate implanted, which enabled continuous alendronate delivery.	[108]
		Alendronate integrated magnesium-doped HAP coated on titanium implants with a PCL top layer.	Reduced initial burst. During the first 24 hours, samples containing 2 and 4 wt% PCL released roughly 34% and 26% of alendronate, respectively.	[109]
	Osteoporosis	Alendronate incorporated implants composed of titanium oxide nanoparticles, strontium, silver, HAP, and chitosan.	Enhanced resistance against bacterial action and corrosion. Sustained release up to 16 days.	[110]

utilized to apply polymeric coatings on implant surfaces. As a result, it can be either passive or active based on external factors like the system's pH or the activity of particular enzymes. Beyond that, the potential release event may be triggered by outside stimuli such as electric fields, photoradiation, or ultrasonic waves.[112] Research based on smart implant coating for the controlled release of alendronate still needs to be explored.

Despite technological advancements, implant-related challenges continue to be a major concern. Implant coatings that are not sufficiently durable tend to peel off, which reduces their ability to release drugs. For a coating to have a therapeutic effect, the drug must be released continuously. Nevertheless, the majority of the time, a drug is initially released too quickly, decreasing its effectiveness.[113]

2.5 Nanoparticles

The development of drug formulations based on nanoparticles has enabled the treatment of difficult diseases, with increased solubility, enhanced bioavailability, and the capacity to cross biological barriers. These effects are attributed to their small size and large surface area.This property of nanoparticles can enhance the loading efficiency of the drug. The release mechanism of the drug from nanoparticles is shown in Fig. 7. Drug delivery using nanoparticles can be accomplished in a number of ways. During the formulation stage, the drug can be physically encased into biocompatible nanoparticle assemblies. Another technique involves chemically attaching it to a nanomaterial in order to help get the drug to the desired location. Particle size, surface charge, stiffness, and structural topography all affect how nanoparticles behave in the body. A nanoparticle's half-life and biodistribution can be enhanced by modifying its physicochemical characteristics. Typically, positively charged nanoparticles are removed from the

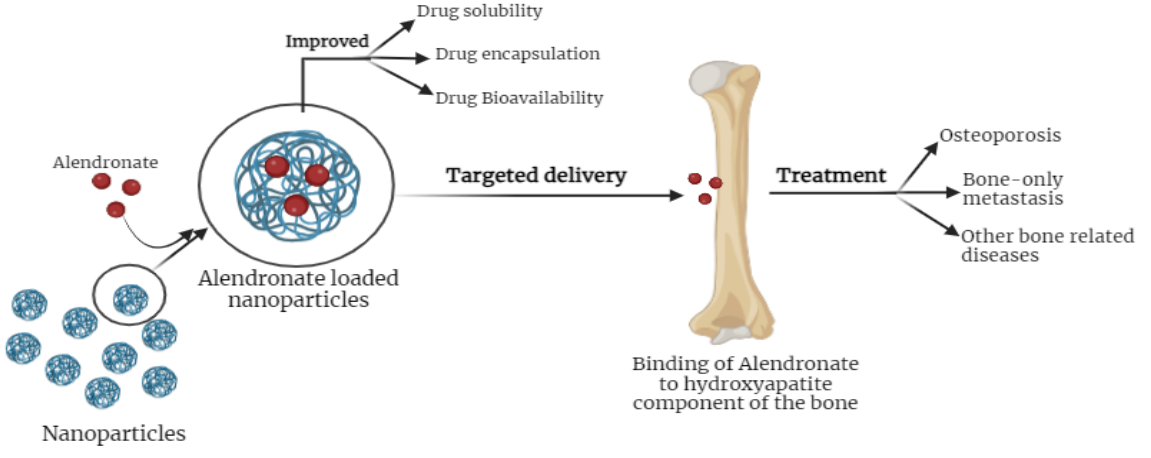

Fig. 7 Illustration representing alendronate delivery through nanoparticles (Created using Bio render).

bloodstream more quickly than highly negatively charged ones. Neutral, slightly positive, and slightly negative nanoparticles on the contrary, have longer half-lives and can circulate in blood.[114] The enhanced specific surface area ensures the effective adhesion of nanoparticles to the surfaces of cells and tissues. While particles bigger than 600 nm can deform the membrane and enter the cells, which could result in the death of the erythrocyte, particles smaller than 100 nm can be effectively adsorbed on the erythrocyte surface without leading to apoptosis or morphological irregularities.[115,116]

Off-target delivery often happens when controlled drug delivery using nanoparticles is used. In an effort to boost local drug concentrations and decrease off-target effects, Swami *et al.* used engineered bone-targeting polymeric nanoparticles that delivered alendronate drugs to the bone in a spatiotemporally controlled manner. These nanoparticles, which were created by combining PLGA, PEG, and alendronate-conjugated polymers, demonstrated improved bone-binding capacity, as revealed by HAP binding assay and vivo imaging.[117] Posadowska *et al.* aimed to fabricate a site-specific delivery system for alendronate that could be easily managed by surgeons and stay in the intended tissue location. They first created PLGA nanoparticles loaded with alendronate and then incorporated them into a drug delivery system based on gellan gum hydrogel.[118]

Hydrophilic molecules such as alendronate encapsulation are difficult to monitor because careful monitoring of the operating conditions is required. Miladi *et al.* addressed this issue by investigating polycaprolactone-based nanoparticles loaded with alendronate. They employed two methods, nanoprecipitation, and double emulsion evaporation, to prepare the nanoparticles. Their study revealed that the double emulsion method yielded superior results, demonstrating increased drug loading and encapsulation efficiency compared to nanoprecipitation.[119] K. Miladi *et al.* further explored the use of chitosan, a safe and biodegradable substance, for drug delivery purposes. The significantly higher positive charges of chitosan facilitated increased electrostatic interactions, allowing for the entrapment of high amounts of alendronate. They employed the ionic gelation technique to prepare chitosan nanoparticles loaded with alendronate.[120] To address the low bioavailability and high toxicity of alendronate at higher doses, Ravan *et al.* created alendronate delivery vehicles with high encapsulation and loading efficiencies: mesoporous bioactive glass and aminated mesoporous bioactive glass. The results of the research indicated that aminated mesoporous bioactive glass released alendronate more sustainably and controlled than mesoporous bioactive glass, which may allay worries about toxicity and low bioavailability.[121] Iles *et al.* created a nanostructured system with biodegradable polymers for the regulated release of alendronate sodium in order to treat the gastric problems brought on by the long-term use of bisphosphonate. A 98.5% drug incorporation rate and nanoparticle size of 51.02 nm were found to indicate effective encapsulation. Biological tests revealed that the gastric lesions had healed, myeloperoxidase and malondialdehyde levels were normal, and that even at high concentrations, there was no adverse effect in osteoblastic cells.[122]

Li *et al.* synthesized a calcification-targeting nanoparticle by conjugating alendronate to PLGA particles. These nanoparticles exhibited low cytotoxicity and good biocompatibility, demonstrating the ability to bind directly to HAP and porous scaffolds, mimicking calcified tissues. These findings suggest potential applications in diagnosing and treating calcification-related diseases.[123] Many cancers, including lung and breast cancer in humans, are able to spread quickly to bone, giving rise to a variety of bone diseases like secondary bone tumors and bone metastases. The physiological environment of bone is ideal for cancer cells to adhere to and multiply. An effective drug for treating bone metastases is alendronate. Co-delivering curcumin and alendronate to boost antitumor activity and stop tumor metastases to bone was made possible by a drug delivery method created by Dong *et al.*, and poly alendronate-hyaluronan-curcumin copolymer with disulphide bond linker is a novel multifunctional polymer-drug that targets CD44 receptor and is redox-responsive.[124]

To improve the biological distribution of the drug in bone tissue, the surface of nanoparticles can also be altered with cell/tissue-targeting groups, such as bisphosphonates or osteoclast/osteoblast-targeting peptides.[125] Alendronate's strong affinity for HAP makes it a valuable tool for targeted drug delivery. Alendronate can be utilized to deliver other drugs to a specific site because of its strong affinity for the HAP component of bone. The bone-targeting Triptolide (TP) nanoparticle is a novel nanoformulation that was created by Wen *et al.* to address the unique clinical requirement of treating bone-only metastases.[126] Using silk fibroin and sodium alginate, Vafapour *et al.* synthesized nanoparticles that were subsequently modified with sodium alendronate to increase the efficacy of chemotherapy for osteosarcoma.[127] Chen *et al.* fabricated a nanoparticle-based delivery system using PLGA as the core coated with alendronate-modified D-α-tocopheryl polyethylene glycol (TPGS) succinate and folic acid-conjugated TPGS for paclitaxel (Taxol) delivery. This system significantly improved treatment efficacy for bone metastatic breast cancer by enhancing alendronate-mediated binding affinity for HAP and stimulating payload uptake by cancer cells overexpressing the folate receptor, resulting in inhibited tumor growth and improved survival rates in vivo.[128] Conners, Christopher *et al.* evaluated gold nanoparticles functionalized with alendronate and pamidronate for treating osteoporotic bone disorders. These nanoparticles-maintained RANKL expression in osteoblast cell lines, laying the groundwork for therapeutic strategies employing bisphosphonate-functionalized gold nanoparticles.[129] Adenosine, as an external molecule, can be used to treat osteoporosis since it aids in the upkeep of strong bones. Adenosine's instability and rapid breakdown in the human

body can cause numerous organs to go into shock when administered directly, which is a problem. Hoque *et al.* developed a functional nanocarrier delivery system that has the ability to target the bones. This nanocarrier was fabricated using emulsion suspension photopolymerization using hyaluronic acid, allowing it to bind adenosine. Alendronate was used as another conjugated molecule to enhance the adhesion capability of the nanocarrier to bones. Adenosine delivery using such a tailored approach significantly decreased bone loss during the osteoporosis-simulated mice's surgical procedures. The mice that received the treatment showed signs of healthy bones.[130]

Alzheimer's disease is thought to be significantly influenced by isoprenoids. Alendronate can be utilized to treat the disease because of its capacity to control isoprenoid levels. By using the ionic gelation process, Zameer *et al.* created alendronate-loaded chitosan nanoparticles that were intended to be administered intranasally to the brain. The size of the nanoparticles was resolved to be 200 nm, and the prolonged release of alendronate from the nanoparticles demonstratedalterations in the deterioration of cognitive function brought on by intracerebroventricular streptozotocin-induced Alzheimer's disease.[131] The development of nanodiamonds linked to alendronate and their potential for tre-

Table 5. Research on drug delivery methods using nanoparticles for various bone-related conditions across various domains.

Field	Condition	Formulation	Results	References
Orthopedic	Osteoporosis	Alendronate incorporated PCL nanoparticles	Improved the drug loading and the encapsulation efficiency. The formation showed a sustained release up to 300 minutes.	[119]
		Alendronate encapsulated chitosan nanoparticles with sodium triphosphate	enhanced the encapsulation efficiency. The drug release was observed to be faster in acidic medium by 360-minutes only 42% of the encapsulated drug had been released.	[120]
		An injectable method based on alendronate-loaded nanoparticles suspended in a gellan gum was created for the intra-bone delivery of alendronate.	The nanoparticles showed a sustained release up to 25 days with an initial burst.	[118]
		Alendronate loaded solid lipid particles	Improved drug loading efficiency and controlled release up to 72 hours.	[133]
	Osteosarcoma	Alendronate loaded mesoporous bioactive glass nanoparticles	Nanoparticles showed a loading efficiency of 63% and encapsulation efficiency of 85%. Sustained release was obtained up to 4 days.	[121]
	Bone Diseases	Acetylated cashew gum or propionic anhydride cashew gum were combined with Angico gum to create the nanoparticles for alendronate encapsulation.	The formulation showed a controlled release up to 420 mins and encapsulation efficiency of 98.5%.	[122]
		The Nanoparticles composed of PLGA, PEG and alendronate	The nanoparticles demonstrated improved bone localization because of its long circulation and ability to target bone minerals. Bortezomib was specifically delivered to the bone marrow microenvironment by the bone-targeted NPs using sustained release polymer technology, producing anti myeloma effects.	[117]
	Bone Metastasis	As a vehicle for paclitaxel, a nanoparticle-based delivery system was created, with PLGA as the hydrophobic core and alendronate-modified D-α-tocopheryl polyethylene glycol succinate and folic acid-conjugated TPGS on top.	This formulation exhibited superior HAP binding.	[128]
		"Bone-targeting" local injectable Triptolide nanoparticles decorated with alendronate	The nanoparticles exhibited an encapsulation efficiency of 97% and a controlled release lasting up to 5 days.	[126]

ating a variety of illnesses by directly reaching the treatment site, *i.e.,* the bones were discussed by Ryu *et al.* Alendronate nanodiamonds demonstrated high adhesion to hydroxyapatite, according to the data. Alkaline phosphatase, an enzyme linked to bone development, was found to be more active when regular and alendronate nanodiamonds were present, with the effect being greater for the latter. The research findings highlight the unique features of alendronate nanodiamonds that make them excellent for targeting bones and, consequently, show significant promise in directly treating disorders like osteoporosis.[132]

Lipid-based drug delivery particles, such as solid lipid nanoparticles (SLPs), offer improved oral and topical administration of alendronate. SLPs combine benefits like incorporating both lipophilic and hydrophilic drugs, controlled release, and increased bioavailability. Gelucire 44/14-based SLPs enhance alendronate's solubility and wettability.[133] Additionally, lipid-coated nanoparticles modified with alendronate, developed by Zhong *et al.*, target bone and serve dual roles in bone cancer treatment and repair.[134]

Table 5 summarizes the research on nanoparticle-based formulations for controlled drug delivery of alendronate. Drug formulations based on nanoparticles are being developed to improve solubility, bioavailability, and targeted delivery, thereby addressing treatment challenges. Alendronate-loaded nanoparticle studies demonstrate how hydrophilic molecule encapsulation can be optimized through techniques like double emulsion and chitosan encapsulation. These developments could lead to better treatment outcomes in a range of medical applications. Among the various formulations developed, injectable PLGA nanoparticles, suspended in a gellan gum showed the best regulated release for 25 days.[118]

Despite an enormous amount of money spent on researching nanoparticles and showing promising results in early-stage studies, not many of these treatments have successfully moved from laboratory research to actual use in hospitals or clinics. Fewer than 60 nanoparticle-based drug formulations have already been authorized for clinical use, which demonstrates challenges in getting these innovative treatments to patients.[135] To comprehend the biodistribution of nanoparticles, predictive models like physiologically based pharmacokinetic (PBP) models must be developed. The biodistribution of nanoparticles can be studied by different imaging and counting techniques. However, most of these studies are based on qualitative or semi-quantitative techniques alone, which may not provide enough information to adequately formulate an accurate quantitative model.[136] Most of the literature studies only calculate the concentration of drug loaded in nanoparticles, which might lead to misleading results because the drug behaves differently in the body once released. In addition, biodistribution data from the nanoparticle are generally sparse, with at most only a few time points studied, and not much information on long-term biodistributions. Biodistribution characterization necessitates weekly observations of points in time across various biological samples and multiple administrations of nanoparticles are necessary, and repetitive dosing may cause alterations in the adsorption, distribution, metabolism and excretion (ADME) behavior of the nanoparticles.[137] Standardized reporting methods may render nanoparticle pharmacokinetics more comparable, and the precision of pharmacokinetic modelling heightened because errors may be introduced in studies through irregular reporting practices. The absence of adequate in-vitro and in-vivo data required to comprehend the factors for the ADME of nanoparticles in preclinical species and humans is one of the main challenges in the development of predictive PBP models for nanoparticles and their successful clinical translation. It's possible that the PBP model's structure and parameters, which were determined by pharmacokinetic data produced for a single type of nanoparticle, may not work for other types. Absence of sufficient quantitative data to support the creation of a PBP model for nanoparticles, despite the abundance of published data available on the biodistribution of nanoparticles.[135]

Table 6 summarizes the merits and limitations of the numerous delivery strategies that are covered in the study based on the literature review.

3. Challenges and prospective view

This review highlights various strategies to address the limitations of current alendronate delivery methods by briefing about the importance of controlled drug delivery to strengthen the drug's bioavailability and efficacy. Regardless of the administration method, challenges persist due to the drug's properties, particularly its hydrophilic and polar nature, which may result in leaching from the formulation. Alendronate's strong affinity for HAP, capable of acting as both a drug carrier and bone mineral reservoir, underscores the importance of HAP in alendronate delivery systems, especially when combined with biopolymeric scaffolds. However, drug binding to natural bone mineral (HAP) surfaces via electrostatic interactions may trigger rapid release upon administration. Continued progress in controlled drug delivery, employing technologies like dendrimers and nanobots for alendronate delivery, could enhance drug loading efficiency and improve targeted delivery precision. Furthermore, the development of user-friendly formulations may expedite their availability in the market.

4. Conclusion and perspective

In conclusion, advancements in drug delivery systems, which give controlled release, targeted delivery, and stable drug protection, have great potential for treating various disorders such as periodontitis, osteoporosis, and other bone-related disorders. The different formulations developed to deliver alendronate in a controlled way are compiled in this review article under several sections, including gel-based, transdermal, microsphere, implant-based, and nanoparticle-

Table 6. Advantages and disadvantages of various delivery methods for controlled drug delivery of alendronate.

Delivery Method	Advantages	Disadvantages
Transdermal	• Non- invasive drug delivery method • Allows self-administration thereby improving patient compliance • Improved bioavailability of the drug buy avoiding the first pass affect. • An efficient method of administering drugs, particularly for pediatric patients and older patients who have trouble swallowing.[77]	• Most drugs have large molecular sizes or high concentrations that hinder skin absorption, making it difficult for them to be absorbed via the skin.[60] • It can be challenging to establish uniform drug dosing since other factors that may impact drug absorption including temperature, skin thickness, and hydration. • The onset of pharmacological effect is typically delayed with transdermal delivery compared to other administration methods.[76,77]
Microspheres	• Drug efficacy and side effect minimization can be achieved by tailoring microspheres to deliver drugs at specific sites of action. •Drugs with low water solubility may benefit from the improved solubility and absorption provided by microspheres, which would increase their bioavailability.[78,79]	• Certain microsphere formulations may not have a high loading capacity. Multiple parameters, such as particle size, polymer type, and environmental factors, might have a direct or indirect impact on the rate of drug release. • Microspheres may have an agglomeration propensity, which could impact their efficacy and dispersion.[78,79]
Implant coating	•Implant coatings that are laden with drugs can be designed to distribute drugs directly to particular tissues or organs, improving therapeutic outcomes while lowering systemic side effects. Drug delivery via implants improves bioavailability by preventing the digestive tract from destroying the medication.	• Implantation requires surgery, which entails risks of infection and problems as well as the potential for a lengthy recovery period. • It's also possible that the coating coated with medications peels off and doesn't release the drugs. • Implants have the potential to promote biofilm formation and bacterial colonization, which raises the risk of infection. • Once implanted, it is difficult to modify the medication or the dosage.
Nanoparticles	• Nanoparticles can be engineered to specifically target particular cells or tissues, thereby minimizing toxicity and optimizing therapeutic effects. • They can be customized to meet the specific drug's requirements as well as therapeutic goals because the materials used to make them can range widely, from lipids to polymers, etc. • Smaller diameters of nanoparticles allow for greater drug delivery effectiveness due to improved cell penetration.	• Some nanoparticles have toxic effects depending on their formula and interaction with biological systems. • Some nanoparticles may induce an immune response.

based formulations. This article briefly discussed the benefits and drawbacks of each polymeric system while highlighting the formulations that provided the best-controlled release of alendronate. Transdermal patches can typically be used to administer small, lipophilic drugs that effectively penetrate the skin barrier. Although transdermal patches are a beneficial, non-invasive way to administer small lipophilic drugs that can successfully pass through the skin's protective layer, hydrophilic drugs, such as alendronate, might not respond well to this approach. Additionally, the longer commencement of action compared to intramuscular or intravenous procedures may make it more challenging for patients to accept and adhere to treatment plans.

However, this drawback of transdermal patch can be addressed by microspheres by employing the right blend and selection of polymers. The implant coating-based controlled drug delivery can deliver the drug in a more targeted manner compared with conventional implant-based drug delivery; however, implants are prone to biofilm formation, and the drug-loaded coating can detach from the implant, thereby decreasing the effectiveness of the delivery method. To overcome some of these drawbacks, the use of nanoparticles can improve the drug-loading capacity of formulation for controlled drug delivery. Moreover, further modification on the surface of nanoparticles has the ability to enhance targeting drug delivery, thus maximizing treatment outcomes.

Hydrogels that react to stimuli, such as temperature, light, pH, or chemical triggers, can be used in targeted and sustained alendronate drug delivery systems. Further research and development are still required to improve its utilization in the treatment of disorders like osteoporosis. This article also provides insight to researchers to determine the ideal polymer combination for more effective and regulated delivery of alendronate. Among the various studies discussed in this article, developing formulations using polymers such as PLGA, PCL, and chitosan offered a good, controlled release of alendronate. Over the years, more work has gone into discovering novel drugs and bringing them to market than designing controlled drug delivery systems for drugs that are currently on the market but have solvable problems in their pharmacokinetic profile or mode of administration. The innovative formulations of alendronate have not succeeded in breaking into the commercial market, despite improvements in controlled delivery systems. Currently, the only available formulations are oral tablets and injections. By understanding the vital role of patient compliance, pharmaceutical companies can help increase the competitiveness of controlled drug delivery system development. Overcoming these challenges through research could offer new avenues for drug delivery of alendronate.

Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

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