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# Targeted drug delivery by bone cements

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ABSTRACT

Bone cement (BC) is one of the most crucial materials for the substitution of damaged bones. Polymer or ceramic can be used as cement materials. Systemic drug delivery to the bone is difficult since human bone has limited perfusion. BC can carry drugs directly to the bone without causing adverse effects on healthy tissues, so it is a good choice for targeted drug delivery. Growth factors in addition to anti-inflammatory, anticancer, analgesic, and antibiotic reagents are just a few of the medicinal chemicals that may be added into BC for various treatment techniques. Our goal in this review is to introduce diverse BCs, drug loading mechanisms in BCs, and ultimately their clinical applications in dental potentials, inflammation therapy, bone infection, treatment of osteoporosis, coating of implants, and cancer therapy.



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## 1. Introduction

Bone is a vital organ in the human body that controls hormones, creates blood cells, and protects and supports other organs [1]. Hundreds of millions of individuals worldwide suffer from musculoskeletal illnesses and disorders like back discomfort, trauma from sports, road traffic accidents and war, bone tumors, bone fractures, osteonecrosis, osteoporosis, arthritis, and spinal problems [2-4]. Based on the Bureau of Labor Statistics in 2014, 32 percent of workplace injuries and illness is related

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to musculoskeletal disorders [5]. Davis et al reported that the compensation system of Ohio workers between 1999 and 2004 incurred an annual cost of about $3 billion for musculoskeletal disorders [6]. Bone injuries and skeletal deformities of a particular critical size or greater are well known for posing significant therapeutic issues due to the inability of bone tissue to heal spontaneously in a reasonable length of time [7, 8]. In developed countries, the aging of the population is happening, and the number of people suffering from joint diseases like osteoarthritis is predicted to rise [9]. When bone is damaged, it may go through a self-healing process. If, on the other hand, a portion of the bone is lost due to a trauma or an unhealthy state, repair is required [10-12]. The size of the incision determines how quickly a bone defect heals. When the extent of the defect exceeds the healing capability of the bone, fibrous connective tissue takes over as the dominant tissue in the bone defect [13, 14].

Xenograft (transplantation between different species), allograft (transplantation within the same species), and autograft (transplantation inside the same body) are all used in the surgical therapy of bone disorders. A xenograft is less costly and more plentiful, but it has drawbacks such as ethical concerns, xenosis, and chronic or hyperacute rejection. Disease transmission and immunogenic rejection are issues with allografts. The third procedure (autograft) is the gold standard in clinical practice; however, it also has drawbacks such as hematoma formation, anatomical constraints, the requirement for a second operation, and donor-site morbidity [15-18]. To circumvent these limits, the use of spontaneously synthesized and manufactured bone graft substitutes intended to direct and guide newly formed bone has garnered interest. A perfect bone replacement would combine osteoinductivity (the ability to induce new bone generation) and osteoconductivity (the ability to grow the bone on the materials' surface) into the design of the synthetic porous graft material, allowing for bone growth while being biocompatible, biodegradable, and mechanically stable [19-21]. In recent years, bone cement (BC) has been in high demand in medicine application because of the population ageing, which is accompanied by bone weakness gradually, and an increment in the number of accidents [22-24]. Biomaterials developed by combining a liquid phase and a powder phase that may be molded and implanted as a paste and set once implanted within the body are referred to as BC [25].

BC can be utilized as a carrier of bioactive compounds, which can protect the implant against battle bacteria introduced during the surgical procedure and other germs, cure local infections in addition to its fracture stabilizing and bone filler functions [26]. Furthermore, although joint replacements are currently the most effective treatment option for severe joint problems, postoperative infection remains a worry, demanding sophisticated and expensive measures. While incorporating a powdered antibiotic in the BC may help reduce the rate of infection, the powder often agglomerates, impairing the cement's mechanical performance and antibiotic release properties [9]. Ayre et al. [9], for example, created a new delivery method comprised of liposomes loaded with antibiotics on a nanoscale for incorporation into polymethyl methacrylate (PMMA) BC. This new technique allowed for a progressive and more regulated distribution of antibiotics over 30 days.

**Table 1.**
Calcium orthophosphates, which are extensively employed in BCs.

| Name of compound | Ca/P ratio | Chemical formula | Abb. |
|---|---|---|---|
| β-Tricalcium phosphate | 1.50 | $\beta$-$Ca_3(PO_4)_2$ | B-TCP |
| α-Tricalcium phosphate | 1.50 | $\alpha$-$Ca_3(PO_4)_2$ | α-TCP |
| Tetracalcium phosphate | 2.00 | $Ca_4(PO_4)_2O$ | TTCP |
| Octacalcium phosphate | 1.33 | $Ca_8H_2(PO_4)_6$ | OCP |
| Monocalcium phosphate anhydrous | 0.50 | $Ca(H_2PO_4)_2.H_2O$ | MCPM |
| Monocalcium phosphate monohydrate | 0.50 | $Ca(H_2PO_4)_2$ | MCPA |
| Hydroxyapatite | 1.67 | $Ca_{10}(PO_4)_6(OH)_2$ | HA |
| Dicalcium phosphate dihydrate | 1.00 | $CaHPO_4.2H_2O$ | DCPD |
| Dicalcium phosphate anhydrous | 1.00 | $CaHPO_4$ | DCPA |
| Calcium-deficient hydroxyapatite | 1.5-1.67 | $Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ (0<x<1) | CDHA |
| Amorphous calcium phosphate | 1.2-22 | $Ca_3(PO_4)_2.nH_2O$ | ACP |

An increase in musculoskeletal problems frequently necessitates medication therapy at the defect/ injury/ surgery site. One of the most critical components of the treatments is increasing drug access to particular bone regions and managing drug release in a way that the target medicine concentration may be maintained within the therapeutic index for extended periods. As a result, a significant amount of work has gone into developing materials capable of releasing pharmaceuticals in a predictable and consistent manner [27-30]. Otsuka et al. [31] developed and evaluated a novel drug delivery technique based on a self-setting bioactive calcium phosphate cement (CPC) composed of tetracalcium phosphate and dicalcium phosphate in vitro, using the anticancer compound 6-mercaptopurine (6-MP) as a model molecule. The rate of release from heterogeneous drug-loaded cements of varying thicknesses (1, 2, and 3 mm) was shown to be a function of thickness, suggesting that the cement formulation design may control release kinetics. As a result, while the majority of these drug carriers are polymers, some inorganic materials can also play a role in the pharmacological therapy of skeletal illnesses.

The major categorization of BC systems is covered in this study, as well as their preparation procedures for bone substitution. Furthermore, our goal is to develop a drug loading mechanism in BC for targeted delivery and therapeutic applications in cancer therapy, implant coating, osteoporosis treatment, bone infection and inflammation treatment, and dentistry applications.

## 2. Bone cement systems

BC was created because of its flexibility in the surgery process, shorter hospital stays, and little secondary harm. It was produced, deeply and thoroughly examined, and subsequently widely employed as one of the bone healing materials. BC is a substance that is self-setting and easy to shape. The solid particles are first poured into the solution, resulting in a viscous liquid with injectability and high fluidity. Consequently, it could immediately be injected into faults or shaped into a certain form. Following the formation of the paste, the material continues to react and undergoes the "self-setting" process, developing strength and allowing it to be utilized as a bone replacement. Because the entire process could be carried out at room or body temperature, and the material could achieve acceptable mechanical strength in a relatively short period (typically a few minutes), the BC ushered in a new era for the mending of bone deformities. During the development of BC, PMMA cement was first developed as a bone replacement to enhance human life quality. PMMA BC had a favorable impact on prosthetic joint advancement and was originally used in bone restoration [32, 33]. PMMA acrylic BC has earned a distinguished place in the realm of synthetic biomaterials since then, and while the composition of the cements has remained mostly the same, dispensing processes and innovative mixing are increasingly being employed to improve the cement's performance. In addition, additives including bioactive glass fillers, fluoride salts, and antibiotics have been studied to improve the therapeutic function of PMMA cement [34].

Ceramics have a negligible chemical reactivity, exceptional wear resistance, excellent hardness, and high melting point, which have led to a broad range of uses as functional materials at high temperatures [35,

36]. CPCs have been examined for neck and spinal reconstruction after burst fractures because of some of the drawbacks of PMMA cements, such as an increased risk of fracture in nearby vertebral bodies [37], high polymerization temperatures, and monomer toxicity. CPCs are resorbable and imitate the mineral component of bone [38], facilitating natural bone ingrowth and remodeling [39, 40]. CPCs are biocompatible and bioresorbable; however, because of their poor mechanical strength, they are mostly employed in maxillo-facial and cranial procedures.

Glass ionomer cements (GICs) are a frequent and beneficial solution for restorative treatment in dentistry for fillings that are not located in high-stress areas. GICs, on the other hand, have numerous benefits over permanent filling materials like resin-based composites, including the anti-cariogenic qualities like long-term fluoride release, dentin without the use of an intermediate agent, and the ability to bind to wet enamel. A low coefficient of thermal expansion and biocompatibility are two more therapeutic features that reinforce their significant position in regular dental treatment [41-45]. In this part, we'll look at three different BC biomaterial types and their applications, as well as some novelties and modifications used by researchers to mitigate their disadvantages.

*2.1. Calcium phosphate bone cement*

CPCs are commonly used to treat bone deformities. Extensive research has been performed to enhance their characteristics since their discovery in the 1980s, and accumulating data supports their expanded use in bone tissue engineering [46]. Because of their chemical closeness to the mineral elements of natural bone, CPCs have several benefits over other calcium phosphate-based materials [47, 48].

CPCs have several drawbacks, including an inflammatory reaction to synthetic polymers, a lack of mechanical strength, a pore size restriction on ingrowth, and the difference between bone degradation and regeneration rates. Efforts are constantly being made to solve these issues [49, 50]. Minimizing foreign body response by employing natural polymers [51, 52], adding materials to improve mechanical strength [53], regulating contact with bodily fluid to increase degradation rate [54], improving mechanical strength, and controlling pore size [55] have all been prioritized. Bone flaws are filled and healed using CPCs. Incorporation of cements into polymers, including collagen, gelatin, cellulose, chitosan, chitin, alginate, and synthetic polymers such as poly (L-lactic acid), (PLLA) polycaprolactone (PCL), poly (lactic-co-glycolic acid) (PLGA), and polyethylene glycol (PEG) are mainly done to fill bone flaws [56].

CPCs allow for the insertion of various components as well as hardening at body or room temperature because of their intrinsic porosity. Cells, physiologically active chemicals, and medications may all be used without their functions being harmed or even losing their activity throughout the procedure. In addition to the osteoconductive property, this modification in the CPCs provides novel features, such as supporting the control of pathologies or illnesses including osteoporosis or bone cancers, and increased capacity for bone regeneration [57].

Studies are also being performed to see if embedding growth factors and medications in cement might improve efficacy [58, 59]. These novel cement paste compositions, according to Vorndran et al. [60], may be employed as a controlled release mechanism for antibiotics (vancomycin, gentamicin). From pre-mixed one- and two-phase cements, both antibiotics experienced a burst release of 7–28 percent, followed by a square root of time release kinetic for vancomycin. In the early days of the release experiment, gentamicin release rates also fell, but after roughly a week, they remained quite stable for many weeks. The sulfate counter ion's participation in the cement setting process modified the drug's solubility, resulting in this unique release kinetic. The drug-loaded cement pastes displayed high antibacterial efficacy against Staphylococcus aureus in an agar diffusion test. In the Loca et al. [61] study, CPC modification with vancomycin-loaded PLA microcapsules decreased the initial burst release of medicine by more than 7 times, with just 30.4 ± 1.3 percent of medication released after 43 days. CPC was transformed with PLA/vancomycin microcapsules filled and coated with nanosized hydroxyapatite after 43 days, resulting in 85.3 ± 3.1 percent vancomycin release. Roy et al. [62] created a composite CPC scaffold using a newly developed resorbable calcium phosphate cement (ReCaPP) formulation with porogen degradable microspheres of biocompatible poly (lactic-co-glycolic acid) (PLGA). Vancomycin's in-vitro release from the composite CPC scaffold suggests that the drug's interaction with the composite scaffolds may be tweaked to achieve regulated release kinetics.

Biomaterials' drug-adsorption properties are substantially determined by their microstructure like grain size, roughness, porous architecture (size distribution, connectivity), specific surface area, and so on [57]. These features are influenced by the processing conditions, such as the form of the starting powder, the particle size, and the liquid/powder ratio [63]. One of the most difficult difficulties for a drug-carrier biomaterial is to maintain adequate mechanical stability, akin to bone tissue while exhibiting adequate macroporosity for bone ingrowth and cellular infiltration [64]. Many CPCs with various compositions are commercially available and have been studied [21, 65]. CPCs are made through a chemical reaction involving two phases – a liquid and a solid–when mixed form a paste that gradually sets and hardens into a solid mass. One or more calcium phosphate molecules make up the solid phase. The liquid is water or a phosphate or calcium -containing solution that may also contain citric acid [66, 67], succinate [68], chondroitin sulfate [68, 69], gelatin [70, 71], hyaluronate [72, 73], alginate [54, 74], or chitosan [21, 75] to facilitate the dissolution of the initial CaP compounds until the solution becomes oversaturated, resulting in crystal reprecipitation. The entanglement of plate-like or the reprecipitated needle-like crystals causes the cement to solidify. In general, a cementing system is a heterogeneous mixture including a hardening liquid (binder) and one or more solid distributed active phases (fillers). Hardening and setting occurs as a result of the interaction of these components. The setting time is determined by changes in phase composition and mechanical characteristics, as well as the presence of heat influences [76]. CPCs can readily meet the requirements in regenerative medicine for producing materials that can act as carriers for the transfer of bioactive compounds and medicines and support bone tissue ingrowth. The ability to manipulate a self-setting paste has been demonstrated to allow for a variety of processing procedures in the manufacture of preset CPC scaffolds or self-setting, as well as CPC-based microcarriers and granules. Furthermore, with the creation of "ready to use" CPCs, several difficulties with the CPCs' attributes being affected by the surgeon's handling can be addressed [64]. All CPCs have a powder phase that contains one or more calcium phosphate molecules (Table 1) [77].

*2.2. Acrylic cement*

Acrylic bone cements (ABCs) are commonly used in arthroplasties as fixing agents between the implant and the bone [78]. ABCs, particularly those based on PMMA systems, are undegradable, biomechanically strong, moldable, and simple to use materials, and when implanted into irregular craniofacial defects, allow for adequate tissue response, increase filling and leveling for memory tissue preservation, and improve load distribution making them perfect for a transitory use [79]. The ABC is available in two forms: liquid and solid. The polymer, the polymerization reaction catalyst, and the radio-opacifier describe the solid phase (powder); the monomer, the reaction accelerator, and the stabilizer characterize the liquid phase [80]. The most often used BC is a two-component solution that consists of a liquid methylmethacrylate (MMA) monomer and a powder PMMA copolymer [81, 82]. Polymerization is catalyzed by an initiator and happens in four stages: mixing,

waiting, working, and hardening [83-85]. After implantation, the hardening phase might last for weeks [83, 84].

Due to the insufficient biological and mechanical qualities of PMMA, several problems have been documented, including loosening and subsequent fracture of adjustment vertebral bodies [86-88]. A low degree of bioactivity and monomer toxicity, for example, are two other drawbacks of PMMA that restrict its clinical use [89-92]. PMMA is also a bioinert substance [93] that prevents osteointegration or chemical bonding with the bone at the implant site [94]. Furthermore, bone necrosis caused by high exothermic temperatures during the polymerization reaction, as well as the susceptibility to some pathogenic bacteria [95, 96], may result in premature failure [97], necessitating additional interventions and increasing patient complications, which are potentially dangerous to the patient's health [98-100]. PMMA modification with biodegradable or bioactive chemicals has shown tremendous promise in concurrently addressing these two issues [91, 101-104]. There are hundreds of fillers with intriguing features are presently under research for BCs. Previously, the inclusion of bioactive reinforcing agent comprising HA, the titania, BG ceramics, and BGs was carried out. However, these composite BCs could scarcely combine adequate bioactive and physicochemical features for the development of therapeutic applications. The employment of developing carbon-based nanomaterials, graphene oxide and carbon nanotubes as a filler, would considerably increase the mechanical endurance and strength of PMMA, therefore minimizes the potential concern posed by early failuree of the implant. The functionalized GO are biocompatible and promote the implant integration to surrounding tissue. PMMA-based BCs would propose enhancing in the biological features, setting properties, mechanical properties and functional qualities with encapsulation of carbon-based and bioactive nanomaterials reinforcing agents [105].

PMMA is also employed as a drug delivery mechanism in practice [106-109]. To decrease the risk of infection, PMMAs are generally loaded with antibiotics (tobramycin, gentamicin, vancomycin, etc.) to use in joints and similar surgeries [108-111]. By using these cements, antibiotics will be released into the environment resulting in the avoidance of infection until the implant-tissue interactions are complete [112]. Antibiotics have long been investigated as a way to minimize the risk of infection after implantation or treatment of current illnesses by including them into BCs, notably PMMA (resulting in the reduction of the chance of recurrence). PMMA cements loaded with antibiotics currently on the market require significant improvement in terms of their elution profiles, mixing methods, loading doses, and antibiotic types, as these factors have a significant impact on cement mechanical strength, bone ingrowth, tissue toxicity, and antimicrobial efficacy [113]. Slane et al. [114], for example, revealed that increasing antibiotic loading in cement does not always imply increased antibiotic elution. To overcome these issues, Ayre et al. [9] created a novel delivery strategy including antibiotic-loaded nano-sized liposomes and inclusion in PMMA BC. This method was evaluated in a commercial cement (Palacos R) and consistently delivered a higher proportion of the integrated antibiotic (22%) than powdered antibiotic cement (9%), showing that less antibiotic is needed than with conventional cement. The new approach allowed for a progressive and more regulated distribution of antibiotics over 30 days. The study by Matos et al. [115] offered a unique modified PMMA BC matrix loaded with minocycline. The BC matrix with 2.5 percent (w/wBC) minocycline and 10.0 percent (w/wBC) lactose showed the best features, completely releasing the loaded minocycline while preserving antibacterial activity and mechanical properties against common orthopedic infection strains. In vitro testing of the selected matrix revealed that neither minocycline nor lactose loading enhanced the cytotoxicity of BC.

**Table 2.**
Parameters that influence BC characteristics.

| | |
|---|---|
| Environmental elements | pH<br>Humidity<br>Temperature |
| Mixing factors | Pre-implantation time period<br>Mixing approach (speed, time, etc.)<br>Liquid/powder ratio |
| Liquid phase | pH<br>Additives (retarders, accelerants) |
| Powder phase | Powder particle size distribution<br>Additives (retarders, accelerants, seeds, etc.)<br>Constituents relative proportions<br>Chemical composition |

In the 1970s, the FDA authorized the use of BCs for the fastening of knee and hip prostheses. Typically, PMMA is referred to as BC. Other commercial BCs, including glass polyalkenoate (ionomer) cements (GPCs) and CPCs, are used in a range of dental and orthopedic applications [116].

Low-frequency ultrasound, centrifugation, vacuum-mixing, and hand-mixing can all be used to make PMMA, which can result in a range of antibiotic elution rates and porosities. The characteristics of PMMA might vary greatly depending on the surgical preparation process [117]. PMMA is created by combining a powered MMA-styrene co-polymer with a liquid MMA monomer. When the two components are mixed, the liquid monomer polymerizes around the pre-polymerized powder particles to form rigid PMMA. Due to an exothermic reaction, heat is created during the process. The inclusion of PMMA, as well as other additions, provides the combination of a set of chemical and physical characteristics. Premature polymerization of the liquid component can be caused by exposure to high temperatures or light. To avoid early polymerization, hydroquinone is added as an inhibitor or stabilizer. At room temperature, an initiator, di-benzoyl peroxide (BPO), is added to the powder, and an accelerator, primarily N, N-dimethyl-p-toluidine (DmpT), is added to the liquid (cold curing cement). To make the cement radiopaque, it is treated with a contrast agent. The exothermic free-radical polymerization process heats the cement. This polymerization heat reaches temperatures of around 82–86 °C inside the body. The relatively thin cement coating, which should not exceed 5 mm, and heat dissipation through blood flow, and the large surface area of the prosthesis contribute to the body's low polymerization temperature [23]. The thermal history and the mechanical characteristics of PMMA BC vary a lot depending on how it is prepared. Due to the exothermic nature of the polymerization reaction, numerous studies have sought to reduce thermal osteonecrosis caused by heat generation by modifying the cement preparation techniques [118]. Bioactive additives are frequently used to alter PMMA BC and to generate a new type called bioactive ABC to increase osteointegration ability, biocompatibility, bioactivity, and other features [119]. Radiopacifier particles, polymerized monomers, and PMMA beads make up ABCs, which are multi-phase materials. Furthermore, various factors such as the presence of blood, oil, other bodily fluids, mixing technique, or probable delaminations caused by introducing the cement into the bone cavity might impact the interfacial microstructure and bulk of the cements, as well as their mechanical performance [25]. Chemical and physical phenomena coexist, influencing the setting process as well as mechanical properties and the microstructure of the set material, which are influenced by factors such as the chemical environment, the physical mixing method, the concentration of the initial liquid and powder components, and chemical composition (Table 2) [25].

### *2.3. Glass ionomer cement*

In 1969, glass ionomer cement (GIC) was developed by Kent and Wilson [98] , And on the other hand Wilson and Mclean [99] Upgrade it in 1970 . GIC is a cement made up of an acidic polymer that sets through

an acid-base interaction and a basic glass. Glass–polyphosphonate and glass–polyakenoate are two subgroups of the GIC term [120, 121]. GICs are acid-base cements that are often used in dentistry [122]. This is due to their groundbreaking properties, which provides benefits including direct attachment to the tooth structure, anti-cariogenic properties, and fluoride release [123-125]. They've lately been employed as BCs [126].

Because of their propensity to release a range of ions, GICs are intrinsically bioactive. Because GIC is more aesthetically pleasing than porcelain, gold, or amalgam, it is frequently used for luting, lining, and repair [127]. The physical features of GICs are influenced by how the cement is created, including the powder liquid ratio, the age of the specimens, the particle size of the glass powder, and the polyacid concentration [128]. GIC is unaffected by temperature fluctuations and has a low thermal expansion coefficient [129]. Despite these benefits, GIC has some limitations as a dental restorative material due to its slow setting rate, poor physical properties due to high solubility, and susceptibility to dehydration, which results in mechanical properties such as low wear resistance, toughness, and fracture strength being compromised. A variety of initiatives have been made to address the issues, which include the use of alternative fillers, such as inclusion of hydroxyapatite, carbon and alumino-silicate fibers, stainless steel powders, and silver-cermets into glass-polyalkenoate [130].

During regular use, GIC glasses contain calcium fluoride, which leaches soluble fluoride into the mouth. Consequently, GICs function as a rechargeable fluoride "reservoir" enabling long-term fluoride release in the vicinity of a GIC repair [131]. Throughout the experiment, the GICs in the Hook et al. [132] research generated chlorhexidine, a broad-spectrum antimicrobial agent effective against a wide variety of oral bacteria. This did not come at the expense of other properties. Antimicrobial nanoparticle replacement did not affect fluoride release in the majority of formulations, and the internal structure seemed unaltered up to and including 10% substitution. Kiri et al. [133] studied drug-loading capacity to enhance the therapeutic potential of GICs, particularly in the treatment of cancer-related fractures. The findings reveal that methotrexate (MTX) was easily released by the GIC without compromising the mechanical usability or the material's handling and the drug's therapeutic potential. Bioactive glasses (BGs) are utilized to rebuild bone by releasing therapeutic ions as they disintegrate [134]. Fuchs et al. [134] sought to combine the advantages of BG with GIC by investigating the use of alkali-free BG (MgO-CaF2-CaO-SiO2) with 0–50% calcium replaced by strontium since strontium's beneficial effects on bone formation are widely documented. When poly (vinyl phosphonic-co-acrylic acid) and BG were combined, ions were rapidly released (up to 90% in 15 minutes at pH 1), resulting in GIC setup. Strontium release from GIC increased linearly with strontium substitution for calcium, enabling customized strontium release according to clinical demands.

Three elements are required for a GIC: water, basic (ion-leachable) glass, and polymeric water-soluble acid [135]. These are normally delivered as a thick paste that hardens fast and is composed of finely split glass powder and a water-based polymeric acid solution that has been blended according to the appropriate technique. Alternative formulations include mixing the glass and acid in the powder and adding clean water to the set, as well as formulations in which part of the acid is combined with the glass powder and the remainder is present as a weak solution in water. As the liquid component, this solution is utilized to create the setting paste. Because these formulations are proprietary and the precise amounts of each component are unknown, the effect of these alterations is unknown. However, it seems that supplying these composites with components distributed differently across the aqueous and powder phases has no detectable effect on the final properties [136]. After mixing, an acid-base reaction produces glass ionomers in 2–3 minutes. The first step is a reaction between hydrated protons from the polyacid and basic sites on the surface of the glass particles. This results in the migration of ions such as $Sr^{2+}$, $Ca^{2+}$, and $Na^{+}$ from the glass into the polyacid solution, followed by $Al^{3+}$ ions. When these ions interact with the polyacid molecules, ionic crosslinks are generated, and the resulting insolubilized polysalt forms the hard framework for the set cement. When this reaction happens, no phase separation occurs and the cement absorbs all the water [137].

## 3. Bone cement-drug loading mechanism

Even in BC [138-143], several options to drug delivery techniques have been extensively researched and published by various researchers [144, 145]. Differences in the articulation of the spacer, spacer surface and geometry, spacer implantation length, the amount and/or ratio of the antibiotic incorporation, the addition of one or more antibiotics, and cement antibiotic impregnation and its type are just a few of the variables that could affect the pharmacokinetic properties in vivo [146].

Although there are two primary methods for incorporating bioactivity into polymer-based PMMA resins [147], none has been able to achieve a totally regulated release of bioactive compounds. The first approach involves the incorporation of water-soluble drugs (most often antibiotics) into the cement formulation to facilitate their elution from the cured product. These admixed cements are straightforward for surgeons to work with and prepare in the operating room, and they need no extra specialized equipment [148]. On the other hand, mixed cements allow limited control over the bioactive compound's release profile, which typically follows a preset burst release pattern within 48 hours after implantation [140, 143, 148-150]. Drugs added to PMMA cements may be at risk of oxidative damage during the free-radical polymerization process that occurs during curing. Additionally, since drug powder particles create focal points of stress within the cement [151], admixed cements containing sufficient medication to have the desired therapeutic effect have reduced mechanical strength, which is unsuitable for long-term orthopedic applications [152-154]. The second strategy for incorporating bioactivity into PMMA materials is to utilize polymerizable bioactive moieties to permanently alter the surface properties of the material. This method is most often used to manufacture dental resins bacteriostatic by adding quaternary ammonium and other bacteriostatic comonomers [147, 155]. To accomplish a similar effect, polymeric prodrugs of medical compounds were added to the BC's solid filler component [156-158]. While this covalent anchoring approach is excellent at keeping bacteriostatic substances from evaporating, it is useless for bioactive compounds that must be taken by cells [159].

To produce BC with sustained drug release, two elements must be considered: (1) the cement's ability to enable the medication contained inside to flow out and (2) the cement's ability to maintain drug release [160]. According to Oungeun et al. [160], the hydrophobic antibiotic ERY does not need encapsulation prior to inclusion in the PMMA cement to mediate the drug's movement out and sustain drug release. Unencapsulated ERY-doped PMMA cement demonstrated that 85 percent of the drug molecules were able to flow out slowly over 42 days, with just a brief burst at the beginning. On the other hand, the cements containing ERY–EC or ERY–PLGA showed a greater burst release during the first week and much lower drug concentrations subsequently. While the unencapsulated ERY emits an adequate amount of PMMA on its own, the hydrophilic VAN must be encapsulated in the suitable carriers before being added to the cement. Burst release was seen within the first 2–3 days after incorporating VAN encapsulated in RGs or unencapsulated VAN, and only 18% of the contained drug could be released from the cements over the 42 days.

Cyphert et al. [107] created a combination antibiotic PMMA composite system by combining rifampicin-loaded β-cyclodextrin (β-CD) microparticles with PMMA packed with a second medicament. In com-

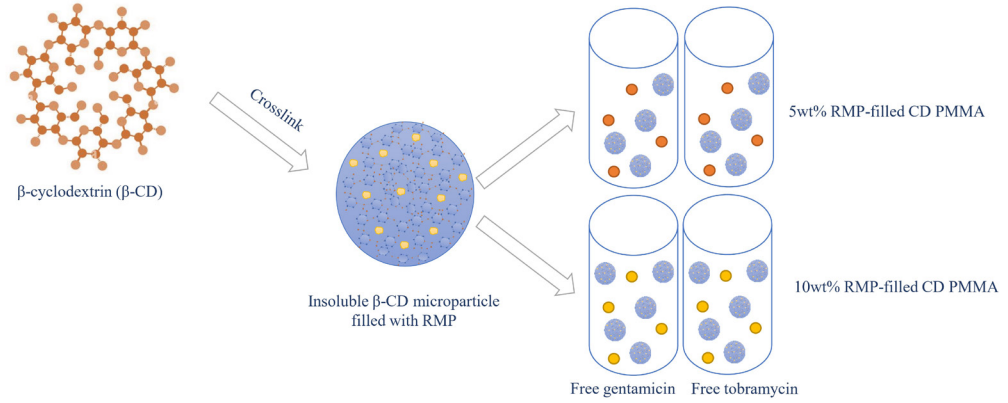


**Fig. 1.** Composite PMMA BC compositions including several medications. Cross-linking of prepolymerized cyclodextrin (β-CD) resulted in the formation of insoluble microparticles containing rifampicin (RMP). During polymerization, various quantities of drug-filled β-CD microparticles (10 or 5% by weight) were introduced to tobramycin or gentamicin (without encapsulation in β-CD).

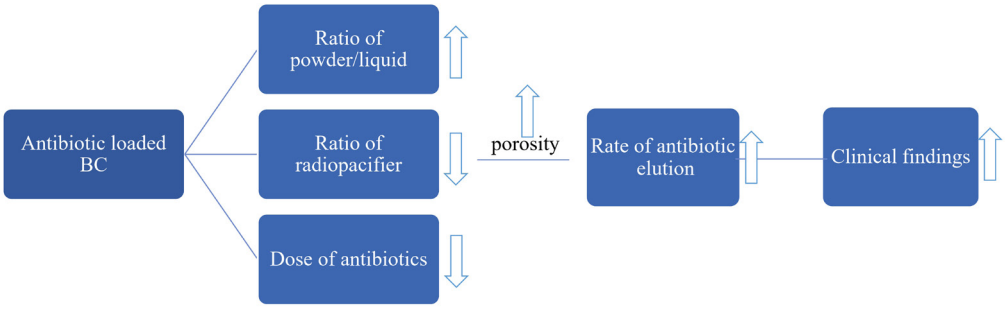


**Fig. 2.** Increasing antibiotic dosages, increasing the radiopacifier ratio, and lowering the liquid/powder ratio may improve antibiotic elution from ABC and thereby improve therapeutic effectiveness against infection.

parison to antibiotic-filled PMMA used in clinical practice, their combination antibiotic PMMA composite system demonstrated an increase in antibacterial activity duration of up to eightfold. Following simulated implantation, the addition of CD microparticles enabled the refilling of additional antibiotics, resulting in numerous therapeutic efficacy windows. Fig. 1 depicts the various PMMA composites, which include a variety of drug combinations and varying amounts of β-CD microparticles.

Because of the detrimental influence on BC mechanical qualities and the probability of consumption during the polymerization operation, direct loading of Tocopherol acetate (ATA) in BC was not feasible [161]. In a study by Bettencourt et al. [161], these constraints were solved by adding ABC containing ATA(PMMA) particles. The emulsion solvent evaporation process was found to be an excellent strategy for generating PMMA particles with good encapsulation characteristics and high yield.

The radical polymerization reaction is an exothermic one that produces heat. Chen et al. [162] conducted research to produce a basic PMMA BC with better mechanical strength and biocompatibility. Surprisingly, their data indicated that multiple components of the BC contributed to antibiotic elution efficacy. The antibiotic content was increased (0.3 g gentamicin in 4 g BC), the radiopacifier ratio was increased (20-30 %), and the liquid/powder ratio was decreased (85 %). This resulted in improved antibiotic elution without affecting the cured BC's mechanical strength (Fig. 2) [162].

The majority of literature research on drug release from CPC scaffolds have focused on two basic aspects: 1) drug research, in which many characteristics of the drug have been explored, as well as the impact of parameters such as loading technique on the release of the drug, loaded amount, and the drug type; 2) matrix features like extra phases addition or not, degradability, crystallinity, porosity, and the chemical composition. In addition to these two fundamental features, other investigations have looked into the impact of various environmental circumstances on drug release kinetics, such as the in-vivo release or the medium of release [163].

How the drug is incorporated into the cement, as seen in Fig. 3, is the first issue to address, since it will impact the drug's interaction with the matrix and dispersion. Typically, drugs are added to CPCs by dissolving them in the liquid phase or by combining the pharmaceutical powder with the solid phase. In both cases, the drug is distributed uniformly throughout the volume of the material, yet when incorporated in the liquid phase, a more homogenous distribution is achieved. An alternative method is to include the medicine by impregnating pre-set CPC granules or solid blocks with a medicinal solution. While injectability is restricted in this circumstance, some benefits remain in comparison to standard ceramic matrices. These advantages derive principally from the fact that material consolidation through a low-temperature dissolution-precipitation process results in hydrated compounds with distinct microtextures and high specific surface areas, which facilitate release mechanisms and drug loading [57].

Because the rate of cement resorption (degradation) was much slower than the rate of drug release in all CPC systems evaluated as drug carriers, the scientists concluded that drug release from a CPC matrix is a diffusion-controlled process. According to Higuchi's research, the amount of drug (F) released at a given time (t) is dependent on several parameters, including the matrix surface area (A), the matrix's solubility in the matrix ($C_s$), the drug's effective diffusion coefficient ($D_{eff}$), and the drug's initial concentration in the matrix ($C_0$). The rate of deterioration of CPC materials is strongly influenced by crystallinity, porosity, and the available surface area. It might explain why porous CPCs release more cephalexin than non-porous ones [164].

Incorporating species into a glass ionomer, on the other hand, necessitates consideration of the inclusions' influence on the mechanical qualities and cement's handling. This is significant both in terms of the set material's ultimate qualities and in terms of the amount of time available for cement manipulation. The structural alterations that occur as the GIC is transformed by the addition of active species may also be shown by such metrics [165]. Several GIC-based medication delivery methods are introduced in the literature. Organic silicone has resilience to age, weather, and heat and superior electrical isolation [166]. Yan et

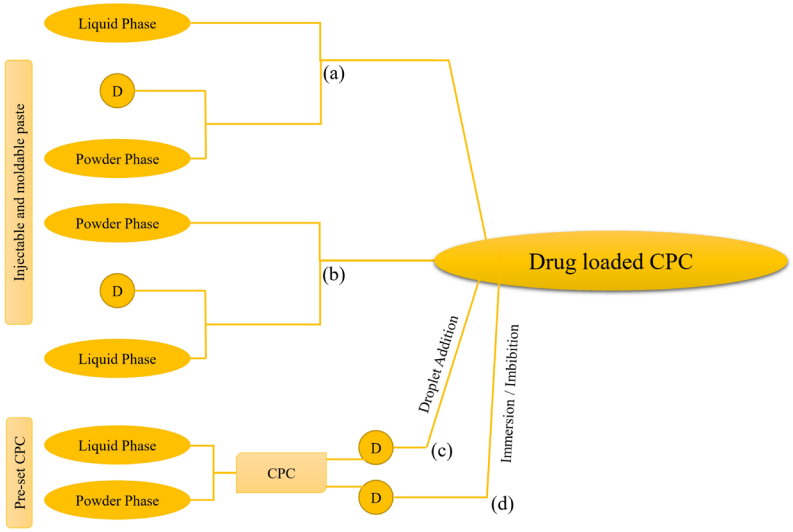


**Fig. 3.** Several methods may be used to insert drugs or biologically active compounds (designated D) into CPCs. Prior to merging the solid and liquid phases of cement, the medicine may be mixed with the cement powder phase (a) or solubilized in the cement liquid phase (b). After the cement has been set, droplet addition (c) or immersion (imbibition) of the cement in the pharmaceutical solution may be performed (d). Due to the need for cement pre-setting in the end procedures (c) and (d), they do not allow for cement injection, hence retaining the textural characteristics of the low-temperature setting reaction.

al. [167], for example, synthesized expanded-pore mesoporous silica nanoparticles (pMSN) to encapsulate CHX, a well-established antimicrobial agent and used the CHX@pMSN to modify dental conventional GIC for the first time, enhancing its antimicrobial performance without impairing its mechanical properties. The findings indicated that at a concentration of 1% (w/w), CHX@pMSN-modified GIC could continuously release CHX and effectively inhibit the development of *S. mutans* biofilms without impairing the mechanical properties of GIC.

## 4. Therapeutic applications

Recently, research has been conducted on the use of antibiotics as a therapy for bone infections or as a preventative measure for infections caused by surgery. Antibiotics aren't the only medications that have been studied; hormones, anticancer agents, and anti-inflammatories have all been mentioned. Additionally, the administration of bone regeneration-promoting chemicals such as transforming growth factors (TGF-β) or bone morphogenetic proteins (BMP) has been explored [168, 169]. BCs may be used in a variety of ways, as seen in Fig. 4.

### *4.1. Bone cancer therapy*

Metastatic bone cancers frequently result in a decrease in bone amount, which can lead to significant discomfort or a compression fracture. Compression fractures of the bone have been treated with conservative therapy. Patients are put on bed rest with the diseased area of the body fixed, and any discomfort is managed with medicines in this therapy. However, with this treatment, patients may be required to stay in bed for a few months, and such a lengthy term of bed rest may raise the risk of dementia in senior people [170]. The most prevalent kind of skeletal cancer is bone metastases. Radiological evidence of skeletal metastases can be seen in around 80% of individuals with advanced cancer [171, 172]. With a 30-50 percent incidence, the femur is the most common metastatic location in the extremities long bones, and patients require structural stability, especially in weight-bearing bone metastases such as tibia, femur, and the pelvic bone [173]. The conventional therapy techniques were unable to provide an effective cure for cancer [174, 175]. Local recurrence with subsequent osteolysis is a concern after intralesional curettage of giant cell tumors of the bone, metastatic carcinoma, and myeloma. Zoledronic acid (zoledronate) has been shown to inhibit osteoclast activity, making it a potentially attractive therapy option, particularly for giant cell tumors with a high number of osteoclasts [176]. The purpose of Zwolak et al. [176] research was to characterize the elution dynamics of zoledronic acid from ABC, as well as its in vitro anticancer activities. Their technique for determining the elution of zoledronic acid from BC and determining its effect on tumor formation is reproducible. Zoledronic acid is released from BC and inhibits the in vitro growth of cell lines derived from giant cell tumors of renal cell carcinoma, myeloma, and bone.

Anticancer chemicals diffused from BC may also slow tumor development, according to several studies [177]. Tanzawa et al. [177] tested whether CPC implants carrying anticancer caffeine and other drugs, which boost anticancer drugs' cytocidal impact, would improve antitumor effects in rats with osteosarcomas (SOSN2 cells). According to the findings, CPC comprising CDDP and caffeine enhances anticancer effects and might be used as a local chemotherapeutic treatment for malignant bone tumors. Liang et al. created a multifunctional BC (DOX/$Fe_3O_4$@PMMA) filled with the anticancer drug doxorubicin and $Fe_3O_4$ nanoparticles for synergistic MH ablation and treatment of OS in another investigation. The proposed DOX/$Fe_3O_4$@PMMA exhibited OS treatment in vivo, synergistic MH ablation, decreased tumor cell growth, increased OS tissue apoptosis, and regulated DOX release.

### *4.2. Implant coating*

Surface biofunctionalization is among the simplest ways to modify the surface characteristics that can increase surface bioactivity, remove or limit the degradation rate, and prevent implant-related infections, among other things, to accomplish biocompatibility and biofunctions on implant materials [178]. Coatings applied on the surface of materials enhance their visual, mechanical, and physical qualities [179-181]. While fixed, cemented implants provide superior long-term stability than uncemented implants, clinical loosening of cemented replacements has been seen [182]. Bone regeneration has been demonstrated to be influenced by hormones, biologically active substances, and a variety of growth factors [183]. Bone regeneration is known to be aided by TGFs, IGFs, PDGF, VEGF, and BMPs [184, 185]. Controlled administration of essential medication dosages that are easily and quickly changeable for individual clinical scenarios is very desirable in order to facilitate efficient bone repair [186].

PMMA BCs in various forms, as well as antibiotic-laced beads, have been utilized in chronic and acute osteomyelitis and hip replacement for more than 40 years [85, 187-189]. Because of the burst and restricted release of implanted antibiotics, FDA-approved drug-eluting PMMA BCs are better employed as a prophylactic measure rather than as a therapeutic because they have no impact on active IRIs [190, 191]. Antibiotics diffuse from PMMA cements primarily as a result of surface erosion, superficial pores, and surface roughness [191-193].

Calcium phosphate materials include hydroxyapatite (HA), beta-tricalciumphosphate (β-TCP), and CPC [65, 193-195]. Injectable CPCs

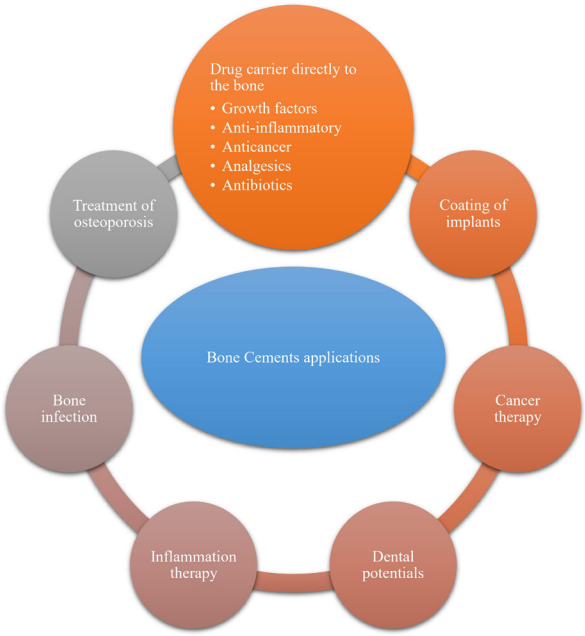


**Fig. 4.** A schematic diagram illustrating the range of possible uses for BCs.

that can be cemented after implantation is currently commercially accessible [65, 194]. Before the CPCs solidify, there are usually two phases: liquid and particles for optimum performance. CPCs have no exothermic reaction that might be damaging to the medicine included and the bone, and have the capacity to self-set and self-mold [193, 195]. CPCs have been limited in clinical use due to their weak biomechanical strength and delayed biodegradation in vivo. Furthermore, CPC microstructures lack macroporosity and are thick, making them unsuitable for cell colonization, penetration, and adhesion, as well as tissue regeneration [191]. Chemical and electrochemical processes are two of the most fundamental methods for the fabrication of composite coatings [196]. Antibiotics like vancomycin [197, 198] and gentamicin [192, 199-202] can be added to the liquid phase of CPC, HA, or β-TCP [203] to combat MRSA and S. aureus. Microcrystals in apatite cements outperform HA particles in terms of formation, size, and biological performance [199], as well as antibacterial activity. Wet chemical precipitation can produce HA nanoparticles, which have a good bactericidal impact on implant-related infections due to the toxic effect of destroying the bacterial membrane [204-206]. To construct a Ti6Al4V implant with a drug-chitosan-HA coating, a drug-chitosan compound was put in a porous HA matrix and then coated onto the smooth surface of the implant [207-209]. The burst releasing peak lasted for several hours, and the sustained release lasted for 4–8 days after surgery. It took more than a month for the remainder to be released. β-TCP seemed to be a better candidate for drug release than HA, despite its superior biomechanical properties. Another form of coating is bi-phasic calcium phosphates, which are composed of HA and TCP (BCP). During the local release, the BCP dissolved additional ions, resulting in an increase in the amount of carbonate hydroxyapatite on the surface [210]. For up to 30 days, a doxycycline-containing β-TCP coating (BonyPidTM) was shown to generate a continuous, zero-order rate of release capable of eliminating contaminating bacteria [206]. Additionally, histological, radiological, and microbiological investigations demonstrate that the poly(lactic acid)(PLLA)/β-TCP coating results in a beneficial infection outcome [197, 211].

### *4.3. Osteoporosis treatment*

Osteoporosis has a substantial influence on the occurrence of fractures among the elderly and affects almost 10 million individuals in the United States alone [212]. By 2040, the global population of the elderly is predicted to quadruple, resulting in a significant rise in the frequency of osteoporotic fractures [213].

BCs act as a mechanical buffer between the prosthetic components of the hip and the bone, absorbing mechanical shocks and decreasing stress [214]. Li et al. [215] evaluated the bone healing capability of CPC in osteoporotic goats using BMP-2-loaded gelatin microspheres (GM). BMP-2/CPC/GM composites induced more mineralization and accelerated bone lesion repair compared to BMP-2/CPC composites. The quicker bone healing was assumed to be due to the CPC/GM combo releasing more BMP-2 than CPC alone. Because injectable acrylic cement is routinely utilized in osteoporotic patients as a temporary support or merely a mechanical permanent filler , and because it is non-degradable, it has not been studied for the delivery of bone anabolic molecules. Internal heat created by the setting and polymerization of the cement reduces the amount of molecules and medications that it may encapsulate. Nonetheless, alendronate was added to an acrylate cement formulation and its biocompatibility was investigated [216]. The possible advantage in an in vivo model, on the other hand, has not been reported. Calcium phosphate and sulphate products make up the majority of other cements. The latter has been investigated in relation to the distribution of anti-resorptive and anabolic drugs to the bones. This is owing to CaP materials' inherent features, including as generally adequate to outstanding osseointegration, protein absorption, breakdown, porosity, and size, even in impaired tissue [217, 218]. Jindong et al. [219] evaluated the properties of a new composite alendronate-loaded CPC in vitro. In vitro, the alendronate-loaded CPC had favorable properties, indicating that it may be useful for osteoporotic bone locally in vivo.

### *4.4. Bone infection treatment*

Infection is a common side effect of prosthesis surgery. The infection has become a catastrophic consequence despite its low occurrence (around 5% — 3%), due to the characteristics of biofilm development, which make eradication difficult [220, 221].

BCs with antibiotics are also drug delivery devices. Artificial implants are known to be particularly vulnerable to bacterial colonization on their surfaces since the germs can then bypass the body's natural defence and create a periprosthetic infection. When antibiotics are applied topically, BCs can act as a carrier matrix [222]. While PMMA has a low inflammatory response and intrinsic toxicity, as well as excellent biocompatibility [223], experience has shown that not all antibiotics meet the inclusion criteria in this cement. Glycopeptides (vancomycin) and aminoglycosides are the two antibiotic classes that meet the most stringent criteria for inclusion in these cements (low serum protein binding, low influence on the mechanical properties of the cement, low or no risk of delayed hypersensitivity or allergy, thermal stability, elution from PMMA in high concentrations for prolonged periods, bactericidity at low concentrations, wide antibacterial spectrum, and availability in powder form) [224]. The most prevalent cause of failure in cemented joint replacements is aseptic loosening of the components, which may occur as a result of mechanical failure of the cement mantle around the implant. As a result, a number of approaches for optimizing the material characteristics of BC have been devised, including adding reinforcing particles/fibers, lowering porosity with vacuum mixing equipment, and altering the initiation chemistry [225]. Other antibacterial agents were utilized by researchers for generating modified PMMA BCs with antibacterial properties: essential oil or essential oils combined in different materials, graphene, hydroxyapatite, gold nanoparticles, silver nanoparticles, and antibiotics. A schematic illustration of the cement preparation technique is provided in Fig. 5.

On-site alternatives such as antibiotic treatment have been utilized

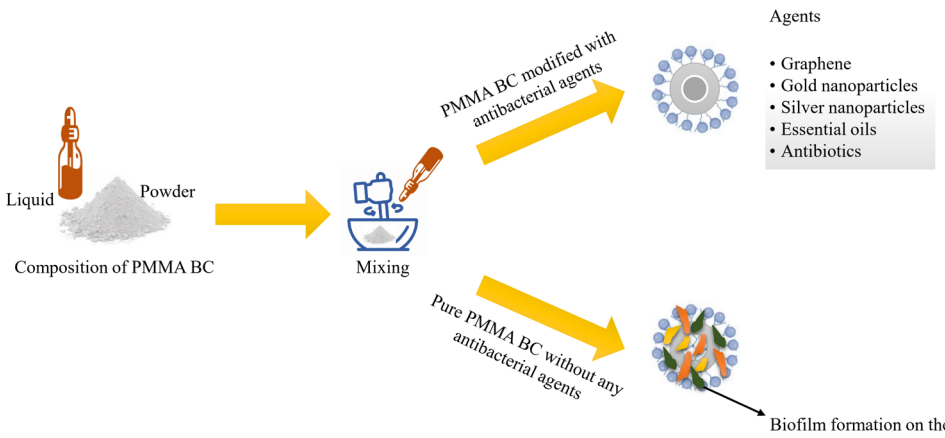


**Fig. 5.** Schematic illustration of the technique for preparing modified PMMA BCs with antibacterial characteristics.

to prevent infections associated with orthopedic surgery, which usually result in bone loss or implant removal [226-228]. This is often performed by encapsulating the medicine in PMMA or encapsulating it in a CPC matrix. PMMA beads are not biodegradable, needing further surgery to remove and replace them with fresh antibiotic-loaded spheres if the therapy is to be extended. To circumvent this constraint, substantial research has been conducted on CPCs as biodegradable materials capable of carrying antibiotics. However, because of the low doses of release, the chance of building bacterial resistance exists. Thus, antibacterial properties have been bestowed on implants by coating them with silver ions and functionalizing the surfaces of biomaterials [229]. However, the absence of additional antibiotics beyond those now commercially available, the inability of antibiotic-loaded ABCs to adhere to bone tissue, as well as impairing their biological activity, continue to be significant limits in their clinical application [230]. Matos et al. [230] aimed to develop a novel BC drug delivery system that incorporates Sr- and Mg-doped calcium phosphate particles as drug carriers inside a lactose-modified acrylic BC. This novel BC composite biomaterial demonstrated sustained levofloxacin release, biocompatibility maintenance, and improved mechanical integrity, with antibacterial activity against Staphyloccocus aureus and Staphyloccocus epidermidis (two common pathogens associated with bone infections) lasting for 8 weeks and concentrations exceeding the minimum inhibitory concentration values after 48 hours.

### *4.5. Dental application*

In recent decades, an increasing variety of dental restorative materials have been dominating the market. Adhesive solutions have been created that maintain healthy tooth structure while also adhering to preventive principles. Direct filling techniques, as opposed to macromechanically engineered, destructive preparations using indirect restorative materials, are gaining popularity as a means of protecting and maintaining tooth hard tissues [231].

In everyday dental practice, a variety of direct restorative materials are employed. GICs and resin composites are the most prevalent, after amalgam. Amalgam is simple to use and affordable, thanks to its lengthy therapeutic history. However, the potential for poor aesthetics and mercury poisoning are drawbacks. Resin composites have acceptable physical qualities and are the most aesthetically pleasing. They have disadvantages in being technique-dependent adhesives, time-consuming, and very costly treatments. Because of their capacity to vary their physical characteristics by modifying the chemical formulation or liquid/powder ratio, GICs may be employed in a wide range of therapeutic applications. GICs provide a more appealing appearance than metallic restorations. They also have chemical adherence to mineralized tissue and strong biocompatibility, and they have an anticariogenic potential due to the incorporation of fluorine. Poor mechanical qualities, such as wear, toughness, and low fracture strength, prevent their widespread usage in dentistry as a stress-bearing filler material. GICs are commonly utilized as a temporary filling material in the posterior dental area. As a result of the need to strengthen such cements, more research into reinforcing concepts is being conducted. Several previous attempts involved the use of glass fibers or second-phase ceramic, as well as metal particles. Compounding reactive glass fibers also showed promising outcomes [231].

GICs are said to be the most antibacterial and cariostatic of all dental restorations, probably because they emit fluoride, which is thought to assist limit germ development, increasing remineralization, and minimizing demineralization. Yearly clinical studies, however, found that secondary caries continues to be the major cause of GIC failure, suggesting that the fluoride delivered by GICs is inadequate to mitigate the effects of bacterial damage or to inhibit bacterial proliferation. Although numerous attempts have been made to enhance the antibacterial activity of dental restoratives, the majority of them have concentrated on the release or slow release of various low-molecular-weight antibacterial agents such as chlorhexidine (CHX), iodine, silver ions, zinc ions, and antibiotics. However, if the release or concentration of antibacterial agents is not carefully controlled, it might result in likely toxicity to adjacent tissues, temporary effectiveness, and loss of the restoratives' mechanical properties over time [232]. Weng et al. [232] reported on the synthesis and evaluation of a novel non-leachable poly(quaternary ammonium salt) (PQAS)-containing antibacterial GIC. The findings indicate that the cements are indefinitely bactericidal, with no PQAS leaching. Because of its persistent antibacterial activity and great mechanical strength, the experimental cement seems to be a therapeutically appealing dental restorative that could be employed for long-term restorations.

CPC may also be placed to build a scaffold for bone ingrowth and shaped into any shape for aesthetic purposes. Extensive reconstructions of the mandible or maxilla following trauma or tumor removal, support of metal dental implants or augmentation of inadequate implant sites, periodontal bone regeneration, and maxillary and mandibular ridge augmentation are all possible craniofacial and dental applications of CPC. Calcium phosphate biomaterials, on the other hand, showed poor bone production and angiogenesis. To overcome this problem, angiogenic growth agents have been employed. In vitro prevascularization of the scaffold is another possible way to solve this problem [233]. The purpose of Sa et al. [234] research was to determine the efficacy of injectable CPC in terms of antibacterial activity and occluding dentinal tubules when loaded with chlorhexidine (CHX). This was believed to be advantageous for minimally invasive dentistry and dental biomimetic reconstruction. When compared to a blank control without CHX, CPC loaded with CHX revealed a significant antibacterial effect and maintained CHX release over a week. As a result of its injectability, tooth-like composition, apatite-mineralization capacity, and unique self-set-

ting ability, the results suggest that CPC may be a viable biomaterial for minimally invasive reconstruction and biomimetic of fractured enamel on exposed dentin. Additionally, because of CPC's superior drug delivery characteristics, it may quickly transfer medications to prevent future pulp infection.

## 5. Future perspective

While some commercially available cements incorporate antimicrobial agents or are lacing to allow surgeons to impregnate them with appropriate antimicrobial agents during surgery, they do not justify the enormous amount of time and research spent in this area, which includes controlling drug release patterns, developing various categories of delivery systems and products, and testing them in animal models, nor do they meet all patient needs. Clinically, commercially available antimicrobial agent-containing cements do not address the variety of personalized conditions that surgeons face, including the patients' general health status and age, the chronicity/severity of their infection-related conditions, the volume and type of the involved bone's tissues, all of which affect the required dose of antimicrobial agent to eradicate the infection without compromising the patients' general health. This is exacerbated further by the diversity of pathogenic microorganisms that cause bone infections, as well as the ongoing development of the necessity and resistance for a wide range of antimicrobials to be included in delivery systems, as well as the constant introduction of novel chemical moieties. Commercially available blank cements, on the other hand, enable surgeons to incorporate proven effective antimicrobial agents at the required concentrations during the operation (whereas in-situ developed scaffolds are not standardized for drug release rate) which means that sufficient drug is delivered to maintain the concentration above the specified infectious organism's minimum inhibitory concentration (MIC) during the operation. Additionally, they are not evaluated for dose dumping of the antibacterial medicine in question in order to minimize effect of toxicity on patients and/or fast scaffold depletion. The findings of the preceding study have led to ongoing individualized research investigations in various orthopedic departments of hospitals and clinics in pursuit of beneficial therapies for their patient's well-being [235]. Furthermore, BC implantation syndrome (BCIS) is a poorly known and sometimes deadly complication of orthopedic surgeries, particularly cemented hip arthroplasty. The real incidence of BCIS is unclear due to its ambiguous nature and wide range of symptoms. BCIS is a common clinical occurrence in cancer patients who have femoral cemented arthroplasty, with an increased risk for patients over 60 and those who have reduced lung function due to lung cancer or metastases. Patients with BCIS are more likely to require a lengthier stay in the hospital after surgery [236]. In any case, the groundwork has been laid for the development of innovative dosage forms for local delivery to bone sites, and there is still a fascinating and lengthy road ahead of us, given the topic's expanding relevance [57]. To achieve long-term attachment, an appropriate BC for the restoration of metastatic bone lesions can have the following properties [237]:

1. Produce a chemotherapeutic action with a therapeutic index that is acceptable.
2. Produce an antibacterial action with a therapeutic index that is acceptable.
3. Set the temperature to body temperature.
4. Have osteoconductive qualities to the maintenance of osteointegration and aid in the speed.
5. Have mechanical qualities that are similar to the trabecular bone to avoid stress shielding.

There are several features of fiber reinforcing that are yet unknown. To generate reinforced cements with outstanding qualities, more study into delivery strategies, fiber content, size, and fiber material is needed [238].

## 6. Conclusions

BC, whether made of polymers or ceramics, is a suitable choice for delivering drugs to the bone since they can transfer the medicine directly to the bone without harming adjacent tissues. Growth factors, anti-inflammatory agents, anti-cancer medicines, analgesics, antibiotics, and other therapeutic chemicals can all be added into BC for a number of therapeutic techniques. therefore, we looked at several BC systems, dental applications, inflammation treatment and bone infection, osteoporosis treatment, implant coating, cancer therapy, and drug incorporation methods. It may be concluded that they offer a great deal of promise for delivering medications locally and for therapeutic purposes.

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