Inorganic cements for biomedical application: Calcium Phosphate, Calcium Sulphate and Calcium Silicate

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Abstract

Inorganic cements have found utility in tissue replacement since the late 19th Century, one of the first examples being calcium sulphates in the augmentation of bone defects. In the intervening period of time countless formulations of calcium phosphate, sulphate and silicate cement have been researched and as a result, many are now commercially available for a variety of biomedical applications. This review summarises the applications, formulations, advantages and drawbacks of such inorganic cements, suggesting future work that will drive progress in this area into the future of biomaterials research.

Keywords

Calcium Phosphate, Calcium Sulphate, Calcium Silicate, Inorganic Cements

1. Introduction

A cement can be defined as a material that may be “used to unite fragments to form a whole.”1 This definition is extremely broad, encompassing materials with respect to biomedical application such as inorganic salts (calcium phosphates, sulphates and silicates) and a range of polymeric materials (e.g. cyanoacrylates, poly(methyl methacrylate) (PMMA). For the purposes of this review, we will focus on the inorganic cements used extensively in restoration of hard tissues such as bone, although it should be noted that PMMA has also found use in orthopaedics and the manufacture of ocular implants.

Following the traumatic loss of bone or tissue excision to treat infection or cancerous growth the surgeon is left with a defect that is typically irregular and the size of which is difficult to predict prior to surgery. The “self-healing” ability of bone means small defects can be replenished by new bone formation in response to the injury. However, defects of a critical size will not be filled in such a manner naturally, instead being with a fibrous tissue.2 The formation of this fibrous tissue will weaken the overall structure of the bone and may result in permanent deformity. To avoid such an outcome, these defects must be augmented with suitable material to prevent fibrous ingress into the defect whilst contributing a degree of biomechanical stability. Bioceramic materials in the form of pellets/granules and pastes have been used to fill critical sized defects. In the case of granules, the irregular nature of defects means migration from the implant site can occur. Such a scenario may be potentially problematic for adjacent tissues. Cements, that may share the same composition of the aforementioned granule bioceramics, overcome migration issues as they can be applied as a paste that fills the defect entirely followed by hardening to provide both mechanical and biological functions.

Many inorganic cements have been used for the augmentation of hard tissues. The most frequently used cements as bone replacements are formed from calcium sulphates, silicates and phosphate cements. This review will focus on these compositions, but in the future developments section, we will also discuss other inorganic cement materials that have significant promise for application within both medicine and dentistry. Each section of this review will briefly discuss the chemistry of the cement materials in addition to modifications that have been made to further enhance the application of these materials in medicine.

2.1 Calcium phosphate cements

The credit for the formulation of the first calcium phosphate cement applicable for use in the clinical setting is rightly given to Brown and Chow of the Paffenbarger Dental Institute.3 These researchers observed that combinations of tetracalcium phosphate (TTCP; Ca4(PO4)2O) and brushite (Dicalcium phosphate dihydrate; DCPD; CaHPO4.2H2O), intended for use as a remineralising paste hardened when allowed to stand on the laboratory bench overnight. In years prior to this, other researchers including Monma had identified that the combination of calcium phosphate salts such as α-tricalcium phosphate (α-TCP, Ca3(PO4)2) with water formed a hardened product.4 Despite the findings, these researchers did not report the first calcium phosphate cement in the modern literature. Indeed, in his seminal paper in 1950, Kingery demonstrated that the combination of CaO and H3PO4 enabled the formation of a hardened product that consisted of monocalcium phosphate monohydrate (MCPM; Ca(H2PO4).H2O).5 The soluble and acidic nature of this compound would not have made this material useful for biomedical application. Modern calcium phosphate cements harden to form one of only two products: if the cement paste has a pH value >4.2, hydroxyapatite (Ca10(PO4)OH2) or more likely the calcium deficient form of the salt (Ca9(PO4)5HPO4OH) is favoured and if the cement has a pH <4.2, brushite (DCPD; CaHPO4.2H2O) is favoured, which under certain conditions may dehydrate to form monetite (DCPA; CaHPO4).3,6,7 The hardening properties of the cement materials rely on the pH dependent solubility’s of these calcium phosphate salts. Typically, one or more cement precursors are mixed with solvent in which they are not thermodynamically stable. The calcium phosphate salt or salts subsequently dissolve and the salt most stable at that stoichiometry and pH value is usually precipitated, hardening to form a solid cement matrix.

The following sections will briefly describe basic formulations and modifications to a range of calcium phosphate cement salts.

* + 1. Apatitic calcium phosphate cements

The majority of the early work on calcium phosphate cements focussed on the optimisation and application of apatite forming materials; the rationale being that apatite is the main constituent of bone mineral and the hardening of this material, in contrast to brushite cements, does not require the use of acidic pH values. Therefore it was considered that this material would be more “biologically relevant”. Monma’s calcium phosphate cement formulation hardened following the hydrolysis of α-TCP to form a calcium deficient apatite in accordance with Equation 1.4

3α-Ca3(PO4)2 + H2O 🡪 Ca9(PO4)5HPO4OH Equation 1

The hydrolysis of α-TCP resulted in the absorption of water into the hardened phase. Since water is the principle source of porosity in most cements, the absorption of water by the setting mechanism can enhance strength when compared with that exhibited by non-hydraulic cement formulations, such as that initially reported by Brown and Chow as shown in Equation 2.3 This formulation was refined to substitute DCPD for DCPA (presumably due to cost and stability).

2Ca4(PO4)2 + 2CaHPO4.2H2O 🡪 Ca10(PO4)6OH2 Equation 2

In the TTCP/DCPD cement formulation, water acted only as a solvent in which the TTCP and DCPD dissolved prior to reprecipitation of the hardened phase. As such, water present within formulation constituted significantly to porosity and thus severely compromised mechanical performance of theF hardened product.8 Minimisation of the excess water that needed to be added to this powder blend to form a workable cement paste formed part of a movement to enhance the strength of these materials. Work by the Barralet group in the early 2000’s achieved compressive strengths in excess of those typically exhibited by cortical bone (>200MPa) by using a combination of compaction and non-toxic superliquefiers.9 The superliquefiying effect of these additives was also utilised to enable extrusion of these materials through a hypodermic needle.

Apatitic calcium phosphate cements may also be formed through the crystallisation of amorphous calcium phosphates. The hardening reactions associated with these materials are advantageous in that they do not exhibit an exotherm or any local pH fluctuations during hardening minimising the chances of detrimental biological response.10 Amorphous calcium phosphates may be formed either by precipitationor by a process of mechanical activation of existing calcium phosphate salts such that they undergo rapid dissolution/reprecipitation reactions when immersed in an aqueous medium. 11,12

Numerous modifications have been made to the above materials to enable drug delivery, bone ingrowth through a macroporous structure or the production of tougher materials through fibre reinforcement or polymer incorporation. The major drawback of apatitic calcium phosphate cements, is their poor solubility in physiological conditions, meaning that they remain *in situ* for a considerable period of time following implantation as they may only be resorbed by osteoclastic action. The relatively weak nature of the majority of apatitic cement formulations means that they present a long-term risk of catastrophic failure following implantation. The recognition of this has driven more recent research into brushite-based cement formulations, which are sparingly soluble in physiological conditions and hence may be resorbed through a combination of dissolution and cellular activity.

* + 1. Brushite-based cement formulations

This section discusses brushite-based cement formulations, which includes materials that initially harden as brushite and subsequently convert to monetite, which has been shown to be beneficial to resorption properties. Since the precipitation of brushite requires acidic conditions, the majority of brushite cement formulations harden following the combination of a calcium phosphate salts such as β-TCP with either an acidic calcium phosphate salt, such as MCPM or MCPA, and water or with a phosphoric acid solution. The former material hardens in accordance with Equation 3 and the latter in accordance with Equation 4. The microstructure of Brushite cement made with β-TCP and phosphoric acid solution observed using SEM is provided in Fig.1.

F:\folder result paper-brushite\Paras-SEM-Granules brushite\K-500.tif

Fig.1. SEM image of a Brushite cement crystal microstructure formulated from mixing β-TCP and orthophosphoric acid at powder to liquid ratio of 3g/mL13

β-Ca3(PO4)2 + Ca(H2PO4)2.H2O + 7H2O 🡪 4CaHPO4.2H2O Equation 3

β-Ca3(PO4)2 + H3PO4 + 6H2O 🡪 3CaHPO4.2H2O Equation 4

Notable in Equations 3 and 4 is that the material consumes water during hardening, meaning that the fraction of the water consumed by the hardening reaction does not contribute to the pore volume of the material. Lemaitre *et al*., reported the first reported brushite-based cement formulation.14 Subsequent seminal work by Bohner identified cement additives including citrate ions, sulphate ions and pyrophosphate ions enabled the production of material that hardened in a clinically applicable timeframe.15 In the absence of such setting inhibitors, brushite cements set too quickly to be of practical use.16,17 As with apatitic cements, brushite cements have been extensively refined in order to optimise strength, deliver therapeutic quantities of drugs and to resorb at a rate appropriate to a variety of applications.17

Despite the more soluble nature of brushite than apatitic salts in physiological conditions, brushite cements have been shown to exhibit an unpredictable resorption rate ranging from almost complete resorption through to long-term stability. Significant work has gone into generating an understanding of this variability and it is now widely acknowledged that a reduction in the rate of resorption is directly related to the conversion of brushite to apatite in physiological conditions. Work published by one of the coauthors of this review has identified that this conversion is strongly influenced by initial cement composition, media composition, media refreshment rate, media volume and cement volume.18 Work to inhibit this reaction and prevent long-term stability has modified the cement matrix with a magnesium salt (magnesium is an inhibitor of apatite formation)19 and an additional pyrophosphate phase.20 The latter was also shown to be successful in enabling extensive resorption of the hardened material in an ovine model.21 Other workers have demonstrated that if brushite is converted to monetite, by heating or adjusting cement stoichiometry, conversion to apatite occurs more slowly and this has also prevented long-term stability in an animal model.

In addition to being used as a cement for application in paste form, the rapid setting nature of brushite cement has been utilised to enable the production of defined 3 dimensional structures using a process of 3D printing.22 Although not widely clinically used, this method has enabled workers to identifying new methods to enable blood vessel growth into hardened cement blocks (through modification with copper ions).23

3.1. Calcium sulphate (CS) cements

Calcium sulphate (CS) has been long-used as an orthopaedic biomaterial. It is considered as safe to handle and store and is cheap. It is available in medical grade purity and can be provided as cement components or as pre set pellets. The forms of CS are summarised in Table.1. The three main forms are fully hydrated CS, CaSO4.2H2O (gypsum), partly hydrated CS, CaSO4.0.5H2O (hemihydrate) and fully anhydrous CS, CaSO4 (anhydrite).

Table.1 Various calcium sulphate forms and stages (Adapted from [24])

|  |  |  |  |
| --- | --- | --- | --- |
| Molecular formula | Molecular mass (g mol-1) | Forms/stages | Common names |
| CaSO4.2H2O | 172.17116 | n/a | Calcium sulphate dihydride+  Gypsum+  Raw Gypsum  Byproduct gypsum  Hardened gypsum |
| CaSO4.0.5H2O | 145.14824 | Alpha\*  Beta\* | Calcium sulphate hemihydrate+  Plaster of Paris+  Alpha  Alpha form  Alpha plaster  Alpha hemihydrate  Beta  Beta form  Beta plaster  Beta Hemihydrate |
| CaSO4 | 136.1406 | Anhydrate III\*  Stages:  Beta anhydrite III  Beta anhydrite III’  Alpha anhydrite III  Anhydrate II\*\*  Stages:  AII-s (slowly soluble)  AII-u (insoluble)  AII-E (Estrich gips)  Anhydrate I\*\*\* | Calcium sulphate anhydrite+ |

+ Common names used in biomaterial literature

\* Metastable in dry air

\*\*Stable between 40-1180oC

\*\*\*Stable at >1180 oC

Upon heating fully hydrated CS, it is readily inclined to lose its attached water molecules. This loss of water can result in hemihydrate or anhydrate. The dehydration reactions are as follows:

CaSO4.2H2O + heat🡪 CaSO4.0.5H2O + 1.5H2O Equation 5

CaSO4.2H2O + heat 🡪 CaSO4 + 2H2O Equation 6

Addition of water rehydrates anhydrous CS to give fully hydrated CS in a slightly exothermic reaction. The rehydration reactions are as follows:

CaSO4.0.5H2O+ 1.5H2O 🡪 CaSO4.2H2O + heat Equation 7

CaSO4 + 2H2O 🡪 CaSO4.2H2O + heat Equation 8

Adding water to an anhydrous form of CS will rapidly lead to the solution becoming supersaturated with CaSO4.2H2O, which precipitates out via crystal nucleation and growth, which continues until a point below saturation. A cycle of dissolution and precipitation repeats, eventually resulting in a solid material consisting of hydrated CS.25 Setting time is relatively fast. Korte and Brouwers have modeled CS hydration to provide more understanding of this mechanism.26 Setting kinetics can be quickened or disrupted by additives termed accelerators and retardants respectively.27

To obtain a cement paste with a workable consistency, more water is added than the molar equivalents suggested by the hydration equations. The smaller the powder to water ratio (p/w) employed, the more likelihood cement is to be weaker. Excess volume of free water leads to porosity in the bulk structure after setting. Barralet *et al*., have shown that porosity has a negative exponential effect on cement mechanical performance.28 Thus, increasing p/w can increase cement strength.

The two forms of hemihydrate, alpha and beta, are rarely differentiated in the literature of CS research. The difference between the alpha and beta hemihydrates shouldn’t be underestimated. Alpha hemihydrate crystal structure is described as being structurally well formed and larger than the beta hemihydrate counterpart. The alpha hemihydrate also produces much stronger cement compared to the beta hemihydrate crystals, which are flakey, rugged and generally less structured/ordered.24,29 As alluded to by Dewi *et al.,* gypsum degradation rate can differ by the hemihydrate employed.[29]

Different gypsum dehydration pathways can produce the hemihydrates.24 Synthesis of beta hemihydrate is achieved by heating gypsum to between 45-200oC under vacuum or dry air. To acquire alpha hemihydrate, gypsum must be heated to above 45oC in an acidic or salt solution. Alternatively, the process can be achieved in water at 97.2oC under pressure. Careful further heating of the resulting hemihydrates at 50oC under vacuum leads to the formation of the respective alpha and beta anhydrites.

An investigation into the powder morphology of hemihydrate conducted by Wang *et al.,* demonstrated powder morphologies with lower aspect ratios produced cements with improved mechanical properties, in particular compressive strength.30 The method involved varying the concentration of CaCl2 in solution, of which a mixture of Ca(OH)2 that had been treated with sulphuric acid and succinic acid was added and boiled to achieve the different hemihydrate powders. Chen *et al.,* also synthesised CS hemihydrates with tunable morphologies by varying the presence of MgCl2, sodium citrate and sodium dodecyl benzene sulfonate modifiers during gypsum dehydration.31

Since its first use *in vivo* in 1892 by Dressmann to treat tuberculous osteomyelitis, CS has been used for filling bone defects.32 In the 1950’s, Peltier demonstrated use of CS to repair large bone defects, including that of the tibiae of dogs.33 The treated area displayed new bone formation. This work demonstrated CS is partially or completely resorbed with no foreign body reaction elicited, indicating it is well tolerated by local tissues *in vivo*. Peltier and Jones used CS to fill cavities left over from removal of bone cysts.34 The patients discussed had cavities filled with CS pellets, which were absorbed and replaced by new bone. Minimal side effects were reported. Early CS reports should be treated with care due to variance of reported outcomes, possibly from inconsistent crystal structure, purity and CS quality being assessed at the time.35

Stubbs *et al.,* show that CS applied as paste or pellets supports new bone formation, however complete filling of rabbit tibia defects was not observed and only residue CS remained after 3 weeks.36 Residual CS can either continue to provide an osteoconductive scaffold or undesirably impede further bone formation by further continuation of dissolution.37 Handling properties of other osteoconductive scaffold materials such as ProOsteon® 200R (hydroxyapatite and calcium carbonate), were much improved when added to CS paste. Whilst the CS resorbs quickly, ProOsteon® 200R was shown to provide an osteoconductive scaffold for at least a year.36

Orsini and colleagues have shown that both cement and pre-set forms of CS perform equally well.38 CS poses minimal risk of *in vivo* side effects,39,40,41 although it has been reported that severe inflammation is experienced in 20% of patients when treated with OSTEOSET®T pellets.29,37,42,43 The relatively short time frame it takes CS to undergo *in vivo* dissolution could lead to inflammation from resulting calcium rich fluids. Transient hypercalcemia is an expected side effect.44 Further research has attributed these complications to impurities. Similar CS OSTEOSET® pellets were used by Stubbs *et al.,* with no inflammation.36 Wilkins *et al.,* report of 50 patients treated with CS Osteoset pellets, no complications arose.45

CS is unable to bring about osteogenesis, but potentially encourages the formation of bone through its dissolution.46 Consequences of CS dissolution include release of resorbable Ca2+ ions and localised acidity. The release of Ca2+ ions may also help to stimulate osteoblasts by shifting the bone degradation/bone reforming balance and halting the actions of osteoclasts.47 Acidity is thought to help influence the bone formation that occurs in place of CS at implant sites by inflicting demineralisation of local bony tissue to release growth factors like BMPs, that may enhance osteoblast differentiation from mesenchymal cells as to enhance bone formation.48

Sidqui *et al.,* investigated both osteoblast adherence and osteoclast resorption upon CS.49 Before their investigation, little was known of the activities of these cells upon CS. Successful demonstration of osteoblast attachment was presented. Osteoclasts also adhered. Formation of lacunae and pitting from osteoclastic degradation were reported, suggesting osteoclast resorption might partially account for degradation *in vivo*. Due to fast disappearance of CS *in vivo*, rapid dissolution as opposed to cell mediated degradation and subsequent bone formation may be the dominant cause of CS disappearance from defect sites.43

Compared to calcium phosphate materials, typically hydroxyapatite and beta-TCP, CS degrades a lot quicker *in vitro* and *in vivo*. Fast resorption properties often means lone CS may not be suitable on its own with a bony defect as the rate new bone formation cannot always match the rate CS disappearance. Simply, the scaffold necessary for new bone growth is lost too quickly within a given defect. For hard tissue replacement, degradation rate should be acceptable to allow new bone formation whilst retaining a degree of mechanical integrity.

Composite formulation associated with CS is a prominent research area. Combining with other biocompatibles, such as calcium phosphates, to produce composites that elongate the period of osteogenesis provided in order for new bone to replenish a damaged site. Podaropoulos *et al.,* studied a composite consisting of CS/beta-TCP compared to beta-TCP in defects of the iliac crest of dogs. CS/beta-TCP allowed for more new bone formation compared to beta-TCP after a period of 4 months.50 Hing *et al.,* showed that CS degradation and resorption occurs to a far greater extent compared to beta-TCP and porous silicate calcium phosphate.43 Osteoclastic and phagocytic activity upon the woven bone formed at the defect edges treated with CS was observed. Fibrous tissues had surrounded remaining CS material within defects. At 6 weeks, bone at the outer edge appeared less inflicted by osteoclastic activity and by 12 weeks the CS had failed to completely fill the defect with new bone, but more so than beta-TCP. Neither material performed as well as silicate calcium phosphate.

Cai *et al.,* report the development of a poly(propylene fumarate) (PPF)/CS/beta-TCP composite material for bone replacement.51 Non-linear dynamic ageing in PBS demonstrated potential suitability as a cancelleous bone substitute in terms of mechanical properties over 6 weeks; starting compressive strengths were between 12.0±4.8MPa and 61.9±6.6MPa prior to ageing and fell to 0.5±0.1MPa and 20.6±2.9MPa across the formulations assessed prior to ageing. Mechanical properties were tailored by altering CS/beta-TCP ratio incorporated into the final composite and varying amount of *N*-vinyl pyrrolidinone used in polymer crosslinking. The same group demonstrated the composites were biocompatible and acts as suitable hard tissue scaffold in rabbit tibia defects. Postulated in both works, and demonstrated in the latter, CS/beta-TCP degrades faster than the PPF network leaving behind an increasingly porous network for bone formation, demonstrating CS as a ceramic porogen.51,52

As opposed to being simply osteoconductive, osteoinductive CS materials are of interest for advancing the role of CS in its applications. Intini *et al.,* reports a novel CS/platelet rich plasma (PRP) biomaterial for the regeneration of bone requiring simple preparation.53 The idea is that introduction of high Ca2+ levels from CS coupled with growth factors from activated platelets would help to initiate the biological processes for new bone growth. Kutkut *et al.,* also worked with a CS/PRP formulation as a dental extraction socket preservation graft material and compared it to collagen resorbable plug dressing as control.54 16 patients were examined, half having received the CS/PRP that led to 66.5%±10.4% vital new bone formation in comparison to 38.3±9.3% in control material after 3 months.

Oral and maxillofacial surgery often requires filling of bony voids. Endosseous implants require suitable bone quantity and quality for optimal results within the before edentulous region. Augmentation of the maxillary sinus is a procedure required to achieve suitable bone quantity for dental implants. Issues lie with choice of grafting material. CS was shown to be a suitable maxillofacial sinus augmentation grafting material compared to autologous bone, demineralised freeze-dried bone allograft, synthetic hydroxyapatite and others typically used.55 The histological analysis carried out demonstrates 100% living new bone growth and cellular activity throughout the implant biopsies from participants whom received CS graft. More recently, AlGhamdi invested a combination of CS and bovine bone at a 4:1 ratio for maxillary sinus augmentation.56 The author suggests the addition of the faster resorbing CS acts as a porogen, which in turn provides opportunity for bony ingrowth. CS provided a matrix for the bovine particles, which holds them in place during the healing process.

Any improvements to CS must maintain the current advantages such as low cost and biocompatibility. Not only is it accepted by the body with little risk of side effects, it also acts as a fully resorptive scaffold for the formation of new bone in a defect space. Research should target controllable degradation, mechanical enhancement and osteoinductive enhancement for new bone formation.

Table.2 Summary of examples regarding various *in vivo* studies of lone CS and in some instances in combination with other materials for treating bone defects

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| No. | CS defect filling material | Form | Experimental model | Defect site | Remarks | Ref. |
|  |  |  |  |  |  |  |
| 1 | CS (Surgiplaster, Classimplant) | Granular | Human | Peri implant site | New bone formation.  No innflamatory response.  Resorptsion in 4 months. | [39] |
| 2 | CS (Surgiplaster, Classimplant) | Granular | Human | Dental extraction socket | Fully resorbed within 3 months.  Replaced by new trabecular bone formation. | [57] |
| 3 | CS pellets (Osteoset®,  Wright Medical Corp.) | Granular | Human | Metacarpal, proximal phalanx, middle phalanx and distal phalanx | Complete resorption by 6 weeks.  New bone formation was completed by 10 weeks in all cases. | [58] |
| 4 | CS pellets (Stimulan, Biocomposites Ltd) combined with bone marrow stromal cells | Granular | Human | Tibia | 9 year nonunion healed within 2 months. | [59] |
| 5 | CS paste (Stimulan Kit, Biocomposites Ltd.) | Paste | Human | Distil radius | New bone formation after CS resorption.  No inflammatory response.  Fully resorpted within 3 months. | [41] |
| 6 | Dehydrated CS (Merck), (Capset, Lifecore Medicals) and (Surgiplaster, Classimport) | Granular | Rabbit | Femur | New bone formation observed with use of all three CS brands.  Resorption within 30 days. | [60] |
| 7 | Particulate Bioglass covered by a  CS (Calcigen™ Oral, Biomet 3i) barrier | Paste | Rat | Skull | Well-formed bone at periphery of the defect.  Minimal CS remained at 4 weeks. | [61] |
| 8 | CS (Galveston Shriners Burne Hospital’s orthotic laboratory) | Granular | Sheep | Lumbar vertebrae | New bone formation observed.  Biomechanically superior fusion mass compared to control Ti cage. | [62] |
| 9 | Biphasic calcium sulfate and beta-TCP putty (Genex Paste, Bio- composites, Ltd.) | Paste | Sheep | Lumbar vertebrae | Almost completely resorbed and replaced by new bone.  No inflammatory response.  Resorbed within 2 months (only ~1% material remained) | [63] |

4.1 Caclium silicates

Calcium silicate has been well known as the main component in Portland cement in concrete field, but has only as a two decades history as a biomaterial. Depending on Ca/Si molar ratio, there are three kinds of calcium silicate: monocalcium silicate (CaSiO3, MCS), dicalcium silicate (Ca2SiO4, C2S), and tricalcium silicate (Ca3SiO5, C3S). C2S and C3S, which are the main components of Portland cement, are hydraulic and can be hydrated and hardened when mixed with liquid phase. C2S have been known to have five polymorphs, designated by using the symbols α, α’H, α’L, β and γ. The γ form is stable at room temperature, where it is inactive against hydration. The β form is unstable but it has hydration activity at room temperature.64 Synthesis of pure β-C2S has been widely studied. Several techniques, including sol–gel, evaporative decomposition of solutions, chemical precipitation and Pechini process have been used to produce pure β-C2S.65 It seems that the Pechini process is the better way to produce pure β-C2S.66 β-C2S hydrates much slower than C3S and is the probably the most significant limitation for the use of this kind of cement.67 When hydrated, the silicate phases undergo a series of physico-chemical reactions resulting in the formation of a nanoporous gel phase of calcium silicate hydrates (CSH) and a soluble fraction of calcium hydroxide Ca(OH)2 or portlandite. Monocalcium silicate is a mineral in nature and has two main forms: the low-temperature phase wollastonite (β-CaSiO3) and the high-temperature phase pseudowollastonite (α-CaSiO3).68 MCS, though not hydraulic, still attracts attention as a biomaterial due to its good bioactivity and biocompatibility.

Since the discovery of Bioglass by Hench et al. in 1971, various types of biomaterials containing CaO-SiO2, such as bioactive glasses, AW glass-ceramics, and calcium silicate cement, have been investigated as biomaterials for hard tissue repair or replacement.69 The element silicon is an important trace element in the early stages of bone formation. The soluble form of silicon may contribute to the stimulation of collagen type I synthesis and osteoblastic differentiation in human osteoblast-like cells.70 Throughout the literature it is shown that biomaterials containing CaO-SiO2 appear to have excellent bioactivity and can bond to living bone and soft tissue. This occurs through the development of a biologic apatite layer on the surface of the implanted material.71 Mineral trioxide aggregate (MTA), derived from a Portland cement parent compound, has been investigated for dental applications since the early 1990s and was given approval for endodontic use by the U.S. Food and Drug Administration in 1998.72 In 1996 when D. Lamy et al. used C2S as a bond coat for improving the bonding of hydroxyapatite coatings on Ti alloys substrates.73 Then in 2002, X.Y. Liu et al. investigated the bioactivity of C2S coating and indicated that the C2S coating possessed excellent bioactivity74 Then in 2004 and 2005, Chang Jiang group studied the self-setting property and bioactivity of β-C2S cement75,76 and C3S cement,77,78 showing that calcium silicate cement might be suitable for potential applications in the biomedical field. Since then, calcium silicate cements have attracted more attention in the field of bone or dental repair and drug delivery since they showed good biocompatibility, bioactivity, excellent marginal adaptation and sealing ability.79,80

Compositional modification by ion substitution or doping with ions such as titanium (Ti4+), strontium (Sr2+), magnesium (Mg2+) or europium (Eu3+) has been extensively studied in the literature and the findings are summarised in Table.3. Physicochemical and biological properties are typically improved by the incorporation of an additional inorganic component. For example, a major drawback of the CaSiO3 ceramics is their high dissolution rate, resulting in increased pH values in the surrounding environment that may be detrimental to surrounding tissues.81 Ti4+ or Sr2+ incorporation into CaSiO3 can improve its chemical stability and bioactivity.82

Table.3 Summary of element or ion substituted or doped calcium silicate research

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| No. | Element | Composites | Synthesis methods | Remarks | Potential applications | Ref. |
| 1 | Ti | Sphere CaTiSiO5 ceramic | Sol-Gel | Improved chemical stability and bioactivity | Skeletal tissue regeneration and as coating onto orthopedic/dental implants | [81] |
| 2 | Sr | Mesoporous Sr-CaSiO3 | using P123 as template | Decreased the dissolution rate of Ca and Si ions from mesoporous CaSiO3 and Enhanced the ability to stabilise the pH environment. | Bone tissue regeneration | [82] |
| 3 | Mg | Mesoporous CaMgSi2O6 | P123 as template; precipitation | Good bioactivity, degradability and cytocompatibility | Bone substitute | [83] |
| 4 | Ag | Ag/CS core-shell Nanoparticles | Precipitation |  | Biomedical materials | [84] |
| 5 | Eu3+ | mesoporous Eu doped CS | P123 as template; precipitation | Bioactive,  luminescent | Drug delivery | [85] |
| 6 | Eu3+/Tb3+ | Mesoporous Eu3+/Tb3+ doped CS microspheres | Using mesoporous silica spheres as the templates | Mesoporous structure, good biocompatibility and luminescent | Drug delivery | [86] |

P123: EO20PO70EO20 (polyethylene oxide)(20)(polypropylene oxide)(70)(polyethylene oxide)(20)

Another way of composition modification is to fabricate hybrid composites. Materials that have been incorporated with calcium silicate include: inorganics such as calcium phosphates, calcium sulphate and calcium carbonate; synthetic biopolymers such as PLGA, PCL and PLLA; and natural biological polymers, such as silk fibrin, chitosan and gelatin. The composites usually have improved mechanical properties and better biocompatibility and bioactivity comparing to the single-phase calcium silicate. A summary of the calcium silicate composites is provided in Table.4.

Calcium silicate or calcium silicate/polymer hybrid nanoporous/mesoporous spheres, hollow microspheres, nanowires, nanobelts, nanofibres and nanofoils have been fabricated.80 This provides an array of applications for calcium silicate beyond being cement. Spheres can be used for drug delivery. One-dimensional (1-D) nano-materials have potential applications within advanced functional materials and devices, and also could be used as additives to improve the mechanical properties of composite materials, owing to their unique physical, chemical and biological properties.87

Until now, calcium silicate cements have been primarily utilised as root-end filling, root repair, pulp capping and other dental repair materials.79 The application for CS in bone repair is actively being researched. Recently, the application of calcium silicate for drug delivery has drawn more interest. Jin Wu et.al88 reported that CSH was made into nanostructured mesoporous spheres using a low-cost, surfactant-free sonochemical method (Fig.2 (a)&(b)). The drug loading capacity was 2.29g ibuprofen (IBU) per gram. During the release of loaded IBU in SBF, CSH gradually transformed to HAP, implying the good bioactivity and biodegradability. The authors also80 have prepared amorphous CSH/mPEG-PLGA (CSHP) nanoparticles through a facile block copolymer assisted route (Fig.2 (c)&(d)). The IBU loading capacity of the CSHP nanoparticles was about 1.9 g IBU per gram CSHP. The loaded IBU can release in SBF for a long period of time (about 300h), during which the CSHP is completely transformed to hydroxyapatite. The loading capacity of the anticancer drug DTX in the CSHP hybrid nanoparticles is about 82 mg DTX per gram of CSHP. More importantly, the release of the loaded DTX in PBS at pH 5.5 is obviously faster than that at pH 7.4, which is promising for the application in cancer therapy.

Chang Jiang89 group synthesised hollow CSH microspheres by a surfactant-assisted sonochemical route (Fig.1 (e)&(f)). The drug loading capacity was about 260mg gentamicin per hollow CSH. All these results suggest that CSH might be used for preparation of bone grafts with drug delivery properties. Another group studied Eu3+ and Tb3+ doped MCS as the drug carries.85,86 Of interest is that the drug-loaded samples show the characteristic emission lines of Eu3+ (5D0–7F1-3) and/or Tb3+ (5D4–7F3–6) under UV irradiation. The PL intensity of Eu3+ in the drug carrier system increases with the cumulative released amount of IBU, allowing the drug release to be tracked via change of Eu3+ luminescence. This material demonstrates a great potential for drug delivery and disease therapy.

图片1.emf

Fig.2. Morphologies of several kinds of calcium silicate materials: (a)&(b) SEM and TEM images of hierachically nanostructured mesoporous spheres CSH, prepared by the surfactant-free sonochemical method;88 (c)&(d) TEM micrographs and XRD pattern of amorphous CSH/mPEG-PLGA hybrid nanoparticles80; (e)&(f) SEM and TEM images of the hollow CSH microspheres synthesised by a surfactant-assisted sonochemical route.89

Table.4 Summary of Calcium silicate based biocomposites research

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Composition | | | Fabrication methods | Shape | Effects/Advantages | Potential applications | Ref. |
| 1 | CaSiO3 | HAP | Electrodeposition | | Porous coating | Higher bond strength;  better cell response | Improving the property of titanium | [90] |
| β-CaSiO3 | Sol-Gel method | | Nano-composite | Enhanced mechanical properties | Bone substitute, especially in load bearing sites | [91] |
| Ca2SiO4 | Fast Hot-Pressing | | Bulk composite | Homogeneous ceramic material characterised by controlled phase composition; improved mechanical strength | Load-bearing bone substitutes | [71] |
| 2 | CaSiO3 | CPC | chemical  precipitation | | disk-shaped composite | Excellent biocompatibility; better cell adhesion and spreading | Bone repair | [92] |
| 3 | β-Ca2SiO4 | Calcium sulfate | Sol-Gel method | | Bulk cement composites | Improved the self-setting properties; higher mechanical strength; shorter setting time | Tissue repair substitute | [93] |
| Ca3SiO5 | [94][95] |
| 4 | CS | Calcium carbonate | CO2 bubble template method | | Hollow microspheres | Enhanced drug loading capacity; better biocompatibility | Drug delivery | [96] |
| 5 | CS | PLGA | P123 and CTAB as templates | | Nanoporous | Improved bioactivity and biocompatibility | Bone repair | [97] |
| 6 | Amorphous CSH | mPEG-PLGA | Co-precipitation route | | core/shell hybrid nanoparticle | High drug loading capacity; nearly 100% loading efficiency | Drug carriers | [80] |
| 7 | CSH nanowire | PLLA | Electrospinning and hot press processing | | Nanoparticles | Improved mineralisation ability and cellular responses | Bone graft substitutes | [98] |
| 8 | nano-CaSiO3 | PCL | Solvent-casting method | | Bulk composite | Enhanced bioactivity and biocompatibility | Bone repair | [99] |
| 9 | Mesoporous CS | Silk fibroin | Solvent casting method | | Film | Excellent physicochemical and biological properties | Bone tissue engineering | [100] |
| 10 | β-Ca2SiO4 | Gelatin | Sol-Gel and Pressing-hydrothermal method | | Bulk composite | Higher compressive strength and Weibull modulus; bioactive, nontoxic, and osteogenic | Load-bearing tissue repair | [101][102] |
| 11 | β-Ca2SiO4 | Chitosan oligosaccharide and gelatin | Sol-Gel method | | Bulk cement | Nondegradable and highly active | Dental and orthopedic applications | [103] |

mPEG-PLGA: block copolymer monomethoxy(polyethyleneglycol)-block-poly(lactide-co-glycolide);

PLLA: poly(L-lactic acid);

PCL: poly (epsilon-caprolactone)

P123: EO(20)PO(70)EO(20);

CTAB: hexadecyltrimethyl ammonium bromide;

CSH: Calcium silicate hydrate;

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