Cold-sintered bioceramics for medical applications: State of the art and further perspectives

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ABSTRACT

Cold sintering has recently emerged as a promising approach for preparing dense ceramic materials and composites at low temperatures. It relies on utilizing transient, typically externally introduced, liquid phases to accelerate material diffusion and densification under applied pressure. Cold-sintered bioceramics, especially those prepared at temperatures below 100°C, may open up numerous possibilities, not only in producing dense ceramics with refined microstructural properties and reduced time/energy costs, but also in developing multifunctional platforms containing bioactive compounds, therapeutics, growth factors, and signaling molecules for enhanced and targeted biological responses. Cold sintering in the presence of liquids inherently involves dissolution and nucleation, which become particularly intricate under applied pressures and elevated temperatures. Pseudo bio-mineralization, an auspicious approach for tailoring synthetic bone grafts toward targeted mechanics, may serve as a viable route for enhancing the densification mechanisms inherent to cold sintering. We have carefully analyzed the current state of the art in cold-sintered bioceramics and the results achieved, with a focus on the chemistry of the employed liquids and the corresponding changes upon sintering, the selection of transient phases, and mineral nucleation, while also addressing the potential for developing new biomaterials. Despite the widely accepted classical dissolution–precipitation strategy, no clear roadmap can yet be defined regarding the type and amount of liquid phase that should be applied, at least in the case of hydroxyapatite (HAp) densification–the most important representative of calcium phosphates. We strongly advocate the use of water as the transient liquid of choice in the cold sintering of HAp-based bioceramics, instead of strong acids/bases, and emphasize the importance of understanding the various processes and parameters that govern and connect solution chemistry to mineral nucleation. This understanding will enable the advancement of cold sintering protocols in a target-oriented manner, and we provide perspectives on future developments, including practical advice.

Keywords:
Cold sintering; Calcium phosphates; Bioceramics; Nucleation; Solution chemistry; Biomedicine; Mechanical properties; Biomaterials translation

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1. Introduction

Ceramic-based materials, either alone or as composites with polymers and/or metals, have found broad applications in bone tissue repair. Among different bioceramic materials, the vast majority of studies focus on calcium phosphate ceramics, particularly hydroxyapatite (HAp) and β-tricalcium phosphate (β-TCP), or their mixtures, known as biphasic calcium phosphate, due to their chemical similarity to bone mineral, biocompatibility, and bioactivity. However, their insufficient mechanical properties limit load-bearing applications; therefore, they are often combined with traditional ceramics such as alumina and zirconia or subjected to grain boundary or interface engineering to enhance their structural reliability. Nevertheless, novel ceramic systems have also emerged for biomedical applications, e.g., biocompatible $MgFeCO_3$ layered double hydroxide, which exhibits surface

reactivity and the ability to intercalate different ions for therapeutic effects,[1] or biodegradable calcium sulfate.[2]

The preparation of bioceramics and related composites by sintering remains the leading technology for producing structural components used in bone tissue repair. Originating from traditional high-temperature firing, sintering approaches have gradually evolved toward microstructural optimization and grain size refinement in sintered pieces, aiming to achieve enhanced functional properties of nanoceramics, improved mechanical performance, stronger interactions with biologically relevant molecules (e.g., proteins), and better cell attachment and proliferation. Decreasing the sintering temperature, as in two-step sintering,[3,4] or both the temperature and duration, as in microwave[5] and spark plasma sintering,[6] has proven beneficial not only for reducing grain size while maintaining high relative density but also in terms of cost savings, environmental protection, and enhanced biological behavior. Laser sintering has demonstrated excellent capability for producing complex structural parts;[7] however, these techniques still face technological challenges for large-scale applications.

Affordable, green, and convenient low-temperature sintering applicable on an industrial scale has the potential to revolutionize manufacturing processes and materials preparation. Over the past decade, an increasing number of publications have focused on the cold sintering of diverse ceramic materials. Cold sintering has emerged as a logical extension of liquid-phase and reactive sintering. It is performed at very low temperatures (however, it can reach up to 300°C or even occur at room temperature) by applying external pressure and using a transient liquid phase, which together promote enhanced material diffusion and densification. Remarkable results have been achieved, spanning applications from solid-state electrolytes and electronic circuits to biomaterials.[8] A literature survey on cold-sintered ceramics for biomedical applications reveals extensive efforts to adapt cold sintering procedures using either crystalline or amorphous phases; transient liquids ranging from pure water to strong mineral acids and bases; temperatures from room temperature to 300°C; and uniaxial pressures up to several hundred MPa. Cold sintering requires lower energy for densification than conventional sintering, implying non-equilibrium conditions at the solid–liquid interface.[9] It is a promising technology for fabricating biomimetic ceramics with enhanced functional properties[10] and nanocomposites with incompatible processing windows (e.g., polymers cannot be densified at high temperatures like ceramics) to produce high-density monoliths.[11]

Herein, we critically analyze current achievements and challenges in the cold sintering of bioceramic materials intended for bone tissue repair by revisiting the underlying chemistry of solid–liquid systems; the resulting microstructural and functional (mechanical, optical, and biological) properties; existing gaps in understanding nucleation processes; and the potential to develop new biomaterials. Furthermore, we propose novel strategies and practical approaches that can be applied in cold sintering and explore its potential expansion through the incorporation of various biomolecules and reinforcing phases. The interplay between solution chemistry, nucleation control, and interfacial engineering may open new possibilities in materials science for the development of advanced composites for bone tissue engineering. This paper focuses exclusively on cold sintering studies and excludes other low-temperature sintering approaches (e.g., spark plasma or microwave sintering), as well as pure compaction techniques and materials other than calcium phosphates.

2. Cold sintering of bioceramics: Current achievements

Most cold sintering studies of materials related to bone tissue engineering concern calcium phosphates, including both amorphous and crystalline phases. Although biomimetically grown calcium carbonate polymorphs are of great significance in the biomedical field,[12] their cold sintering behavior is excluded from this work. Here, we present the most important results on the cold sintering of anhydrous dicalcium phosphate (DCPA), dicalcium phosphate dihydrate (DCPD), β-TCP, amorphous calcium phosphate (ACP), HAp, and related composite systems.

DCPA ($CaHPO_4$), a hard-to-stabilize calcium phosphate phase, was obtained by cold-sintering DCPD ($CaHPO_4{\cdot}2H_2O$) at 250°C. Using water as an additive, DCPA with a relative density of 95% was synthesized, highlighting the crucial role of water-mediated hydration. The obtained ceramics exhibited a flexural strength of 46.17 MPa and Young's modulus approaching that of natural bone tissue.[13] β-TCP was cold sintered at 200°C with the addition of S53P4 bioglass. The bioglass played a critical role in the densification mechanism, achieving a theoretical density of up to 85%, while no improvement in densification was observed for pure β-TCP,[14] implying a possible role of structural hydroxyl groups. Such cold-sintered β-TCP–bioglass composites demonstrated apatite formation in simulated body fluid (SBF) solution after 7 and 14 days.[14]

ACP was densified through cold sintering at temperatures ranging from room temperature to 150°C using 20 wt.% of water as a transient liquid. Regardless of whether a transient liquid or an increased temperature was applied, ACP could be sintered to no more than approximately 75 % relative density compared to ACP processed at room temperature, with no significant improvements at higher sintering temperatures.[15] Cold sintering is very promising for the preparation of transparent ceramics.[16] Seo *et al.*[17] synthesized transparent HAp ceramics by cold sintering at 180°C and a uniaxial pressure of 800 MPa, achieving more than 80% transmittance and

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mechanical properties comparable to conventionally sintered ceramics. They applied a so-called "pseudo-biomineralization" approach, using SBF as a transient liquid phase to induce the formation of newly precipitated crystalline HAp on the HAp grains of the starting ceramics. This led to grain rearrangement and refinement in high-density compacts, providing optical transparency at 550 nm comparable to other reported HAp sintered bodies.[17] Increasing the amount of SBF did not result in a consistent density increase, while higher applied pressures, sintering temperatures, and durations played a more significant role in densification and transparency enhancement. The study also revealed that pseudo-biomineralization, as a key mechanism contributing to the final densification, required 6 h to achieve optimal density–transparency functionality, emphasizing the importance of the process kinetics. Finally, the prevention of grain growth and the preservation of structural OH groups were identified as crucial for obtaining transparent ceramics, consistent with a previous study of HAp using non-isothermal heating densification.[18]

In addition to water, acetic and phosphoric acids have also been used to enhance the cold sintering behavior of HAp. Kumar *et al.*[19] investigated the cold sintering of HAp at 200°C and 360 MPa using water, acetic acid, and phosphoric acid as transient liquids. They found a correlation between the relative density of the cold-sintered HAp and the concentration of the liquid phase, reaching the highest relative density of 90% for 2 M phosphoric acid. Interestingly, 0.5 M phosphoric acid did not perform significantly better than pure water. Galotta *et al.*[20] used acetic acid, phosphoric acid, and ethylenediaminetetraacetic acid (EDTA) at a concentration of 0.1 M and a weight fraction of 0–30 wt.% to sinter mussel shell-derived HAp (initially obtained as $CaCO_3$, which was then transformed into HAp) at 200°C under 300–600 MPa, achieving a maximum relative density of 82%. The addition of EDTA up to 20 wt.% increased the relative density compared with dry-pressed HAp, but the effect then plateaued. On the other hand, increasing the applied pressure and holding time had a positive effect on densification. The cold-sintered bioceramic was non-toxic, and human bone marrow-mesenchymal stem cells formed interconnected clusters on the ceramic surface, exhibiting favorable proliferation. Shen *et al.*[21] used water, 14 M ammonium hydroxide, and 1 M acetic acid as transient liquids to sinter HAp at 250°C for 15 min under a uniaxial pressure of 250 MPa. However, the acid and base liquid phases did not improve final densification compared with using only water, reaching a relative density of 92%. Moreover, using only dry powder, a relative density of 90% was achieved, with an average grain size of 20–30 nm.[21] HAp was also cold-sintered at 200°C at 500 MPa for 60 min, reaching a relative density of 98% without any added transient liquid. This effect was ascribed to surface chemistry and the presence of an amorphous hydrated layer around HAp nanoparticles, which not only facilitated particle sliding but also contributed to densification through dehydration, yielding slightly lower microhardness than conventionally sintered HAp. The loss of this amorphous hydrated layer through calcination and HAp crystallization was detrimental to densification during cold sintering and could not be recovered by external water addition.[22]

Combining HAp with fracture-resilient ceramics has been explored to improve the inherent brittleness of calcium phosphates. Recently, cold sintering was applied to consolidate HAp-encapsulated nano-alumina (Al_2O_3) powder. HAp was reinforced with up to 45 wt.% of alumina and sintered at 300 °C for 10 min under 500 MPa, resulting in a nonporous microstructure. The dense HAp/nano-Al_2O_3 composites exhibited good hardness and demonstrated protein adsorption, indicating potential as biocompatible bioceramic materials. Successful densification was achieved without the addition of transient liquid phases, which was attributed to the effect of water on the HAp surface.[23] Silica was also used to improve the performance of HAp bioceramics. HAp reinforced with 35 mol.% of silicon dioxide was sintered at 250°C under 750 MPa using 35 wt.% of deionized water as an added liquid phase, reaching a relative density of 92.4 %.[24] The resulting glass-ceramics exhibited good mechanical properties, with a Vickers hardness of 5.4 GPa, a fracture toughness of 0.62 MPa·$m^{1/2}$, and a compressive strength of 602 MPa.[24] Cold sintering using oleic acid was also applied to induce the self-assembly of layer-ordered HAp nanowire arrays, which proved beneficial for oil/water separation.[25]

Cold sintering offers substantial potential for consolidating or co-sintering materials with very different thermal behaviors such as polymers, metals, and ceramics. This opens numerous opportunities for creating composite materials with durable mechanical properties for applications in bone tissue engineering. Regarding the cold sintering of HAp/polymer composites, several studies have recently been reported. For example, HAp–gelatine multilayered composites (70 wt.% of HAp) with embedded gold nanoparticles were cold sintered at 50°C for 20 min at a pressure of 1 GPa, without transient phases or binders, exhibiting good integration without delamination.[26] Recently, cold sintering has been applied to HAp and poly(lactic acid) (PLA) to fabricate a bone-mimicking nanocomposite. The focus was on the consolidation of HAp in the PLA matrix by exploiting the plasticization effect. The system was cold sintered at 250°C and 360 MPa. The HAp-to-PLA ratio was a critical parameter, and the system containing 80 wt.% HAp and 20 wt.% PLA exhibited the optimal consolidation behavior. The resulting mechanical properties of the nanocomposite were suitable for load-bearing applications, such as the cortical bone reconstruction.[27] At this HAp-to-PLA ratio, the system achieved higher densification than a previously reported similar composite,[28] which was attributed to the more fluid-like behavior of PLA under the applied cold sintering conditions and the plasticization effect of tributyl citrate.

One of the pioneering efforts in using cold sintering to produce a drug-delivery platform based on mussel shell-derived apatite/chitosan composites loaded with strontium ranelate has also been reported. Cold sintering was performed at a pressure of 1.5 GPa at room temperature for 10 min, achieving a relative density of 90%. Densification was enhanced not only by the increased pressure but also by the addition of chitosan and strontium ranelate. The composite exhibited controlled release of strontium ranelate for 19 days and showed no cytotoxicity.[29]

Figure 1 summarizes the main approaches (**Figure 1A**) and key achievements (**Figure 1B**) in the cold sintering of

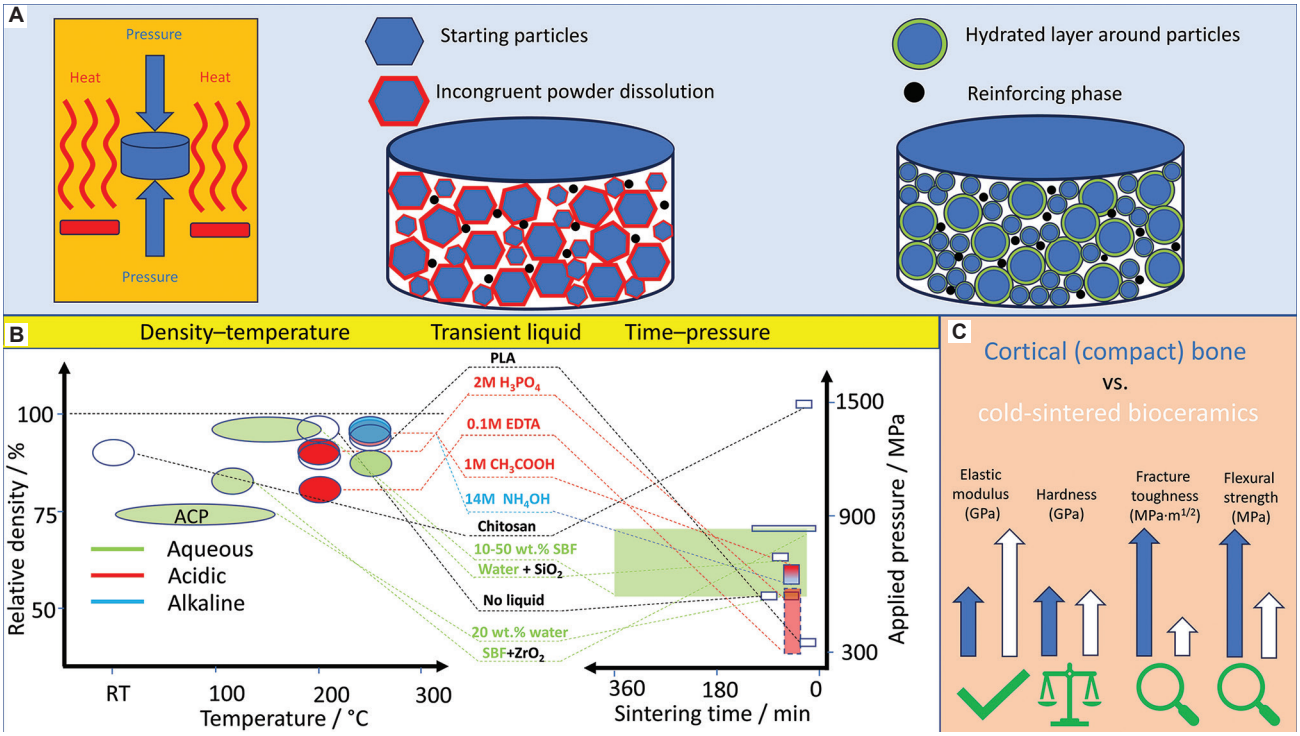

Figure 1. Current achievements in the cold sintering of calcium phosphate-based bioceramics, mostly hydroxyapatite (HAp), highlighting the effects of acid/base and water as transient liquids, and comparing the mechanical properties of engineered samples with cortical bone. (A) Schematic representation of the cold sintering procedure, showing model examples of initial green bodies: incongruently dissolved particles when acids are used as a transient liquid (as for HAp) and hydrated particles with externally added water or a hydrated layer. (B) Key results using different acids, bases, and water as transient liquids, showing employed processing parameters (temperature, time, pressure) and achieved relative densities. The left plot depicts sintering temperatures versus relative densities, while the right plot shows sintering time– pressure conditions. Red denotes acidic transient liquids, blue represents alkaline conditions, and green stands for water; transparent features indicate no added transient liquids, and black indicates external, reinforcing phases. (C) Illustration of the mechanical properties of cold-sintered bioceramics compared with cortical (compact) bone.
Note: Data points were extracted from Rubenis *et al.*,[15] Seo *et al.*,[17] Kumar *et al.*,[19] Galotta *et al.*,[20] Shen *et al.*,[21] Ul Hassan *et al.*,[22] Huang *et al.*,[24] Hu *et al.*,[25] Kumar *et al.*,[27] Galotta *et al.*,[29] and Seo *et al.*[30] Figure created by the authors.
Abbreviations: ACP: Amorphous calcium phosphate; RT: Room temperature.

calcium phosphate bioceramics. The relative densities of HAp bioceramics (as the main calcium phosphate representative) processed through cold sintering fall within a well-defined range of 80–99%, typically employing sintering temperatures between 200 and 250°C, pressures from 300 to 800 MPa, and sintering times of up to 1 h (although exceptions exist). This demonstrates the method's suitability for preparing fully dense sintered bodies at relatively low temperatures, though still above room temperature. There are examples of dense bioceramics bodies obtained at lower temperatures, but these required much higher pressure. Regarding the use of transient liquids, there are no clear indications that acidic or alkaline environments enhance densification compared to water or even an externally added liquid phase, in terms of either relative densities or mechanical and biological performance. The use of SBF as a transient phase can be positively evaluated, likely due to its promotion of pseudo-biomineralization, a process that can assist the final densification. The proposed densification mechanisms include dissolution–recrystallization, dehydration, sliding over amorphous grain boundary phases, pseudo-biomineralization, pressure-induced solution creep, and hydrated precursor-assisted densification.[15,17,19-22,24,25,27,29-31] However, the exact mechanism is strongly system-dependent and likely involves multiple concurrent processes. Although reported mechanical properties are difficult to compare due to variations in measurement methods, testing direction, sample quality, and reinforcing phases, the literature reports elastic moduli for cold-sintered bioceramics ranging from 25 to 84 GPa, hardness from 2.17 to 5.4 GPa, fracture toughness from 0.62 to 1.11 MPa·m$^{1/2}$, and flexural strength from 23 to 63 MPa. Compared with cortical bone (**Figure 1C**),[32] the elastic modulus and hardness of cold-sintered calcium phosphate bioceramics are well-matched, while their fracture toughness and flexural strength remain lower than those of natural bone tissue (considering the aforementioned limitations in determining mechanical properties). The biomaterials translation stage of cold-sintered bioceramics is still at the initial basic research and discovery; however, protein adsorption and stem cell spreading have been clearly demonstrated.

A more detailed overview of the most significant cold sintering studies related to calcium phosphates, including the type and amount of liquid phase, potential reinforcement, cold sintering conditions (i.e., temperature-time-pressure), achieved relative density, densification mechanism, functional performance, and the BTS is presented in **Table 1**. The list is not intended to be exhaustive but, in our opinion, highlights the most important

Table 1. Current state of the art of cold-sintered bioceramics

Ceramic system	Transient phase/ liquid (amount, %)	Added reinforcement (amount)	Sintering temperature (°C)/time (min)/ applied pressure (MPa)	Relative density (%)	Densification mechanism	Performance	BTS	Reference
β-tricalcium phosphate	Deionized water (10 wt.%)	S53P4 bioglass (0–60 wt.%)	200/-/166	76–85	Bioglass as a densification aid	Enhanced apatite formation in SBF after 7 and 14 days	BR&D	14
ACP	Water (20 wt.%)	-	RT, 100–150/15/500	76	Hydrated structure of ACP	Biaxial flexural strength (32.3±4.6 MPa), average grain size on the nanometer level	-	15
HAp	-	-	200/60/500	98.8	Surface chemistry, dehydration of and sliding over the amorphous layer	Microhardness (2.17±0.23 GPa)	-	22
HAp	NH_4OH (14 M), CH_3COOH (1 M) (up to 20 wt.%)	-	250/15/650	92	Ion substitution and lattice water	Average grain size of 20–30 nm	-	21
HAp	SBF (10– 50 wt.%)	-	100–200/30–360/500–800	98.5	Pseudo-biomineralization	80% transparency at 550 nm, Vickers hardness (3.88±0.22 GPa), fracture toughness (0.62±0.03 MPa m1/2), biaxial flexural strength (41.69±1.23 MPa), Young's modulus (78.1±2.04 GPa)	BR&D	17
HAp	Water, H_3PO_4, CH_3COOH, 0.5–2 M (10 wt.%)	-	200/10/360	90	Dissolution–recrystallization, ionic substitution	-	-	19
Mussel-shell-derived HAp	CH_3COOH, H_3PO_4, EDTA, 0.1 M (0–30 wt.%)	-	200/15/300–600	82	Pressure-induced solution creep	Fast adhesion and spreading of hBM-MSCs, with flexural resistance of 23 MPa	BR&D	20
HAp	-	nano-alumina (≤ 45 vol.%)	300/10/500	100	Water at the HAp surface	Hardness 3 GPa, good plasma protein adsorption/ osseointegration	BR&D	23
HAp	Water (35 wt.%)	SiO_2 (35 mol.%)	250/30/750	92.4	Dissolution–reprecipitation, plastic deformation	Vickers hardness 5.4 GPa, fracture toughness 0.62 MPa·$m^{1/2}$, high compressive strength 602 MPa	-	24
HAp	Oleic acid ($C_{18}H_{34}O_2$) (0–20 wt.%)	-	80/20/200	99	-	Excellent oil/water separation performance	-	25
HAp/gelatin	-	Au structures	50/20/1000	-	Gelatine-enhanced densification	No delamination	-	26
HAp/PLA	PLA (20 wt.%)	Tributyl citrate plasticizer	250/10/360	95.6	PLA-enhanced densification, plasticization effect	Mechanical properties comparable to cortical bone, hardness HV20 112.5, elastic modulus 25 GPa	-	27
Mussel shell-derived HAp/chitosan	Chitosan (10 wt.%)	Strontium ranelate (5 wt.%)	RT/10/1500	90	Chitosan	Bioactivity, sustained drug release for 19 days, no toxicity	BR&D	29
HAp	SBF (20 wt.%)	ZrO_2 (50–20 vol.%)	130/10-120/800	88	Biomineralization	Vickers hardness (3.68±0.18 GPa), fracture toughness (1.11±0.10 MPa·$m^{1/2}$), biaxial flexural strength (63.72±2.35 MPa), Young's modulus (83.91±1.93 GPa)	-	30
HAp	-	$CaHPO_4{\cdot}2H_2O$ (DCPD) (10–90 wt.%)	80–150/20/500	95	Hydrated precursor-assisted densification	Elastic modulus 55 GPa, compressive strength~135 MPa, flexural strength~50 MPa	-	31

Abbreviations: ACP: Amorphous calcium phosphate; Au: Gold; BR&D: Basic research and discovery; BTS: Biomaterials translational stage; $CaHPO_4$: Dicalcium phosphate; CH_3COOH: Acetic acid; DCPD: Dicalcium phosphate dihydrate; EDTA: Ethylenediaminetetraacetic acid; HAp: Hydroxyapatite; hBM-MSCs: Human bone marrow-mesenchymal stem cells; H_2O: Water; H_3PO_4: Phosphoric acid; NH_4OH: Ammonium hydroxide; PLA: Poly (lactic acid); RT: Room temperature; SBF: Simulated body fluid; SiO_2: Silicon dioxide; ZrO_2: Zirconium dioxide.

achievements available in the literature. This survey proves that cold sintering, although a relatively novel technology, has gained momentum toward becoming a method of choice for consolidating versatile bioceramic materials and expanding their application range and potential for use as multifunctional biomedical platforms. The mechanical performance of cold-sintered systems based on calcium phosphates is comparable to or slightly lower than that of conventionally sintered counterparts. However, there are still no data on the electrical properties— piezoelectric or conductive—of these materials, although such functionality could be important for bone healing. The consolidation of HAp with different polymeric systems has been demonstrated, opening many possibilities for further research. The level of translation into actual biomaterial applications remains at a very early stage, and no *in vivo* tests are currently available. Nevertheless, the densification mechanism under cold sintering conditions is still poorly understood. The choice of transient liquids—whether acids, bases, or water—appears to have reached a dead-end street, without a clear conclusion as to the optimal cold sintering pathway, implying the need to reconsider the problem from different perspectives.

3. Critical analysis of dissolution in cold sintering of calcium phosphate bioceramics

Excessive temperatures or pressures, as well as abrupt solvent evaporation during cold sintering, may cause macroscopic structural defects such as fractures, delamination, or closed porosity, requiring precise adjustments of all processing parameters. The classical dissolution–precipitation pathway is considered a critical mechanism and driving force for cold sintering.[21] The main concept is that the liquid phase and applied pressure enhance material dissolution; therefore, the liquid phase in cold sintering is sometimes referred to as a solvent. Subsequently, capillary forces and chemical potential differences drive material diffusion. Solvent or liquid evaporation increases supersaturation, ultimately leading to precipitation. The transient liquid phase typically constitutes approximately 4–25 vol.%[9] and facilitates mass transport to and from the particles of the processed material. It is assumed to be fugitive, i.e., to leave the pellet during densification.[11] However, dissolution at the solid–liquid interface under applied pressure and high temperature is complex and system-specific. Dissolution can be congruent or incongruent (see below), and the kinetics of the process depend on factors such as liquid composition/concentration, temperature, and pressure,[11] making cold sintering mechanisms extremely complex and difficult to predict.

As dissolution is considered essential for densification during cold sintering, many studies have employed strong acids and bases to promote it. For calcium phosphate bioceramics, as described in the previous section, acetic acid, phosphoric acid, EDTA, and ammonium hydroxide have been used.[15,20,21] However, excellent results were also obtained using water or even dry powders with hydrated layers surrounding HAp nanoparticles.[21,22] Indeed, structurally bound water may play a significant role in densification during cold sintering, possibly through hydrogen-bond formation between particles.[15]

The solubility of HAp is of great importance in dentistry and medicine but remains a nontrivial issue. The addition of highly concentrated acids, such as 3 M hydrochloric acid, has been used to dissolve HAp and subsequently reprecipitate ACP by creating a highly alkaline environment.[33] Galotta *et al.*[20] used 0.1 M acetic acid, phosphoric acid, and EDTA in weight fractions of 0–30 wt.% to sinter mussel shell-derived HAp at 200°C and 300–600 MPa. The pH values of 0.1 M solutions of acetic acid, EDTA, and phosphoric acid range approximately from 4 to 1, respectively, yet all cold sintering experiments resulted in a similar relative density of ~75%.[20] Kumar *et al.*[19] employed up to 2 M acetic acid and phosphoric acid as transient liquid phases for the cold sintering of HAp, with pH values of 1.70 and 0.75, respectively. Shen *et al.*[21] reported very mild effects of 14 M ammonium hydroxide or 1 M acetic acid liquid solutions, regardless of their amounts, on the densification of HAp.

Solid titration experiments were performed to study the solubility of HAp at pH values 3–4, showing that the phase precipitating after reaching supersaturation is also HAp, but with slightly lower crystallinity.[34] Furthermore, the dissolution of HAp in acid is incongruent, meaning that the resulting solution does not have the same stoichiometry as the dissolving solid,[34] due to the underlying aqueous phosphate buffer equilibrium and these and other pH-dependent changes in speciation. When a large amount of solid HAp is exposed to an acidic environment, material dissolution predominantly occurs at the particle surface rather than in the bulk, leaving chemically but also structurally inhomogeneous regions within this interfacial zone. This also alters the calcium/phosphorus ratio in the "interphase" between the surface and the bulk material, further complicating the densification process.

Acetic and phosphoric acids are also of interest due to their role in caries formation. Margolis and Moreno[35] reported that the dissolution kinetics depend on the degree of solution saturation. Remarkably, the rate of HAp dissolution in partially saturated phosphoric acid was lower than in organic acids and buffers of the same initial pH, provided that the saturation degree was the same.[35] While the use of phosphoric acid is beneficial for final densification, as shown above, its efficiency in dissolving HAp may be limited because both the liquid and solid contain the same phosphate anion. According to Le Chatelier's principle, this will suppress further HAp dissolution, at least if sudden reprecipitation is delayed.

Regarding HAp dissolution in small-molecule organic acids, citric acid is more effective than acetic acid,[36] although it has not yet been studied as a transient liquid in the cold sintering of HAp. EDTA is known as an efficient chelating agent for calcium ions and is used in potentiometric quantitative calcium determination. Thus, its use may cause significant changes in mineral stoichiometry and a decrease in the calcium/phosphate ratio of the forming HAp phase, introducing potential structural instability in the system. Acids can enhance material flow but may also generate structural defects and affect functional properties.

Fourier-transform infrared spectroscopy spectra of cold-sintered HAp processed in the presence of acetic and

phosphoric acids exhibited bands corresponding to acetate residuals and showed slight changes in crystal chemistry due to the incorporation of some hydrogen phosphate groups, which is related to incongruent dissolution in an acidic environment.[19] This is an important factor that must be understood when designing cold sintering experiments, as residual chemical species may lead to adverse biological effects, e.g., during the osseointegration or resorption of cold-sintered implant materials. The use of strong acids in the cold sintering of HAp is also detrimental to its crystal chemistry, given that such acids will inevitably neutralize hydroxide ions, whose presence is important for numerous functionalities, including electrical conductivity and protein adsorption.

On the other hand, the synthesis of stoichiometric and crystalline HAp is more favorable in alkaline environments, typically around pH 11. Sodium hydroxide and ammonium hydroxide are the most commonly used bases. Exposing low-crystalline or amorphous HAp to highly alkaline environments may lead to its crystallization or the loss of the favorable amorphous layer surrounding HAp nanoparticles. Thus, the rationale for using ammonium hydroxide as a transient liquid for the cold sintering of HAp remains questionable and requires further investigation.

Water, as a transient liquid in cold sintering of HAp, β-TCP, or BCP, can facilitate mass transport along particles under pressure, but it does not cause any dissolution of the material, as none of these phases is soluble at near-neutral pH values. On the other hand, water can have a profound influence on amorphous or less stable calcium phosphate phases, e.g., DCPD. The solubility of HAp in water at near-neutral pH values at room temperature is very low, estimated to be 4 ppm,[21] and characterized by an activity-based solubility product of ~10^{-57}–10^{-52}.[37] X-ray powder diffraction analysis of ACP cold-sintered at 100°C without and with 20 wt.% of water as a transient phase showed that the amorphous phase crystallizes to nanocrystalline HAp only in the presence of water, while the cold-sintered dry powder remains amorphous.[15] This sheds light on the role of water not only as a diffusion-facilitating and moisturizing agent but also as a medium in which the pseudo-hydrothermal crystallization is viable between closely packed and heated nanoparticles, even at the water evaporation temperature. Hydrated amorphous precursors have been shown to play a critical role in designing nacre-like aragonite crystals through water-mediated crystallization and densification.[12,38] The power of water as a densification medium was also demonstrated in the water-mediated densification of bulk van der Waals materials from respective nanosheets at 45°C in only 10 min.[39] The assumed dissolution–precipitation mechanism has been questioned, however, in a recent study on the densification of amorphous silica.[40]

Considering the previously favorable results obtained using water as a liquid medium for HAp densification by cold sintering, there is no clear rationale for using strong acids or bases instead of water to induce the dissolution of HAp as a prerequisite for a successful cold sintering process. Harsh acid–base chemistry is inconsistent with green and soft approaches and may also cause premature failure of the employed equipment, leading to adverse effects in physiological environments, as the chemical constituents of the strong acids and bases will probably never completely leave the bioceramics system. Based on the principles of green and soft chemistry, as well as on existing studies, rational argumentation, and the currently achieved densification levels and functional properties (**Figure 1** and **Table 1**), together with the employed sintering temperature, pressure, and duration, we propose that water should be the focus of further cold sintering studies of HAp-based bioceramic materials. Aqueous environments are inherent to the surface and crystal chemistry of HAp, and a better understanding of the corresponding chemistry of dissolution and nucleation phenomena within the applied temperature–pressure windows will allow the optimization of these chemical environments for low-temperature HAp consolidation.

4. The role of nucleation in cold sintering of calcium phosphate bioceramics

Traditional high-temperature sintering results in highly crystalline ceramics in which different crystal orientations meet at grain boundaries, even when low-crystalline starting powder is used.[3,4,18] Crystallization that occurs during sintering is a thermally driven process; therefore, amorphous materials often cannot be densified to high levels. In contrast, cold sintering can help stabilize amorphous structures. Such amorphous phases are advantageous in biomedical applications, as they exhibit higher solubility and bioavailability and can transform into native biominerals, contributing to bioactivity. Assuming that cold sintering experiments rely on the dissolution–precipitation mechanism, once the material is dissolved, its subsequent nucleation is critical for densification.

While the choice of a transient liquid system in cold sintering is important regarding the material's dissolution, as discussed above, the next step in the dissolution–precipitation cascade is the onset of mineral precipitation or formation. Nucleation from a supersaturated solution formed by congruent high-pressure dissolution has been discussed in terms of strain, temperature, curvature gradient, or solvent evaporation.[11] It is assumed that precipitates form from the liquid phase due to increased supersaturation, which is caused by gradual solvent evaporation during cold sintering above room temperature. This, however, seems to be a rather simplified view that neglects the physicochemical aspects of the solid–liquid interface,[11] which may play a decisive role in mineral formation.[41]

The fundamental basis of mineral formation during cold sintering is the nucleation process. Besides homogeneous nucleation, a supersaturated solution may also precipitate through secondary nucleation on the same mineral or through heterogeneous nucleation on a chemically different system. Heterogeneous nucleation is faster and requires lower supersaturation than homogeneous nucleation, and in our opinion, is the dominant nucleation pathway during cold sintering. However, the formal applicability of classical nucleation theory and its milestone concepts of supersaturation for calculating the size of critical nuclei is challenging here for at least several reasons: (i) the exact

state of saturation/supersaturation can hardly be determined following established experimental protocols (see below); (ii) if dissolution is incongruent, as for HAp dissolution in acids, the solution stoichiometry differs from the stoichiometry of the solid due to the intimately pH-dependent speciation; as pH and activity coefficients during sintering are largely unknown, the definition of the supersaturation ratio, S, as ion activity product (IAP) over solubility product (K_{sp}), i.e., $S = IAP/K_{sp}$, is inconvenient to use as a parameter to pinpoint nucleation thermodynamics; (iii) if the solid phase remaining after dissolution differs from the starting phase, e.g., exhibits different crystallinity, amorphous structure, then K_{sp} changes, i.e., the solid phase may have higher or lower solubility under the given physicochemical conditions; (iv) the challenge of defining supersaturation is further complicated by the crystal chemistry of HAp, which is highly flexible toward various substitutions, reflected in the vast and partly contradicting literature on the solubility of HAp (e.g., McDowell *et al.*[42] and Prakash *et al.*[43]). This highlights that "one HAp" does not seem to exist and that pH, temperature, pressure, ionic strength, the presence of spectator ions, and other conditions will not only crucially determine mineral dissolution but also strongly affect its nucleation.

Regarding the cold sintering of HAp-based bioceramics, the central question is how HAp nucleates and mineralizes. However, this is a very complex system that includes different ion associations and related mechanistic pathways, including solution clustering and speciation, and the fundamental understanding of mineralization at near-physiological pH values is still developing.[44] The "non-classical" prenucleation cluster approach suggests the importance of the solution dynamics and solute PNC species for nucleation, which occurs through dense liquid and solid transient amorphous phases.[45,46] Notably, there is evidence that prenucleation clusters also play a crucial role in secondary nucleation processes and thus in the heterogeneous scenarios important in cold sintering. HAp has a low solubility product, i.e., dissolution in small volumes will create a strong thermodynamic driving force for nucleation even upon just slight evaporation, at least in the neutral to basic pH regime. Even under well-controlled laboratory conditions, the exact mechanisms underlying HAp nucleation are difficult to explore experimentally.[47] It has been recently reported that, under physiological conditions, HAp forms through acidic or basic routes. Along the acidic route, which seems to be of higher importance for cold sintering studies, HAp mineralization starts with DCPD over transient ACP, i.e., hydrogen phosphate-based species form first and then transform into the more stable, fully deprotonated minerals.[48] Furthermore, HAp powders with different crystallinities can be obtained over a wide range of pH values by governing the reaction kinetics. A study of calcium phosphate nucleation between pH 7 and 8 has shown that higher addition rates of calcium into phosphate buffer (e.g., 1 mL/min) delay the onset of nucleation toward higher levels of supersaturation. Unexpectedly, slower additions at pH 7.3 resulted in DCPD formation from lower levels of supersaturation, while faster additions led to the nucleation of poorly crystalline HAp from higher levels of supersaturation. Above pH 7.4, no DCPD formed regardless of the addition rate.[49] All of this implies that phosphate- and hydrogen phosphate-based minerals form along distinct thermodynamic pathways within a complex, yet unknown, phase diagram governed by pH, temperature, and pressure. Indeed, the literature on calcium phosphate nucleation is vast (e.g., Omelon *et al.*[50]), and this small excerpt merely reflects the complexity of the studied chemical system.

It was reported that pressure may lead to strong amorphization (at 10 GPa) in calcium phosphates.[51] The pressure applied in cold sintering is an order of magnitude lower, but the presence of liquid and vapor phases (due to evaporation), as well as high curvatures and nanoscale confinement, could locally induce even higher pressures, contributing to the formation of amorphous layers, which is favorable for densification. Increased connectivity between phosphate anions and the loss of long-range order were found in simulation experiments on calcium and zinc orthophosphates at pressures of 7–23 GPa; however, it was noted that hydrogenation of metal phosphates might induce a lowering of the amorphization,[52] implying the potential role of hydrogen bonding and the exchange between hydrogen and dihydrogen phosphates. Moreover, it was reported that at high supersaturations, which indeed exist during cold sintering in the presence of transient liquids, small differences in the size of nanoconfinement may lead to the formation of different calcium phosphate phases, from ACP to brushite and monetite.[53]

Considering this, we suggest a hypothetical phase diagram for aqueous mineral systems, including a miscibility gap, which might contribute to a better understanding of nucleation under cold sintering conditions, i.e., temperatures and pressures higher than ambient.

The literature survey in Section 2 indicates the dominant use of strong acidic systems or water in the cold sintering of calcium phosphate bioceramics. Using a mineral acid as a transient phase, a portion of the material will undergo strong dissolution according to its solubility in the respective acid. In practice, the extent of dissolution can be lower than the theoretical value, due to spatial–kinetic effects, i.e., insufficient contact or time between the liquid and solid phases for equilibration. Nevertheless, this might shift the system even further away from the conditions necessary for HAp formation. In contrast, water, as a transient liquid, causes only slight mineral dissolution, while its efficiency, either as externally added water or as that in the hydration layer of HAp nanoparticles, has already been demonstrated in cold sintering, as described above.

Instead of using strong acids and bases as transient liquids, material nucleation and subsequent crystallization during cold sintering can be conducted under physicochemical environments analogous to those in biomineralization. Such pseudo-biomineralization-assisted densification was reported for HAp–zirconium dioxide ceramics at 130°C under 800 MPa, reaching a relative density of 88% and good mechanical properties.[30] Solid DCPD was applied in the cold sintering of HAp as a hydrated precursor for HAp formation to assist densification, achieving good mechanical properties. No other liquid phase was applied.[31]

After elaborating on the current achievements in cold sintering of HAp-based ceramics, our critical analysis of the liquid transient phases used, and the challenges of the nucleation-related aspects of cold sintering, we can formulate further perspectives toward low-temperature consolidation of HAp-based bioceramics. In our opinion, cold sintering studies should be designed and performed based on insights from nucleation studies of the investigated chemical system. Such studies, e.g., those based on potentiometric titrations,[57] allow the quantitative establishment of phase behavior for the given physicochemical conditions (**Figure 2**), as well as the identification of (meta)stable, often very reactive reaction intermediates, allowing for their isolation and application as transient liquid phases. It will be especially crucial to study the pressure dependence of aqueous mineral phase behavior, which has not been explored for the liquid–liquid separation process at all. It is quite possible that "non-classical" pathways are thermodynamically and kinetically enhanced under cold sintering conditions with added water. In that way, well-defined liquid states with respect to the formation of the most stable mineral phase can be used in the sintering process. When a chemical solution system optimally compatible with the consolidating solid phase is used, the structure and chemistry of the existing solid will not be disrupted, which is the case when strong acids are employed rather than water. If an HAp powder is mixed with its suitable "prenucleation" liquid phase containing corresponding prenucleation species or amorphous precursor phases, and if pressure and temperature changes are taken into account, the liquid will form a suitable layer around and between compacted particles. In the case of a supersaturated transient liquid phase, the nucleation process could be further promoted by the heterogeneous nucleation of HAp on HAp through optimized intermediates, facilitating consequent material densification.

The nucleation of a solid may also be altered by using other ionic or molecular species. The crystal lattice of HAp is known for its ability to accommodate different ions, both cations and anions. Thus, the liquid phase can be enriched with an entire palette of metal species, such as magnesium, strontium, lithium, iron, copper, etc., all important for biological functions, giving the final cold-sintered material excellent potential for, e.g., a therapeutic release of different ions or postoperative control imaging. Furthermore, the added transient liquid phase can be enriched with therapeutic molecules, which, in the case of mild processing parameters, may remain functional and ready to release upon material integration into the surrounding bone tissue, provided that the HAp nucleation behavior in their presence remains favorable. Moreover, it is also possible to use a small amount of a reinforcing and non-toxic material, e.g., nanocellulose, alginates, or chitin, which will then be naturally dispersed along grain boundaries formed during cold sintering, opening the pathway toward rational grain boundary engineering. Such phases may be an efficient

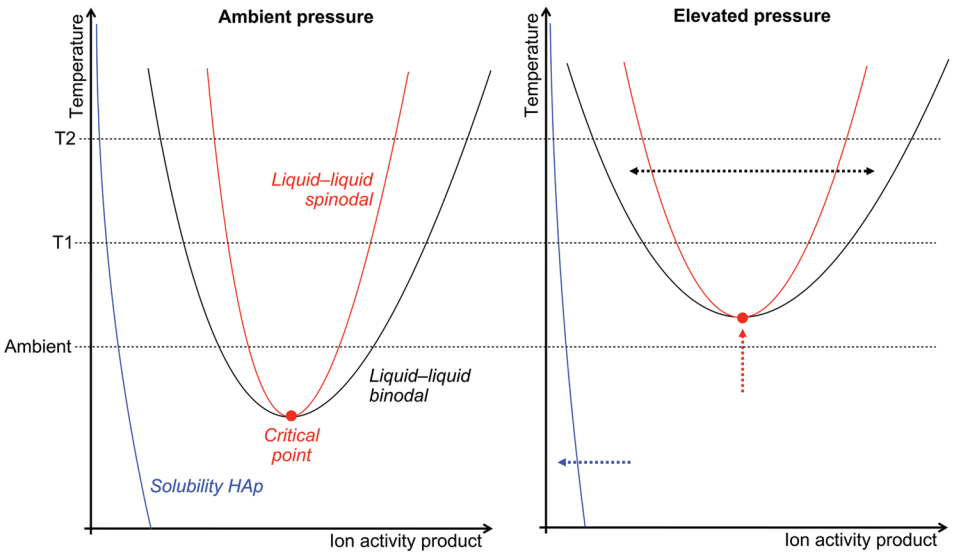

Figure 2. Hypothetical, simplified phase diagrams for aqueous mineral systems including a metastable liquid–liquid miscibility gap (left, ambient pressure; right, high pressure). In the case of calcium carbonate, solid amorphous phases form through prenucleation clusters that demix into dense liquid minerals, which subsequently dehydrate and transform into crystals.[54,55] In view of existing literature, e.g., Nudelman *et al.*,[56] it may be speculated that similar phase behavior would exist for calcium phosphates. As the solubility of HAp is retrograde (exothermic dissolution), the liquid–liquid phase behavior could be governed by a lower critical solution temperature. When the pressure is increased (right), in metastable equilibrium and at the same temperature, the dense liquids could become denser and the mother solutions leaner than at ambient pressure, shifting the critical point upwards and decreasing the solubility of HAp (dashed bold arrows). If this situation reflects a real scenario, the miscibility gap could no longer be entered at ambient temperature and high pressure (although accessible at ambient temperature and pressure), while at sintering temperature T_1, the supersaturation required to enter the dense liquid regime would be higher at elevated than at ambient pressure. By contrast, at sintering temperature T_2, the supersaturation required to enter the dense liquid regime at higher pressure would be even lower than at ambient pressure. This illustrates that the choice of temperature and pressure could strongly affect the precipitation pathway and, with it, the role of dense liquid and solid amorphous phases nucleating transiently during cold sintering. Future research is crucially needed to clarify the phase behavior of calcium phosphate in the presence of added water in cold sintering approaches. Figure created by the authors.

means of dispersing mechanical energy and increasing the fracture toughness of implanted materials. It is well-known that numerous macromolecules and polymers may promote or suppress mineral formation.[58-60] This is very important in biomineralization studies,[61,62] which may be exploited, along with controlled nucleation, to further boost the cold sintering of HAp-based bioceramics.

Finally, the existing cold sintering protocols need to be addressed, specifically the practice of adding a liquid phase by dropping it onto the mineral powder, followed by manual homogenization in a mortar, which is largely irreproducible, and the obtained results may differ strongly among individual experimenters. In addition, it suffers from the inevitable formation of inhomogeneities at the solid–liquid interface, which may introduce further technological issues. A better approach is immersing the powder into the intended transient liquid, providing homogeneous surface wetting and uniform solid–liquid interactions with low solubility. After separating the solid and liquid phases, the amount of the retained liquid phase may be determined gravimetrically but also controlled by subsequent low-temperature drying, keeping the system moisturized. Adding suitable analytics, such as a pH electrode and/or a calcium-ion-selective electrode (suitable for HAp) in the mixed solution, or analyzing the calcium and phosphate amounts in the separated liquid, provides direct quantitative insights into the induced chemical changes, i.e., cold sintering can be conducted from a much better-known starting point. In that way, additional functional molecules can be introduced and homogeneously distributed, tentatively along forming grain boundaries, and the composition of the transient liquid can be conveniently adjusted to achieve improved functional properties. The initial nucleation behavior should be studied before implementing cold sintering experiments to achieve a better understanding of the mechanistic aspects of the process and to further advance the field.

We summarize the main gaps in the current understanding of cold sintering of bioceramics and sort them into three different groups of a physicochemical, structural, and technical nature.

The physicochemical aspect refers here to the lack of understanding or neglect of the dissolution behavior of, e.g., HAp in the employed solvent (acid, base, or water) at a specific concentration or exposure time. Dissolution seems to be applied generically to provide a facilitated material diffusion. Considering that HAp is a complex inorganic compound, both chemically and structurally, and that it also dissolves incongruently in acids, i.e., it remains unclear how much of the main material is actually dissolved under the applied conditions. This leads to a complex scenario in which we fail to know the chemistry of both the formed liquid and the remaining solid before applying the actual cold sintering conditions. Even more critical is the understanding of nucleation during cold sintering. The nucleation of HAp is difficult to understand even under well-controlled conditions and atmospheric pressure, while its nucleation behavior under high pressures in compact samples is still to be investigated. The presence of different chemical species originating from the solvent itself further complicates the cold sintering of bioceramics. Thus, to further improve the cold sintering strategies, attention must be paid to the dissolution and nucleation behavior in the respective transient liquids.

The structural aspect is related to structural changes occurring on the surface and in the bulk of the material upon dissolution. Incongruent dissolution may leave specific defects in the crystal lattice, the extent of which should be determined to understand the nucleation behavior and, eventually, the densification mechanisms. In this regard, the use of acids for the dissolution step is critical, considering the inevitable dehydroxylation. This may lead to exhausted diffusion along the *c*-axis, the central axis in the apatite crystal structure, and make the material prone to structural collapse upon exposure to mechanical stresses that bioceramics are expected to be subjected to, or affect its biological performance.

Finally, the technical aspect should not be forgotten, as no standardized protocols exist for the cold sintering of bioceramics. Specifically, every single experimenter approaches the mixing of a transient liquid/solvent and the mineral phase differently, varying in the amount of chemicals, concentration, pH, time, volume, and drying conditions. This is reflected in the observed dissolution behavior and, consequently, in the cold sintering behavior. Thus, standardized cold sintering protocols are highly desired to make the starting conditions before cold sintering as well defined and reproducible as possible.

Accordingly, we formulate several practical recommendations to implement in cold sintering studies. The idea is to show that the mineral dissolution and nucleation processes need to be better understood, including those under increased pressure and temperature, to govern the solid/liquid interaction during cold sintering.

(i) Select water as the transient liquid of choice for the cold sintering of HAp-based bioceramics.
(ii) Approach the phase separation point by carefully preparing a near-supersaturated/supersaturated aqueous calcium phosphate solution at a near-neutral or slightly acidic pH according to literature data or perform on-site experiments. Possibly use thermostated systems.
(iii) Immerse the powder to be cold-sintered in the prenucleation liquid; optimize the immersion time and stirring by determining the changes in pH and the concentrations of calcium and phosphate ions.
(iv) Apply simple drying after centrifugation to adjust the water content.
(v) Cold-sinter the uniformly moisturized powder following the standard cold sintering procedures, starting from room temperature.
(vi) In extension of point (ii), modulate the nucleation behavior of the calcium phosphate phase by adding appropriate nucleation additives, e.g., peptides, polymers, or ionic species, which will (partly) remain in the transient liquid. Use experimental protocols existing in the literature or perform on-site studies.
(vii) In extension of points (ii) and (vi), consider adding reinforcing phases for grain boundary engineering.

Given that cold sintering occurs under high temperatures and pressures, the nucleation behavior might differ (**Figure 2**), but

in most cases, it is expected to be promoted toward mineral formation and densification, more closely approaching real scenarios compared to the existing endeavors.

5. Biomedical challenges

This section discusses key biomedical challenges—specifically sterilization, scalability, and regulatory pathways—that must be addressed for cold-sintered bioceramics to advance toward clinical applications. At present, no studies have been reported on these aspects. Dry heating, steam sterilization (autoclaving), and gamma irradiation are the most common means used for sterilizing calcium phosphate bioceramics.

Dry heating is not expected to cause any chemical or structural changes in cold-sintered calcium phosphate bioceramics, as the current cold sintering temperatures are well above 100°C. By contrast, steam sterilization can alter the physicochemical properties[63] and lead to phase transformations in some calcium phosphate phases.[64] Saturated water vapor during hydrothermal autoclaving can influence crystallization kinetics and induce the crystallization of ACP.[65] These studies confirm that this sterilization method must be employed with caution. However, it should not be excluded that it might be used meaningfully to cold-sinter and sterilize the material simultaneously, given that steam sterilization is performed at temperatures of 100–200°C—temperatures not far from those currently used for cold sintering calcium phosphates.

Gamma irradiation is a powerful means of sterilization. Nevertheless, it may cause chemical changes, especially if calcium phosphates are co-sintered with some softer, polymeric materials (e.g., Gomes *et al.*[66]), ultimately influencing the mechanical and biological response. If applied, the dose of gamma irradiation must be carefully determined to avoid any adverse effects.

Scalability represents a major challenge in cold sintering when processing larger implant components, considering the relatively high pressures required for successful densification. Scaling up may be possible by applying a vertical geometry; for instance, a single die with a long body containing five specimens of the same diameter was used to scale up cold sintering from a single-piece to a batch process.[67] One of the advantages of cold sintering is the possibility of incorporating different materials into a single compact, which might be suitable for scaling up. Specifically, a metal or a plastic mesh can be used to connect multiple green bodies separately placed into specially designed dies in a horizontal geometry, enabling the construction of larger devices with adjustable spacing in between bioceramic bodies. This metal or polymer mesh may provide additional mechanical support, provided that the processing windows for the bioceramics and metal/polymer are appropriately determined.

Regulatory pathways for cold-sintered bioceramics do not exist at the moment, but they will need to go through a complete procedure, including the determination of the device type, establishing a quality management system, preclinical testing, regulatory submission, and post-market analysis; necessary tests and documents might differ depending on the country and the agency in charge, but the regulatory system is expected to be established in the near future.

6. Conclusions

Cold sintering is one of the most promising technologies for the fabrication of multifunctional bioceramics. A literature survey on cold-sintered ceramics for biomedical applications indicates that significant effort has been devoted to identifying appropriate transient liquid phases to promote densification at low temperatures (up to 300°C) and relatively low pressures (up to 600–800 MPa) through dissolution–precipitation mechanisms. The main bioceramic systems studied are calcium phosphates, ranging from amorphous systems to β-TCP, HAp, and DCPD. Promising results have been achieved in attaining high relative densities (~99%) and nanometer-scale grain sizes, particularly for HAp, with mechanical properties comparable to those of conventionally sintered counterparts. At present, the translation of cold-sintered bioceramics into real-world applications remains limited, with most studies still at the early stages of basic research and discovery. Although acids and bases are favorable for enhancing mineral dissolution—a critical initial step for successful cold sintering—there is no clear evidence of their advantages over water as a transient liquid, which raises questions about the understanding of the main densification mechanism. In this context, we critically analyzed the transient liquid systems employed and correlated cold sintering behavior with nucleation studies of HAp, the most important bioceramic material. The nucleation aspect has been poorly integrated into existing cold sintering strategies, despite being decisive for densification under cold sintering conditions, as most attention remains focused on dissolution. Promising pseudo-biomineralization approaches have also emerged, which may or may not improve conditions for effective nucleation. We strongly recommend using water as the transient liquid of choice in the cold sintering of HAp-based bioceramics and designing experiments based on insights from nucleation studies. These may include the addition of various ionic and molecular species as additives, nucleators, reinforcing phases, therapeutic molecules, growth factors, and medicaments. Finally, we have provided a set of practical recommendations for revisiting cold sintering protocols, aiming to further advance the development of bioceramic materials for bone tissue reconstruction.

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Ethics approval and consent to participate
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Availability of data
Not applicable.

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